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FORMULATION, OPTIMIZATION, AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF TOFACITINIB CITRATE

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ABSTRACT
The objective of the present study was to study the effect of polymer on the sustained release of Tofacitinib Citrate from tablets. Compatibility was studied using Fourier transform infrared spectroscopy and UV-Visible spectroscopy. The tablets were prepare using the wet granulation method using HPMC K4M and Xanthan gum. The prepared matrix tablets were evaluate for their physicochemical parameters such as weight variation, hardness, thickness, friability, content uniformity, and in-vitro dissolution. Both pre-compression and post-compression parameters were evaluated, and all were found to be within the acceptable range. The drug release data were subjected to different models to evaluate the kinetic mechanism of drug release. Formulation (F-3), F-6), (F-9) were selected as best formulation as they sustained their drug release.

KEYWORDS: Sustained Release, HPMC K4M, Xanthan gum, Matrix Tablet.

1. INTRODUCTION

The term "sustained release" refers to a relatively new technology in the field of pharmaceuticals. As a result, research in this area has been extensive, leading to many significant discoveries. Sustained release term used to identify drug delivery systems that are designed to gain prolonged therapeutic effects by continuously releasing medication over an extended period after administration of a single dose [1].
Sustained-release matrix tablets are designed to release the active pharmaceutical ingredient (API) slowly over an extended period, maintaining a consistent drug concentration in the blood. Matrix type of drug delivery system contains a semisynthetic and natural polymer involved for showing controlled release respectively [1].
Tofacitinib is a Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). In cellular settings. This study aimed to prepare matrix tablets of Tofacitinib Citrate using varying proportions of the HPMC K4M and Xanthan gum.

2. Materials and methods [2,3]

2.1 Drug and Excipients

Tofacitinib Citrate was received as a gift sample from Unichem Laboratory, Ltd. (Goa, India), HPMC K4M, Xanthan gum, Lactose, Magnesium stearate, and Talc.

2.2 Method of Preformulation study

2.2.1 Organoleptic characters

The drug's color, odor, and taste were documented using descriptive terms.

2.2.2 Melting point determination

The melting point of the drug was determined by the capillary fusion method.

2.2.3 UV -Visible spectroscopy

UV-Visible spectra can be used to confirm the identification of tofacitinib citrate in the tablet formulation. The characteristic absorption peaks of tofacitinib citrate can be compared to reference spectra to confirm the presence of the API of product.

2.3 Preparation of sustained release matrix tablet by wet granulation method

Matrix tablets of Tofacitinib Citrate were prepared by wet granulation method by using varying proportions of polymers in combination. The drug was mixed with the HPMC K4M, Xanthan Gum as a polymer, and lactose at different ratios.

The powders were granulated with isopropyl alcohol, sieved using a mesh 20 screen, and dried at 50 ºC for 30min. The dried granules were again sized by a mesh 20 screen and mixed with talc and magnesium stearate for 2 min. The final weight of each trial formulation was kept at 500mg and compression of the tablet was done by a tablet punching machine. The appropriate amount of the mixture was weighed and then compressed using 10-station rotary tablet presses equipped with punches at a constant compression force required to produce the hardness of tablets. All the tablets were stored safely in airtight containers for further use [4,5].

2.4 Identification of FTIR spectrometry

Tofacitinib citrate plates were prepared by pressing tofacitinib citrate with potassium bromide and obtained a spectral range of 4000 to 400 cm^{-1} under operating conditions and spectrum observed for any occurrence and disappearance of characteristic drug peak and compared with the standard references [6,7].

2.5 Micromeritic Properties of granules for Tofacitinib Citrate Tablets [8,9]

Bulk Density: Measures the powder's mass per unit volume, including void spaces.

$$BD = \frac{Mass\ of\ powder}{Bulk\ volume}$$

Tapped Density: Measures the powder's density after tapping, indicating packing efficiency.

$$TD = \frac{Mass\ of\ powder}{Tapped\ volume}$$

Carr's Index (CI): Indicates compressibility and flowability of the powder.

