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PREPARATION AND EVALUATION OF OSMOTIC TABLET OF TOFACITINIB CITRATE

Sheetal B. Gondkar[1], Saba R. Shaikh[*2], Pradnya K. Gangurde[3], Rishikesh S. Bachhav[4], Nitin Hiray[5]

[1]Department of Pharmaceutics, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik 422213 (M.S.), India
[2*]Department of Pharmaceutics, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik 422213 (M.S.), India
[3]Department of Pharmaceutics, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik 422213 (M.S.), India
[4]Department of Pharmacology, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik 422213 (M.S.), India
[5]MVP's Institute of Pharmaceutical Sciences, Adgaon, Nashik, 422207 (M.S.), India

***Corresponding Author:** Saba R. Shaikh
Address: Department of Pharmaceutics, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, India
Email: sabashaikh1410@gmai.com

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ABSTRACT:

The aim of this research is to create Controlled Porosity Osmotic Tablets incorporating Tofacitinib Citrate aimed at treating Rheumatoid Arthritis. These tablets operate on the principle of osmosis. Using a 3^2 factorial design, nine formulations were prepared. The formulation involved a wet granulation method, with the core tablet comprising osmotic agent (NaCl), release retardant (HPMC), and other excipients. A cellulose acetate coating served as the semipermeable membrane, which upon contact with aqueous fluid forms a microporous structure. The evaluation included pre compression parameters, and also post compression parameters. Also SEM analysis was done. Batch F8 exhibited a drug release of 99.80% within 24 hours. Dissolution kinetics were evaluated utilizing multiple pharmacokinetic models including Korsmeyer-Peppas, First order, Higuchi model and zero-order models across all batches.

KEY WORDS: Tofacitinib citrate, Osmotic pump, Osmogen, Semipermeable membrane, Osmotic pressure

1. INTRODUCTION

An osmotic drug delivery system (ODDS) is a type of controlled-release system designed to administer medication steadily over an extended period. This study focuses on formulating Controlled Porosity Osmotic Tablets (CPOP). The osmotic delivery system employs osmotic pressure as both the energy source and the mechanism driving drug release [Thanki K. et al.,2011]. The objectives of this study include achieving sustained drug release over an extended duration, maintaining drug concentrations within therapeutic ranges, improving drug efficacy while minimizing harmful side effects and improving patient adherence through reduced dosing frequency. Importantly, drug release in osmotic systems remains unaffected by physiological factors such as pH, food presence, or gastric motility [Sultana A. et al.,2017].

The CPOP is osmotic pump in which the drug is released from the pored formed in semipermeable wall. Semipermeable membrane is made up of water soluble additives, which when come in contact with gastric fluid get dissolved and the microporous membrane is formed. The parameters that influence the drug design includes solubility, osmotic pressure and semipermeable membrane. Through the osmotic drug delivery system the zero order kinetics can be achieved [Gong T. et al.,2006].

Tofacitinib citrate is utilized for treating rheumatoid arthritis, a chronic autoimmune condition that affects lining of synovial-joints, resulting in progressive disability and premature mortality, and significant socioeconomic burdens. It acts as a JAK inhibitor, exhibiting 74% oral bioavailability and a half-life elimination of 3 hours, and undergoes metabolism via cytochrome P450 enzymes [Guo Q. et al.,2018].

2. MATERIALS AND METHODS

Materials:

The gift sample of drug Tofacitnib Citrate was received from R&D center of Glenmark (Sinner, Nashik), Hydroxy Propyl Methyl Cellulose K100 M, Poly vinyl pyrolidone K30, Magnesium stearate, Talc, Acetone, PEG 400, and Cellulose acetate obtained from Research Lab Fine Chem, Mumbai, Sodium Chloride form Loba-Chemie Pvt. Ltd, Sodium Lauryl Sulphate form Thomas Baker (Chemicals) Pvt. Ltd (Mumbai).

Methods:

Formulation design was conducted using the Design Expert Software (Version 7.0).

EXPERIMENTAL WORK

Preformulation Study:

Organoleptic Properties: The observation of the drug was done by its appearance, Oduor, colour and texture

Melting Point: The Tofacitinib citrate melting point was identified using a melting point apparatus. This apparatus slowly heats the sample, which is observed under a microscope. The temperature at which the first appearance of liquid is observed indicates the melting point.

Solubility: The solubility of Tofacitinib citrate was evaluated in various solvents including water, ethanol, DMSO, methanol, and hydrochloric acid (HCl).

UV-Visible Spectroscopy:

Determination of λ max of Tofacitinib citrate: Drug of 10mg was precisely weighed and then dissolved in methanol to achieve a final volume of 100 ml. From this stock solution, a dilution was made to obtain a 100 µg/ml of concentration. A 1 ml sample from this dilution was taken and further dil. upto 10 ml with the methanol, resulting in a 10.0 µg/ml of concentration. The resultant solution was scanned from 200 to 400 nm using a

spectrophotometer, and spectra were recorded to ascertain the wavelength of maximum absorption [Mahajan R. R. et al.,2023].

Preparation of Calibration curve: 100 µg /ml of stock solution was made in methanol. Dilutions ranging from 2 to 10 µg /ml was subsequently made from this stock solution in their respective solvents. Solutions absorbance was measured at 287 nm by using their respective blank solvents with a UV-visible spectrophotometer [Mahajan R. R. et al.,2023].

Fourier Transform Infrared Spectroscopy (FTIR)

Compatibility Study: A mixture of pure drug and excipient was carefully ground and blended with potassium bromide (at a ratio of 1:100) for 3-5 minutes using a mortar. The resulting mixture was subsequently compressed into discs under 10 kg/cm² pressure using hydraulic press. These mixture was then placed in sample holder and analyzed by scanning from 4000 to 400 cm^{-1} using an FTIR spectrophotometer (Agilent Resolution Pro) [Sahoo C.K. et al.,2018].

