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Formulation and Characterization of Polycaprolactone-Based Buccal Patches for Sustained Release of Irbesartan

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This research focuses on the formulation and characterization of polycaprolactone-based buccal patches for sustained release of irbesartan. The incorporation of polymers, specifically HPMC and polycaprolactone, met the criteria for developing a high-quality buccal film. In vitro dissolution data for formulation F3 batch showed a release rate of 91.49%, while in vitro drug release through cellophane membrane from F3 batch was 58.71%. The percent swelling index of irbesartan buccalpatches from the F3 formulation was found to be 59.61%. Preformulation studies of allexcipients were conducted using UV and FTIR techniques. Overall, this study presents promising results for the development of sustained-release buccal patches for irbesartan delivery.
Keywords: Polycaprolactone, Buccal Patches, Sustained Release, Irbesartan, Drug Release, Swelling Index.

1. Introduction

Oral drug delivery systems have remained a cornerstone of pharmaceutical development due to their convenience, cost-effectiveness, and high patient compliance. However, certain therapeutic agents, such as irbesartan, present challenges when administered orally due to extensive first-pass metabolism and inconsistent bioavailability.[1-3] To address these limitations, alternative drug delivery systems, such as buccal patches, have gained considerable attention. Buccal patches offer distinct advantages, including bypassing the hepatic first-pass metabolism, sustained drug release, and ease of administration. These attributes make them an ideal candidate for delivering antihypertensive agents like irbesartan, which requires consistent plasma concentration for optimal therapeutic effect.[4]

In this study, polycaprolactone (PCL), a biodegradable polymer, and hydroxypropyl methylcellulose (HPMC), a hydrophilic polymer, were utilized to formulate buccal patches for sustained release of irbesartan. The synergistic use of these polymers aimed to enhance the mechanical strength, drug loading capacity, and sustained-release characteristics of the buccal film. Comprehensive preformulation studies, including UV and FTIR analyses, were conducted to evaluate the compatibility and stability of the excipients with irbesartan. The formulation was further characterized for its drug release profile, swelling index, and in vitro performance. The F3 formulation exhibited promising results, with a controlled release of 91.49% over an extended period and favorable swelling behavior, demonstrating its potential as a sustained-release delivery system for irbesartan.[5-7]

This research emphasizes the potential of polymer-based buccal patches in overcoming conventional drug delivery challenges, presenting a viable approach for enhancing the therapeutic efficacy of irbesartan.

2. Materials and Methods

Materials

The chemicals were obtained from different sources and used as received. Irbesartan was a gift sample from Cipla Pharmaceuticals, India.HPMC, Eudragit L 100, Aspartame, Ethyl cellulose, Dimethyl sulfoxide, Propylene glycol, Ethanol were obtained from Research-Lab Fine Chem Industries, Mumbai.

Methods

1. Preparation of Backing Membrane[8-11]

The ethyl cellulose backing membrane was prepared by solvent casting technique. Ethyl cellulose was dissolved in 30 ml mixture of acetone and isopropyl alcohol and kept for 1 hour in magnetic stirrer for continuous stirring. Dibutyl phthalate was added in above solution as plasticizer. This solution was poured in a petridish and kept overnight for drying at the room temperature to obtain the backing membrane.

Table 1. :Composition of backing membrane

Ingredient	Quantity
Ethyl cellulose	1.5 gm
Acetone	19 ml
Isopropyl alcohol	11 ml
Dibutyl phthalate	2 ml

Table 2. : Composition of buccal patch of Irbesartan

Batch	Irbesartan (mg)	HPMC (mg)	Polycaprolactone(mg)	Propylene glycol (ml)	Aspartame (mg)	Ethanol (ml)
1	75	110	80	2	0.2	25
2	75	85	110	2	0.2	25
3	75	110	50	2	0.2	25
4	75	60	80	2	0.2	25
5	75	110	110	2	0.2	25
6	75	85	50	2	0.2	25
7	75	60	110	2	0.2	25
8	75	85	80	2	0.2	25
9	75	60	50	2	0.2	25

2. Folding endurance[12]

A strip of film (2× 2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

3. Drug content[13]

The patches (2 cm^2) were cut and added to a volumetric flask containing 10 ml of phosphate buffer of pH 6.8 (solution) from this solution 0.1 ml solution was taken and the volume was made (20 ml) with phosphate buffer saline (pH 6.8). The contents were filtered using Whatman filter paper and the filter was examined for the drug content against the reference solution consisting of phosphate buffer (contains no drug) at 242 nm specrtophotometrically.

