Research Article

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Formulation and evaluation of Baricitinib Buccoadhessive tablets

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ABSTRACT

Baricitinib is used to treat rheumatoid arthritis. It helps decrease pain, tenderness, and swelling in the joints. The main objective of the study was to formulate and evaluate bioadhesive buccal tablets Baricitinib. Bioadhesive buccal tablets were prepared by direct compression method using bioadhesive polymers like Carbopol, Sodium CMC, Sodium alginate and Hydroxy propyl methyl cellulose K4M in different ratios. The physicochemical compatibility of drug and polymers was studied by FT-IR spectroscopy. Prepared tablets were evaluated for *in vitro* drug release,bioadhesion strength, swelling index, moisture absorbance, surface pH. Among the prepared formulation containing Sodium alginate (Fc2)was found to be best formulation which showed the higher bioadhesive strength of 2.68±0.03 N (peak detachement force) and 0.95±0.08 mJ (work of adhesion).

Keywords: Baricitinib, Bioadesive buccal tablet *in vitro* drug release, Bio adhesion strength.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing .Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) A vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promote the residence time and act as controlled release dosage forms.

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The use of many hydrophilic macromolecular drugs as potential therapeutic agents is their in adequate and erratic oral absorption. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs can not be delivered effectively through the conventional oral route.

Baricitinib (Olumiant™) is a type of drug known as a JAK inhibitor. These drugs work by interfering with the inflammatory processes within the immune system that lead to the symptoms of rheumatoid arthritis. Baricitinib is a long-term treatment.

MATERIALS

Baricitinib Provided by Sura Labs, Dilsukhnagar, Hyderabad. Carbopol 934was gift sample from Lucid pharma, Sodium CMC,Sodium alginate and Mannitol was gift sample from Universal laboratories. HPMC K4M was gift sample from Loba chem. Pvt ltd, Mumbai. Magnesium stearate was gift sample from Magnesium stearate. Aerosil was gift sample from Nice chemicals Ltd.

METHODOLOGY

Preformulation parameters

The various characteristics of blends Angle of repose, Bulk density, Tapped density,Carr's index , tested as per Pharmacopoeia.

Formulation development of Tablets

Baricitinib and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with Magnesium stearate. The tablets were prepared by using direct compression method.

Table 1: Formulation Chart

INGREDIENTS	FORMULATION CHART								
	Fa1	Fa2	Fa3	Fb1	Fb2	Fb3	Fc1	Fc2	Fc3
Baricitinib	2	2	2	2	2	2	2	2	2
Carbopol 934	25	35	45	-	-	-	-	-	-
Sodium CMC	-	-	-	25	35	45	-	-	-
Sodium alginate	-	-	-	-	-	-	25	35	45
HPMC K4M	30	30	30	30	30	30	30	30	30
Magnesium stearate	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5
Mannitol	33	23	13	33	23	13	33	23	13
Total weight (mg)	100	100	100	100	100	100	100	100	100

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content as per IP.

***In vitro* release studies**

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 272nm.

Surface pH

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffer (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3).

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:

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Swelling Studies

Buccal tablets were weighed individually (designated as W_1) and placed separately in petri dishes containing 5 mL of phosphate buffer (pH 6.8) solution. At regular intervals (1, 2, 3, 4, 5 and 6 hrs), 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).This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq**.**

$$\text{Swelling index} = \frac{(W_2 - W_1) \times 100}{W1}$$

***Ex vivo*bioadhesion strength**

Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced force guage equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK) according to method describe as it is fitted with 25kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the buccal tablet to be tested was adhered to another cylindrical stainless steel adaptor similar in diameter using a cyanoacrylate bioadhesive. Mucin 100 µL of 1 %w/v solution was spread over the surface of the buccal mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5mm/sec until the tablet was completely detached from the mucosa. 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.

$$\text{Force of adhesion} = \frac{\text{Bioadhesion strength} \times 9.8}{1000}$$

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

Application of Release Rate Kinetics to Dissolution Data

The obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model to analyze the mechanism of the drug release.

Stability studies

For the determination of stability of prepared different formulations, accelerated stability studies were carried out on optimised formulation. Tablets were stored according to ICH guidelines at 40±2°C/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. After completionofrequired duration time, samplewaswithdrawnandtestedfordifferent testssuchashardness,drug contentand*in vitro* drug release.