Fourier Transform InfraRed spectroscopy: The KBr was mixed with drug and compressed into discs under pressure of 10 kg/cm² using a hydraulic press. These discs were then analyzed by scanning from 4000 to 400 cm^{-1} using an FTIR spectrometer (Agilent Resolution Pro) [Sahoo C.K. et al.,2018].

Formulation of Osmotic Tablets:

Factorial Design: The 3^2 factorial design was used in this method, where 2 factors were each evaluated at three levels. Experimental trials was conducted each of the 9 possible combination, as illustrated in Tables 1, which detail the coded levels and the complete 3^2 factorial design [Shahi S. R. et al.,2012].

Independent Variables:

X1- NaCl (Osmogent), X2- HPMC (Release retardant)

Dependent variable: Y1= Drug release (%)

Table 1: Variables of factorial design

Code Level	Actual value in mg	
	X- 1	**X- 2**
-1	5	50
0	10	65
+1	15	80

FORMULATION OF OSMOTIC TABLETS:

A core tablet containing Tofacitinib citrate was manufactured using the method of wet granulation and the core tablets composition is given detailed in Table 2. Tofacitinib citrate was blended with NaCl, HPMC, and sodium lauryl sulfate in a mortar for 15-20 minutes. PVP K30 and IPA were incorporated into this mixture as binders. The damp mass was sieved through a #22 sieve, then subsequently for 2hrs dried in a hot air oven at 50°C. After drying, the lubrication of granules was done by talc and magnesium stearate. The granules underwent testing for flow parameters and powder characterization. Tablets were then prepared using a tablet compression machine (Rimek Minipress-1-Karnavati) with an 8 mm punch, resulting in tablets weighing 220 mg [Shah N. et al.,2013].

Table 2: Formula for CPOP

Ingredients	**Formulation code**								
Quantity (mg)	**TC 1**	**TC 2**	**TC 3**	**TC 4**	**TC 5**	**TC 6**	**TC 7**	**TC 8**	**TC 9**
Tofacitinib citrate	11	11	11	11	11	11	11	11	11

Sodium chloride	5	5	5	10	10	10	15	15	15
PVP K30	15	15	15	15	15	15	15	15	15
HPMC	50	65	80	50	65	80	50	65	80
Starch	119	104	89	114	99	84	109	94	79
Sodium lauryl sulphate	15	15	15	15	15	15	15	15	15
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight (mg)	220	220	220	220	220	220	220	220	220

All formulations listed above were made according to the above composition and then compressed.

Table 3: Functional category of ingredients in formulations

Sr. No.	Ingredients	Functional category
1.	Tofacitinib citrate	Antirheumatic agent
2.	Sodium chloride	Osmogent
3.	HPMC	Release retardant
4.	Starch	Diluent
5.	PVP K30	Binder
6.	Sodium lauryl sulphate	Solubilizing agent
7.	Magnesium stearate	Lubricant
8.	Talc	Glidant

Evaluation of Powder Bulk for Tablets:

Bulk Density: Substance per unit volume, indicating how densely packed or compacted the material is known as Bulk Density [Edavalath S. et al.,2011].

$$\boldsymbol{Bulk\ density\ (\rho) = m/V}$$

Tapped density: Highest density that a powder or granular material can reach when subjected to tapping or vibration, typically expressed as mass per unit volume after tapping is Tapped Density [Edavalath S. et al.,2011].

$$\boldsymbol{Tapped\ density\ (\rho) = M/V}$$

Angle of repose: The funnel method is used for calculating angle of repose with diameter of 20 to 30 mm attached to the burette stand. The funnel is adjusted at height such that its tip touch to apex of powder and graph is placed bellow the funnel. And circle is drawn along the powder heap [Edavalath S. et al.,2011].

$$\boldsymbol{tan\theta = h/r}$$

Compressibility index (CI): The compressibility index is a metric utilized to quantify the extent to which a powder or granular substance can reduce in volume when subjected to pressure. It serves as an indicator of the material's compressibility or compactibility [Gondkar S. B. et al.,2015].

$$Compressibility\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Hausner's ratio (HR): Assessing the flowability of powders by comparing their tapped density to their bulk density is known as Hausne's ratio. It assesses how effectively a powder can pack under tapping or vibration, with lower ratios indicating superior flowability [Gondkar S. B. et al.,2015].

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Evaluation of Tablets:

Precoating evaluation:

Friability: Friability of tablet was calculated using Roche friabilator test device by taking 20 tablets. Friability was determined by calculating the percentage of weight lost by the tablets [Jadhav M. M. et al.,2012].

$$\%\ \boldsymbol{Friability} = \frac{\boldsymbol{Initial\ weight\ of\ tablet - Final\ weight\ of\ Tables}}{\boldsymbol{Final\ weight\ of\ tablet}} \times \mathbf{100}$$

Weight uniformity: In this test, 20 tablets individually was weighed, and average weight was calculated of them. Every tablet weight was compared to average weight, and percentage deviation was calculated accordingly [Gondkar S. B. et al.,2015].

Content Uniformity: Twenty tablets individually was weighed and subsequently ground into fine powder using a mortar and pestle. The powder, containing 11 mg of Tofacitinib citrate, was extracted by mixing it with 100 mL of phosphate buffer at pH 6.8 and then resulting mixture was filtered by using a Whatmans filter paper, and concentration of Tofacitinib citrate in filtrate was determined through measurement of its absorbance at 287 nm using a double-beam UV spectrophotometer, with appropriate dilution as necessary [Bala S. N. et al.,2023].

Hardness: Tablets must possess a specific level of strength, known as hardness, to withstand mechanical stresses encountered during manufacturing, packaging, and transportation. By using a Monsanto hardness tester the tablet hardness was determined [Jadhav M. M. et al.,2012].

