CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.10019500

https://www.iajps.com/volumes/volume10-august-2023/37-issue-08-august-23

Available online at: http://www.iajps.com ***Research Article***

FORMULATION AND EVALUATION OF MUCOADHESIVE FEBUXOSTAT MICROSPHERES

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Article Received: June 2023 **Accepted: July 2023** **Published: August 2023**

Abstract:

The objective of the present study was to prepare and evaluate the mucoadhesive microspheres of Febuxostat. Febuxostat microspheres were prepared by ionotropic gelation method using polymers such as HPMC (K 100 M), Carbopol 940P, sodium CMC, sodium alginate, ethyl cellulose, methyl cellulose. Totally 12 different formulations of Febuxostat were prepared by using the above polymers. The microspheres were characterized for entrapment efficiency, mucoadhesive property by in vitro wash-off test and in-vitro drug release. The formulation F10 was selected as an ideal formulation based on the in vitro release profile which shows an extended drug release of 97.22 % upto12 hrs in phosphate buffer of pH 6.8. Surface morphology (SEM analysis) and drug-polymer interaction studies (FT-IR analysis) were performed only for the ideal formulation, F10. The microspheres were discrete, spherical in shape and had ideal surface morphology as confirmed by SEM and FT-IR studies indicated the lack of drug-polymer interactions in the ideal formulation, F10. The in vitro release data of all microsphere formulations were plotted in various kinetic equations to understand the mechanisms and kinetics of drug release. The ideal formulation, F10 followed Higuchi kinetics and value of "n," is calculated to be 0.36 indicated that the drug release shows Fickian diffusion.

Keywords: *Carbopol 940P, HPMC (K 100 M), Ionotropic gelation method, Febuxostat, Sodium Alginate, Sodium CMC.*

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Please cite this article in press ***Bhukya Madhulatha*** *et al,* ***Formulation And Evaluation Of Mucoadhesive Febuxostat Microspheres*** *, Indo Am. J. P. Sci, 2023; 10 (08).*

INTRODUCTION:

Taking drugs for a long period of time and taking several medicines simultaneously can lead to an increase in noncompliance to the patient [1]. This problem tends to be serious for drugs with short biological half-lives because they must be taken more frequently.

Buccal systems are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system [2,3]. The main objective of developing these systems is to increase the safety of a product to extend its duration of action and decrease the side effects of drugs. In buccal drug delivery systems, Mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form [4]. Gout is a rheumatic condition due to the deposition of monosodium urate crystals (tophi) in the joints or soft tissues and synovial fluid due to its saturation in blood. It is associated with increased serum uric acid levels. At high levels, uric acid crystallizes in surrounding tissues, resulting in an attack of gout. Gout occurs more commonly in those who eat a lot of meat, drink a lot of beer, or are overweight [5,6].

Febuxostat is a thiazole derivative and inhibitor of Xanthine Oxidase that is used for the treatment of hyperuricemia in patients with chronic GOUT. Febuxostat is an orally available, non-purine inhibitor of xanthine oxidase with uric acid lowering activity. Upon oral administration, Febuxostat selectively and noncompetitively inhibits the activity of xanthine oxidase, an enzyme that converts oxypurines, including hypoxanthine and xanthine, into uric acid. By inhibiting xanthine oxidase, uric acid production is reduced and serum uric acid levels are lowered. [7]

MATERIALS AND METHODS:

Materials:

Febuxostat was obtained from MSN Labs, Hyd. Calcium chloride, Ethyl cellulose was obtained from Sigma Aldrich. Methyl cellulose, Ethanol, HPMC K 100 M, Carbopol 940 was obtained from S.D. Fine chemicals, Mumbai.

Methodology:

Ionotropic Gelation Method:

All polymers and medication were separately processed via sieve number 60. To create a homogeneous polymer solution, enough sodium alginate and bioadhesive polymer were added in filtered water. To create a viscous dispersion, the drug febuxostat was further to the polymer solution and vigorously stirred. The resultant dispersion was then manually added drop by drop using a size 18 syringe needle into a $CaCl_2$ (10% w/v) solution [8]. To finish the curing reaction and create the spherical hard microspheres, the calcium chloride solution was maintained with the additional droplets for 15 minutes. The microspheres were decanted, collected, and after being thoroughly washed with water, they were dried for 12 hours at 450 degrees.

Table 1: Development of Mucoadhesive Microspheres Preparations

Batch Code	Coat Composition	Ratio
F1	Drug: Sod. Alginate	1:3
F2	Drug: Sod. Alginate : Carbopol (940)	1:1.5:1.5
F3	Drug: Sod. Alginate : Hydroxy Propyl Methyl Cellulose (K100M)	1:1.5:1.5
F4	Drug: Sod. Alginate : Sodium Carboxy Methyl Cellulose	1:1.5:1.5
F5	Drug: Sod. Alginate : Ethyl cellulose	1:1.5:1.5
F6	Drug: Sod. Alginate : Methyl cellulose	1:1.5:1.5
F7	Drug: Sod. Alginate	1:4
F8	Drug: Sod. Alginate : Carbopol (940)	1:2:2
F9	Drug: Sod. Alginate : Hydroxy Propyl Methyl Cellulose (K100M)	1:2:2
F10	Drug: Sod. Alginate : Sodium Carboxy Methyl Cellulose	1:2:2
F11	Drug: Sod. Alginate : Ethyl cellulose	1:2:2
F12	Drug: Sod. Alginate : Methyl cellulose	1:2:2

EVALUATION OF MUCOADHESIVE MICROSPHERES:

Drug polymer interaction (FTIR) study:

The FTIR spectra of the medication and the drug-polymer mixture were logged by the KBr pellets [9]. It may be inferred from the characteristic peaks in the formulations that there was no chemical contact amid febuxostat and the polymer, and that the characteristic bands of the febuxostat were unaffected upon successful loading.

