International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 1, 2023

Original Article

DESIGN, DEVELOPMENT AND EVALUATION OF NOVEL MOUTH DISSOLVING FILM OF TOFACITINIB CITRATE

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Received: 14 Aug 2022, Revised and Accepted: 04 Nov 2022

ABSTRACT

Objective: The aim of the present study was to design and evaluation of mouth dissolving oral films of tofacitinib citrate allowing fast reproducible drug dissolution in oral cavity thus bypassing the first-pass metabolism to enhance the patient convenience and effective treatment for rheumatoid arthritis.

Methods: Films have been prepared by way of solvent casting technique by using Hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, sodium alginate, and gelatin had been used as the hydrophilic film-forming polymeric bases and glycerol as plasticizer. The prepared film evaluated for *in vitro* disintegration time, tensile strength, content uniformity, folding endurance, swelling index, and *in vitro* drug release.

Results: The results of prepared film pH of all the selected formulation were ranging between 6.1 to 7.5. Thickness of the films was found in the range of 0.07 to 0.19 mm. The folding endurance was found to vary between 95.7 to 105.4-fold, Disintegration time was found 25 to 35, Drug content was found to be for F3 and F6 formulation i.e., 99.035±1.37 and 99.014±0.79.

Conclusion: Thus, the current study successfully designed, developed an optimized Tofacitinib citrate formulation.

Keywords: Tofacitinib citrate, HPMC, Solvent casting technique, Glycerol, Sodium starch glycolate

DOI: https://dx.doi.org/10.22159/ijap.2023v15i1.46064. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Mouth Dissolving Tablets (MDTs) dissolve or disintegrate in saliva and are swallowed without the need of water. MDTs offer an advantage over conventional tablets because of their convenience of easy manufacturing, self-administration, Compactness. Therefore it improves the onset of action, increases bioavailability, and stability which helps to improve the choice of the dosage form in the current market [1]. Mouth Dissolving Tablets are appreciated by a significant sector of populations, particularly those who have difficulty to swallow. It has been reported that dysphasia (difficulty in swallowing) is common for all age groups and more specific with pediatric, geriatric populations along with institutionalized patients, psychiatric patients, and patients with nausea, vomiting, and motion sickness complications MDTs with good taste and flavor increase the acceptability of bitter drugs by various groups of the population. The ability to change the disease progress, cost-effectiveness, drug safety should be essential factors for all the treatments, and all these factors can be fulfilled by Mouth dissolving Tablets [2, 3].

Tofacitinib citrate is a Janus kinase JAK1/JAK3 inhibitor class. It is currently developed by Pfizer for treating severe active rheumatoid arthritis in adult patients. It is used for the treatment of severe active rheumatoid arthritis in adult patients, Ulcerative colitis, Psoriatic arthritis. Janus kinases (JAKs) comprise a family of four enzymes, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), which are centrally working in cell signaling processes important in cancer and immune-inflammatory diseases. Progression in the Pharmaceutical field has taken a recent step forward with the approval of Tofacitinib [4-6].

Tofacitinib act as a non-specific protein-tyrosine kinase inhibitor and an antirheumatic drug. Also used to treat Atopic dermatitis, solid organ malignancy, and lymphoma in rheumatoid arthritis patients [7, 8] The aim of this study to prepare mouth-dissolving tablets of Tofacitinib Citrate used to treat certain types of arthritis film [9, 10]. The aim of the present study was to design and evaluation of mouth dissolving oral films of Tofacitinib citrate, allowing fast reproducible drug dissolution in oral cavity thus bypassing the first pass metabolism to enhance the patient convenience and effective treatment for rheumatoid arthritis [11, 12].

MATERIALS AND METHODS

Materials

Tofacitinib citrate API was procured from Hetero drugs Ltd. Hyderabad. HPMC procured from Granules India Ltd. Hyderabad. Glycerol, SSG, Sodium saccharin and methanol procured from SD Fine Ltd, Mumbai.

