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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF TOFACITINIB CITRATE

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ABSTRACT

In this study, an effort was made to develop tofacitinib citrate extended-release tablets to provide an extended-release dosage form, in order to improve efficacy, reduce total dose frequency, and improve rates survive. Patient satisfaction. Infrared spectroscopy and differential scanning calorimetry confirmed that there were no drug-polymer interactions. In this study, tofacitinib citrate sustained-release tablets were prepared by a hot granulation technique using carnauba wax, cetyl alcohol, and stearic acid as slow-release polymers. In this work, only physicochemical characteristics such as reset angle, Carr index, Hausner ratio, weight change, hardness, thickness, friability and drug content were performed and only evaluation was performed. print studies. in vitro of tofacitinib citrate matrix tablets. Along with in vitro studies, in vivo drug research is the most important. In the future, in vivo studies are needed to establish the in vitro-in vivo correlation (IVIVC) required for formulation development and long-term stability studies are needed. All tests show that the particles exhibit excellent flow characteristics. In the present studies, the F3 substrate formulation containing carnauba wax may exhibit maximal delay in drug release and an abnormal diffusion mechanism. For these reasons, the F3 formula is considered the best of the nine formulas.

KEYWORDS: Tofacitinib citrate, Sustained Release, Matrix tablet, DSC.

INTRODUCTION

Oral administration has been the most commonly used and convenient way to administer the drug. The oral route has received more attention in the pharmaceutical sector, due to its greater flexibility in dosage form design compared to drug delivery design for other routes.

Medication intake depends on various factors such as the type of delivery system, the disease being treated, the patient, the duration of treatment, and the properties of the drug. Most orally controlled drug delivery systems (OCDDS) rely on diffusion, dissolution, one or a combination of two mechanisms, for controlled release of drug into the gastrointestinal tract (GIT).[1]

The physicochemical properties include crystalline nature, solubility, partition coefficient, intrinsic solubility, etc. The dosage form properties are controlled and optimized for the physicochemical properties of the drug and related GI environmental factors. Other factors considered were disease status, patient compliance and duration of treatment.[2]

The goal of an oral drug delivery system is to achieve better therapeutic success than conventional dosage forms of the same drug. This can be achieved by improving pharmacokinetic profiles, patient comfort and adherence. The oral route has been known for many decades as the most widely used route of all routes for understanding systemic drug delivery through pharmaceutical products manufactured in a variety of dosage forms. each other.[3]

Tofacitinib citrate is the most widely used antidepressant in the treatment of major depression. The disease has low bioavailability, due to poor absorption. It undergoes hepatic metabolism and the mean half-life (5 hours) of the drug requires frequent dosing, different recent drug release control techniques, the matrix system provides many Various advantages are easier better control of drug release profiles and better patient compliance.[4]

The marked variability caused by the use of common drugs is likely to produce a period of therapeutic effect when the concentration falls below the minimum therapeutic concentration of the drug and can be controlled within narrow treatment using a sustained release system. This will minimize the severity of side effects.[5]

Hydrophobic polymeric matrix systems are widely used to design sustained-release oral dosage forms due to their versatility to provide desirable drug release profiles, cost-effectiveness, and acceptability. widely prescribed. Large-scale production requires simpler formulations with the most economical and least expensive dosage forms. The matrix pelletization by wet granulation is the most accepted in large-scale production.[6]

MATERIALS

Table No. 1: List of materials with the source.

Name of ingredients	Name of supplier
Tofacitinib citrate	PharmaTech Solutions.
Carnauba wax	Shasun pharmaceuticals, Puducherry.
Cetyl alcohol	Tristar formulations Pvt. Ltd., Puducherry.
Stearic acid	Tristar formulations Pvt. Ltd., Puducherry.
Lactose	Loba chemie Pvt.Ltd., Mumbai.
Talc	Loba chemie Pvt.Ltd., Mumbai.
Hydrochloric acid	S d fine-chem limited, Mumbai.
Methanol	Qualigens fine chemicals, Mumbai.
Acetone	Loba chemie Pvt.Ltd., Mumbai.
Sodium hydroxide	S d fine-chem limited, Mumbai.

Equipment used

Table No. 2: List of equipment with model make.

Equipment	Model/ Make
Electronic balance	Shimadzu BL-220H, Japan.
Bulk density apparatus	Indolabs VTAP/MATIC-II, Chennai.
Standard sieves	Jayant scientific, India.
Hot air oven	Precision scientific Co., Chennai.
Sixteen punch tablet compression machine	Cadmach, Ahmadabad, India.
Friability apparatus	Veego scientific VFT-DV, Mumbai.
Hardness tester	Monsanto
Vernier caliper	Indolabs, Mitutoyo.
Humidity chamber	Labtech, Ambala.
USP dissolution test apparatus Type I	Veego scientific VDA-8DR, Mumbai.
UV-Visible spectrophotometer	Elico-SL 159 UV-Visible spectrophotometer, Japan.
FTIR spectrophotometer	Shimadzu, Japan.
Differential scanning calorimeter	Shimadzu, Japan.