Percentage Yield:

The measured mass was divided by the sum of all the non-volatile ingredients that went towards making the microspheres. The formula can be used to calculate percentage yield.:

% yield = Whole mass of excipient and medication / Actual mass of product x 100

Encapsulation Efficiency:

A weighed quantity (10 mg) of Mucoadhesive microspheres were suspended in 50 ml of ethanol and subjected to a 15-minute sonication process in order to completely extract the medication that was contained within them [10]. After filtering the solution, 1 ml of it was taken out and diluted to 50 ml with pH 6.8 phosphate buffer solution. The amount of drugs in this solution was measured using a UV spectrophotometer at 315 nm.

EE (%) = Actual Medication Content / Theoretical Medication Content X 10

Particle Size:

By utilising optical microscopy, the average particle size of mucoadhesive microspheres laden with febuxostat was determined [11]. A tiny amount of microspheres was spread out on a spotless glass slide, and the average size of the microspheres in each batch was calculated.

Degree of Swelling:

The swellability was resolute in the Phosphate buffer solution pH 6.8 precisely balanced 100 mg of microspheres were absorbed in slight extra of buffer solution for 24hrs and washed [12].

$\alpha = (Ws-Wo) / Wo$

α is the degree of swelling;
Wo is the mass of microspheres before swelling;
Ws is the mass of microspheres after swelling.

In vitro dissolution studies:

The dissolution vessel was filled with 900ml of pH 6.8 phosphate buffer, and the USP dissolution apparatus II was put together. The medium was given time to reach equilibrium at 37°C ±0.5°C. The dissolution vessel was filled with microspheres, covered, and the equipment was run at 50 rpm for 12 hours. The 5 ml of the dissolving fluid was removed, sieved, and replaced with a new 5 ml blank sample at prearranged time intervals [13]. With the aid of the dissolution fluid, the samples were diluted appropriately, and a UV-spectrophotometer was used to analyse them spectrophotometrically at a maximum wavelength of 315 nm.

DRUG RELEASE KINETICS:

Zero Order

$\% R = kt$

First Order

Log (fraction unreleased) = kt/2.303

The model can be used to analyze the release outlines of pharmacologic dosage forms, such as those that incorporate water soluble medicines in porous matrix, as well as hydrolysis kinetics [14].

Matrix (Higuchi Matrix)

$$R = kt^{0.5}$$

Hixson - Crowell Equation

$$(Fraction\ unreleased)^{1/3} = 1 - kt$$

When using this model, it is presumable that drug particle dissolving rate rather than potential diffusion through polymer matrix limits the release rate.

Peppas Korsmeyer Equation

To inspect the release mechanism of Febuxostat from the microsphere formulations, the release data was fitted into Peppa's equation,

$$M_t / M_\infty = Kt^n$$

Where,
M_t / M_∞ is the fractional release of medication,
't' signifies the release time,
'K' characterizes a constant integrating structural and geometrical characteristic of the device, 'n' is the diffusional exponent
If n < 0.5, the polymer relaxation does not mark the molecular transport, hereafter diffusion is Fickian.
If n > 0.5, the solid transport will be non – fickian and will be relaxation controlled.

Stability studies:

By maintaining the mucoadhesive microspheres powder at accelerated stability conditions, i.e., 40°C±2°C and 75% RH 5% RH, the percent entrapment efficiency was evaluated. The formulation is kept in glass vials with aluminium foil seals for the duration of the trial. The samples were taken at various times over a period of one month to three months, and the formulations' % entrapment efficiency was analysed spectrophotometrically [15]

RESULTS AND DISCUSSION:

Compatibility studies:

The fact that the main IR absorption peaks suggests that there is no interaction between the drug and the polymer, according to spectral studies. The same peaks matching to the functional groups and characteristics demonstrate that neither the polymer nor the preparation technique has had an impact on the stability of the medication.