Methods

Solvent casting technique

Drug (Tofacitinib Citrate) containing fast dissolving films were fabricated by the solvent casting Method. The optimized amount of HPMC was dissolved in 5 ml of water and stirrer continuously for 1-hour, optimized amount of Plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2 ml of water and kept on sonication for proper dispersion [13, 14]. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed [15, 16]. The aqueous solution was cast in a glass mould having 2.5 x 2.5 cm 12 film areas and was dried at controlled room temperature (25 °-30 °C, 45%RH) as well as with increased temperature (microwave oven). The film took approximately 48 h to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing [17, 18].

Calculation of the amount of drug to be poured per plate

An oral dose of Tofacitinib citrate	= 5 mg
bioavailability, Therefore, actual bioavailable dose	= 74%
	= 5 × 74/100
	= 3.7 mg
	= 3.7 mg
Therefore, amount of drug to be loaded per 2 × 2 cm2 film	= лr2
	= 3.14 × (4.75)^2
Area of Petri plate	= 70.84 cm^2
Therefore, number of films	= 70.84/4
	= 17.71
Drug amount required	= 17.71 × 3.7 mg
	= 65.527 mg

Experimental design

3^2 full factorial designs were used for the optimization of the polymer-plasticizer ratio. In this design, 2 factors were evaluated each at 3 levels, and experimental trials were performed in all 9 possible combinations [19]. The amount of polymer HPMC 5 cps (X1) and amount of plasticizer, glycerol (X2) were selected as independent variables and each factor being studied at-1, 0,+1 level. Table 1 give the levels of independent variables used and the full factorial design layout of the variables, respectively. The composition of various mouth-dissolving films is given in table 2 [17, 20].

Table 1: Independent variables design

Factor	Level used, actual (coded)		
Independent variables	**Low (-1)**	**Medium (0)**	**High (+1)**
X1 = Concentration of polymer (% w/w)	45%	50%	55%
X2 = Concentration of plasticizer (% w/w)	10%	15%	20%

Table 2: Composition of various films prepared using 3^2 Full Factorial design [21]

Name of ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tofacitinib (mg)	5	5	5	5	5	5	5	5	5
HPMC (% w/w)	45%	45%	45%	50%	50%	50%	55%	55%	55%
Glycerol (% w/w)	10%	15%	20%	10%	15%	20%	10%	15%	20%
Saccharin Sodium	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
SSG (% w/w)	4%	4%	4%	4%	4%	4%	4%	4%	4%
Methanol	0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.05 ml
DM water (ml)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Evaluation of MDF

Morphological properties of prepared films

Properties such as homogeneity, color, transparency, and the surface of MDF were tested visually. All the formulations were wrapped in butter paper and then in aluminum foil, stored at room temperature (25 °C) with a relative humidity of 65±5% Rh and were tested periodically for 3 mo [22].

Tack test

Tackiness was evaluated gently by pressing the film between fingertips and results were noted in qualitative terms as tacky or non-tacky [23].

Thickness evaluation

It is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose distribution in the film. The thickness of the film was measured by calibrated digital Vernier Calipers. The thickness was evaluated at five different locations (four corners and one at the center) [24, 25].

Weight variation

This test was carried out by taking 2 × 2 cm^2 of the film cut at three different places from the cast film. The weight of each film was taken individually using an electronic balance. Average of three readings was taken for the weight variation study [26].

Folding endurance

Folding endurance which is related to the flexibility of a film was measured manually by firmly holding and folding the film repeatedly through the middle. The number of folds on the same crease, required to produce a crack in the film was noted as the value of folding endurance [27].

pH evaluation

The surface pH of the MDFs was determined to investigate the possible side effects due to changes in pH *in vivo*, since an acidic or alkaline pH may irritate the oral mucosa. The surface pH was determined by using the pH meter. The film was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 h. at room temperature. The pH was noted down by bringing the electrode in contact with the surface of the film, allowing it to equilibrate for 1 min and the pH was recorded [28].