Preformulation study[7]

Identification by FTIR spectroscopy

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. Absorption maximum in the spectrum obtained with the substance being tested corresponds in position and magnitude relative to that of the reference spectrum.[8]

Identification by melting point

Melting point of the drug was determined by capillary tube method.[9]

Organoleptic properties

The color, odor and taste of the drug were recorded using descriptive terminology.[10]

Solubility study

It is important to know the solubility characteristics of a drug in an aqueous system as it must possess some limited water solubility to elicit a therapeutic response. The solubility of the drug has been recorded using different descriptive terms indicated in the Indian Pharmacopoeia, 2007.[11]

Loss on drying

Drying loss is the loss in weight expressed as a mass percent/w due to water and volatiles of any kind that can be ejected under specified conditions. 1 g of the accurately weighed sample is transferred to a shallow glass stoppered weighing vessel and accurately weighed. The bottles were transferred to the drying oven and the material was dried at 105°C for 3 h. The bottle has been removed from the oven and reweighed; The loss on drying is calculated according to the following equation.[12]

$$LOD = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

Determination of λ max

The absorbance peak of the standard solution was scanned between the 200-400 nm regions on a Shimadzu-1700 Pharma spec UV-Visible spectrometer. Absorption maximums obtained with the substance under test correspond to the position and intensity relative to the values of the reference spectrum.[13]

Preparation of standard curve of Tofacitinib Citrate in 0.1N HCl

A stock solution of tofacitinib citrate was prepared by dissolving 100 mg of the drug in 0.1 N HCl and the final volume was brought to 100 mL to give a solution concentration of 1000 µg/ml. From the stock solution, pipette 10 ml into a 100 ml volumetric flask to obtain a concentration of 100 µg/ml. From the standard tofacitinib citrate stock solution, pipette appropriate aliquots 1, 2, 3, 4, and 5 mL into a 25 mL volumetric flask, and the final volume was prepared with 0.1 N HCl. To obtain concentrations of 4, 8, 12, 16, and 20 µg/ml. The absorbance spectra of each solution for 0.1 N HCl as a blank were measured at 287 nm using an Elico-SL 159 UV Visible Spectrophotometer.[14]

Preparation of standard curve of Tofacitinib Citrate in pH 6.8 phosphate buffer

Stock solution of tofacitinib citrate was prepared by dissolving 100 mg of the drug at pH 6.8 and the final volume was brought to 100 mL to give a solution concentration of 1000 µg/mL.

From the stock solution, pipette 10 ml into a 100 ml volumetric flask to obtain a concentration of 100 µg/ml. From the standard tofacitinib citrate stock solution, pipette appropriate aliquots 1, 2, 3, 4, and 5 mL into a 50 mL volumetric flask and the final volume formed with a pH of 6.8. To obtain concentrations of 4, 8, 12, 16 and 20 µg/ml. The absorbance spectra of each solution against pH 6.8 as a blank were measured at 287 nm using an Elico-SL 159 Ultraviolet Visible Spectrophotometer.[15,16]

Determination of percentage purity of drug

Accurately weigh 100 mg of tofacitinib citrate dissolved in a small amount of pH 6.8 phosphate buffer and the volume adjusted to 100 ml with the same prepared standard solution of 1000 µg/ml concentration. From the above solution, 5 ml of solution was transferred to a 25 ml volumetric flask and a final volume was made 25 ml with pH = 6.8. The absorbance values of these solutions were measured against the blank (pH 6.8) at 287 nm using a UV-VISIBLE spectrophotometer. The percent purity of the drug was calculated using the calibration histogram method (least squares method).[17]

Determination of drug-polymer compatibility

Differential scanning calorimetry, Fourier transform infrared spectroscopy studies are used to evaluate physicochemical compatibility and interactions, helping to predict drug-polymer interactions. Each polymer used in the formulations has been blended with actual drug levels down to the final dosage form. Each polymer has been carefully mixed with the drug to increase the drug-polymer molecular contact to speed up the reaction where possible.

Differential scanning calorimetry

Any possible drug polymer interaction can be studied by thermal analysis. The DSC analysis of pure drug, drug with carnauba wax were carried out using Shimadzu to evaluate any possible drug- polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.[18]

Method of preparation

All the ingredients mentioned in Table were pre-weighed and passed the drug through mesh #80. The waxes were molten and then required quantity of drug was slowly added to the molten wax. After cooling, the mass was subjected to granulation by passing through mesh #16. Granules were mixed with lactose and talc and also used for evaluation of flow

characteristic.[19]

Table No. 3: Composition of Tofacitinib Citrate SR matrix tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tofacitinib Citrate	5	5	5	5	5	5	5	5	5
Carnauba wax	53	106	159	-	-	-	-	-	-
Cetyl alcohol	-	-	-	53	106	159	-	-	-
Stearic acid	-	-	-	-	-	-	53	106	159
Lactose	204	151	98	204	151	98	204	151	98
Talc	48	48	48	48	48	48	48	48	48
Total weight (mg)	310	310	310	310	310	310	310	310	310

Evaluation of pre-compression granules[20,21]

Angle of repose

The angle of repose was determined by the funnel method. An accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$$\tan(\theta) = \frac{h}{r}$$

Where „h" and „r" are the height and radius respectively of the powder cone.