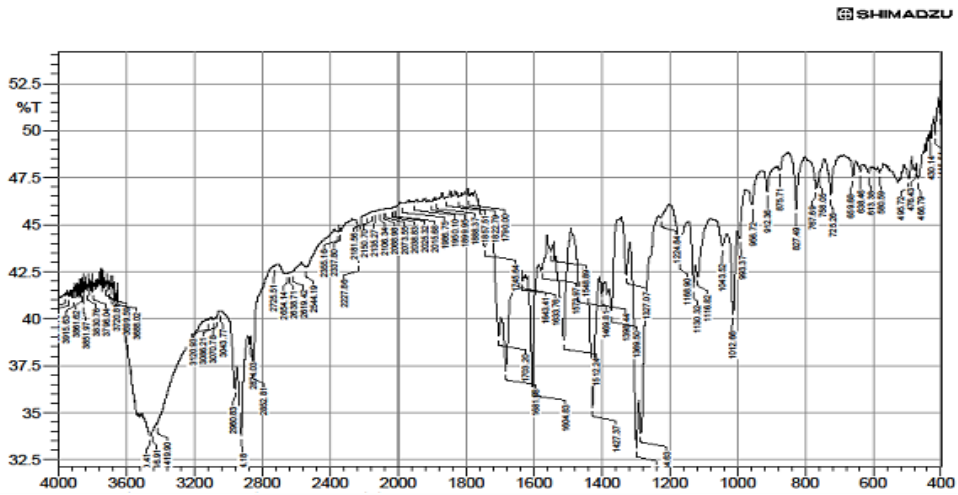

Figure 1: FTIR Graph of Febuxostat

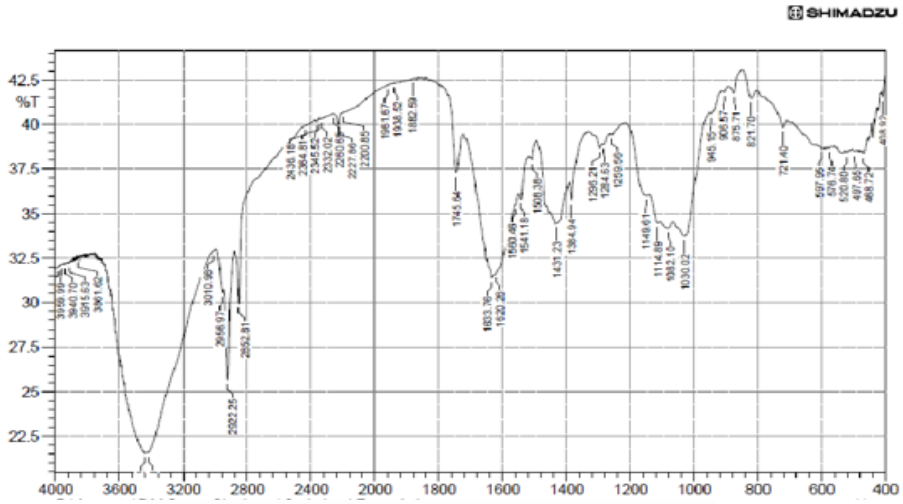

Figure 2: FTIR Graph of Optimized Formulation

Table 2 : IR Spectra data for Febuxostat

SI No.	Category of Vibrations	Frequency (cm-1)
1	C=O Stretching (Amide group)	1633.76
2	O-H Stretching	3861.62
3	C-H Stretching	2852.81

Percentage yield:

As the drug: polymer ratio augmented, the percentage yield too improved. The little produce in some preparations may be owing to adhesion of microspheres to the beaker throughout the formulation process or microspheres misplaced through the washing procedure. The % yield was found to be from 44.0% to 81.72%.

Table 3: Percentage yield of all formulations (F1 to F12)

Formulation code	Percentage yield (%)
F1	57.4%
F2	61.0%
F3	55.83%
F4	65.73%
F5	44.0%
F6	57.5%
F7	66.8%
F8	73.1%
F9	67.50%
F10	81.72%
F11	61.25%
F12	67.37%

Drug entrapment efficiency:

The percentage of Febuxostat mucoadhesive microspheres that successfully trapped the drug varied from 52% to 82%. With an increase in the amount of the polymers, the produced microspheres' ability to trap drugs improved over time.

The viscosity of the dispersed phase increases as the polymer concentration rises. With increasing viscosity, the particle size grows exponentially. It would be anticipated that when the polymer concentration increased, the polymer solution's increased viscosity would prevent medication from diffusing into the exterior phase, increasing the entrapment efficiency.

Table 4: Drug entrapment effectiveness of F1 to F12

Formulation code	Drug Entrapment efficiency (%)
F1	65 %
F2	79 %
F3	76 %
F4	62 %
F5	59 %
F6	52 %
F7	68 %
F8	82 %
F9	78 %
F10	66 %
F11	61 %
F12	55 %

Particle size analysis:

By using optical microscope, several formulations' particle sizes were evaluated. The range of the average particle size was determined to be between 237.3 and 682.3 m. According to the type of polymer employed to prepare the microspheres, the mean particle size greatly differed; this could be because the viscosity of the polymer solution

varied. Because shattering emulsion droplets needs a lot of shearing energy owing to the high viscosity of the polymer solution.

Because carbopol solution has more viscosity at the same concentration, carbopol microspheres are larger than sodium alginate-sodium CMC microspheres. Microsphere size increases when polymer concentration in the internal phase increases because at greater concentrations, the polymer solution is more viscous and requires more energy to break up the droplets of the dispersion phase.

With an upsurge in polymer concentration, the microspheres' particle size and drug entrapment effectiveness both went up. It's fascinating to see that the increase in particle size and the rise in entrapment effectiveness are comparable.

Table 5: Particle Size Analysis of all formulations (F1-F12)

Formulation code	Average particle size (µm)
F1	445.7
F2	493.5
F3	474.4
F4	365.2
F5	325.7
F6	237.3
F7	475.6
F8	682.3
F9	660.8
F10	423.2
F11	375.4
F12	295.1

Degree of swelling:

The amount of water present in the hydrogel at any one time throughout swelling is used to express the edema's degree. It is a crucial quality because it influences the mucoadhesion and medication release profiles of polymeric drug delivery systems. Phosphate buffer pH 6.8 was used to study the in-vitro swelling characteristic.

Data on swellability showed that the amount of polymer has a significant impact on solvent transfer. From the results, it can be inferred that as polymer concentration rises, so does swelling intensity.

The swelling index increased from 1.02 to 1.67 for the various formulations from F1 to F12. When sodium alginate and sodium CMC were cast-off as polymers in the F10 preparation, the most swelling was seen.