Tensile strength

The tensile strength of the films was evaluated by using a TAXT Plus Texture Analyzer (Texture Technologies, Scarsdale, NY) and miniature tensile grips TA-96B according to the procedure described below: A 2 × 2 cm^2 film free from air bubbles or physical imperfections was held longitudinally in the tensile grip on texture analyzer. The test was performed at 6 mm of initial grip separation from both sides at a crosshead speed of 2 mm/sec till the film broke 16. All measurements were conducted in triplicate for each film [29].

***In vitro* disintegration of films**

In vitro disintegration time of 2 cm^2 film was determined visually in a petri dish containing 25 ml of phosphate buffer pH 6.8 at 37.0±0.5 °C. The time when the film started to break or disintegrate was recorded, which is the disintegration time of the film [20].

Percentage moisture loss

Percentage moisture loss was calculated to check the integrity of films in dry condition. Film was cut into 2 cm^2 and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 h the film was removed and weighed again. The decrease in the weight of the film gave the amount of moisture loss. The % age loss in moisture was calculated by using the following formula [29].

$$\% \text{ Moisture loss } = \frac{(\text{Initial weight} - \text{final weight})}{(\text{Initial weight})} \times 100 \ldots\ldots (1)$$

Percentage moisture absorption

The moisture uptake was determined by cutting the film into 2 cm^2 patches. These films were put for one day in a desiccator containing a saturated solution of potassium sulphate (relative humidity 75%) at room temperature. The increase in the weight of the film was observed, which was due to absorption of moisture. The % age gain in the moisture by the films was calculated using the following formula [30].

$$\% \text{ Moisture absorption } = \frac{(\text{Initial weight} - \text{final weight})}{(\text{Initial weight})} \times 100 \ldots\ldots\ldots (2)$$

Swelling index

A pre-weighed drug-loaded film was placed on a 2% agar plate. An increase in the weight of the film was noted until the constant weight was obtained [31].

Drug content uniformity

Drug content of all formulations was determined by the UV-spectrophotometric method. For this 2 × 2 cm^2 film was cut and dissolved in 100 ml of phosphate buffer pH 6.8. The solution was filtered, and absorbance was recorded at 206 nm. Drug content was

calculated from the calibration curve of the drug. All the readings were taken in triplicate [27].

In vitro dissolution and drug release study

The *in vitro* dissolution test was carried out in a USP II paddle dissolution apparatus. The film of appropriate size (2 × 2 cm^2) was cut and placed in dissolution media. The dissolution medium consisted of 300 ml freshly prepared phosphate Buffer (pH 6.8), maintained at 37±0.5 °C and stirred at 50 rpm. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were subjected to UV analysis at 206 nm (λ max) [26].

Accelerated stability studies for optimized formulation

Accelerated stability studies were carried out according to ICH Q1A (R^2) guidelines. The chose formulation F3 and F6 were assessed for accelerating stability study. Each film (2 × 2 cm^2) was wrapped in butter paper, followed by aluminum foil and placed in an aluminum pouch, which was heat-sealed at the end**.** Stability study was carried out at 40±2 °C and 75±5% Rh for 2 mo. Samples were withdrawn after 15 d interval and evaluated for physicochemical properties. The similarity factor was applied to study the effect of storage concerning its physical appearance, *in vitro* disintegration time, tensile strength and drug content after storing at 40 °±2 °C/75±5 % Rh for 2 mo [32].

FTIR spectral analysis

The FTIR spectra of pure drug, physical mixture and formulation F3 (after storage at accelerated conditions) were recorded using a FTIR spectrophotometer (Agilent Cary 630). The samples were scanned over a range of 4000-500 cm^{-1} [33].

Differential scanning calorimetry (DSC) studies

Tofacitinib Citrate (pure drug) and Excipients were studied using DSC to see if there was any difference in the drug's melting enthalpy, glass transition temperature, or interactions with ingredients.

The research was conducted using DSC Q1000 TA equipment. Approximately 2-5 mg of sample was deposited in standard aluminum pans and scanned in the range of 5 °C to above its melting point with a temperature increment speed of 10 °C/min under dry nitrogen (flow rate 50 ml/min) as effluent gas [18, 34, 35].