Loose bulk density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder

Tapped bulk density

A precisely weighed powder mix of each recipe is gently shaken to break down agglomerates form and it is fed into a graduated cylinder. The cylinder is knocked until no further change in volume is observed, resulting in an adjusted volume. The mining block density of the powder mixture is determined according to the following formula.

Tapped bulk density = Total weight of powder / Total volume of tapped powder

Hausner's ratio

It is related to inter-particulate friction and could be used to predict powder flow properties. Hausne's ratio was determined by following equation,

Hausner's Ratio = Tapped bulk density / Loose bulk density

A Hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

Carr's compressibility index

It is a simple index that can be determined on small quantities of powder. The compressibility indices of the powder blends was determined using following formula,

Carr's compressibility index (%) = [(TBD-LBD)/ TBD] x100

Preparation of sr matrix tablets

Hot melt granulation method:

All ingredients listed in Table were pre-weighed and the drug passed through the #80 grid. The wax was melted and then the required amount of drug was slowly added to the melted wax. After cooling, the mass is granulated by passing through mesh no. 16. The granules are mixed with lactose and talcum powder and compressed on a 16-station rotary tablet press using double- concave circular holes 11 mm. The drug polymer ratio was developed to tailor drug release to the theoretical release profile and keep the total tablet mass constant for all batches produced under experimental formulation conditions. The total weight of the matrix tablet is 350 mg with different drug polymer ratios such as 1:0.7, 1:1.4 and 1:2.1. The various polymers used are carnauba wax, cetyl alcohol, and stearic acid. In formulated formulations, retarders include carnauba wax, cetyl alcohol, and stearic acid. Lactose is used as a diluent and 5% talc as a lubricant and thickener.

Evaluation of tofacitinib citrate sustained release matrix tablets

Appearance[22,23]

The tablets were visually observed for capping, chipping and lamination.

Dimension (Thickness and Diameter)

Pellet thickness and diameter are important for pellet size uniformity. The thickness and diameter of the pellets are determined with a caliper. Ten tablets of each formulation type were used and average values were calculated.

Tablet hardness

For each formulation, the hardness of 10 pellets was determined using a Monsanto durometer. The tablet was held along an elongated axis between the tester's two jaws. At this point, the reading should be 0 kg/cm2. Then, a continuous force is applied by turning the knob until the tablet breaks. Values at this stage are recorded in kg/cm2.

Percent friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber that revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in a Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows. Endurance is a measure of a tablet's strength. This test tests several tablets for the combined effects of impact abrasion using a plastic chamber that rotates at 25 rpm, dropping the pellets at a distance of 6 inches with each revolution. A pre-weighed sample of tablets is placed in a Roche chiller, which is then operated for 100 revolutions. The tablets were then removed and reweighed. A loss of less than 1% in weight is generally considered acceptable. The percent friability (% F) is calculated as follows.

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

Weight variation

To detect weight differences, 20 tablets of each formulation were individually weighed using an electronic balance, the average weight was calculated, and the individual pellet weights were then compared with the mean. to find out the difference in weight. The check is done by the regular method. The degree of significant weight change during compression of the tablet part, each and at each interval, we need to check the weight of the pill. If we do not maintain the change in weight, it will create a deviation in the drug content as well as the yield of the tablet.

Drug content

The drug content of each formulation was determined by crushing 20 tablets and a powder equivalent to 100 mg of tofacitinib citrate was transferred to a standard 100 ml volumetric flask. 50 ml of pH 6.8 phosphate buffer was then added. It is gently stirred for 15 minutes.

Then add phosphate buffer pH 6.8 to the mark. The solution was filtered through Whatman filter paper, appropriately diluted, and the absorbance of the resulting solution was measured with an Elico-SL 159 UV Visible Spectrophotometer at 287 nm using pH. 6.8. Phosphate buffer as a blank.

In vitro release studies[24]

The release rate of tofacitinib citrate from the matrix tablet was determined using the US Pharmacopoeia I Dissolution Test Device (Basket Method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed at 50 rpm, using 900 ml of pH 1.2 buffer for the first 2h and phosphate buffer of pH 6.8 for 2 to 10 h at 37 ± 0.5 °C. One sample (5 ml) of solution was removed from the dissolution device every hour and the samples were replaced with a fresh dissolution medium. Samples were filtered through a 0.45 µm membrane filter and diluted appropriately. The absorbance of these solutions was measured at 287 nm using the Elico-SL 159. UV-Vis Spectrophotometer. For each formulation, experiments were performed in triplicate. Release data were analyzed to investigate release kinetics using a first-order, zero-order and Korsmeyer-peppas matrix equations using PCP disso V3 software.

