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Formulation Development and Evaluation of Tofacitinib Citrate Effervescent Floating Tablet

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ABSTRACT

The objective of the present study was to formulate and evaluate Effervescent Floating tablets of Tofacitinib citrate for the treatment of Antirheumatic agent. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, and Carbopol 934 and were evaluated for drug-excipients compatibility, density, buoyancy test, drug content, and *In-Vitro* release profile. Sodium bicarbonate and citric acid were used to produce the base for the buoyancy of tablets. Analysis of drug release from tablet indicates drug release by zero order, first order rate kinetics. No significant change was observed in physical appearance, drug content, floatability, or in-vitro dissolution pattern after storage at $45^0C/75^0C$ RH for three months.

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INTRODUCTION

Oral drug administration remains the route of choice for the majority of clinical applications some drugs have ideal characteristics for good absorption to occur desirable for optimizing the therapeutic benefit of the drug[1]. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance, and flexibility in formulation[2]. Attempts have been made to be 8-10 hr. From mouth to colon, is relatively brief with considerable fluctuation. One of the important determinants of G.I transit is the residence time in the stomach. The oral controlled delivery of drugs hold an absorption window which continuously delivers the drug before the absorption window for a prolonged duration. Thus ensuring adequate bioavailability[3]. A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating tablets and Floating capsules are common examples of floating system[4, 5].

Effervescent Floating Drug Delivery System:

A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT) thus enhancing the opportunity for absorption. Various approaches have been proposed to control the gastric residence of the drug delivery system in the upper part of the GIT including a floating drug delivery system. High-density DDS, bioadhesive systems, swelling and expanding DDS, modified shape systems, and other delayed gastric devices[5,6]. FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs act locally in the stomach, and for drugs that are poorly soluble or unstable in the intestinal fluid DDS systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged duration. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* non-effervescent and effervescent system, have been used in the development of FDDS[6,7,8].

The matrices system prepared with swellable polymers and components *e.g.* sodium bicarbonate and citric acid or stearic acid. In non- FDDS, the drug mixes with a gel forming agents or hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier[9].

Merits of Effervescent Floating Drug Delivery System:

1. Increases the oral bioavailability of drug.

2. Enhanced first pass biotransformation. Sustained drug delivery/ reduced frequency of dosing.

3. Reduced fluctuations of drug concentration. Improved receptor activation selectivity.

4. Reduced counter-activity of body.

5. Extended time over critical (Effective) concentration.

6. Minimized adverse activity at the colon.

7. Receptor activation selectivity is improved. Site specific drug delivery.

Demerits of Effervescent Floating Drug Delivery System:

1. Floating drug delivery requires sufficient high level of fluids in the stomach.

2. Not suitable for the drug that have solubility or stability problem in GIT.

3. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food.

4. These factors are never constant and hence the buoyancy cannot be predicted.

MATERIAL AND METHOD

MATERIAL

Preformulation study of Drug:

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of the physical and chemical properties of a drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable dosage forms, which can be mass-produced[10, 11].

Identification Tests

a) Organoleptic Properties:

The sample of Tofacitinib citrate was studied for organoleptic characteristics such as color, odor, and appearance[10, 11].

b) Melting Point:

The melting point of Tofacitinib citrate was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate and the average value was noted[10, 11].

c) IR Spectroscopy

The FT-IR spectrum of the obtained sample of the drug was compared with the standard FT-IR spectra of the pure drug.

d) Solubility analysis:

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

e) Differential Scanning Calorimetry:

The powdered sample (3 mg) was hermetically sealed in Alumnium pans and heated at a constant rate of 10^0C/min, over a temperature range of 30-300^0C with a nitrogen flow rate of 30ml/min. Thermograms of the samples were obtained using differential scanning Calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indian standard was to calibrate the DSC temperature and enthalpy scale.