RESULTS & DISCUSSION

Preformulation parameters of powder blend

Table 2:Physical Properties of Precompression Blend

Formulation Code	Angle of repose (θ)	Bulk density (g/mL)	Tapped density(g/mL)	Carr's index (%)	Hausner's ratio
Fa1	25.16±0.8	0.628±2.5	0.714±1.6	14.27±0.12	1.17±0.5
Fa2	27.54±2.5	0.662±1.2	0.763±1.3	13.23±0.1	1.15±0.05
Fa3	24.68±1.2	0.560±0.5	0.631±1.2	11.25±0.15	1.12±0.08
Fb1	22.9±1.4	0.672±1.2	0.742±1.2	12.2±0.1	1.21±0.2
Fb2	28.3±2.2	0.643±2.1	0.624±0.7	14.2±0.9	1.11±0.2
Fb3	24.84±0.4	0.654±1.6	0.755±1.4	13.12±1.8	1.12±0.06
Fc1	28.68±0.8	0.782±1.2	0.869±0.8	11.0±1.2	1.11±0.2
Fc2	24.65±2.5	0.695±1.5	0.823±0.8	15.5±0.08	1.18±0.1
Fc3	26.76±1.2	0.526±1.8	0.612±1.6	14.0±0.02	1.16±0.1

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

Physicochemical characterization of buccal tablets

Table 3: Physico-chemical parameters of Baricitinib buccal tablets

Formulation Code	Average Weight (mg)	Thickness (mm)	Hardness ($kg/cm^{2)}$	Friability (%)	Assay (%)
Fa_1	100.74 ± 0.61	2.37 ± 0.03	5.2±0.14	0.55	99.65 ± 0.44
Fa_2	99.04 ± 0.80	2.34 ± 0.02	5.3±0.29	0.63	99.13 ± 0.75
Fa_3	100.38 ± 0.71	2.36 ± 0.03	5.2±0.49	0.66	99.28 ± 0.92

Fb_1	99.45 ± 0.64	2.36 ± 0.02	5.4±0.17	0.58	98.77 ± 1.00
Fb_2	100.91 ± 1.01	2.21 ± 0.02	5.5±0.28	0.64	98.96 ± 0.44
Fb_3	99.98 ± 0.82	2.34± 0.01	5.9±0.24	0.47	98.81 ± 0.92
Fc1	100.38 ± 0.80	2.68± 0.02	6.8±0.17	0.66	99.77 ± 0.72
Fc2	100.04 ± 0.71	2.34± 0.03	6.5±0.49	0.65	99.81 ± 0.44
Fc3	99.94 ± 0.75	2.22± 0.02	6.0±0.19	0.43	99.15 ± 0.75

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

Weight variation test

The average weight of the tablet is approximately in range of 99.94 ± 0.75 to100.74 ± 0.61mg, so the permissible limit is ±7.5% (>100 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

The results showed that the hardness of the tablets is in range of5.2 – 6.0 kg/cm^2,which was within IP limits.

Thickness

The result showed that thickness of the tablet is raging from 2.21 to 2.68 mm.

Friability

The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

From the drug content studies it was concluded that all the formulations were showing the % drug content values within 98.69±1.00 to 99.81±0.04%.All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In vitro* drug release studies**

Table 4:*In vitro* drug release profile

Time (hrs)	Fa1	Fa2	Fa3	Fb1	Fb2	Fb3	Fc1	Fc2	Fc3
0	0	0	0	0	0	0	0	0	0
1	49.67	10.965	21.85	29.125	7.037	14.32	33.8	51.62	35.425
2	66.05	13.257	32.15	42.22	9.24	20.867	43.05	58.92	54.675
3	80.05	32.11	47.62	47.12	22.536	27.9	54.82	70.06	83.475
4	84.3	38.44	51.22	56.05	29.9	30.85	60.88	82.53	85.925
5	90.02	38.74	53.85	61.6	32.11	34.62	62.22	97.85	87.75
6	92.23	43.09	58.98	65.7	38.4	39.07	69.05	98.32	89.32