Table 6: Degree of swelling of all formulations (F1 to F12)

Formulation	Degree of swelling
F1	1.02
F2	1.15
F3	1.32
F4	1.09
F5	1.21
F6	1.45
F7	1.49
F8	1.27
F9	1.36
F10	1.67
F11	1.31
F12	1.54

In-vitro drug release study:

In-vitro dissolution study of Febuxostat from ready microspheres showed a biphasic pattern. The release of Febuxostat from microspheres was considered by an initial stage of burst effect (higher release), which was owing to the existence of medication particles on the surface of the microspheres shadowed by a second phase of modest release.

The *in vitro* release profile of Febuxostat from microcapsules displayed that with augmenting the concentration of drug: polymer, the release of the medication from the polymer matrix was retarded. The cumulative percent drug release of Improved preparation F10 was found to be 97.22 % at 12 Hrs.

Table 7: *In-vitro* dissolution profiles of Febuxostat mucoadhesive microspheres formulations F1-F6

Time (Hrs.)	% Cumulative drug release*					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
0.5	25.77±0.15	27.18±0.04	27.54±0.07	29.13±0.07	31.21±0.06	29.46±0.044
1	39.57±0.21	35.76±0.01	34.50±0.05	32.45±0.02	33.86±0.06	31.30±0.01
2	44.45±0.13	38.83±0.02	39.10±0.14	37.16±0.03	39.76±0.01	36.44±0.03
3	52.65±0.16	45.88±0.06	44.34±0.04	46.12±0.09	43.72±0.04	40.43±0.05
4	61.22±0.09	53.87±0.01	53.38±0.05	52.24±0.04	47.26±0.03	44.65±0.02
5	69.85±0.13	60.07±0.08	61.02±0.009	57.46±0.01	53.89±0.02	51.25±0.03
6	76.21±0.005	71.03±0.02	65.58±0.09	61.35±0.04	59.64±0.001	56.72±0.01
7	84.23±0.04	77.07±0.002	74.64±0.03	67.30±0.007	64.88±0.08	61.73±0.02
8	89.16±0.03	84.15±0.09	79.63±0.02	70.29±0.06	70.24±0.03	66.61±0.05
9	95.14±0.03	87.38±0.07	87.15±0.05	76.37±0.06	76.74±0.01	72.37±0.03
10	95.59±0.06	92.31±0.03	94.38±0.03	82.19±0.05	82.36±0.02	76.87±0.09
11	96.12±0.02	92.87±0.04	94.85±0.009	87.52±0.01	87.24±0.02	79.94±0.07
12	----	93.30±0.03	95.38±0.039	88.00±0.004	87.74±0.03	80.43±0.04

* Mean ± S.D (n=3)

Table 8: *In-vitro* dissolution profiles of Febuxostat mucoadhesive microspheres formulations F7-F12

Time (Hrs.)	% Cumulative drug release*					
	F7	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0
0.5	32.83±0.04	30.44±0.04	31.64±0.01	33.63±0.04	31.56±0.06	26.66±0.01
1	38.83±0.24	34.38±0.01	37.87±0.14	38.03±0.003	35.03±0.003	30.58±0.004
2	41.83±0.008	41.17±0.001	41.64±0.03	43.80±0.01	42.62±0.04	34.96±0.04
3	49.16±0.02	47.28±0.01	45.85±0.01	49.20±0.02	44.74±0.05	39.14±0.04
4	52.74±0.01	52.89±0.07	50.85±0.04	54.72±0.06	52.82±0.01	43.16±0.02
5	58.47±0.02	57.93±0.05	57.35±0.02	62.05±0.03	56.82±0.003	52.84±0.01
6	64.69±0.04	64.85±0.05	64.03±0.002	72.03±0.02	63.04±0.01	60.67±0.02
7	71.07±0.01	68.14±0.04	71.72±0.02	79.37±0.07	68.34±0.03	67.14±0.01
8	78.73±0.04	73.13±0.02	76.23±0.02	83.60±0.08	74.51±0.01	71.35±0.05
9	84.70±0.05	79.67±0.04	85.93±0.01	89.82±0.008	83.22±0.05	78.74±0.01
10	94.72±0.01	85.37±0.03	90.06±0.01	92.26±0.007	87.33±0.007	82.74±0.02
11	95.25±0.03	90.95±0.03	91.88±0.11	96.92±0.027	90.50±0.03	86.25±0.03
12	95.66±0.05	91.42±0.02	91.63±0.17	97.22±0.08	91.03±0.01	86.66±0.03

* Mean ± S.D (n=3)