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

Hausner's Ratio : A ratio of tapped to bulk density, showing flow characteristics.

A ratio close to 1 indicates a good flow

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

Angle of Repose (θ): Measures the powder's ability to flow freely.

$$tan\ tan\ (\theta) = \frac{Height\ of\ powder\ cone}{Radius\ of\ the\ base}$$

Table 1: Formulation of Sustained release matrix tablet of Tofacitinib Citrate by using 3^2 factorial design [10]

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tofacitinib Citrate	10	10	10	10	10	10	10	10	10
HPMC K4M	85	85	85	95	95	95	105	105	105
Xanthan Gum	60	65	70	60	65	70	60	65	70
Lactose	295	290	285	285	280	275	275	270	265
Magnesium stearate	30	30	30	30	30	30	30	30	30
Talc	20	20	20	20	20	20	20	20	20

2.6 Post-compression parameters [11,12]

2.6.1 Weight variation - This is done to ensure that each tablet contains the correct amount of API and excipients.

$$Weight\ variation = \frac{Individual\ tablet\ weight - Average\ tablet\ weight}{Average\ tablet\ weight} \times 100$$

2.6.2 Hardness - Tablet hardness ensures the tablet can withstand mechanical stress during handling. It is measured using a tablet monsanto hardness tester.

2.6.3 Friability - Friability is calculated by measuring the loss in weight after subjecting a sample of tablets to abrasion in a Roche friabilator [13].

$$Friability = \frac{Initial\ tablet\ weight - final\ tablet\ weight}{Initial\ tablet\ weight} \times 100$$

2.6.4 Thickness – It is measured by using a tablet thickness gauge. This ensures uniformity in size and appearance[14].

2.6.5 Dissolution Testing – It measures how the drug is released over time. A USP dissolution apparatus (usually Apparatus II-Paddle) is used and the percentage of drug released is measured at different time points [15].

$$Tablet\ thickness = \frac{Total\ tablet\ thickness}{No.of\ tablets\ measured}$$

3. RESULTS AND DISCUSSION

3.1 Result of Preformulation Study

Organoleptic parameter of drug has been studied. Drug powder is white and odourless. Melting point of drug was found to be 200 - 202°C. Solubility study of tofacitinib citrate was carried out and it shown freely soluble in water, freely soluble in methanol and sparingly soluble in acetone. FTIR study carried out to study of drug with excipients. Standard graph of Tofacitinib citrate in pH 7.4 Phosphate buffer was carried out. The graph of absorbance vs concentration for Tofacitinib citrate was found to be linear in the concentration range of 5 to 25 µg/ml. So, the drug obeys Beer Lambert's law in the range of 5-25µg/ml [16,17].

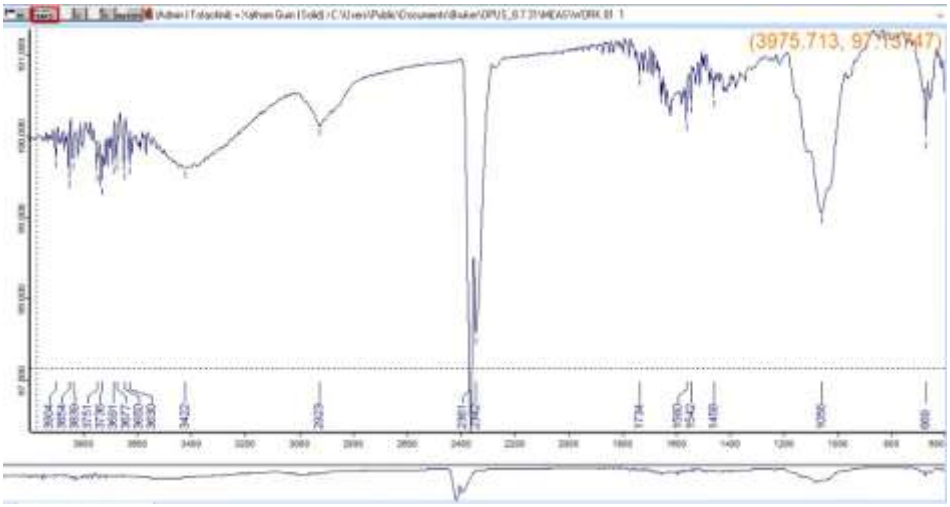

Figure 1: Calibration curve of Tofacitinib Citrate

3.1.1 FTIR Spectral analysis

Infrared spectra of drug, drug with polymers, drug with all the excipients are examined. It has been found in this investigation that there is no chemical interaction between among them. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between drug and all the excipients [18,19].