4. In vitro drug release through cellophane membrane.[14-15]

The release profile of drug from buccal films was performed by using Franz diffusion cell. The formulation was placed on cellophane membrane mounted between the donor and receptor compartment of the diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 6.8) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 242 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the cellophane membrane was determined as a function of time.

5. In vitro drug release[16]

The in vitro releases study was carried out using USP dissolution apparatus type 2 in 300ml phosphate buffer 6.8 at 50 rpm. A 2cm^2 patch was taken and attached to a glass slide in order to prevent floating of patches over the dissolution media. The in vitro release study was carried out for six hours. 5ml of sample were withdrawn at various time intervals. Replacing with fresh medium each interval. Absorbance of the sample was measured at 242 nm and the cumulative percentage release was calculated.

6. Swelling studies[17]

The degree of swelling of bioadhesive polymer is an important factor affecting adhesion. The swelling rate of buccoadhesive patch was evaluated by placing the patch in phosphate buffer solution pH 6.8 at 37 ± 1ºC. The patches of each batch were cut and weighed (W1). The patches

were placed in phosphate buffer and were removed at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr. Excess water on the surface was carefully absorbed using filter paper and swollen patches were reweighed. The average weight W2 was calculated and the swelling index was calculated by the formula:

Swelling index = [(W2 -W1) ÷ W1] × 100

Where, W1 = Initial weight of the patch

W2 =Final weight of the patch

7. Surface pH[18]

The surface pH of the patch was determined by the method similar to that used by Bottenberg et al. (1991). The patches were allowed to swell by keeping them in contact with 1drop of distilled water for 2 h at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 min.

3. Result

1. Characterization of drug:

Table no. 3. General description of Drug

Tests	Specifications	Observation
Color	White	White
Odour	Odorless	Odorless
Taste	Tasteless	Tasteless
Physical appearance	Solid crystalline powder	Solid crystalline powder

2. Melting point determination:

Melting point of the Irbesartan was determined by capillary fusion method; one Sided closed capillary filled with drug and put into the melting point apparatus. Temperature was noted at which solid drug changes into liquid. It was found to be 180-181 0 c.

3. Spectroscopic analysis:

a. Determination of λ max:

The standard solution of Irbesartan of concentration 10 µg/ml showed maximum absorbance at the wavelength of 242 nm (Fig 1). Hence the λ max of Irbesartan was found to be 242 nm.

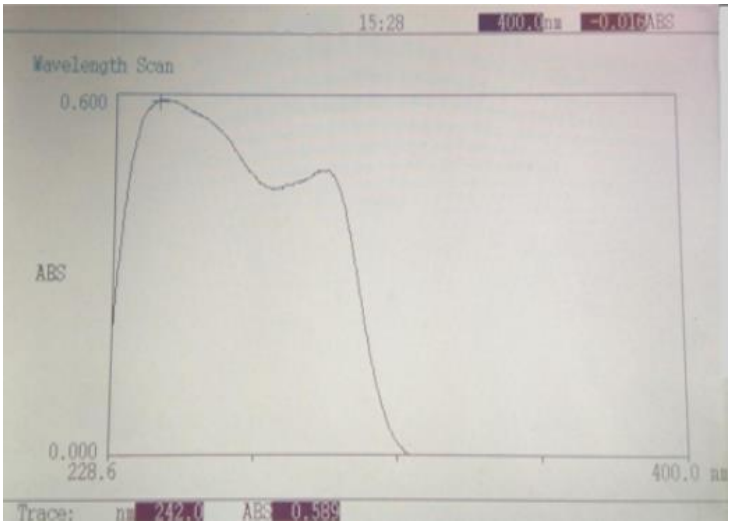

Figure: 1. UV spectrum of Irbesartan in phosphate buffer (pH 6.8).

b. Calibration curve of Irbesartan:

Standard calibration curve of Irbesartan was obtained by plotting absorbance vs. concentration using UV spectroscopy. Calibration curve of Irbesartan in phosphate buffer, (pH 6.8).