Stability study[25]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of Study and Storage conditions

- Long-Term Testing: 25 C ± 2 C at 60% RH ± 5% for 12 Months
- Accelerated Testing: 40 C ± 2 C at 75% RH ± 5% for 6 Months

In present study the selected formulation VF3 exposure up to 3-month stability studies at accelerated condition (40 C ± 2 C at 75% RH ± 5% RH) to find out the effect of aging on hardness, friability, drug content and in vitro drug release. Stability studies were carried out at accelerated condition (40 C ± 2 C at 75% RH ± 5% RH) for the optimized formulation VF3. The matrix tablets were stored at 40 C ± 2 C at 75% RH ± 5% RH for the accelerated

temperature in closely packed with aluminum foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month, and 3rd month. The samples were analyzed for its hardness, drug content and in vitro drug release.

RESULT AND DISCUSSION

Preformulation parameters- Identification of drug

Identification by FTIR spectroscopy

The FTIR spectrum of Tofacitinib citrate was shown in Figure and the interpretations of FTIR frequencies were showed in Table.

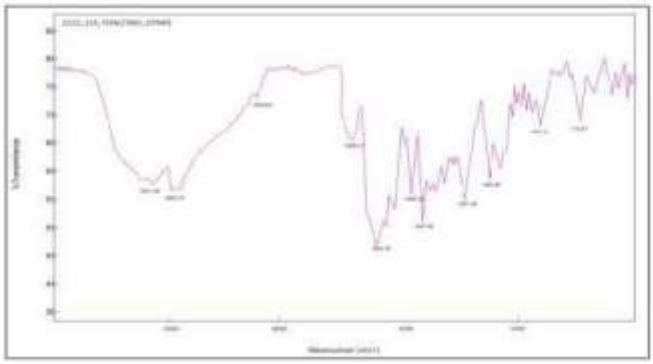

Figure no. 1: FTIR spectrum of tofacitinib citrate.

Interpretation of FTIR Spectrum

Major functional groups present in Tofacitinib citrate shows characteristic peaks in FTIR spectrum. Table shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to the functional group of Tofacitinib citrate. Hence, the sample was confirmed as Tofacitinib citrate.

Table no. 4: Characteristic frequencies in FTIR spectrum of Tofacitinib citrate.

Functional Group	Reported Peak(cm-1)	Observed Peak (cm-1)
N-H Stretch	3200-2945	2992.15
C-N Stretch	2050-1950	2018.64
C=C Stretching	1680-1600	1629.37
C-H bending	1700-1550	1604.26
C-H bending (Aromatic)	1250-1200	1207.38

Melting point

Melting point of Tofacitinib citrate sample was found to be 2010C. The reported melting point for Tofacitinib citrate was in range of 198 to 2020C. Hence, experimental values are in good agreement with official values.

Physicochemical parameters of drug

Organoleptic properties

Colour: White or almost white powder.

Odour: Odourless.

Solubility study

Table no. 5: Solubility of Tofacitinib citrate in different solvents.

Name of solvents	Solubility
Distilled water	Freely Soluble
Methanol	Freely Soluble
Acetone	Sparingly Soluble
Phosphate buffer (pH 6.8)	Soluble
0.1N HCl	Soluble

Loss on drying

The percentage loss on drying after 3 hours was represented in Table 8.3.

Table no. 6: Percentage loss on drying for Tofacitinib citrate.

Percentage LOD	Average percentage LOD
0.107	0.107
0.112	
0.104	

The sample passes test for loss on drying as per the limit specified (N.M.T.1%).

Determination of absorption maximum in 0.1 N HCl

The absorption maximum for Tofacitinib citrate in 0.1N HCL was found to be 287nm and absorption maximum was shown in Figure.

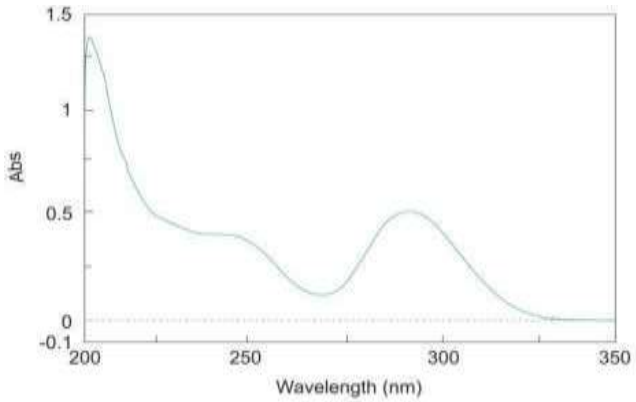

Figure no. 2: λ max observed for Tofacitinib citrate in 0.1N HCl.

Determination of absorption maximum in pH 6.8 phosphate buffer

The absorption maximum for Tofacitinib citrate in pH6.8 phosphate buffer was found to be 287nm and absorption maximum was shown in Figure.