Thickness of Tablet: Digital vernier caliper was used for the measurement of Thickness of tablet and average thickness was recorded [Bala S. N. et al.,2023].

Coating of Osmotic Tablets: Tofacitinib citrate core tablets were coated with a solution composed of 5% w /v cellulose acetate dissolved into a 1:1 mixture of acetone and alcohol. This cellulose acetate solution acted as a semipermeable membrane. To enhance flexibility, 15% v/v PEG 400 was incorporated as a plasticizer. Before application, tablets were gently warmed to 40±2°C to enhance coating adhesion and ensure uniformity. Further details regarding the specific composition of the coating solution can be found in Table 4. For coating of tablet dip coating method was used. This process was repeated until the 10% weight was gained. Following coating, the tablets underwent drying into the hot air oven set at the 50°C for a duration of 10 hours [Gondkar S. B. et al.,2015].

Table 4: Formula for coating of tablet

Ingredient	Quantity (for 100ml)
Polyethylene glycol 400	1%
Cellulose Acetate	5%
Alcohol: Acetone (1:1)	50:50 (ml)

Post coating evaluation of osmotic tablets:

Thickness of tablet: After applying the coating, thickness measurements of all tablets were performed using a digital vernier caliper to precisely determine the thickness of the applied coat. Each measurement was meticulously taken in triplicate [Bala S. N. et al.,2023].

Thickness of film:

Film thickness is calculated by using the following formula -

$$\boldsymbol{Thickness\ of\ coat} = \frac{\boldsymbol{Thickness\ of\ coated\ tablet - Thickness\ of\ uncoated\ tablet}}{\mathbf{2}}$$

Scanning Electron Microscopy (SEM): The SEM analysis was done for the estimation of surface of tablet before coating and after coating microporous membrane [Banerjee A. et al.,2015].

In Vitro Dissolution Test: Dissolution testing was conducted using a dissolution test apparatus I-IP with both acidic and buffer stages (Electrolab TDT 08L). The testing employed a paddle-type apparatus rotating at 50 rpm, under controlled temperature conditions of 37°C ± 2°C [Bhagwat D. A. et al.,2016].

Dissolution Kinetics: To explore the release mechanism from the tablets, the release data were analyzed using zero-order kinetics, first-order kinetics, Higuchi's model, and the Korsmeyer-Peppas model [Dasankoppa F.S. et al., 2013].

3. RESULT & DISCUSSION

Preformulation Study:

Organoleptic properties: Tofacitinib citrate was tested for organoleptic parameters like color, texture, and odour. The outcomes presented are listed below.

Table 5: Comparison of result of identification tests of Tofacitinib citrate with the reported standards

Identification test	Result	Literature Value
Colour	White to offwhite powder	White to offwhite powder
Odour	Odourless	Odourless
Texture	Smooth	Smooth

Melting Point: Tofacitinib Citrate MP is shown in table (6) below:

Table no 6: Melting-Point of Tofacitinib citrate

Melting point	
Practical Value	**Reported Value**
214-218°C	109-202 °C

Solubility:

Table 7: Solubility of Tofacitinib citrate

Sr. No.	Solvent	Observation	Inference
1.	Distilled water	Turbid solution	Insoluble
2.	Ethanol	Less turbid solution	Slightly-soluble
3.	0.1 N HCl	Clear solution	Soluble
4.	Methanol	Clear solution	Soluble

UV Spectroscopy Study:

λ max of Tofacitinib citrate in Methanol: Tofacitinib citrate solution was dissolved in methanol and subjected to UV spectrophotometric analysis across a wavelength range from 400 to 200 nm. The resulting spectrum exhibited a prominent absorption peak at 287 nm. Based on concentrations typically encountered in in-vitro release studies and the anticipated theoretical maximum, operational maximum wavelength (working max) was established as 287 nm. Refer to Figure 1 for the UV absorption spectrum of Tofacitinib citrate in methanol.

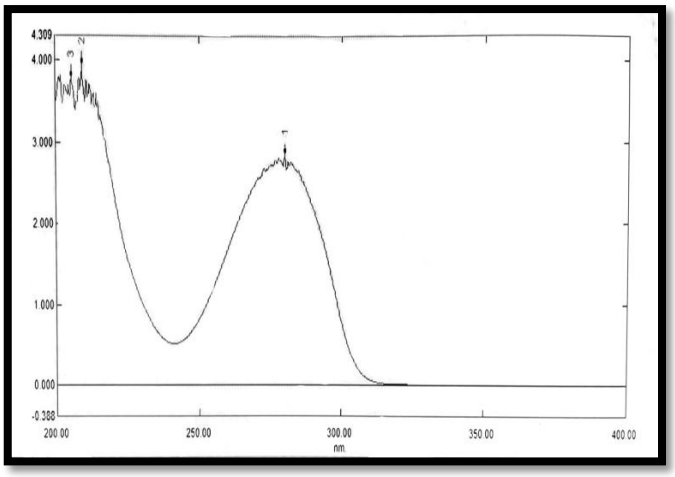

Figure 1: Tofacitinib citrate UV spectrum in Methanol

Calibration curve (In Methanol): The calibration curve for Tofacitinib citrate was established in methanol, chosen for its ability to dissolve the compound effectively. The drug solution in methanol was clear and facilitated straightforward examination using a UV spectrophotometer. The calibration curve exhibited linearity across 2-10 µg/ml concentration range, as detailed in below table, with a coefficient of regression (R^2) 0.9921 value. The equation of the line was determined as y = 0.3017x + 0.239, illustrated in the corresponding figure. Please refer to the figure 3 depicting the calibration curve of Tofacitinib citrate in methanol for visual representation.