4. Saturated Solubility studies of Irbesartan:

Saturated solubility is important parameter that will affect the bioavailability of drug because of its poor solubility in aqueous media it possesses limitation in absorption of drug. Here saturation solubility of Irbesartan was performed in distilled water and phosphate buffer pH 6.8. Saturation solubility of Irbesartan in distilled water and phosphate buffer pH 6.8 was shown in table from the result it suggested that Irbesartan has very less solubility in water and phosphate buffer pH 6.8. The solubility of IRB in distilled water was found to be 0.002731 mg/ml, and phosphate buffer (pH 6.8) 0.3884 mg/ml. The pH of solution showed a significant impact on the solubility of IRB. IRB exhibited low solubility in water and phosphate buffer pH 6.8. Solubility of Irbesartan was determined in distilled water and phosphate buffer of pH 6.8. It is shown in table no.4.

Table no.4: Solubility of Pure drug in Distilled water and 6.8 Phosphate buffer

Solvent	Solubility (mg/ml)
Distilled Water	0.002731
pH 6.8 Phosphate buffer	0.003884

Table 5: Evaluation of buccal patch thickness, folding endurance and drug content of buccal patches

Formulation	Thicknes (mm)	Weight (mg)	Surface pH study	Folding endurance (mg)	Drug content (%)
F1	0.71±0.16	177.33±1.25	6.74±0.11	222±1.24	90.31±0.51
F2	0.70±0.13	176.33± 1.87	6.67±0.24	208±2.37	86.49±0.26
F3	0.71±0.09	174.66± 0.16	6.75±0.20	219±1.56	92.94±0.14
F4	0.63±0.10	175.33±1.28	6.73±0.17	197±2.41	89.50±0.25
F5	0.72±0.58	166.33±2.74	6.40±0.16	232±3.12	89.17±0.56
F6	0.68±0.21	170.66±0.49	6.58±0.15	205±2.74	91.22±0.16
F7	0.70±0.54	173.66±0.84	6.52±0.24	206±1.49	86.61±0.37
F8	0.69±0.79	173.66±1.23	6.72±0.15	215±2.33	87.28±0.41
F9	0.62±0.34	176.66±1.58	6.71±0.17	198±3.61	89.63±0.33

*All values represents mean ± standard deviation (n=3)

5. Thickness

Thickness of the formulated patches was measured on three different places to ensure the uniformity of patches. Average and standard deviation of all three readings were calculated and recorded in table 5. Thickness was found to be in the range of 0.62 ± 2.34 mm to 0.72±1.58 mm. From the results obtained it was confirmed that all the patches were uniform and did not have any significant differences in the thickness at different points. F9 batch showed the minimum thickness while F5 batch showed the maximum. Thickness of the patch was increasing with increase in concentration of polymers.

6. Weight Uniformity

Weight uniformity of all the batches were determined by weighing three 2 x 2 cm2 sections of each patch and then average weight was calculated. From the results shown in table 5, it was observed that all the batches were uniform in weight and there was no significant difference in the weight of the individual formulations from the average value and the variations were all within normal limits. Weight uniformity was found to be in range of 166.33±2.74 mg to177.33±1.25 mg

7. Surface pH

Surface pH of patches of all the batches was determined by using pH meter and recorded in table 5. Surface pH ranged from 6.40±0.16 to 6.75±0.20. Surface pH of all formulations was near to neutral pH hence, should not cause any irritation in the buccal cavity.

8. Folding Endurance

The recorded folding endurance of the formulations was the range between 197±2.41 to 232±3.12. Which indicates good flexibility? Table 5. Shows the folding endurance value of all the formulations.

9. Drug content

The patches (2 cm^2) were cut and added to a volumetric flask containing 10 ml of phosphate buffer of pH 6.8 (solution) from this solution 0.1 ml solution was taken and the volume was made (20 ml) with phosphate buffer saline (pH 6.8). The contents were filtered using Whatman filter paper and the filter was examined for the drug content against the reference solution consisting of phosphate buffer (contains no drug) at 242 nm specrtophotometrically.Maximum drug contain was observed in batch F3 (92.94%) while batch F7 showed minimum drug contain (86.61%). Maximum swelling percentage was observed for F3 batch because of more release.