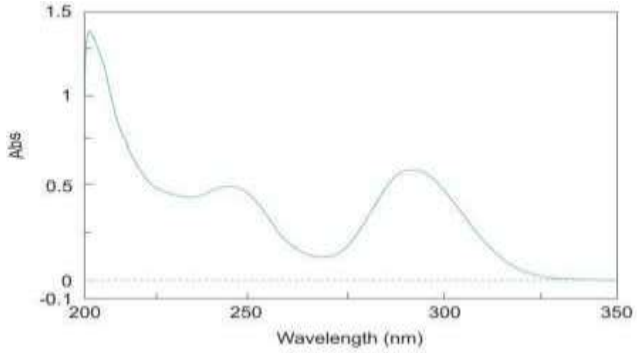

Figure no. 3: λ max observed for Tofacitinib citrate in pH 6.8 phosphate buffer.

Preparation of standard graph of Tofacitinib citrate in 0.1NHCl

Absorbance was obtained in various concentrations of Tofacitinib citrate in 0.1N HCl were given in Table 8.4 and shown in Figure. The graph of absorbance vs. concentration for Tofacitinib citrate was found to be linear in the concentration range of 5-25 µg /ml. The calibration curve parameters shown in Table. So the drug obeys Beer- Lambert‟s law in the range of 5-25 µg/ml.

Table no. 7: Concentration and absorbance of Tofacitinib citrate in 0.1N HCl.

Concentration (µg/ml)	Absorbance
5	0.1123
10	0.2856
15	0.4961
20	0.6938
25	0.8964

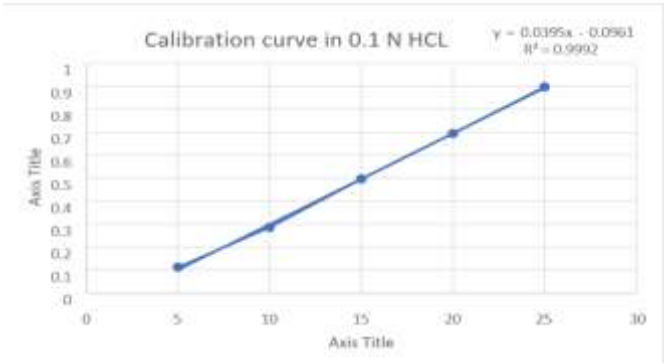

Figure no. 4: Calibration curve of Tofacitinib citrate in 0.1N HCl.

Table no. 8: Calibration parameter values in 0.1 N HCl.

Parameters	Values
Correlation coefficient (r)	0.9992
Slope (m)	0.0395
Intercept (c)	0.0961

Preparation of standard graph of Tofacitinib citrate in pH 6.8 phosphate buffer

Absorbance obtained for various concentrations of Tofacitinib citratein pH 6.8 phosphate buffer were given in Table 8.6 and shown in Figure 8.5. The graph of absorbance vs concentration for Tofacitinib citrate was found to be linear in the concentration range of 5-25µg /ml. The calibration curve parameters shown in Table 8.7. So the drug obeys Beer-Lambert‟s law in the range of 5-25µg /ml.

Table no. 9: Concentration and absorbance of Tofacitinib citrate in pH 6.8 phosphate buffer.

Concentration (µg/ml)	Absorbance
5	0.1216
10	0.3078
15	0.5146
20	0.7349
25	0.9384

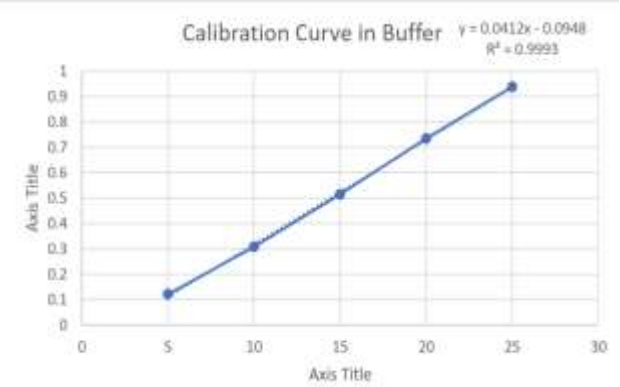

Figure no. 5: Calibration curve of Tofacitinib citrate in pH 6.8.

Table no. 10: Calibration parameter values in pH 6.8 phosphate buffer.

Parameters	Values
Correlation coefficient (r)	0.9993
Slope (m)	0.0412
Intercept (c)	0.0948

Percentage purity of drug

The percentage purity of drug was calculated by using calibration graph-method and

represented in Table.

Table no. 11: Percentage purity of Tofacitinib citrate in pure drug.

Percentage purity (%)	Avg. percentage purity (%)
99.98	100.09
100.12	
100.17	

The reported percentage purity for Tofacitinib citrate was 99 to 102%.

Compatibility testing of drug with polymer

Compatibility of drug and polymers was found to be as following methods such as Fourier transform infrared spectroscopy and differential scanning calorimetry.

Fourier transform infrared spectroscopy

The FTIR spectrums of Tofacitinib citrate with the different polymers used in the formulation are shown in the Figures.