3.1.2 FTIR Spectral analysis of Tofacitinib Citrate

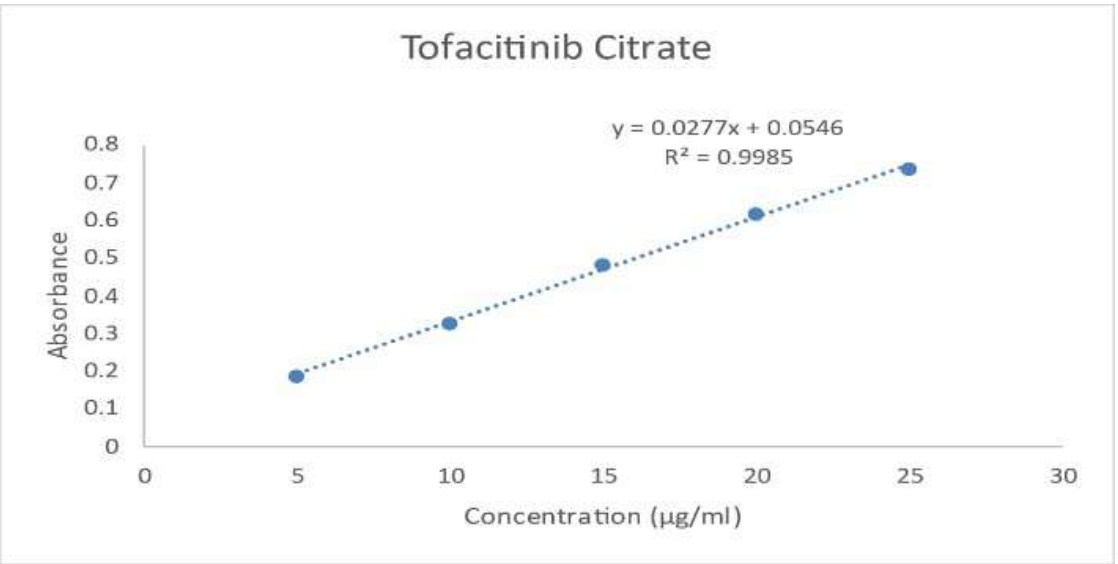

Figure 2: FTIR of Tofacitinib Citrate

3.1.3 FTIR Spectral analysis of Tofacitinib Citrate + HPMC K4M

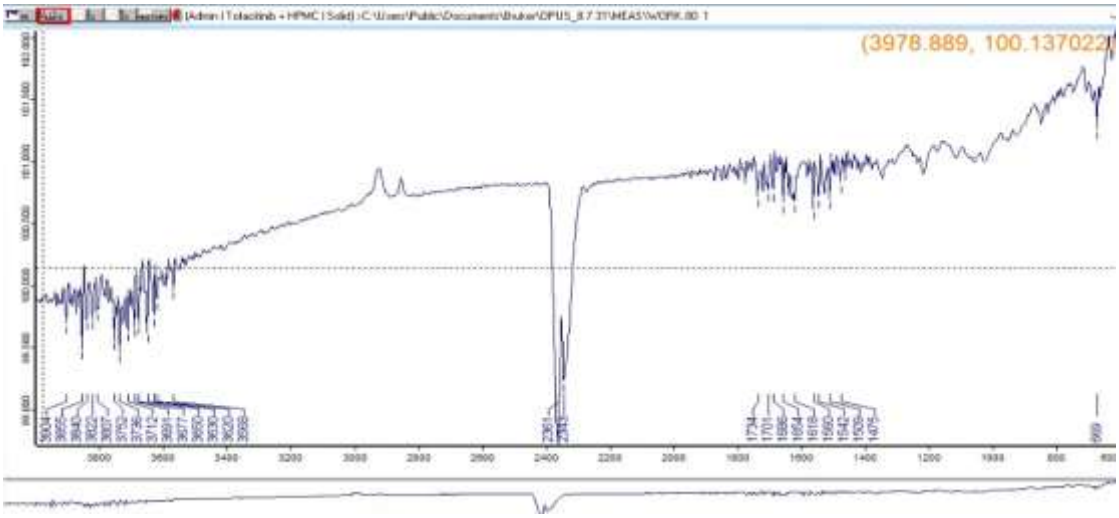

Figure 3: FTIR of Tofacitinib Citrate + HPMC K4M

3.1.4 FTIR Spectral analysis of Tofacitinib Citrate +Xanthan gum

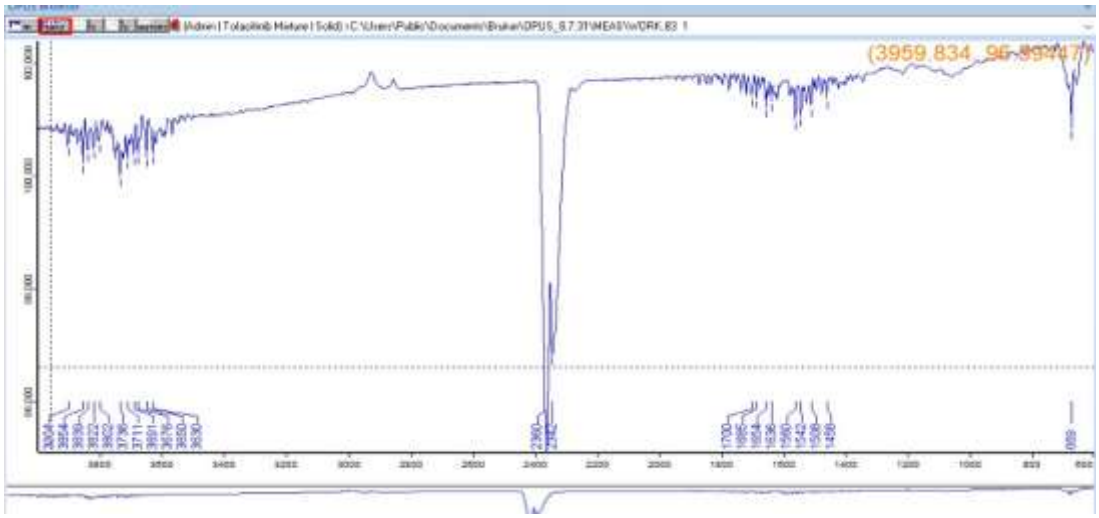

Figure 4: FTIR of Tofacitinib Citrate +Xanthan gum

3.1.5 FTIR Spectral analysis of Tofacitinib Citrate + Excipients

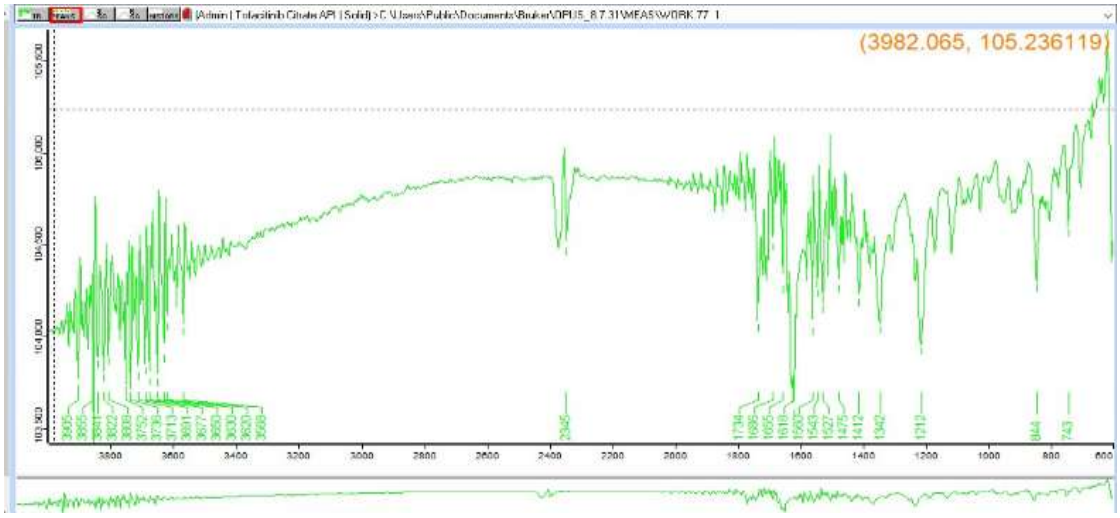

Figure 5: FTIR Spectral analysis of Tofacitinib Citrate + Excipients

4. Pre-compression parameters

The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, and compressibility index, and their values are shown in Table 1. The bulk density of 0.45 to 0.52 g/ml and Powder blend indicated excellent flow properties with an angle of repose values ranging from 27.02 to 30.96. The compressibility index for all the formulations was found to be less than 15%, which indicates that the powder mixture has good flow properties. Hausner's ratio was also calculated, ranging between 1.10 and 1.17 [20].