10. Swelling Index

Swelling studies of prepared patches were performed using 6.8 pH phosphate buffers for 6 hr and the results are shown in table no. 6. Swelling behavior of a buccal drug delivery system is an important property for uniform and prolonged release of the drug and effective mucoadhesion. The effect of various compositions of patches on the swelling index of the patches was studied by plotting the graph between percent swelling and time as shown in fig 2 and table 6 Maximum swelling was observed in batch F3 (59.61%) while batch F7 showed minimum swelling (54.43%). Maximum swelling percentage was observed for F3 batch because of more release.

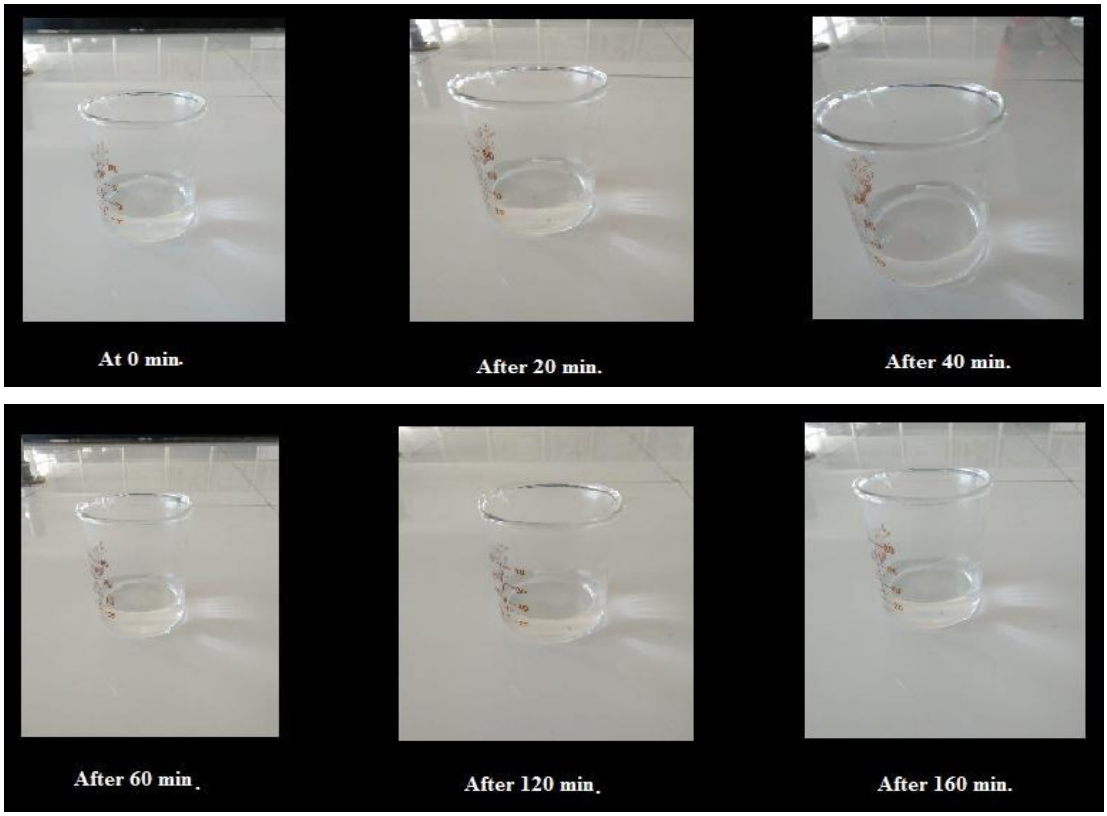

Figure 2: Swelling ability of patches batch F3

Table 6. Percent Swelling Index of Irbesartan Buccal Patches from F1 to F9 Formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
20	10.52±0.27	09.22±0.41	11.63±0.55	11.83±0.08	11.23±0.61	10.89±0.63	08.41±0.71	13.01±0.35	13.17±0.63
40	23.23±0.15	20.35±0.19	22.29±0.48	21.34±0.50	22.46±0.55	23.41±0.37	20.51±0.62	25.37±0.52	24.87±0.33
60	31.82±0.43	29.40±0.62	32.14±0.43	29.67±0.26	31.25±0.36	31.46±0.44	28.35±0.49	32.06±0.05	32.71±0.23
120	42.11±0.23	43.25±0.27	41.32±0.21	41.34±0.12	43.21±0.32	45.62±0.12	41.93±0.18	44.52±0.34	43.95±0.19
160	59.42±0.51	55.15±0.85	59.61±0.17	56.19±0.45	56.07±0.48	58.31±0.88	54.43±0.84	58.02±0.56	57.82±0.84

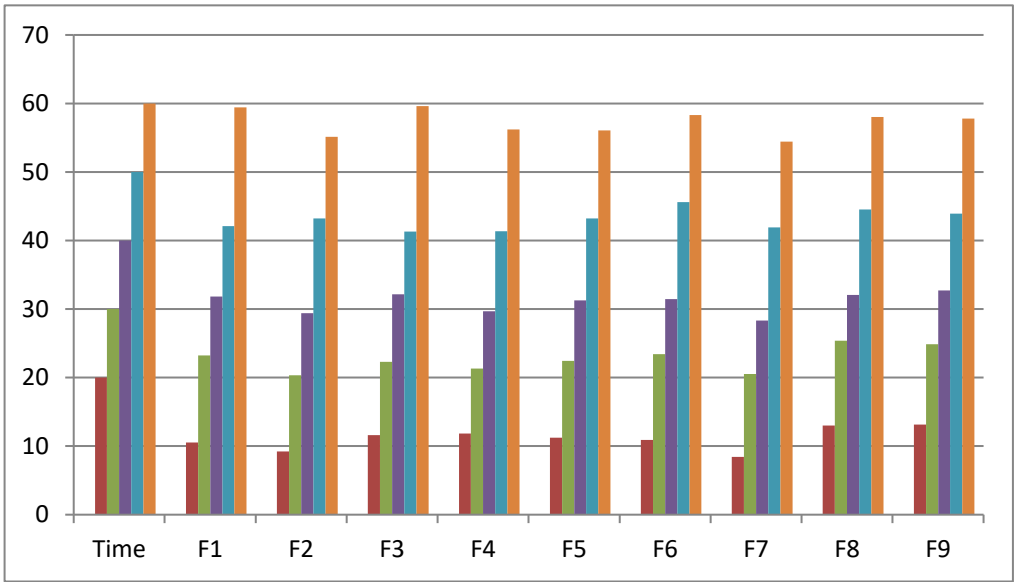

Figure. 3. Comparative Swelling index of All Formulations.

11. In vitro drug release through cellophane membrane.