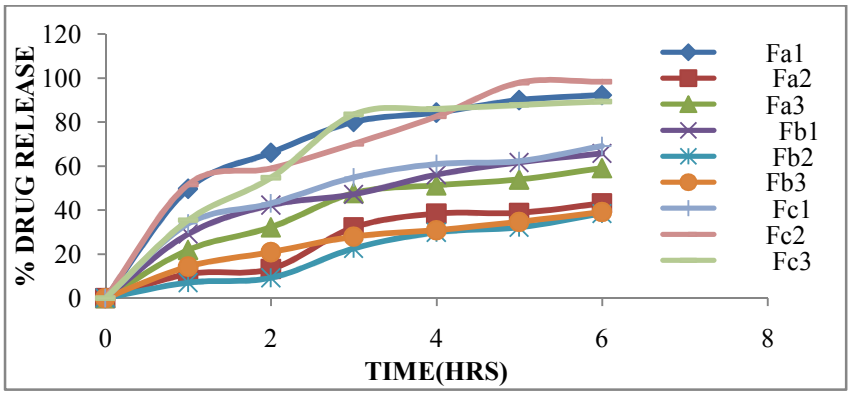

Figure 1: Dissolution profile of Baricitinib

Table 5 :Moisture absorption, Surface pH, Bioadhesive strength values of various formulations

Formulation code	Moisture absorbance	Surface pH	Bioadhesive strength	
			Peak detachment force (N)	Work of adhesion (mJ)
Fa1	30.83± 0.25	6.96±0.16	1.89±0.55	0.47±0.28
Fa2	25.66 ± 0.25	6.86±0.43	2.34±0.02	0.62±0.04
Fa3	32.45 ± 0.25	6.9±0.35	2.05±0.42	0.5±0.28
Fb1	17.51 ± 0.30	6.5±0.12	1.24±0.38	0.34±0.17
Fb2	9.61±0.25	6.66±0.23	2.42±0.06	0.74±0.02

Fb3	20.83±0.25	7.43±0.15	1.30±0.12	0.40±0.38
Fc1	14.16±0.25	6.8±0.43	2.30±0.26	0.61±0.13
Fc2	13.33±0.30	6.77±0.24	2.68±0.03	0.95±0.08
Fc3	19.16±0.30	6.67±0.13	2.44±0.47	0.69±0.41

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

Table 6: Swelling studies of buccal tablets

% Swelling index									
Time (hr)	**Fa1**	**Fa2**	**Fa3**	**Fb1**	**Fb2**	**Fb3**	**Fc1**	**Fc2**	**Fc3**
0	0	0	0	0	0	0	0	0	0
1	19.6	28	4.0	11.2	2.4	3.8	33.8	14.9	18.8
2	39.6	75.4	10.7	18.6	12.2	14.4	77.5	39.3	26.3
3	80.4	84.7	44.0	46.0	15.8	17.9	85.5	62.0	58.9
4	132	114.4	99.8	46.8	35.4	36.4	126	102.9	102.5
5	175.6	155.9	148.1	71.7	37.8	42.3	130.7	137.5	123.4
6	197.5	212.4	197.3	91.2	41.5	49.7	142.8	143.7	135.7

Table7: Release kinetics and correlation coefficients

Formulation code	**Mathematical models(Release kinetics)**				
	Zero order	**First order**	**Higuchi**	**Korsemeyer - peppas**	
	R^2	**R^2**	**R^2**	**R^2**	**n**
Fc2	0.866	0.892	0.982	0.946	0.39