Table 2: Result of Pre-compression parameters for sustained release matrix tablets of Tofacitinib Citrate F1 to F9.

Formulation Batch	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	30.96±0.14	0.47±0.07	0.55±0.10	14.54±0.1	1.17±0.1
F2	28.36±0.2	0.47±0.110	0.52±0.9	9.61±0.2	1.10±0.4
F3	27.47±0.2	0.45±0.096	0.54±0.69	13.46±0.1	1.15±0.1
F4	28.73±0.9	0.48±0.135	0.56±0.2	14.28±0.3	1.16±0.1
F5	29.67±0.4	0.46±0.108	0.53±0.2	13.20±0.2	1.15±0.1
F6	27.24±0.1	0.45±0.160	0.55±0.2	14.18±0.1	1.14±0.1
F7	27.92±0.4	0.52±0.195	0.61±0.1	14.15±0.1	1.17±0.1
F8	29.68±0.4	0.50±0.17	0.58±0.18	13.79±0.1	1.16±0.2
F9	27.02±0.5	0.46±0.145	0.54±0.13	13.96±0.2	1.14±0.1

5. Evaluation of post-compression parameters [21,22]

Sustained release matrix tablets of Tofacitinib Citrate were prepared by wet granulation method. A total of 9 formulations were prepared. The tablet