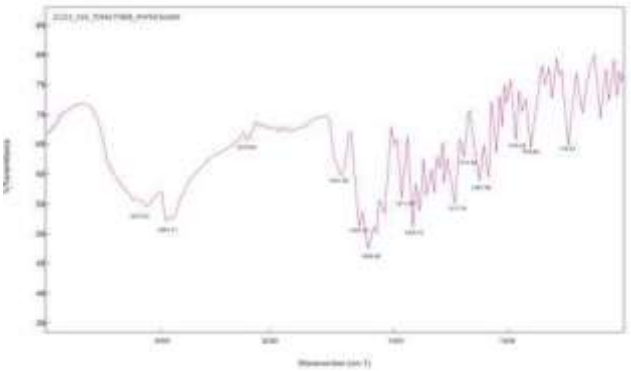

Figure no. 6: FTIR spectrum of Tofacitinib citrate with carnauba wax.

Table no. 12: FTIR peaks observed for Tofacitinib citrate with different polymers used in formulations.

Functional Group	Peaks	
	Pure drug	Physical mixture
N-H Stretch	Yes	Yes
C-N Stretch	Yes	Yes
C=C Stretching	Yes	Yes
C-H bending	Yes	Yes
C-H bending (Aromatic)	Yes	Yes

FTIR spectrums were compared, it could indicate that there was no incompatibility between drug and polymer. According to Table 8.1 and 8.8 and Figures 8.1, 8.6, 8.7 and 8.8, FTIR

spectrum showed that there was no major difference in peak when compared between pure drug of Tofacitinib citrate and Tofacitinib citrate with different polymers. Therefore, it could indicate that there was no incompatibility between drug and different polymers.

Differential scanning calorimetry

The compatibility and interactions between drug and best formulation polymer were checked using differential scanning calorimetry and the results were shown in Figure.

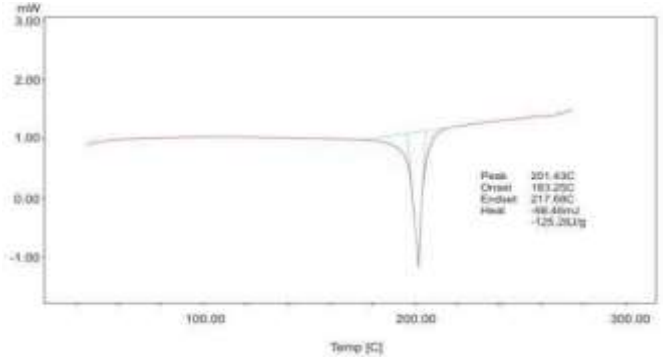

Figure no. 7: DSC thermal analysis of Tofacitinib citrate.

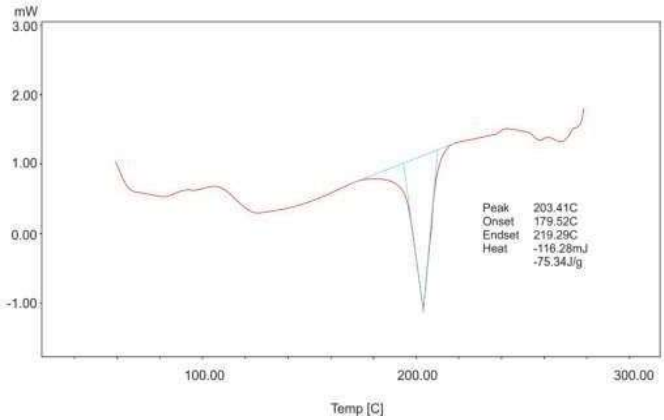

Figure no. 8: DSC thermal analysis of Tofacitinib citrate physical mix.

According to Figures DSC thermos-gram showed that there was no major difference in onset temperature and peak temperature when compared with pure drug thermos-gram. Therefore, it could indicate that there was no incompatibility between drug and best formulation polymer.

Table no. 13: DSC thermos-gram parameters of Tofacitinib citrate + Excipients.

DSC thermos-gram	Onset temperature (°C)	Peak temperature(°C)
Tofacitinib citrate	183.25	201.43
Physical Mixture	179.52	203.41

According to Figures 8.9 and 8.10 and Table 8.10, DSC thermos-gram showed that there was no major difference in onset temperature and peak temperature when compared with pure drug's thermos-gram. No interaction was found between drug and polymer.

Evaluation of granules

The granules of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows

Angle of repose

Angle of repose ranged from 21.31°± 0.05 to 23.27°± 0.43. The results were found to be below 25o and hence the blend was found to have excellent flowability.

Loose bulk density and tapped bulk density

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.454 ± 0.00 to 0.476± 0.00 g/ml; and 0.526 ± 0.00 to 0.555 ± 0.00 g/ml respectively.

Table no. 14: Flow characteristics of powder blends.

Formulation Code	Angle of repose (o)*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner ratio*	Carr's index (%)*
F1	22.43±0.02	0.476±0.00	0.555±0.00	1.16±0.01	14.28±0.62
F2	21.72±0.01	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
F3	23.12±0.03	0.476±0.00	0.555±0.00	1.16±0.01	14.28±0.62
F4	22.23±0.06	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
F5	21.31±0.05	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
F6	22.82±0.12	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
F7	23.27±0.43	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
F8	22.74±0.39	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
F9	23.24±0.51	0.454±0.00	0.526±0.00	1.15±0.01	13.68±0.44

Compressibility index (Carr's index)

The compressibility index (%) ranged from 13.68 ± 0.44 to 14.28 ± 0.62. The blend was found to have excellent flowing property as the result were found to be below 15%.