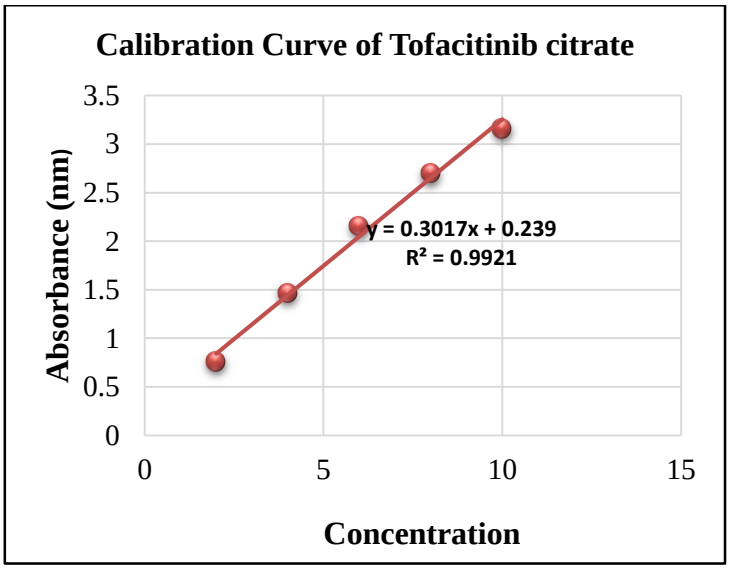

Figure 3: Calibration curve of Tofacitinib citrate in methanol

Table 2: Tofacitnib citrate absorbance in Methanol at 287nm

Sr. no.	Concentration	Absorbance
1.	2	0.761
2.	4	1.469
3.	6	2.153
4.	8	2.701
5.	10	3.162

The FTIR spectrum of Tofacitinib citrate is shown is figure below (Figure 4).

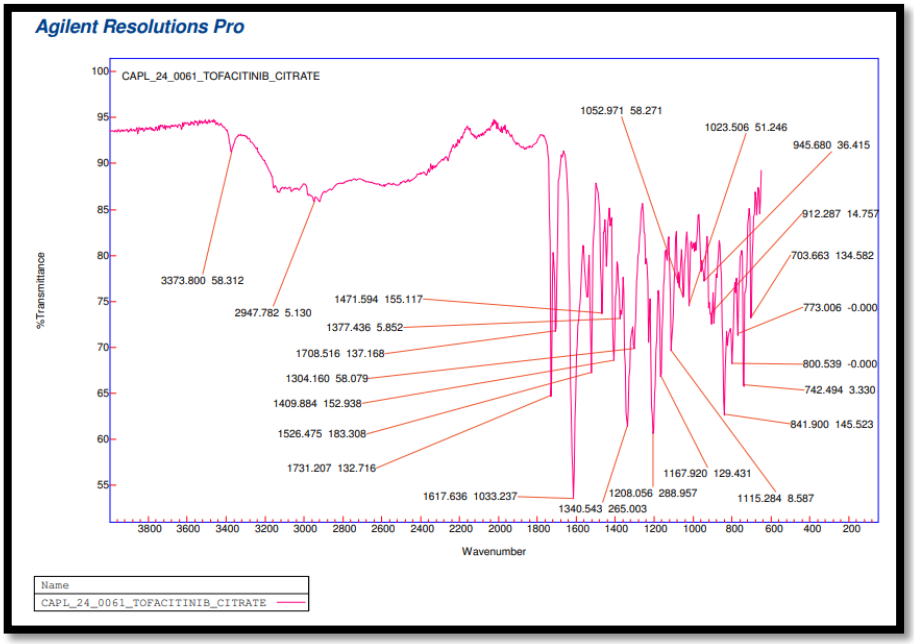

Figure 4: FTIR Spectra of Tofacitinib citrate.

Table 3: IR frequencies of Tofacitinib citrate functional group

Sr. No.	Functional Group	Standard Frequency	Observed Frequency
1.	N-H Stretch	3300-3500	3373
2.	C=O-Stretch	1650-1750	1708.5
3.	C-N-Stretch	1200-1350	1052.9
4.	C-H	3300-2700	1377
5.	COOH Stretching	1700-1750	1708.5
6.	O-H Bend (carboxylic acid)	3200-3500	3373.8

Compatibility Study of Drug and Excipient: The FTIR spectra of both pure Tofacitinib citrate and its excipients were analyzed, indicating no interactions were observed among the drug, polymer, and excipients. A comprehensive analysis of FTIR (spectrum) of the physical mixture is provided in accompanying table. 4.

Table 4: Analysis of FTIR spectrum of physical blend

Sr. No.	Functional Group	Peaks		
		Standard Ranges	Pure Drug	Physical mixture
1	N-H stretching	3300-3500	Yes	Yes
2	C=O-Stretching	1650-1750	Yes	Yes
3	C-N-Stretching	1200-1350	Yes	Yes
4	C-H	3300-2700	Yes	Yes
5	COOH Stretching	1700-1750	Yes	Yes
6	O-H Bend(carboxylic acid)	3200-3500	Yes	Yes

There were no observed peak shifts or disappearances seen in the spectrum of FTIR in physical mixture of drug with polymers. All functional groups of drug were found to be present into the physical mixture, confirming the compatibility of the drug with polymers.