hardness, thickness, friability, and Weight Variation for each formulation are shown in Table 5. The weight variation test indicated that the percentage deviation of all tablet formulations was found to be within the pharmacopoeia acceptable limit. The hardness of all the tablets was within the range of 2.8-3.5 kg/cm. The drug content in all the batches was determined by measuring the absorbance of the sample at 287 nm using a UV spectrophotometer.

Table 3: Result of Post compression parameters for sustained release matrix tablets of Tofacitinib Citrate F1-F9.

Formulation Code	Hardness	Thickness	Friability	Weight variation
F1	3.3±0. 20	3.84±0.02	0.47±0.02	501.10±0.17
F2	3.0±0.05	3.8±0.04	0.71±0.12	500.11±1.06
F3	3.5±0.05	3.82±0.08	0.40±0.05	502.10±0.63
F4	3.4±0.23	3.83±0.15	0.60±1.35	503.10±1.25
F5	3.3±0.11	3.70±0.07	0.59±0.13	501.12±0.86
F6	3.5±0.15	3.80±0.19	0.42±0.01	502.13±0.44
F7	3.3±0.25	3.74±0.21	0.68±0.16	500.17±0.69
F8	3.3±0.11	3.77±0.06	0.59±0.10	501.3±0.73
F9	3.4±0.75	3.80±0.26	0.40±0.17	502.10±0.