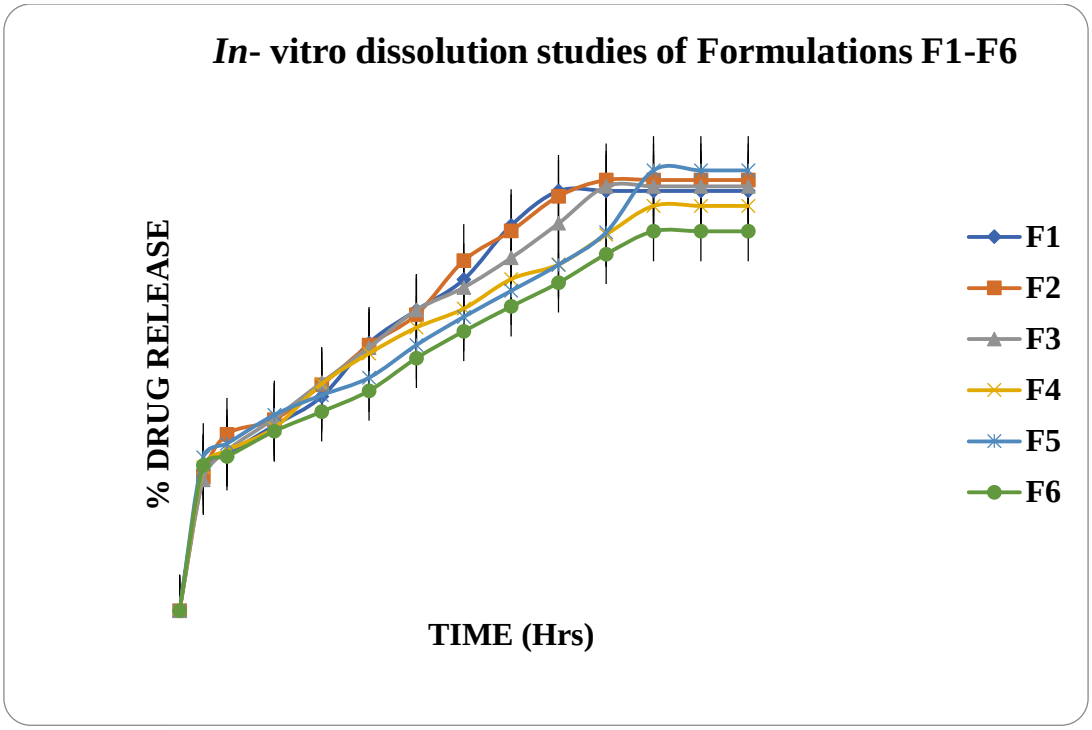

Figure 3: *In-vitro* dissolution profiles of Febuxostat mucoadhesive microspheres F1-F6

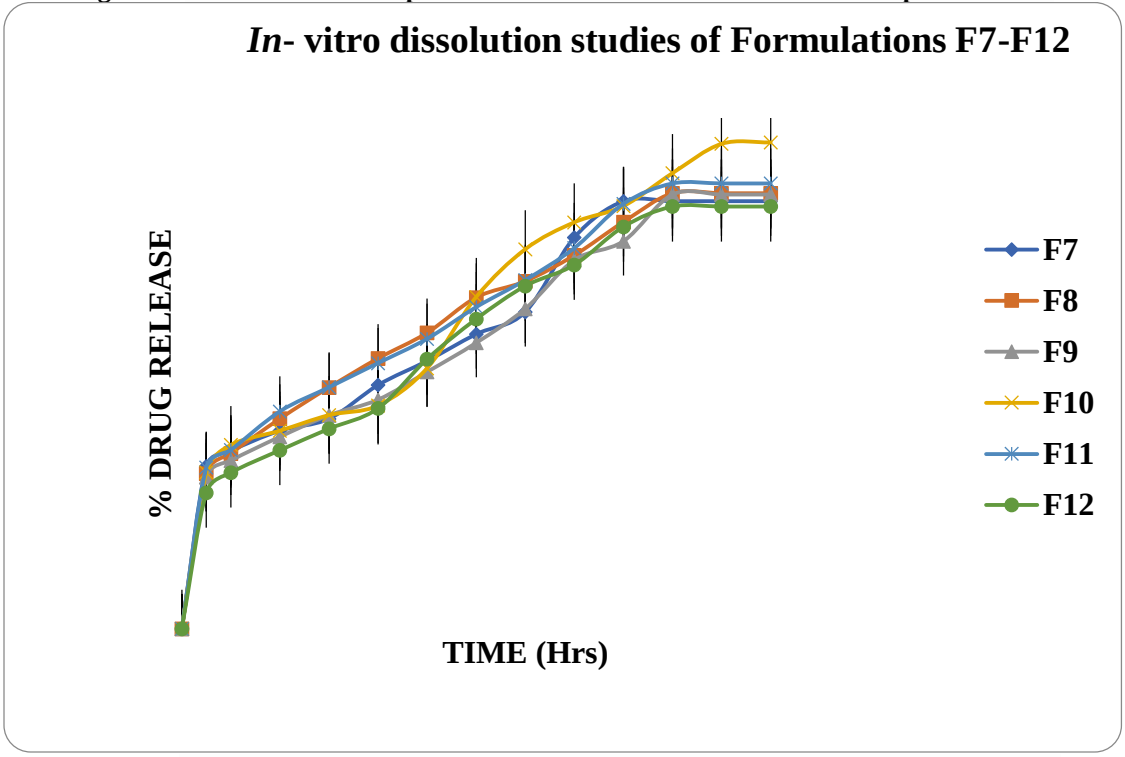

Figure 4: *In-vitro* dissolution profiles of Febuxostat mucoadhesive microspheres F7-F12

Comparison of cumulative medication release of pure drug, marketed formulation and optimized preparation (f10) of febuxostat:

Cumulative drug release of pure drug, marketed formulation and Optimized formulation (F10) was compared and it was found to be 50.90 %, 90.58 % and 97.22 % at 12 hrs. respectively.