Table 5: Drug Excipients Compatibility

Ingredient	Ratio	Initial	Condition (40℃for 1 month)
Tofacitinib citrate	NA	White	NCC
Sodium Chloride	1:1	White	NCC
HPMC	1:1	White	NCC
Starch	1:1	White	NCC
PVP K30	1:1	Off-White	NCC
Sodium Lauryl Sulphate	1:1	White	NCC
Magnesium stearate	1:1	White	NCC
Talc	1:1	White	NCC

Precompression Evaluation of Tablets:

Table 6: Evaluation of Granules for Tablets

Formulation code	Angle of repose (θ^0)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibiliy Index (%)	Hausner's ratio
F1	27.53±0.97	0.2950±0.006	0.3112±0.004	5.18±2.27	1.055±0.025
F2	28.19±0.78	0.2859±0.001	0.3191±0.001	10.39±0.39	1.116±0.004
F3	28.19±0.64	0.2933±0.005	0.3164±0.004	7.29±2.71	1.079±0.031
F4	28.35±0.29	0.2920±0.003	0.3121±0.004	6.41±2.49	1.069±0.028
F5	28.03±1.01	0.2885±0.008	0.3151±0.006	8.44±1.18	1.092±0.014
F6	27.85±0.75	0.2949±0.003	0.3135±0.008	6.05±1.95	1.063±0.020
F7	28.36±0.78	0.2921±0.016	0.3134±0.004	6.84±4.09	1.074±0.046
F8	27.7±1.01	0.2967±0.003	0.3144±0.002	5.61±1.72	1.074±0.046
F9	27.7±1.16	0.2910±0.007	0.3134±0.001	7.12±2.81	1.077±0.032

Postcompression Evaluation of Tablets:

Precoating evaluation: All 9 batches were evaluated by the post compression parameters. Evaluated data is shown in (Table 7)

Table 7: Postcompression parameters

Formulation Code	Average Weight (mg)	Weight Variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	219.67±0.697	1.81±0.31	3.02±0.01	3.24±0.03	0.68±0.46	97.64±0.20
F2	219.39±0.822	5.19±0.37	2.42±0.41	3.29±0.07	0.47±0.13	98.53±0.12
F3	219.76±0.71	3.88±0.71	2.90±0.10	3.23±0.05	0.47±0.07	98.29±0.54
F4	219.63±0.74	1.42±0.33	3.35±0.10	3.26±0.05	0.61±0.18	98.29±0.50
F5	220.77±0.64	3.29±0.29	2.88±0.02	3.28±0.10	0.83±0.21	96.66±0.21
F6	220.2±0.78	5.16±0.35	3.2±0.1	3.23±0.05	0.71±0.27	98.33±0.42
F7	219.95±0.94	6.45±0.42	3.15±0.07	3.23±0.05	0.60±0.10	99.85±0.02
F8	219.88±0.90	1.48±0.41	2.94±0.04	3.26±0.05	0.58±0.90	99.89±0.06
F9	219.91±0.75	1.94±0.34	3.20±0.07	3.23±0.05	0.30±0.69	97.03±0.50

According to the data provided earlier, it has been verified that the uncoated tablet meets the standard specifications for hardness, weight consistency, friability, thickness, and drug content.

Post Coating Evaluation of Tablet: The tablet thickness, weight variation, and film thickness were assessed for each batch of prepared coated osmotic tablets. The investigation

revealed that the weight variance and tablet thickness of the coated tablets fell within acceptable ranges, indicating consistent coating. The difference in thickness between the coated and uncoated tablets allowed for determination of the film thickness.

Table 8: Postcoating evaluation (Osmotic Tablet)

Formulation code	Average Weight (mg)	Weight variation	Thickness of coated tablet	Thickness of film (mm)
F1	229.5±0.89	1.84±0.39	4.09±0.06	0.42±0.04
F2	229.48±0.83	6.81±0.36	4.32±0.41	0.51±0.24
F3	229.42±0.80	4.95±0.35	4.06±0.03	0.41±0.02
F4	229.54±0.75	6.19±0.32	4.06±0.03	0.4±0.01
F5	229.54±0.80	5.57±0.35	4.08±0.01	0.4±0.04
F6	230.46±0.32	1.05±036	4.06±0.03	0.41±0.02
F7	229.50±0.78	9.90±0.33	4.23±0.31	0.50±0.12
F8	231.51±0.77	6.18±0.33	4.1±0.09	0.41±0.05
F9	229.53±0.94	1.12±0.41	4.24±0.39	0.50±1.67

Based on the previously provided data, it is confirmed that the uncoated tablets showed drug content, weight variation, friability, hardness, and thickness within the specified limits.

Scanning Electron Microscopy (SEM): Analysis of the coating layer before and after dissolution testing showed the formation of aqueous pores. These pores enable the drug solution to pass through the Cellulose Acetate barrier due to osmotic pressure generated within the tablet core. SEM analysis of the coating layer confirmed this observation (refer to Figure 5).

a) Before Dissolution of coated tablet **b) After Dissolution of coated tablet**

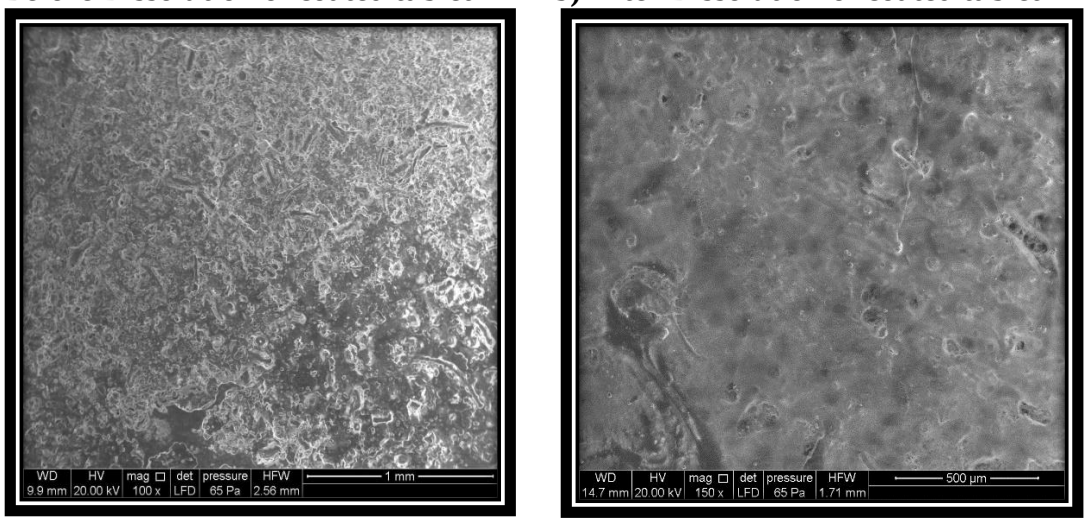

Figure 5: Scanning Electron Microscopy (SEM) of coating tablet (Before dissolution and After dissolution)