Statistical analysis

The results are presented as mean (±SD) and were analyzed by using the GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA, USA). Optimization of the formulation was done by using Design expert software Ver. 13.0, A difference below the probability level of P-value = 0.05 was calculated using ANOVA.

RESULTS AND DISCUSSION

Optimization of formulation and process variables

Table 3: Optimization design showing the effect of an independent variable on the dependent variable

Run	Ludiflash	SSG	Friability	Disintegration time (sec)	Wetting time (sec)	Drug content	% Drug release
1	20	5	0.778±0.118	59.56±1.564	56.083±1.497	99.88±0.116	0
2	30	5	0.444±0.117	51±1.557	50.74±1.491	99.71±0.357	3.73413±4.973
3	40	5	0.416±0.115	44±1.535	43.68±1.469	99±0.382	8.53299±7.465
4	20	10	0.77±0.114	46.5±1.53	37.323±1.464	99.37±0.311	15.8302±10.293
5	30	10	0.636±0.111	45.7±1.506	44.346±1.441	99.44±0.304	26.7031±12.606
6	40	10	0.572±0.088	41.25±1.325	37.323±1.269	99.96±0.294	40.9672±15.648
7	20	15	0.402±0.076	40.5±1.243	40.923±1.19	99.96±0.34	57.9603±16.99
8	30	15	0.772±0.076	37±1.243	29.613±1.189	99.37±0.417	74.9491±13.843
9	40	15	0.536±0.073	29.75±1.506	27.89±1.464	99.96±0.347	91.8709±16.955

Values are expressed as mean±SD (n = 3).

Table 4: Fit statistics showing R^2 response values

Response	R^2	Adjusted R^2	Predicted R^2
R1: Weight Variation (%)	0.9841	0.9898	0.9897
R2: Disintegration time (Sec)	0.9948	0.9980	0.9998
R3: % Drug Release	0.9914	0.9936	0.9966
R4: Drug Content	0.9966	0.9933	0.9978

The predicted R^2 value of 0.9841, 0.9948, 0.9914 and 0.9966 were found to be in reasonable agreement with no need to adjust R^2 value. The Model F-values of 4.850E+07, 9.718E+08, 2.294E+09 and 3.894E+07 implies that the model is significant.

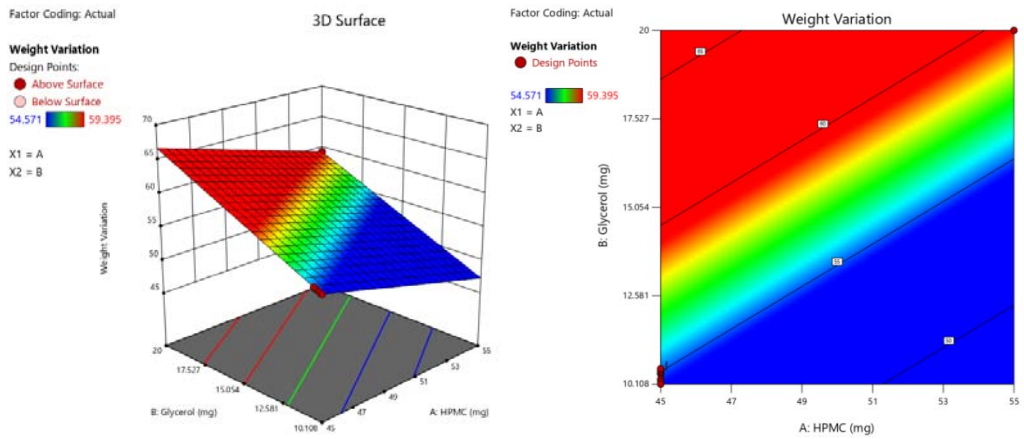

Fig. 1: Responses surface plots showing effect of concentration of HPMC and glycerol on measured responses (a) weight variation %