Table 9: Comparison of % CDR of Pure Drug, Marketed Formulation and Optimized Formulation (F10) of Febuxostat mucoadhesive microspheres

	PURE DRUG (PD)	MARKETED FORMULATION	F10
Time (min)	% CDR	% CDR	% CDR
0	0	0	0
0.5	17.79±0.48	20.48±0.75	33.63±0.04
1	20.55±0.65	28.15±0.99	38.03±0.003
2	23.20±0.39	35.08±0.53	43.80±0.01
3	25.73±0.56	37.86±0.91	49.20±0.02
4	28.93±0.56	41.06±0.50	54.72±0.06
5	32.49±0.81	46.76±0.20	62.05±0.03
6	34.70±0.60	53.92±0.70	72.03±0.02
7	36.60±0.07	60.57±0.69	79.37±0.07
8	39.51±0.58	68.48±0.78	83.60±0.08
9	42.61±0.58	73.01±0.80	89.82±0.008
10	45.68±0.09	81.80±0.07	92.26±0.007
11	48.19±0.52	86.12±0.96	96.92±0.027
12	50.90±0.54	90.58±0.85	97.22±0.08

* Mean ± S.D (n=3)

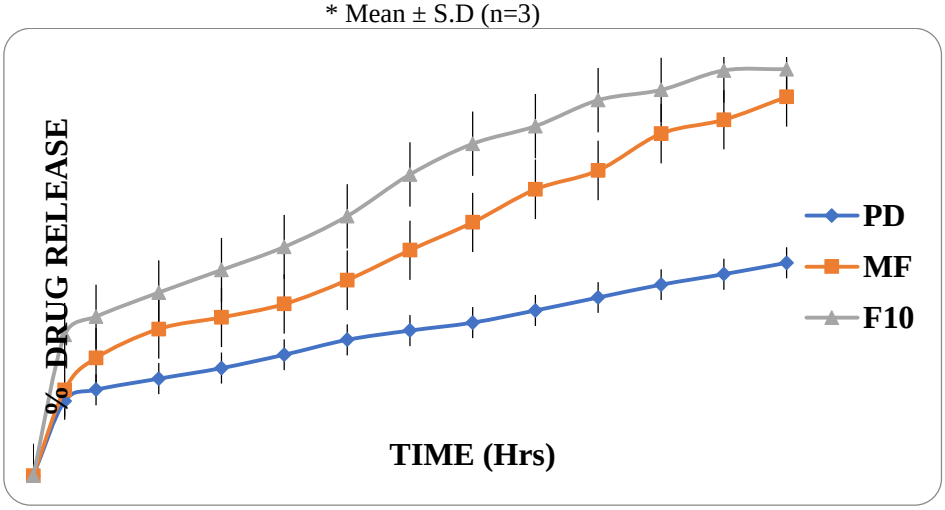

Figure 5: Comparison of % CDR of Pure Drug, Marketed Formulation and F10

Kinetic release models:

The correlation coefficient (R^2) values attained showed that all the formulations (F1 to F12) had highest R^2 values for First order plots indicating that the dissolution data fits into First order equation when compared to Zero order equation and R^2 values. Therefore, all the preparations F1 to F12 found to follow first order release kinetics.

Table 10: Order of release for Formulations F1 to F12

SI. No.	Formulation code	Zero order (R^2)	First order (R^2)
1	F1	0.9017	0.9640
2	F2	0.9300	0.9671
3	F3	0.9350	0.9380
4	F4	0.9174	0.9677
5	F5	0.9198	0.9567
6	F6	0.9115	0.9777
7	F7	0.9189	0.9030
8	F8	0.9173	0.9516
9	F9	0.9182	0.9355
10	F10	0.9111	0.9359
11	F11	0.9174	0.9561
12	F12	0.9398	0.9741