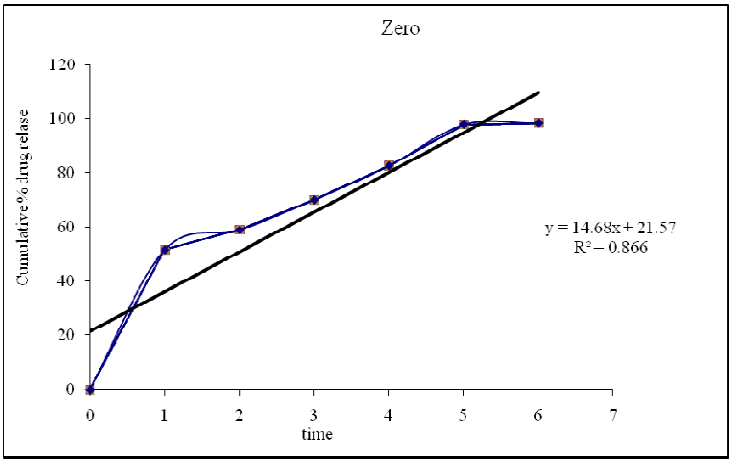

Figure 2: Zero order release kinetics

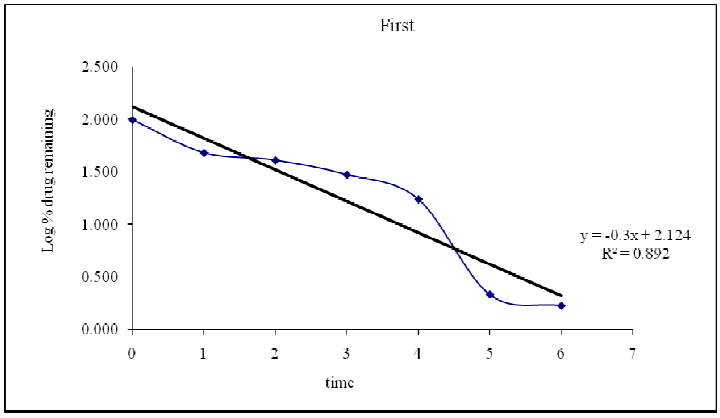

Figure 3: First order release kinetics

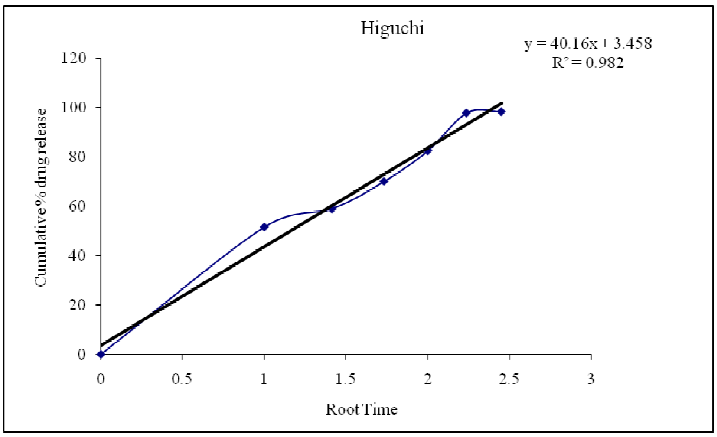

Figure 4 : Higuchi release kinetics

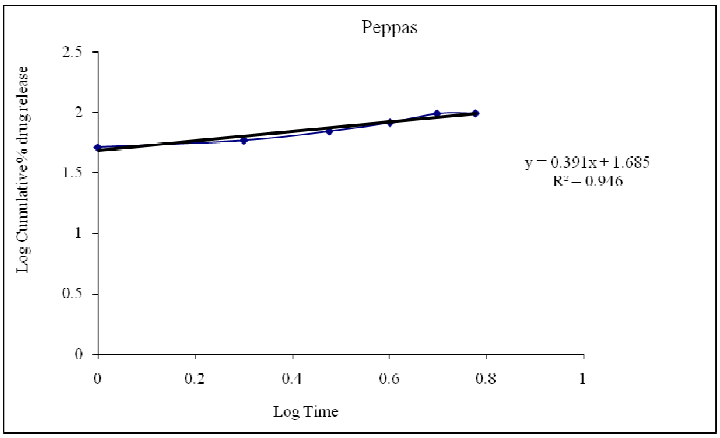

Figure 5 : Peppas release kinetics

The optimized formulation such as Sodium alginate (Fc2) follows First order and Higuchi order of release kinetics governed by Fickian diffusion mechanism.

Accelerated stability studies

The stability study of the optimised tablets were carried out according to ICH guidelines at 40±2°C/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. The results from stability studies are shown in table.