Compatibility studies

a) *IR Spectroscopy*

A compatibility study was carried out by using Fourier Transform Infrared Spectrophotometer (BRUCKER). IR study was carried out on pure drug. A physical mixture of drug and excipients were prepared and samples were stored for 1 month at 40^0C. The infrared absorption spectrum of Tofacitinib citrate and physical mixture of drug and excipient was recorded using diamond disc[12, 13].

b) Preparation of o.1 N HCL

8.5 ml of concentrated HCL was taken and diluted with distilled water up to 1000 ml.

c) Preparation of Standard Calibration curve of Tofacitinib citrate

The UV spectrum of Tofacitinib citrate was obtained by using UV (Shimadzu UV - 1800, Japan). Accurately weighed 10 mg of the drug was dissolved in a sufficient quantity of 0.1 N HCl and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 1 ml of aliquot was withdrawn and made volume up to 10 ml using 0.1 N HCl to obtain the concentration of 10 µg/ml. The resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of maximum Wavelength in respective solvents[10, 11].

Formulation and Preparation of Effervescent Floating Tofacitinib citrate tablet by direct compression

Weight all the ingredients accurately fist add polymer HPMC K4M in a mortar then Carbopol 934 & Sodium bicarbonate mix it well for 10 min then add a drug, magnesium stearate & lactose blend for 10 min at the last magnesium stearate 1% add mix all ingredient homogenously to form a tablet mix for direct compression[14].

EVALUATION OF POWDER:

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index, and Hausner's ratio[3,4,15].

Table No 1: Formulation Chart of Effervescent Floating Tablet of Tofacitinib citrate:

Ingredients	**Formulation code**								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
TOFACITINIB CITRATE	20	20	20	20	20	20	20	20	20
HPMC K4M	50	50	50	60	60	60	70	70	70
Carbopol 934	10	15	20	10	15	20	10	15	20
Sodium Bicarbonate	40	40	40	40	40	40	40	40	40
Citric acid	30	30	30	30	30	30	30	30	30
Mg Stearate	3	3	3	3	3	3	3	3	3
MCC	25	25	25	25	25	25	25	25	25
Lactose	47	42	37	37	32	27	27	22	17
Total Weight	225	225	225	225	225	225	225	225	225

Determination of Floating capacity:

Three individual tablets from each formulation were put in an individual flask containing 400ml of 0.1 N HCl solutions. Then note the time in minutes for each tablet to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated.

***In-vitro* Disintegration Time:**

Disintegration time was determined using USP disintegration apparatus with distilled water. The volume of the medium was 900 ml and the temperature was 37 ± 0.2^0C. The time in minutes taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured. Test complies, all tablets should disintegrate within 15 minutes.

Drug Content:

Units were selected at random and drug content was determined as specified in the monograph. The tablet preparation complies with the test, only if each content lies between 85 to 115% of the average content[4].

***In Vitro* drug release kinetics studies**

The kinetic model described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. To study the exact mechanism of drug release from the tablets, drug release data were analyzed according to zero orders, first order, Higuchi square root, and Korsmeyer Peppas model.

RESULT:

Compatibility study by IR spectroscopy:

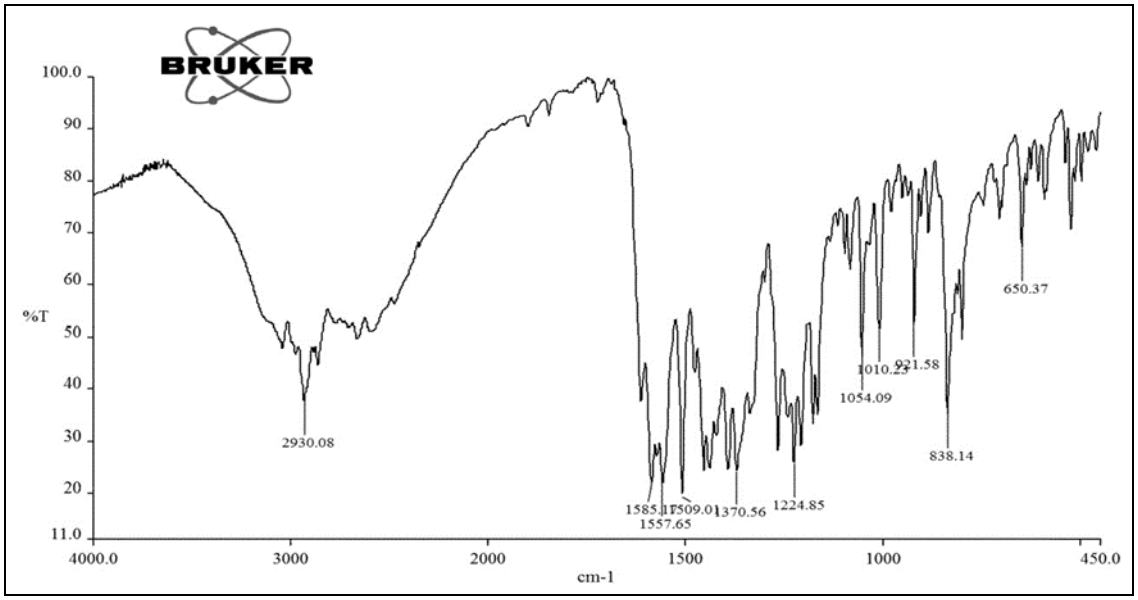

Figure No. 1: FTIR Spectrum of Tofacitinib citrate

The FTIR spectra of pure Tofacitinib citrate showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Evaluation of Formulation:

The Tofacitinib citrate tablets were prepared by direct compression method. Ingredients were accurately weighed and passed through the mesh. The powder blend was studied for

rheological characteristics. The homogeneous blend of powder was then compressed in a 10-station tablet punching machine using 12 mm flat faced punches[16].

Before compression powder beds of all formulations were studied for various rheological characteristics bulk density, true density, compressibility index, and Hausner's ratio. The results of the studies indicated that the powder bed is easily compressible, and hence can be compressed into a compact mass of tablets. The angle of repose is an indicative parameter of powder Flowability from hopper to die cavity[17].

A repose angle between 25^0 to 30^0 indicates excellent Flowability of the powder bed. In this work, the angle of repose was found to be varying between 22.81^0 and 26.72^0 when glidants were incorporated. These studies indicated that the powder beds of all formulations are easily flowable.

Evaluation of Pre-compressed parameters:

All formulations were studied for various rheological characteristics bulk density, true density, compressibility index, Hausner's ratio, and angle of repose. The results of the studies indicated that the powder blend is easily compressible.

Table 2: Pre-Compressed Evaluations:

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	The angle of Repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.369±0.0054	0.454±0.0014	28.56±0.51	9.45±0.32	1.14±0.025
F2	0.391±0.0035	0.432±0.0076	24.89±0.04	15.98.01±0.08	1.96±0.015
F3	0.313±0.0032	0.452±0.0098	27.23±0.50	12.33±0.69	1.91±0.008
F4	0.329±0.0037	0.452±0.0026	19.57±0.56	20.02±0.55	1.14±0.006
F5	0.319±0.0032	0.429±0.0026	23.82±0.61	08.38±0.72	1.96±0.009
F6	0.376±0.0015	0.492±0.0025	19.64±0.54	14.03±0.24	1.91±0.003
F7	0.312±0.0036	0.439±0.0064	25.29±0.37	9.13±0.46	1.94±0.006
F8	0.325±0.0035	0.488±0.0060	20.35±0.52	20.80±0.16	1.37±0.024
F9	0.352±0.0021	0.468±0.0049	23.53±0.42	14.91±0.13	1.84±0.018

Evaluation of Post-Compressed Characteristics:

The results of Hardness, Disintegration time, Drug content, Friability, Swelling index, and Floating time all are summarized in the table given below:

Table 3: Post-Compressed Evaluations:

Formulation code	Hardness (kg/cm^2)± S.D.	Drug content (%) ± S.D.	(%) Friability ± S.D.	Swelling Index %	Thickness (mm)	Weight Variation (mg)
F1	3.42±0.058	88.35±0.040	0.166±0.033	42.25±0.53	3.76 ±0.26	224.13± 1.7
F2	3.51±0.074	89.00±0.027	0.219±0.047	38.33±0.56	3.87±0.15	223.81±0.01
F3	3.54±0.077	98.42±0.018	0.296±0.081	46.35±0.25	3.98±0.21	224.07±0.01
F4	3.32±0.055	91.69±0.029	0.341±0.181	46.36±0.36	3.91±0.41	224.3±0.023
F5	3.53±0.050	90.61±0.010	0.368±0.041	49.25±0.25	3.99±0.68	225.19±1.69
F6	3.58±0.079	95.53±0.017	0.372±0.028	48.25±0.62	3.90±0.12	225.12±0.16
F7	3.56±0.085	93.22±0.023	0.511±0.026	44.54±0.51	3.90±0.49	224.8±0.018
F8	3.57±0.05	92.65±0.030	0.534±0.33	48.22±1.61	3.91±0.16	224 ± 0.018
F9	3.77±0.011	95.14±0.025	0.610±0.23	48.45±0.23	3.93±0.08	225.35±0.15

***In-Vitro* Floating Duration:**

Table 4: Floating duration time and Floating lag time:

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Floating time (hr.)	12	12	12	12	12	12	12	12	12
Floating lag time (sec)	57	65	85	112	130	156	171	217	232

Appearance:

The developed formulation met all the pre-requisite to became an Effervescent floating tablet, swelled and floated instantaneously at the acidic condition of the stomach.

Figure No. 2: Appearance Effervescent floating tablet of Tofacitinib citrate

***In-Vitro* release study:**

Table 5: Dissolution rate study:

Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.36 ±1.98	6.64 ±5.95	7.57 ±2.15	9.12 ±2.42	7.78 ±2.06	8.84 ±1.90	8.06 ±2.02	4.90 ±2.10	5.70 ±1.53
2	17.29 ±2.38	21.68 ±1.93	19.27 ±2.25	15.79 ±1.74	16.43 ±2.83	16.67 ±2.32	15.58 ±4.11	10.15 ±2.04	10.57 ±2.08
3	25.42 ±2.06	27.57 ±1.83	25.14 ±2.05	25.34 ±2.31	19.06 ±1.99	23.18 ±2.501	17.46 ±2.05	19.25 ±2.07	12.86 ±2.84
4	35.88 ±2.52	31.58 ±2.54	32.99 ±2.21	31.70 ±1.58	21.81 ±2.61	29.81 ±2.49	18.03 ±2.56	24.45 ±2.83	23.46 ±2.01
5	39.84 ±1.87	39.84 ±2.22	40.14 ±1.94	42.31 ±2.41	25.34 ±1.91	36.72 ±1.92	22.24 ±1.93	30.41 ±1.95	30.41 ±1.90
6	46.40 ±2.02	48.55 ±2.39	48.55 ±2.11	47.24 ±2.15	28.29 ±2.15	38.05 ±1.9	33.08 ±2.07	37.90 ±1.90	39.25 ±1.89
7	55.16 ±2.10	57.31 ±2.62	57.39 ±1.99	53.01 ±1.94	31.84 ±1.95	45.69 ±2.34	36.87 ±2.00	45.43 ±1.43	47.58 ±4.95
8	61.10 ±2.04	65.66 ±2.19	68.37 ±2.04	62.00 ±2.17	43.97 ±2.06	49.72 ±2.06	45.22 ±2.15	53.01 ±2.11	50.86 ±2.47
9	64.98 ±2.07	73.26 ±2.04	75.24 ±2.54	69.41 ±2.00	54.99 ±2.00	65.32 ±1.98	53.29 ±2.01	62.43 ±1.92	55.16 ±1.81
10	71.44 ±2.64	80.21 ±2.03	82.71 ±2.36	76.94 ±1.86	64.87 ±1.63	76.74 ±2.45	65.36 ±2.56	70.44 ±1.36	59.30 ±1.56
11	76.73 ±2.42	79.53 ±2.69	86.63 ±1.96	79.53 ±2.62	82.36 ±1.25	83.18 ±2.48	70.61 ±2.00	75.90 ±2.33	65.37 ±2.06
12	79.53 ±2.48	84.48 ±2.09	96.35 ±2.08	81.72 ±2.08	89.63 ±1.98	88.82 ±2.63	87.43 ±2.53	77.87 ±1.88	69.97 ±1.32