Table 4: In-vitro drug release data of formulation F1-F3

Time (hrs.)	F1		F2		F3	
	Cumulative Drug Release (CDR)	% Cumulative Drug Release (%CDR)	Cumulative Drug Release (CDR)	% Cumulative Drug Release (%CDR)	Cumulative Drug Release (CDR)	% Cumulative Drug Release (%CDR)
0	0	0	0	0	0	0
2	0.184	28.69	0.120	27.56	0.128	24.78
3	1.0862	41.88	1.063	39.6	1.0862	35.3
4	2.149	58.1	2.138	56.23	2.149	52.6

5	2.982	77	2.537	74.59	2.582	70.65
6	3.085	86.3	3.0633	83.01	2.992	80.4
8	4.024	99.79	3.256	97.11	4.024	94.11

Table 5: In-vitro drug release data of formulation F4-F6

Time (hrs.)	F4		F5		F6	
	Cumulative Drug Release (CDR)	% Cumulative Drug Release (%CDR)	Cumulative Drug Release (CDR)	% Cumulative Drug Release (%CDR)	Cumulative Drug Release (CDR)	% Cumulative Drug Release (%CDR)
0	0	0	0	0	0	0
2	0.172	26.8	0.94	23.4	0.9	20.9
3	1.0853	45.4	1.024	42.21	1.30	37.4
4	1.983	56.9	1.854	52.5	1.923	50.91
5	2.563	75.04	2.493	70.51	2.456	68.17
6	3.078	85.46	3.182	82.36	2.721	79.61
8	4.288	98.19	4.246	97.38	4.187	94.02

Table 6: In-vitro drug release data of formulation F7-F9

Time (hrs.)	**F7**		**F8**		**F9**	
	Cumulative Drug Release (CDR)	**% Cumulative Drug Release (%CDR)**	**Cumulative Drug Release (CDR)**	**% Cumulative Drug Release (%CDR)**	**Cumulative Drug Release (CDR)**	**% Cumulative Drug Release (%CDR)**
0	0	0	0	0	0	0
2	0.153	25.9	0.917	22.8	0.87	20.60
3	1.267	38.41	1.201	35.95	0.968	32.92
4	2.263	57.24	1.893	54.58	1.981	52.08
5	2.560	75.77	2.605	73.16	3.752	69.81
6	3.834	85.91	2.890	81.69	2.654	79.12
8	4.392	98.74	3.890	97.2	4.963	94.90