InVitro Dissolution study:

In vitro drug release experiments were conducted on osmotic tablets using simulated gastric and intestinal fluids. The dissolution protocol consisted of 2 hours in 0.1 N HCl followed by 22 hours in phosphate buffer at pH 6.8. The findings are outlined in Table 9. The results showed that higher concentrations of osmogen (NaCl) increased drug release from the tablets, whereas higher concentrations of the release retardant (HPMC) decreased drug release.

Table 9: Cumulative Drug Release

Time (Hrs)	Cumulative Drug Release (%)								
	TC 1	**TC 2**	**TC 3**	**TC 4**	**TC 5**	**TC 6**	**TC 7**	**TC 8**	**TC 9**
1	0.888 ±0.06	0.531 ±0.01	0.029 ±0.009	0.060 ±0.03	0.180 ±0.13	0.85 ±0.01	0.839 ±0.01	1.22 ±0.6	0.76 ± 0.03
2	2.518 ±0.06	2.268 ±0.08	1.35 ±0.14	2.102 ±0.12	2.31 ± 0.05	1.31 ±0.12	2.366 ±0.16	3.31 ±0.17	1.94± 0.02
3	4.525 ±0.40	4.243 ±0.02	5.535 ±0.32	14.25 ±0.01	5.231 ±0.01	4.248 ±0.01	7.305 ±0.10	10.35 ±0.09	8.49 ± 0.06
4	12.55 ±0.09	8.315 ±0.23	7.425 ±0.02	20.29 ±0.05	11.29 ±0.06	9.401 ±0.16	12.27 ±0.06	15.62 ±0.24	12.43 ± 0.15
5	13.31 ±0.09	12.3 5±0.01	10.35 ±0.21	24.24 ±0.01	18.32 ±0.11	16.32 ±0.11	20.26 ±0.16	18.48 ±0.07	17.42 ±0.14
6	15.30 ±0.05	18.45 ±0.19	11.45 ±0.20	24.28 ±0.06	21.30 ±0.09	20.14 ±0.01	24.23 ±0.01	22.38 ±0.13	35.29 ± 0.05
9	26.34 ±0.17	23.42 ±0.15	29.61 ±0.15	34.12 ±5.86	37.33 ±0.13	34.25 ±0.01	37.46 ±0.08	38.51 ±0.08	40.34 ± 0.18
12	38.50 ±0.08	42.31 ±0.07	38.47 ±0.07	52.34 ±0.03	49.28 ±0.05	47.17 ±0.06	50.18 ±0.05	51.26 ±0.02	46.33 ± 0.07
15	55.30 ±0.04	47.34 ±0.24	45.41 ±0.36	62.41 ±0.10	59.45 ±0.28	57.21 ±0.07	65.23 ±0.01	63.31 ±0.07	65.26 ± 0.03
18	65.27 ±0.07	62.35 ±0.05	59.51 ±0.09	78.24 ±0.01	68.32 ±0.11	67.28 ±0.06	80.34 ±0.18	71.42 ±0.11	78.49± 0.11
21	78.27 ±0.04	70.36 ±0.21	65.45 ±0.37	76.24 ±0.01	74.54 ± 0.3	75.3 ±0.10	98.38 ±0.10	89.38 ±0.13	87.47 ±0.19
24	81.26 ±0.05	75.23 ±0.20	72.29 ±0.18	87.43 ±0.19	81.38 ±0.11	83.25 ±0.05	99.84 ±0.05	99.80 ±0.01	93.87± 0.01

TC = Formulation Code

The findings indicate that increasing sodium chloride (NaCl) concentration and reducing HPMC concentration progressively enhance the release rate. The findings indicate that the osmotic tablet effectively prolongs the release of Tofacitinib citrate for about 24 hours. Formulation F8 was chosen due to its in vitro drug release pattern, releasing 99.80% of the medication within the specified timeframe, which demonstrates excellent performance.

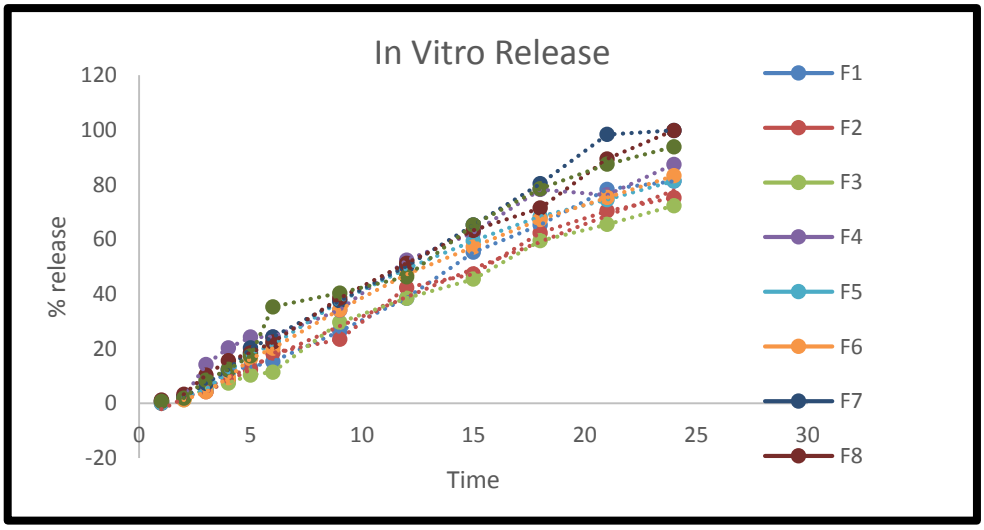

Figure 6: Dissolution Profile

Impact of Osmogen Concentration on Drug Release from Optimized Formulations: Sodium chloride is well-suited as an osmotic agent for moderately or poorly soluble drugs in osmotic tablet manufacturing. Higher concentrations of sodium chloride result in increased drug release from the tablets.