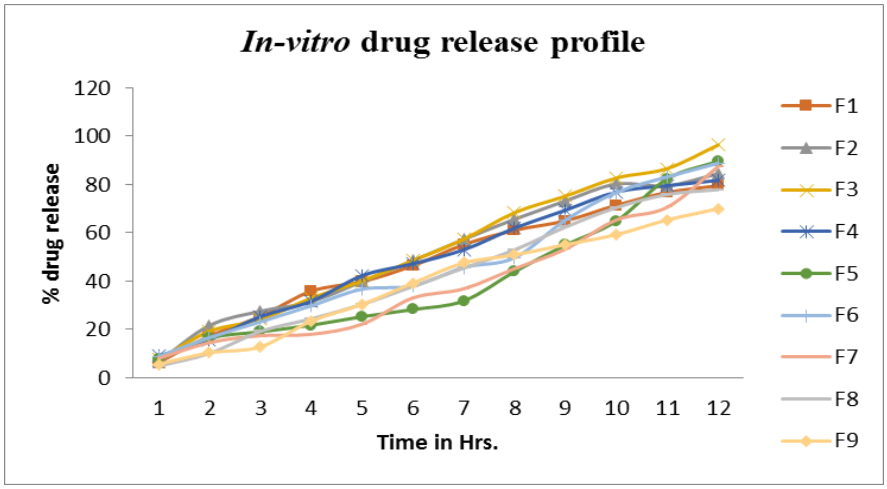

Figure 3: Dissolution Profile of Formulation Batches (F1-F9) (Time Vs %CDR)

A) Surface Response Plots:

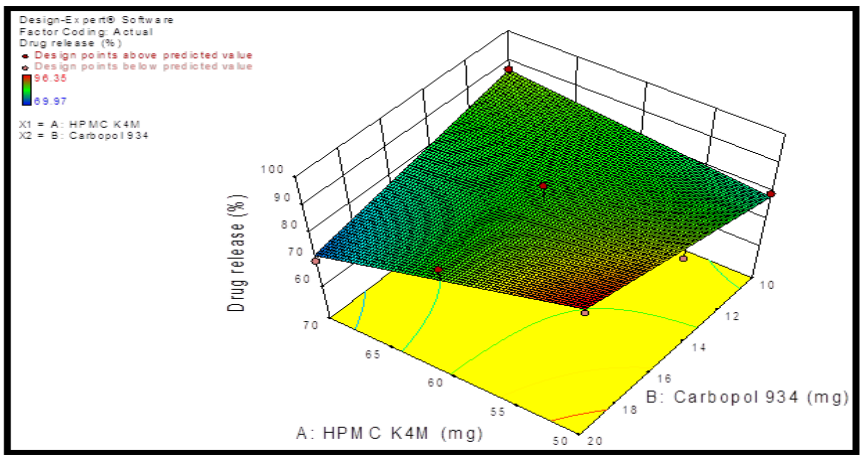

Figure 4: Surface Response plot showing the effect of Carbopol 934 and HPMC K4M on drug release