The release profile of drug from buccal films was performed by using Franz diffusion cell. The formulation was placed on cellophane membrane mounted between the donor and receptor compartment of the diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 6.8. solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (0.1 ml) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 242 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The amount of drug released across the cellophane membrane was determined as a function of time. Maximum in vitro release was found to be 58.71±0.14% over a period of 180 min in batch F3 while minimum in vitro release was found to be 54.43±0.84% in batch F7. These results were further supported by swelling studies results, where highest swelling was shown by batch F3 and hence resulting in faster drug release.

Table No.:7: In vitro drug release through cellophane membrane F1-F9 batches

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
15	8.21±0.25	7.84±0.21	10.84±0.5	8.12±0.23	7.92±0.15	9.10±0.20	7.30±0.43	8.35±0.17	9.45±0.14
30	16.32±0.33	15.54±0.15	17.32±0.11	14.5±0.51	16.63±0.26	16.95±0.42	15.66±0.49	15.58±0.19	15.98±0.44
60	25.58±0.52	22.46±0.26	26.23±0.17	24.44±0.32	21.20±0.28	24.58±0.34	21.84±0.41	22.14±0.22	21.58±0.51
90	31.55±0.11	30.17±0.22	33.41±0.30	31.08±0.25	27.30±0.14	30.22±0.20	27.74±0.23	29.21±0.27	26.84±0.30
120	38.25±0.17	36.47±0.09	41.59±0.3	40.78±0.18	33.86±0.35	37.12±0.51	32.21±0.38	34.29±0.78	32.47±0.29
180	48.13±0.19	44.12±0.24	49.87±0.10	47.35±0.9	46.58±0.41	48.34±0.43	40.55±0.51	46.85±0.16	45.32±0.47
240	56.12±0.29	51.88±0.19	58.71±0.37	54.41±0.14	54.56±0.12	55.81±0.39	47.70±0.21	54.54±0.18	55.17±0.35