Hausner ratio

The Hausner ratio ranged from 1.15 ± 0.00 to 1.16± 0.01. The result indicates the free flowing properties of the powders.

Evaluation of sustained release matrix tablets

Appearance

Surface nature of tablets was observed visually and it was concluded they did not show any defects such as capping, chipping and lamination.

Physico-chemical characteristics

The physical characteristics of Tofacitinib citrate matrix tablets (F1to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table

Dimension (Thickness and Diameter)

The size (diameter) of the tablets was found to be in the range from 11.15±0.02 to 11.19± 0.02 mm and thickness ranged between 4.44 ± 0.01 to 4.53 ± 0.01 mm.

Tablet hardness

The hardness of tablets was found to be in the range from 6.05± 0.05 kg/cm2 to 7.10 ± 0.02kg/cm2. This indicates good mechanical strength of tablet.

Percent friability

Percentage friability of all the formulations was found to be in the range from 0.085 to 0.200 %. This indicates good handling property of the prepared matrix tablet.

Table no. 15: Physico-chemical parameters of Tofacitinib citrate matrix tablets.

F	Dimension		Hardness (kg/cm2)*	iability (%)*	Weight variation (mg)*	Drug content (%w/w)*
	Diameter (mm)*	Thickness (mm)*				
F1	11.16±0.01	4.51±0.01	6.70±0.05	0.114±0.03	350.70±0.75	99.43±0.20
F2	11.19±0.01	4.45±0.02	6.15±0.01	0.185±0.01	353.15±1.12	99.39±0.27
F3	11.15±0.02	4.53±0.01	7.10±0.02	0.085±0.05	350.81±1.23	99.75±0.11
F4	11.17±0.02	4.49±0.01	6.50±0.03	0.142±0.07	351.71±1.24	99.31±0.18
F5	11.16±0.01	4.52±0.01	6.85±0.04	0.100±0.03	350.30±1.68	100.01±0.20
F6	11.19±0.02	4.44±0.01	6.05±0.05	0.200±0.02	352.86±0.17	99.24±0.41
F7	11.18±0.02	4.47±0.02	6.30±0.02	0.171±0.01	352.13±1.50	100.03±0.21
F8	11.17±0.01	4.50±0.01	6.65±0.01	0.128±0.09	351.21±0.10	100.38±0.26
F9	11.18±0.01	4.48±0.02	6.45±0.03	0.157±0.05	352.10±0.65	99.49±0.24

Weight variation

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 400 mg, the pharmacopoeial limit for percentage deviation is ±5%. The percentage

deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoeial specifications IP 2007.

Drug content

The drug content of all the formulations was found to be in the range from 99.24± 0.41 to 100.38 ± 0.26 % w/w, which was within the specified limit as per IP 2007.

In vitro dissolution studies

Table no. 16: Percentage of drugs released in all Formulations.

Time (hours)	Percentage drugs released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	16.02±0.93	14.78±0.71	12.31±0.93	17.87±0.93	15.09±0.46	13.39±0.71	18.95±0.71	15.71±0.71	14.93±0.71
2	28.63±0.47	27.69±0.47	23.04±0.46	31.42±0.92	29.24±0.71	26.30±0.92	29.42±0.71	25.84±0.93	23.98±0.46
3	39.77±0.72	35.73±0.92	30.13±0.93	49.69±0.46	38.53±0.93	35.25±0.46	37.16±0.94	33.56±0.72	30.15±0.93
4	50.34±0.94	43.35±0.47	41.43±0.46	57.85±0.46	50.03±0.70	44.73±0.93	46.18±0.45	41.32±1.18	39.75±0.70
5	60.21±0.98	51.94±0.92	47.68±0.93	71.62±0.93	57.57±0.93	51.93±0.46	54.31±0.94	50.52±0.94	47.69±0.47
6	72.29±0.95	62.27±0.71	56.76±0.45	74.79±0.46	60.98±0.71	59.17±0.93	63.12±0.69	62.55±0.73	59.86±0.96
7	80.41±0.73	76.99±0.71	63.10±0.94	78.45±0.93	72.13±0.45	70.16±0.47	71.81±0.72	77.58±0.49	71.17±0.71
8	84.41±0.74	84.99±0.46	72.72±0.45	81.66±0.46	77.32±1.16	75.65±0.94	75.45±0.69	80.17±0.73	77.43±0.46
9	86.26±0.73	87.31±0.93	81.47±0.94	82.56±0.93	82.38±0.71	82.24±0.69	80.50±0.70	84.78±0.74	82.34±0.71
10	88.27±1.00	90.89±0.70	93.04±0.45	83.47±0.45	86.07±1.88	87.33±0.97	85.88±0.93	86.47±1.44	88.50±0.46