B) Contour plot:

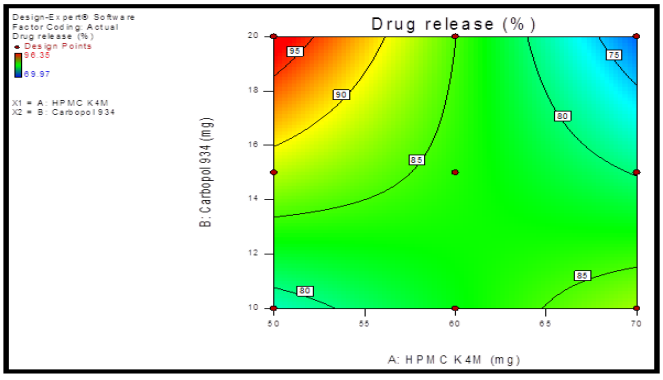

Figure 5: Contour plot showing the effect of Carbopol 934 and HPMC K4M on drug release.

Drug release kinetics:

In the present study, the drug release was analyzed to study the kinetics of the drug release mechanism. The results showed that the factorial design batches followed zero order and first order model kinetics, Higuchi and Connor's model kinetics, and kosemeyer's Peppas model kinetics.

Zero-order comparative evaluation model kinetics:

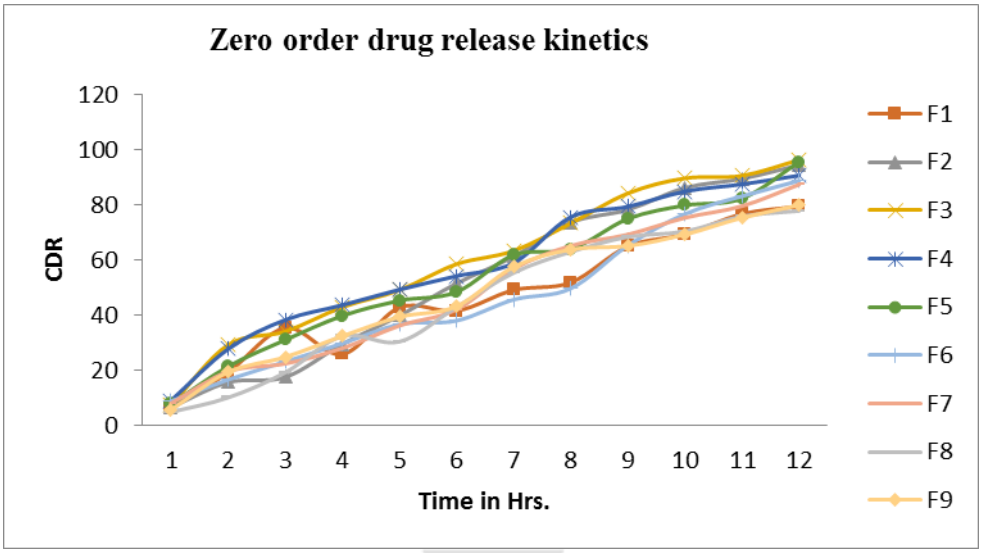

Figure 6: Model graph for comparative evaluation of zero order release kinetics.

First-order comparative evaluation model kinetics:

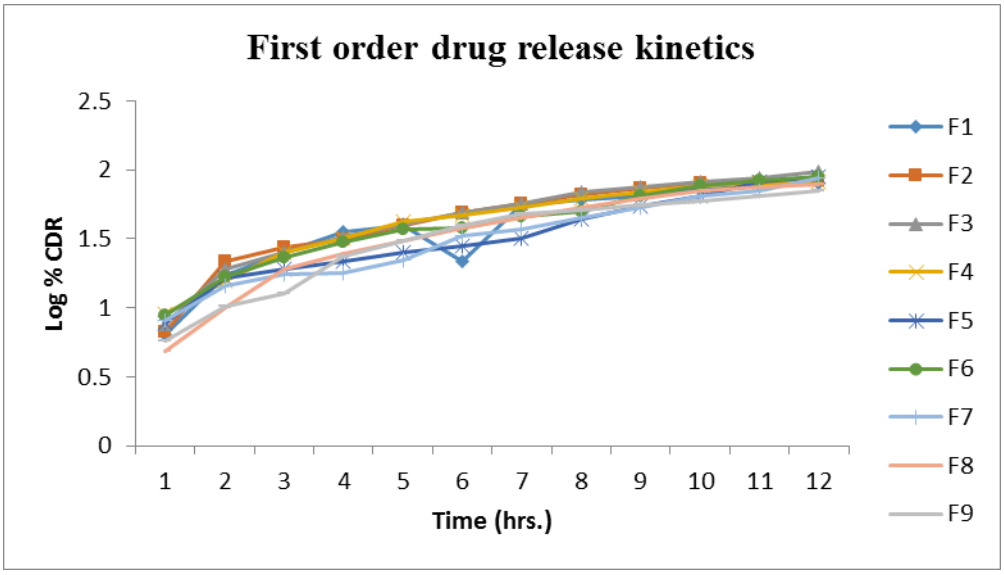

Figure 7: Model graph for comparative evaluation of First order release kinetics

Higuchi and Connor's model release kinetics:

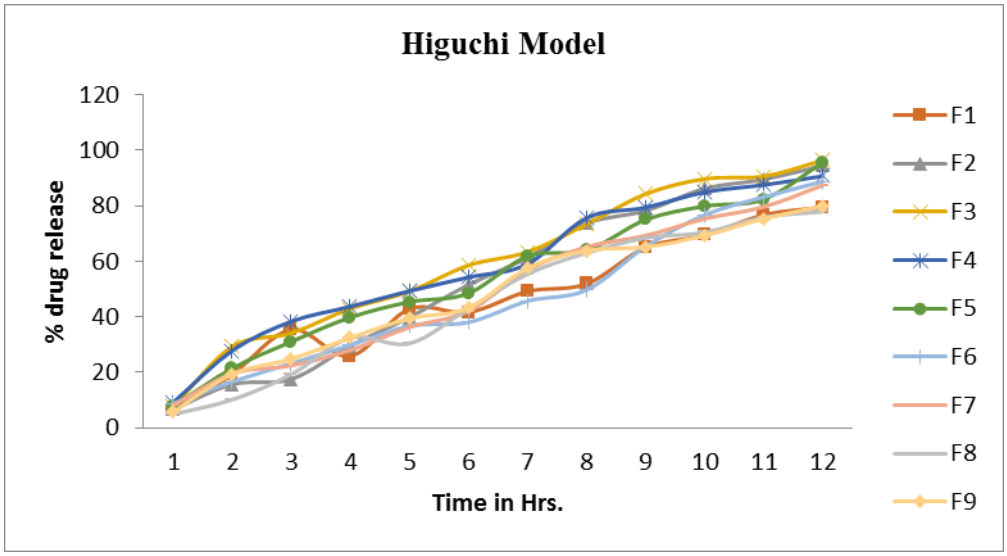

Figure 8: Model graph for comparative evaluation of Higuchi Connor's release kinetics

Korsemeyer's Peppas comparative evaluation model kinetics:

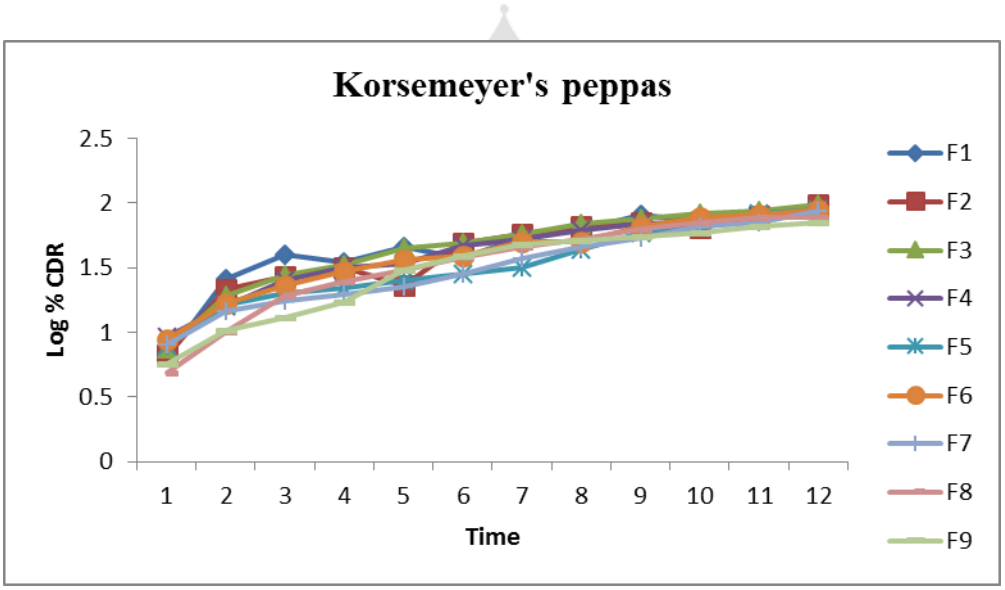

Figure 9: Model graph for comparative evaluation of Korsemeyer's Peppas release kinetics

Stability Studies:

Table 6: Stability study for optimized formulation F3 at 40±2ºC+75% RH:

Formulation code	1 month	2 month	3 month
F3	98.42 % ± 0.018	97.98 % ± 0.060	97.50 % ± 0.032

The selected formulation wrapped in Aluminium foil and stored at 40 ± 2ºC and % RH 75% ± 5% temperature for 3 months. After 3 months the formulation F3were evaluated for the hardness, drug content, and *in-vitro* % drug release. It was observed that there was no significant variation in the physical appearance, average weight, hardness, and loss of drying after placing the tablets at various temperature and humidity conditions for 3 months. Also, the cumulative % drug release data showed that each of the formulation released a drug amount, within the limits laid down as per the ICH guidelines for stability studies.

CONCLUSION:

The present study was carried out to develop the Effervescent floating drug delivery of Tofacitinib citrate using HPMC K4M and Carbopol 934 polymers as the carrier. Tofacitinib citrate is a BCS class II drug having low solubility and high permeability. Its oral bioavailability is less than 55% and its biological half-life is also approximately 3-5 hrs. All the above data are suitable for a gastro retentive drug delivery system. After procurement of the drug sample, it was characterized for identification by FTIR. After identification check the compatibility of the drug with all exipients. It was found that it is compatible with all excipients there is no change in the functional group. The physical property of Tofacitinib citrate tablet i.e. hardness, friability, average weight, and thickness also complies with standard references. The floating lag time of all nine tablet formulations shows within one minute total floating time was more than 12 hrs.

The *In-vitro* drug release profile indicated that batch (F3) was the most promising formulation as the extent of drug release from this formulation was high as in comparison to other formulations, which are suitable for sustained release drug delivery system. The batch F3 shows 96.35% release in 12 hrs, so we concluded that the rate of drug release increases in the acidic environment of the stomach. Release kinetic data of all the formulation how that the F1-F9 formulation follows the Korsmeyer-Peppas model. A stability study was conducted on tablets of batch F3 at 40 ± 2^0C for 3 months. Tablets were evaluated for drug release

pattern, hardness, floating behavior, and In-vitro release. From the discussion, it was concluded that the tablets of batch F3 had considerable mucoadhesion along with considerable floating and swelling behaviors with a good drug release pattern. Tablets of F3 batch was elected as the optimum batch and evaluated for the stability study.

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