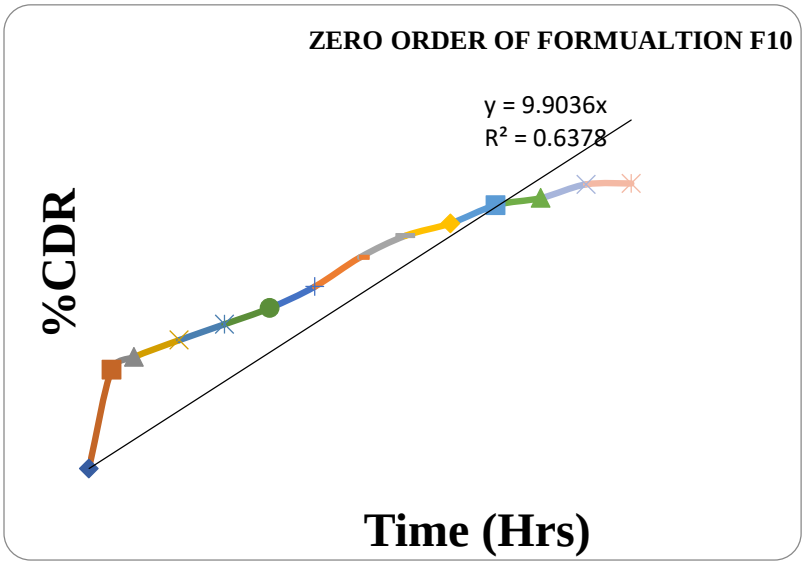

Figure 6: Zero order of Formulation F10

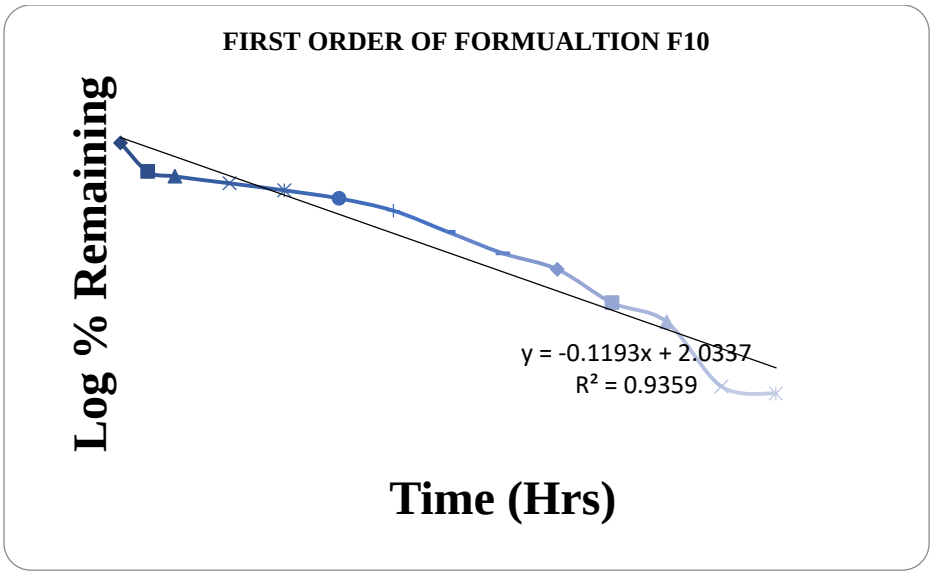

Figure 7: First order of Formulation F10

Release mechanisms:

From the results obtained all the preparations (F1-F12) having n value between 0.3515 and 0.4296. This designates that the preparation shadows release mechanism of Fickian diffusion.

Seeing the R^2 values attained from the dissimilar kinetic equations, the drug release from the all preparations (F1 to F12) were found to follow first order and Higuchi release model.

Table 11: Mechanism of release for different kinetic models

SI. No.	Formulation code	Higuchi (R^2)	Hixson-Crowell (R^2)	Korsemeyer-Peppas (R^2)	n- value
1	F1	0.9896	0.9824	0.9843	0.4296
2	F2	0.9848	0.9833	0.9595	0.4193
3	F3	0.9849	0.9740	0.9603	0.4208
4	F4	0.9859	0.9751	0.9618	0.3753
5	F5	0.9714	0.9676	0.9254	0.3515
6	F6	0.9741	0.9683	0.9216	0.3686
7	F7	0.9694	0.9501	0.9278	0.3592
8	F8	0.9836	0.9718	0.9620	0.3673
9	F9	0.9683	0.9605	0.9281	0.3563
10	F10	0.9800	0.9773	0.9455	0.3695
11	F11	0.9759	0.9704	0.9405	0.3612
12	F12	0.9762	0.9798	0.9302	0.4107