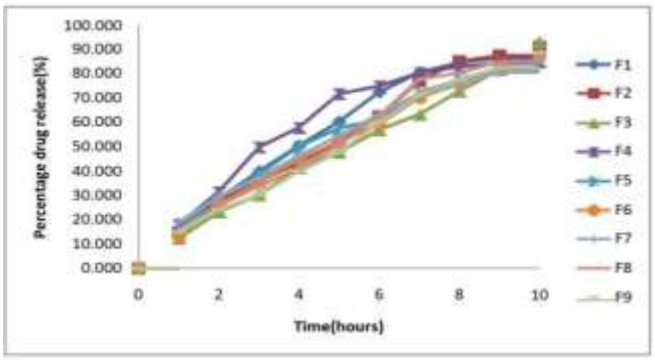

Figure no. 9: In vitro drug release profile of formulation.

Tofacitinib citrate drug was soluble in phosphate buffers and its release from the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The variation in drug release was due to different types of polymers and different concentrations of polymer in all nine formulations. It is expected that the developed formulations should have the following theoretical drug release profile. The drug released from formulation F1 to F3 containing carnauba wax at three concentration levels of 15%, 30%, 45% were found to be 88.27± 1.00, 90.89 ± 0.70, and 93.04 ± 0.45% for Tofacitinib citrate respectively at the end of 10 hours. The drug released from formulation F4 to F6 containing cetyl alcohol at three concentration levels of 15%, 30%, 45% were found to be 86.07± 1.88, 87.33± 0.97and 85.88± 0.93% for Tofacitinib citrate respectively at the end of 10 hours. The drug released from formulation F7 to F9 containing stearic acid at three concentration levels of 15%, 30%, 45% were found to be 85.88 ± 0.93, 86.47 ± 1.44 and 88.50± 0.46% for Tofacitinib citrate respectively at the end of 10 hours. The drug release rate from carnauba wax matrix was found to be high as compared to cetyl alcohol and stearic acid; it was shown in Figure 8.22. This might be due to slow hydration of matrix and its property to form a thick gel layer, it‟s due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration. The overall release rate of Tofacitinib citrate from cetyl alcohol and stearic acid matrices are significantly lesser than that from carnauba wax matrices and which is confirmed by smaller MDT (2.96, 3.89, 3.63 and 4.25, 3.95, 4.45) respectively for cetyl alcohol and stearic acid and higher MDT for carnauba wax matrices. These results are indicating that carnauba wax has higher drug retarding ability for long duration than cetyl alcohol and stearic acid. In addition to concentration of polymer, the type and viscosity of polymer also influences drug release. When drug release data obtained from dissolution study of different polymers at 15%, 30% and 45% concentration is plotted against time respectively, it was observed that low concentration of polymer induces more drug release. High concentration of polymer should be retarding the drug release for longer period of time from the above study, the formulation F3 was concluded as the best formulation among all the nine formulation of this series. Hence the formulation F3 was selected for further stability study.

Stability study

After exposure to accelerated stability conditions the formulation was analyzed for various evaluation parameters.

Table no. 17: Stability studies of best formulation F3 (40°C ± 2°C at 75% ±5%).

Characteristic	Initial	1st Month	2nd Month	3rd Month
Appearance*	Pale yellow	No change	No change	No change
Hardness (kg/cm2)*	7.10±0.02	7.05±0.01	7.00±0.03	6.95±0.01
Friability (%)*	0.085±0.05	0.083±0.03	0.081±0.01	0.080±0.02
Drug content (%)*	99.75±0.11	99.61±0.23	99.43±0.10	99.12±0.14
In vitro drug release at the end of 12 hours*	93.04±0.45	92.86±0.31	92.60±0.27	92.37±0.16

From the above studies there was no significance differences was initiate between the evaluated data from initial and after stability studies and all the values were found in worth accepting limits. The best formulation was showed adequate physical stability at 40oC ± 2oC at 75% ± 5% relative humidity.

CONCLUSION

In this study, an attempt was made to develop tofacitinib citrate extended-release tablets to provide an extended-release dosage form, in order to improve efficacy, reduce total dose frequency, and improve survival. patient compliance. Infrared spectroscopy and differential scanning calorimetry confirmed that there were no drug-polymer interactions. The sustained release tablets are prepared by hot granulation using various polymers such as carnauba wax, cetyl alcohol and stearic acid as slow-release polymers. Particles were evaluated for the collapse angle, density, compression index and Hausner ratio. All tests show that the particles exhibit excellent flow characteristics. In the present studies, the carnauba wax-containing F3 substrate formulation was able to exhibit maximal delay in drug release and an abnormal diffusion mechanism. For these reasons, the F3 formula is considered to be the best of the nine formulas. Based on the values of the release exponent (n), it was concluded that the mechanism of drug release is diffusion coupled with erosion (abnormal transport mechanism). Based on stability studies, there were no significant differences in hardness, friability, drug content and in vitro release profile to give the best formulation.

CONFLICTS OF INTEREST

There are no conflicts of, interest and disclosures regarding the manuscript.

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