5.1 In vitro drug release profile of F1-F9 [23]

5.1.1 Comparative In vitro drug release data of formulation F1-F3.

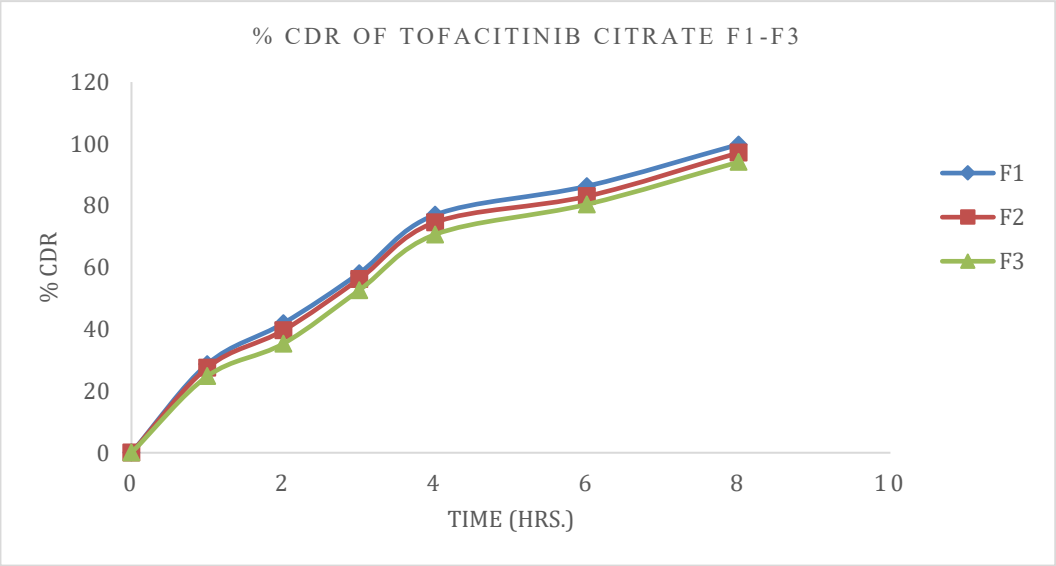

Figure 6: In vitro drug release graph of formulation F1-F3

5.1.2 Comparative In vitro drug release data of formulation F4-F6.

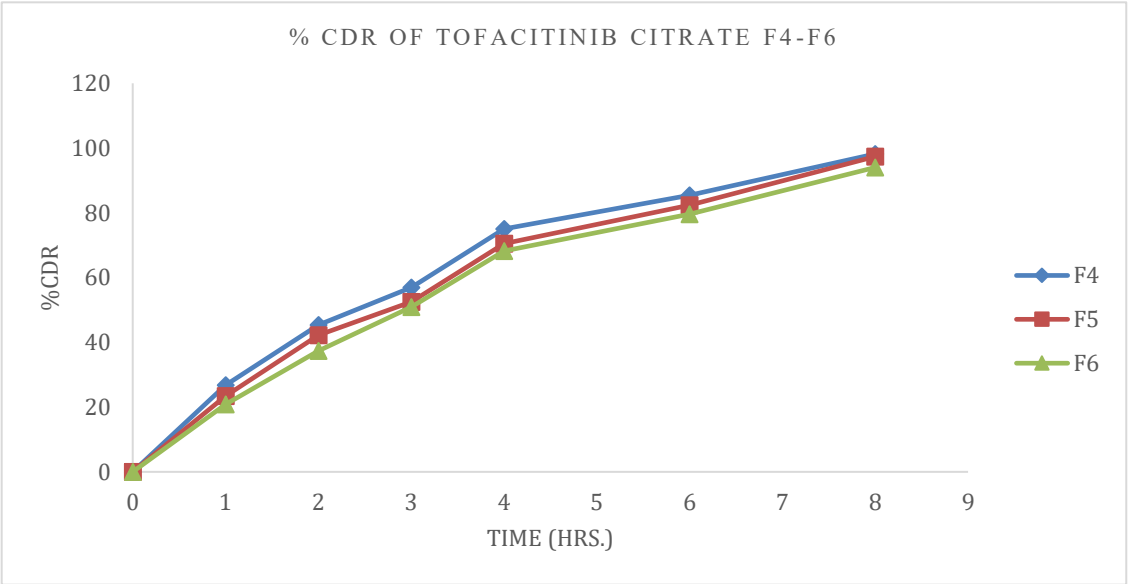

Figure 7: In vitro drug release graph of formulation F4-F6

5.1.3 Comparative In-vitro drug release data of formulation F7-F9.

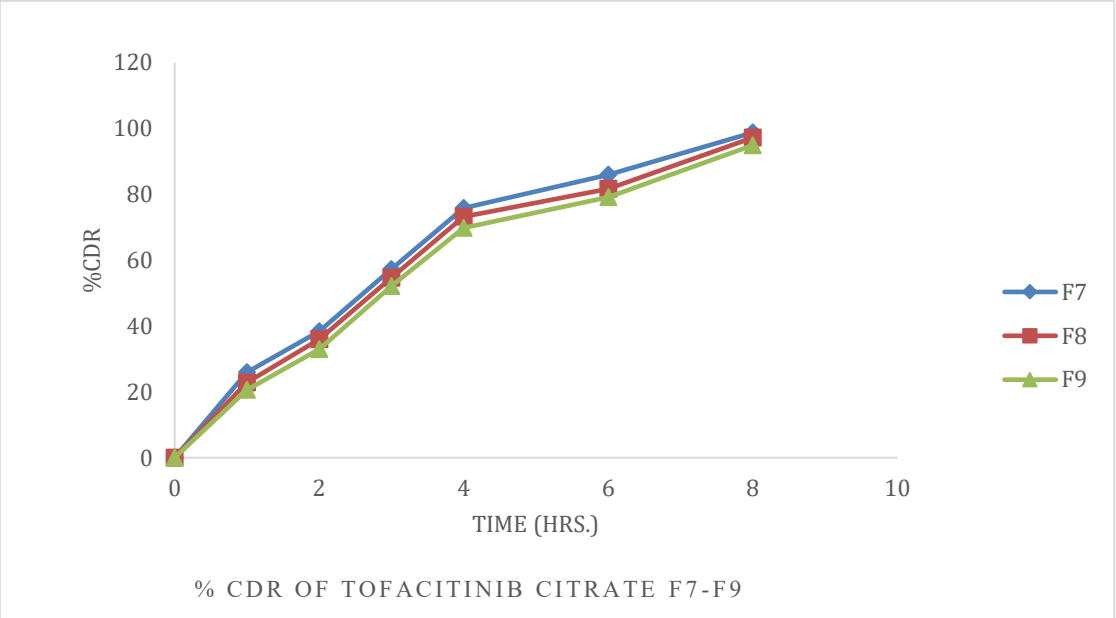

Figure 8: In vitro drug release graph of formulation F7-F9

6. DISCUSSION

6.1 In-vitro drug release data of formulation F1-F3.

In-vitro drug release data of formulation F1-F3 Containing 85 mg of HPMC K4M and 60mg, 65mg, and 70mg of Xanthan Gum respectively. Each of the tablets in all the formulations contains 10 mg of Tofacitinib citrate. The percentage release of drugs from F1, F2, and F3 were found to be 99.79%, 97.11%, 94.11 % respectively. The slope values of release data suggest that as the amount of Xanthan Gum increased rate of release of the drug gradually decreases. Drug release order of the above formulation was obtained in the following manner F3<F2<F1.

6.2 The Result of in-vitro drug release data of formulation F4-F6

In-vitro drug release data of formulation F4-F6 Containing 95 mg of HPMC K4M and 60mg, 65mg, and 70mg of Xanthan Gum respectively. Each of the tablets in all the formulations contains 10 mg of Tofacitinib citrate. The percentage release of drugs from F4, F5, and F6 were found to be 98.19%, 97.38%, 94.02% respectively. The slope values of release data suggest that as the amount of Xanthan Gum increased rate of release of the drug gradually decreases. Drug release order of the above formulation was obtained in the following manner F6<F5<F4.