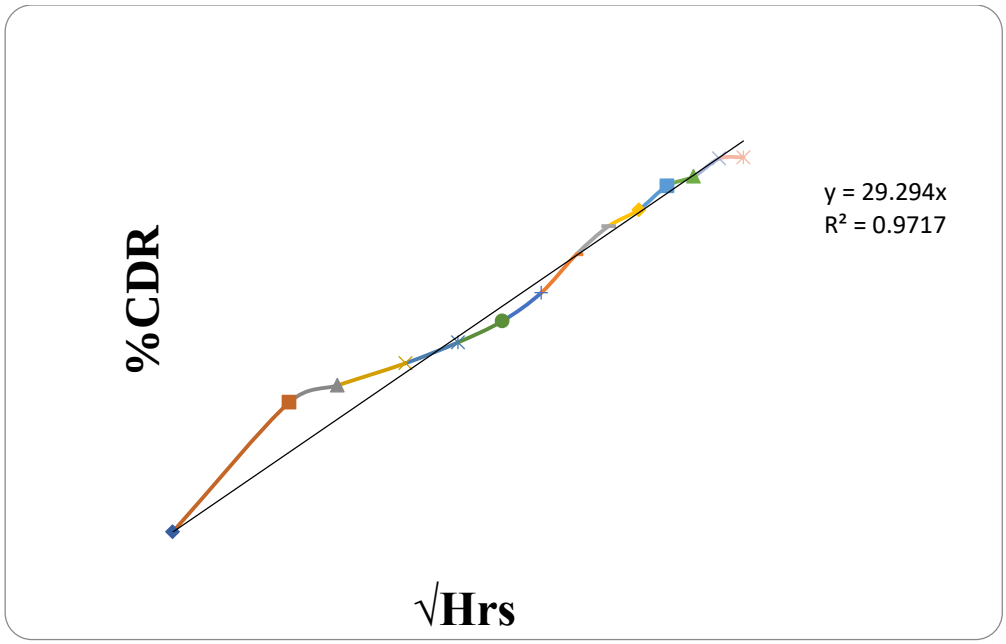

Figure 8: Higuchi model of Formulation F10

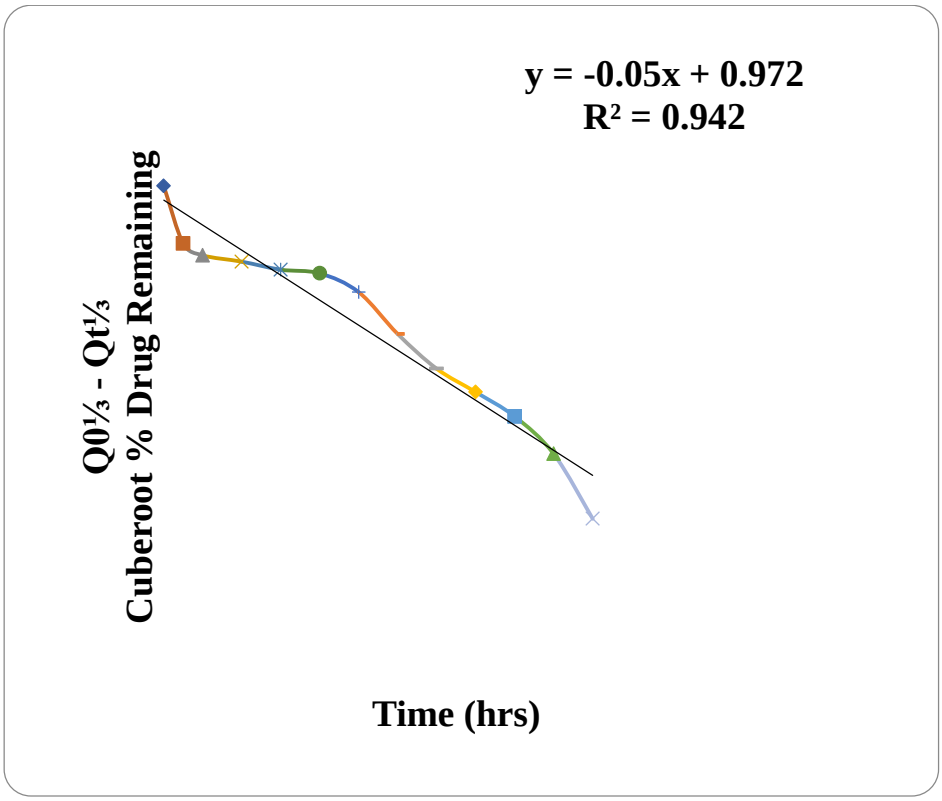

Figure 9: Hixson-Crowell model of Formulation F10

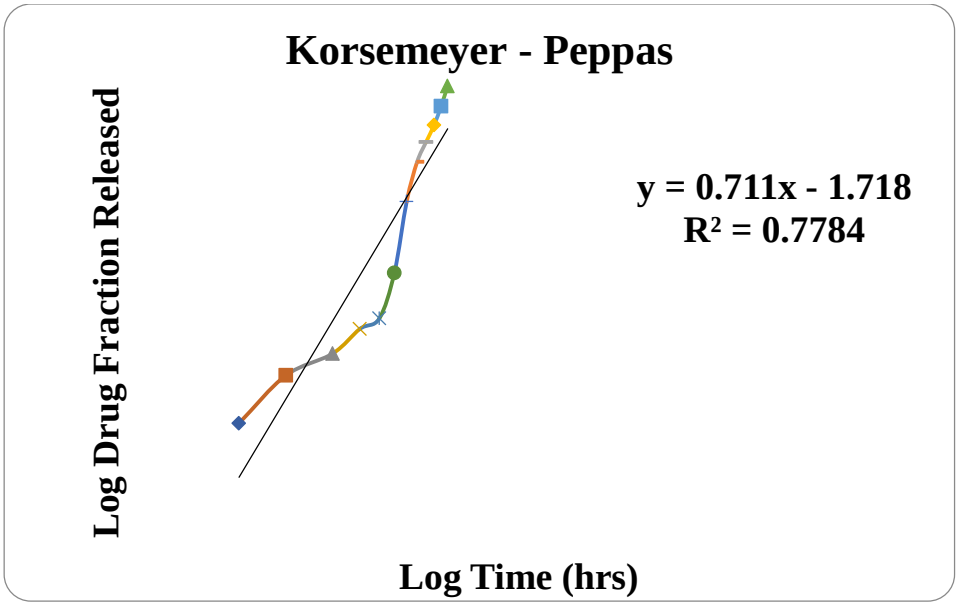

Figure 10: Korsemeyer- peppas model of Formulation F10

Stability studies:

The entrapment efficiency of the optimized formulation at the end of 3 months stored at accelerated stability conditions 40 ± 2 ^{o}C, 75 ± 5 % RH was 80.08 %. Also, there was no alteration in physical appearance and colour change in the formulations. This showed that the formulations are stable at the stored conditions. Therefore shelf-life of the optimized formulation F10 in all possibility is expected to be more than two years

Table 12: Percentage entrapment efficiency of Formulations F10 after three months storage at accelerated temperature conditions

Formulation code	Time in months	Accelerated storage condition	% Drug remaining after 3 months	% Decrease in entrapment efficiency
F10	3 months	40 °C ± 2 °C/75 % RH	80.08	1.92

CONCLUSION:

The current investigation includes formulation and evaluation of mucoadhesive microspheres with Febuxostat as model medication for prolongation of drug release time. The drug: polymer ratio was varied in the microspheres preparation and then they were assessed for percentage yield, % Medication entrapment effectiveness, Particle size analysis, Degree of swelling, in-vitro Mucoadhesion test and morphological study by SEM. According to the FTIR results, there was no chemical reaction amid the medication and the used polymer. Spherical, free-flowing microspheres were produced. The produced microspheres demonstrated a good degree of swelling and had good mucoadhesiveness. The formulations' release patterns were found to be biphasic, with an initial burst release followed by a gradual release. The data from the kinetic model fitting indicates that the medicine is released from the microspheres in accordance with the Higuchi (Matrix) release model. Based on the aforementioned findings, Formulation F10, which contains sodium alginate and sodium CMC, was determined to be the optimal formulation for the administration of febuxostat when all the factors were considered.

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