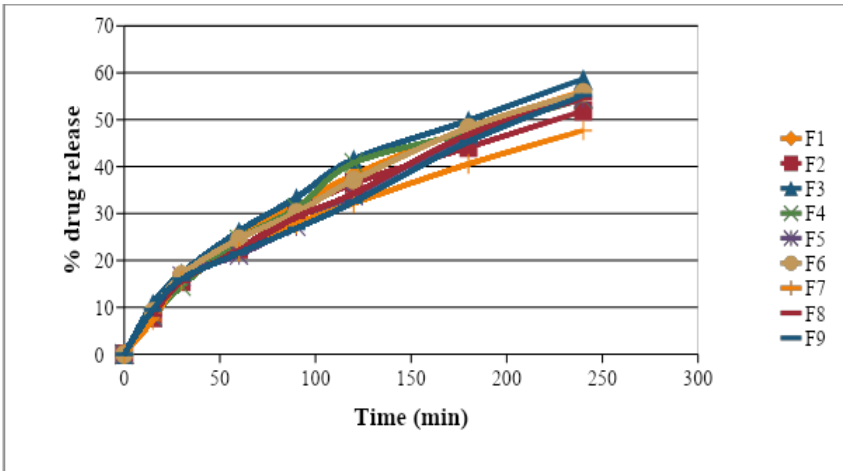

Figure 4: Cellophane membrane Drug release (%) of batch F1-F9

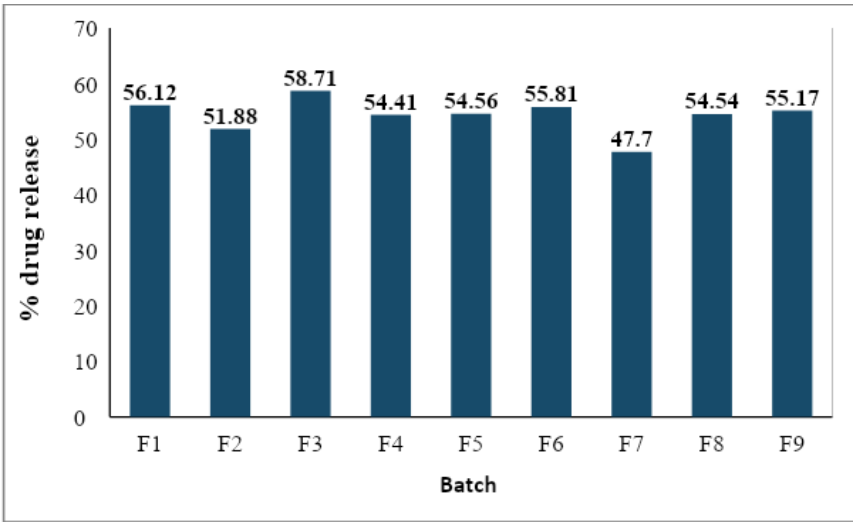

Figure. 5. Comparative Cellophane membrane Drug release (%) of All Formulations.

12. In vitro drug release through Dissolution apparatus

The in vitro releases study was carried out using USP dissolution apparatus type 2 in 300ml phosphate buffer 6.8 at 50 rpm. A $2cm^2$ patch was taken and attached to a glass slide in order to prevent floating of patches over the dissolution media. The in vitro release study was carried out for six hours. 5ml of sample were withdrawn at various time intervals. Replacing with fresh medium each interval. Absorbance of the sample was measured at 242 nm and the cumulative percentage release was calculated. Maximum in vitro release was found to be 91.49±0.41% over a period of 240 min in batch F3 while minimum in vitro release was found to be 87.74±0.73 in batch F7. These results were further supported by swelling studies results, where highest swelling was shown by batch F3 and hence resulting in faster drug release.