Table 8:Stability dissolution profile of Fc2 for 1st, 2nd & 3rd months Dissolution Profile of Baricitinib optimised formulation (Fc2)

TIME(Hours)	Fc2 (1st month)	Fc2 (2nd month)	Fc2 (3rd month)
0	0	0	0
1	51.62	50.11	50.06
2	58.92	58.24	57.92
3	70.06	70.01	69.86
4	82.53	82.12	81.98
5	97.85	96.81	96.80
6	98.32	98.30	97.89

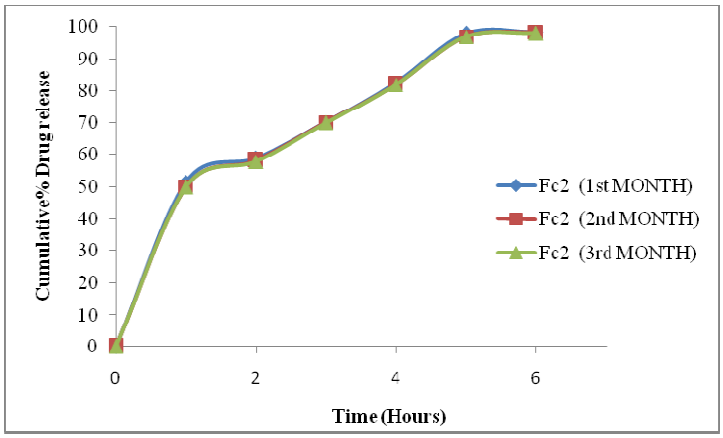

Figure 6: Dissolution Profile of Baricitinib optimised formulation (Fc2) for 3 months

Table 9: Physicochemical parameters of most satisfactory formulation during stability studies for optimised formulation

Time Period (Month)	Hardness (kg/cm^2)	Drug Content (%)
1	6.5	99.71
2	6.3	99.12
3	6.2	98.75

There was no major change in the various physicochemical parameters evaluated like hardness, drug content, *in vitro* dissolution pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability studies.

CONCLUSION

Development of bioadhesive buccal tablets of Baricitinib is one is used to treat rheumatoid arthritis. It helps decrease pain, tenderness, and swelling in the joints. Buccal tablets of Baricitinib were prepared by direct compression method using various bioadhesive polymers like Carbopol, Sodium CMC, Sodium alginate in the combination of Hydroxy propyl methyl cellulose K4M in different concentrations.

The formulated buccal tablets were evaluated for different parameters such as drug excipient compatibility studies, physical properties of precompression blend, weight variation, thickness, hardness, content uniformity, *in vitro* drug release, surface pH, swelling index, moisture absorption studies, *ex vivo* bioadhesive strength tablets. *In vitro* drug release studies performed in phosphate buffer pH 6.8 for 6 hrs in standard dissolution apparatus.

The following conclusions could be drawn from the results of various experiments

- FTIR study concluded that there was no interaction between drug and excipients.
- The physico-chemical properties of all the formulations prepared with different polymers like Carbopol, Sodium CMC, Sodium alginate in the combination of Hydroxy propyl methyl cellulose K4M were shown to be within limits.
- The *in vitro* release studies demonstrate a highest percentage of drug release from the formulation Fc2 containing Sodium alginate.
- *In vitro* drug release studies demonstrated the suitability of developed formulations for the release of Baricitinib.
- The bioadhesive strength was strong in the formulations containing Sodium alginate (Fc2); when compared to formulations containing Carbopol (Fa1) and Sodium CMC (Fb1).
- The surface pH of the formulations Fa1 (6.9±0.16), Fa3 (6.9±0.35), Fc1 (6.8±0.43) and Fc2 (6.77±0.24) and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations does not irritant to the buccal mucosa.
- The moisture absorption studies of selected formulations reveals that the formulation containing Carbopol gum (Fa3) shows maximum moisture absorption capacity than the formulations containing Sodium CMC (Fb2) and Sodium alginate gum (Fc2).
- The formulations containing Carbopol gum (Fa2) showed higher swelling index values (higher water uptake) than other formulations such as Fb1 containing Sodium CMC and Fc2 containing Sodium alginate.
- From the results, it was concluded that the *in vitro* drug release, bioadhesion strength, moisture absorption studies, surface pH, swelling studies of the optimized formulations are suitable for buccal delivery.
- The optimized formulation such as Sodium alginate gum (Fc2) follows First order and Higuchi order of release kinetics governed by Fickian diffusion mechanism.

From the results of this study, it may be concluded that the combination of Sodium alginate and HPMC K4M polymers are suitable for developing bioadhesive buccal tablets of Baricitinib.

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