6.3 The Result of in-vitro drug release data of formulation F7-F9

In-vitro drug release data of formulation F7-F9 Containing 105mg of HPMC K4M and 60mg, 65mg, and 70mg of Xanthan Gum respectively. Each of the tablets in all the formulations contains 10 mg of Tofacitinib citrate. The percentage release of drugs from F7, F8, and F9 were found to be 98.74%, 97.2%, 94.90% respectively. The slope values of release data

suggest that as the amount of Xanthan Gum increased rate of release of the drug gradually decreases. Drug release order of the above formulation was obtained in the following manner F9<F8<F7.

7. CONCLUSION

Sustained release matrix tablets of Tofacitinib Citrate were prepared using different ratios of HPMC K4M and Xanthan Gum and by wet granulation method. The results of the present study demonstrate that the HPMC K4M and Xanthan Gum control the Tofacitinib Citrate release effectively for 8 hrs. It is concluded that sustained release of Tofacitinib Citrate for 8 hours was obtained with formulation (F-3), (F-6), (F-9) containing a high amount of HPMC K4M and Xanthan gum. Sustained-release matrix tablets of Tofacitinib Citrate can reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional Tofacitinib Citrate tablets. Present investigation concluded that amount of Polymer increases the dissolution rate can be decreases (%CDR).

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Conflict of Interest

The authors declare no conflicts of interest.

Authors Contribution

All the authors have contributed equally in this project.

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