Table No. 8: In vitro Dissolution data of formulation F1-F9 batches

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
15	12.72±0.38	13.10±0.27	14.61±0.10	12.83±0.34	11.98±0.13	12.56±0.20	12.41±0.09	13.01±0.12	11.19±0.81
30	27.23±0.42	26.59±0.36	29.47±0.21	26.73±0.30	26.49±0.68	23.41±0.29	28.51±0.72	26.37±0.53	24.87±0.02
60	41.62±0.13	38.48±0.88	42.83±0.33	40.67±0.32	43.54±0.12	36.46±0.56	37.35±0.65	41.06±0.95	38.71±0.44
90	55.10±0.69	53.22±0.29	51.42±0.03	59.34±0.11	51.19±0.46	45.62±0.42	50.94±0.24	52.88±0.19	50.50±0.43
120	68.65±0.41	65.42±0.26	68.17±0.19	68.27±0.53	62.66±0.43	59.24±0.39	61.53±0.25	63.12±0.51	62.99±0.66
180	79.35±0.13	72.66±0.47	79.49±0.23	72.14±0.40	74.36±0.25	75.18±0.41	73.98±0.44	71.53±0.84	70.69±0.90
240	90.52±0.53	87.91±0.55	91.49±0.41	88.05±0.52	89.16±0.65	90.69±0.61	87.74±0.73	88.82±0.50	88.36±0.66

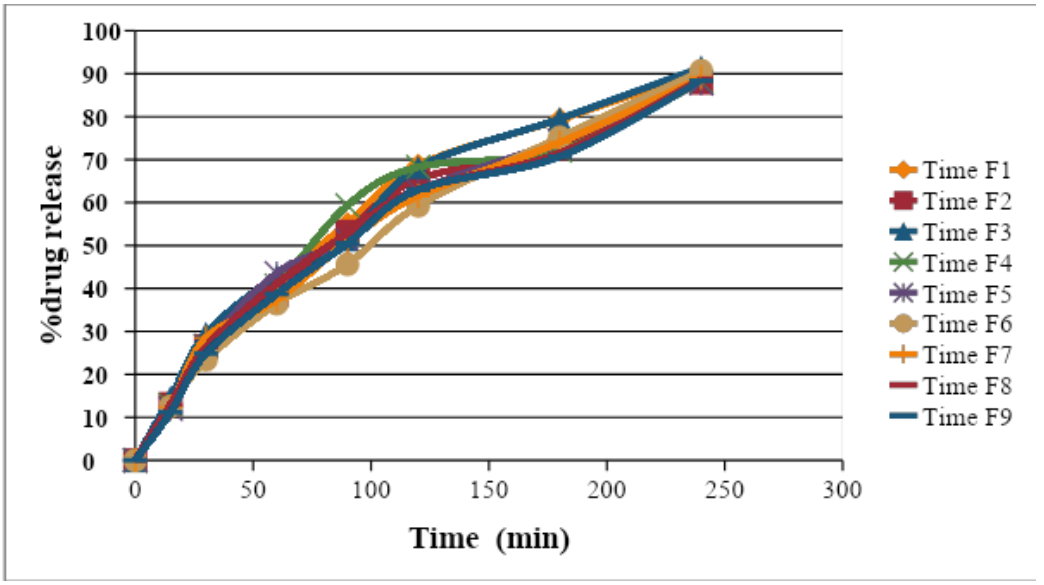

Figure 6: In vitro drug release of batch F1-F9

4. Conclusion

The formulation and characterization of polycaprolactone-based buccal patches for sustained

release of irbesartan demonstrated favorable results in terms of drug release profiles and swelling properties. The use of HPMC and polycaprolactone as polymers showed promise in achieving sustained drug release. The in vitro dissolution data and drug release through cellophane membrane indicate the potential of the developed formulation for controlled drug delivery. The preformulation studies using UV and FTIR provided valuable insights into the compatibility of excipients. This research lays a foundation for further optimization and evaluation of the developed buccal patches for enhanced therapeutic outcomes in irbesartan delivery.

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