Impact of Release Retardant Concentration on Drug Release from Optimized Formulations: To explore the impact of varying the concentration of the release-retardant substance on drug release, it was observed that higher concentrations of this component in the formulation resulted in a decrease in the rate of drug release. Formulation F8, which incorporates a moderate level of the release-retardant substance, successfully delays drug release for a period of 24 hours.

Impact of Variables on Release Profiles (of Optimized Formulation): The optimized formulation (F8) underwent several comparative tests to explore the influence of release retardant substance and osmogen concentrations on its release profile.

Table 10: Optimized formulation comparison with uncoated tablet (Conventional tablet)

Time	% Cumulative Drug Release	
	Uncoated tablet of F8 formulation	F8 Optimized formulation
1	3.28 ± 0.17	1.22±0.6
2	10.48± 0.11	3.31±0.17
3	28.46±0.34	10.35±0.09
4	45.52±0.84	15.62±0.24
5	64.63±0.11	18.48±0.07
6	76.21±0.36	22.38±0.13
9	94.31±0.01	38.51±0.08
12	-	51.26±0.02
15	-	63.31±0.07
18	-	71.42±0.11
21	-	89.38±0.13
24	-	99.80±0.01

When prepared uncoated tablet was evaluated for dissolution testing it shows 94.31% drug release within 9 hrs. optimized formulation shows 99.80% drug release for extended period of 24 hrs.

Dissolution Kinetics:

Release kinetics studies: Different kinetic models were utilized to evaluate the release of Tofacitinib citrate from matrices, encompassing first-order, zero-order, Korsmeyer-Peppas model and Higuchi's square root equation. All batches exhibited zero-order kinetics, indicating constant drug release over time. Specifically, formulation F8 achieved 99.80% drug release within 24 hours, while other batches also showed zero-order kinetics but did not reach the same release percentages of 98 - 99%. Formulation F8, after optimization, exhibited zero-order kinetics with an R-squared value of 0.9971, indicating a stable and predictable release profile.

Table 11: Dissolution Kinetic of prepared Tofacitinib citrate osmotic tablet formulation.

Formulation code	Coefficient of determination (R^2)			
	Zero-order	First-order	Higuchi square-root	Korsmeyer plot
F8	0.9971	0.7429	0.9759	0.9706

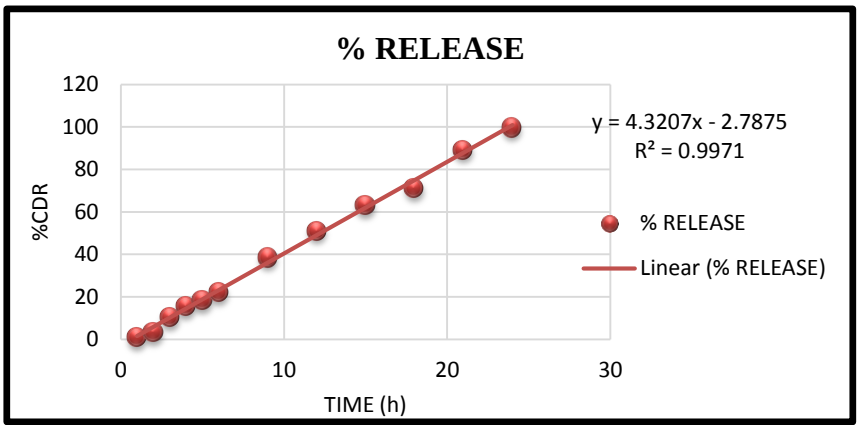

Figure 7: Graph of Zero Order Kinetics of (F8 batch)

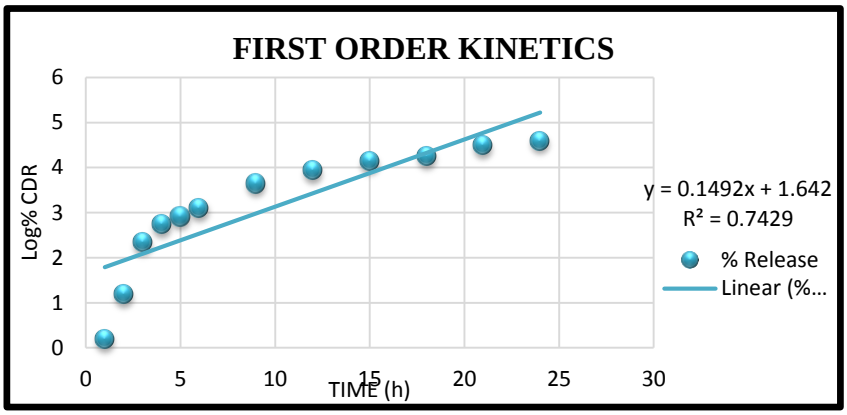

Figure 8: Graph of First Order Release Kinetics (F8 batch)

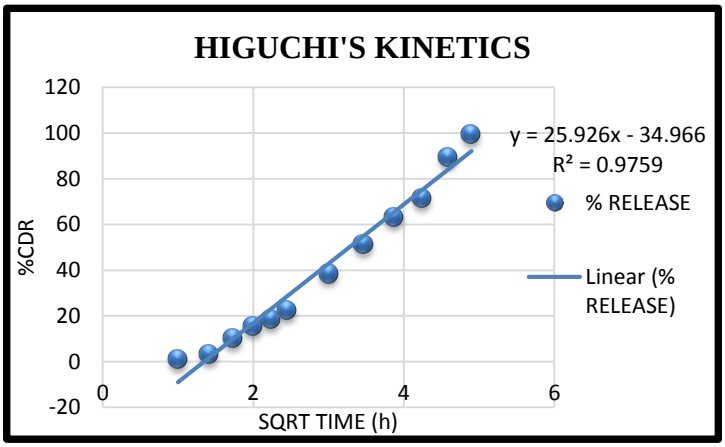

Figure 9: Graph of Higuchi's square root (F8 batch)

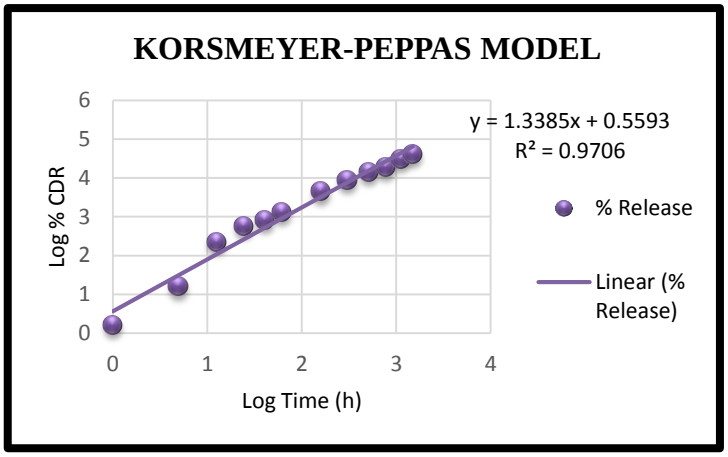

Figure 10: Graph of Korsemeyer's Peppas Model (F8 batch)

Optimization: To investigate the impact of independent variables on responses, software Design Expert 7.0 was used. In other terms, the experimental design involved observing how the dependent variables responded to different factors of the independent variables in nine different batches. Upon analysis, the Fit Summary suggested the Quadratic Vs 2FI approach. The ANOVA results indicated a significant Model F-value of 49.03, affirming the model's significance. Perturbation graphs were generated for each dependent variable, followed by the formulation of mathematical equations representing the models [Wen J X. et al., 2011].

Table 12: The layout of Factorial Design

Runs	Factor1	Factor 2	Response 1
	A: Sodium chloride (%)	B: HPMC (%)	Drug release (%)
1	10	80	81.26
2	5	80	75.23
3	15	50	72.29
4	5	65	87.43
5	10	50	81.38
6	5	50	83.25
7	15	80	99.84
8	10	65	99.80
9	15	65	93.87

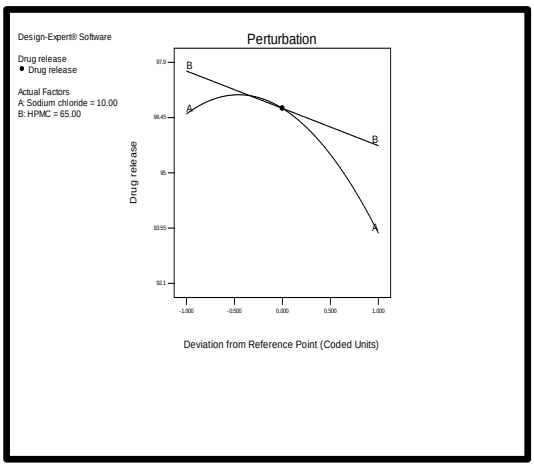

Figure 11: NaCl and HPMC effect on Drug release

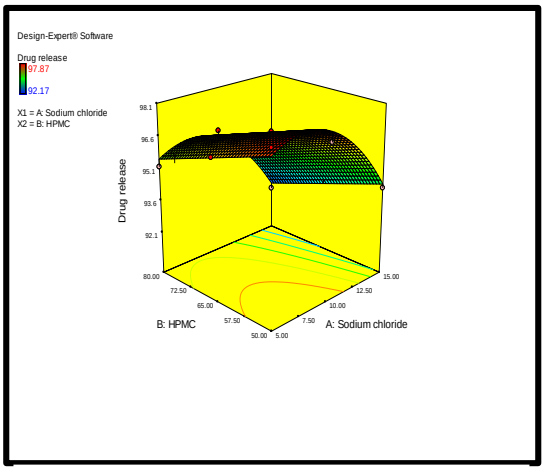

Figure 12: 3D plot for Drug release

The release of the drug shows a relationship where higher concentrations of sodium chloride and HPMC lead to decreased drug release. Specifically, higher concentrations of sodium chloride lead to decreased drug release, while increased concentrations of HPMC also result in decreased drug release.

STABILITY STUDY: The tablets were wrapped in foil and stored in a stability chamber at 40±2°C and 75±5% relative humidity (RH) for a period of 3 months. During this period, the optimized batch exhibited no notable alterations in drug content. Table 13 provides detailed results of the stability analysis for the optimized batch [Singh K. et al.,2014].

Table 13: Stability Study for 3 months

Parameter		**After storage at 40±2°C / 75±5% RH, for 3 months**
Colour		White to pale yellow
Drug content		99.81%
% Drug Released	3 hrs.	10.25
	12 hrs.	50.79
	24 hrs.	99.02

4. CONCLUSION:

The Controlled Porosity Osmotic Pump Tablets (CPOP tablets) were formulated using the wet granulation technique, which included the drug, osmogent, and various other excipients. Examination through SEM confirmed the presence of pores on the tablet membrane. The optimized formulation exhibits drug release following zero-order kinetics. Stability tests, conducted in compliance with ICH guidelines, involved storing the tablets at 40°C with 75% relative humidity for three months, showing no significant change in drug content.

DECLARTION OF COMPITING INTEREST

The authors declare that they have no known competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

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