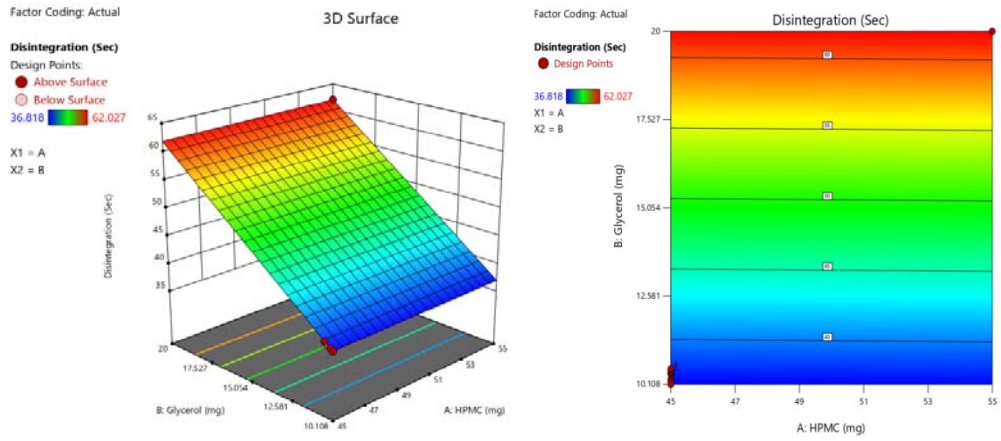

Fig. 2: Responses surface plots showing effect of concentration of HPMC and Glycerol on measured responses (b) Disintegration time (s)

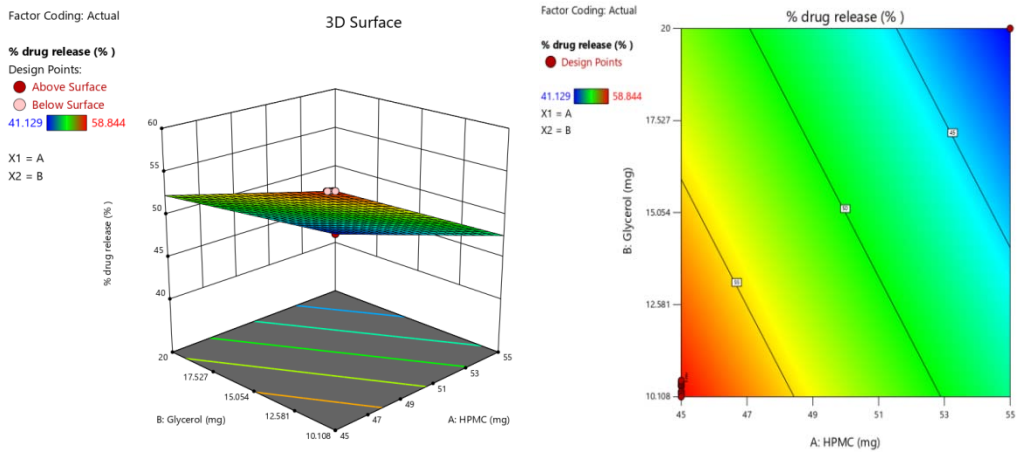

Fig. 3: Response surface plots showing the effect of concentration of HPMC and glycerol on measured responses (c) % drug release

Result of pre-compression parameters

The powder bed was evaluated for rheological properties like Bulk density, Tapped density, Angle of repose, using standard Pharmacopeial techniques and from the results, Carr's index, Hausner's ratio were computed.

Drug content uniformity

The content uniformity test was performed to ensure uniform distribution of the drug. Content uniformity was performed for all the formulations. The results indicated that in all the formulations that there was good uniformity in drug content which ranged between 90.06% to 99.46%. Table 8 shows the drug content and tensile strength of the formulation.

In vitro dissolution study

The data reveals that the percentage of drug release at the end of 5th min

Drug-excipient interaction studies

FTIR and DSC studies were used to study the interaction if any, between the drug and excipients. The FTIR and DSC scan of a physical mixture of drug and excipients exhibited peaks similar to that of the pure drug, indicating that there was no interaction between the drug and the excipients.

Table 5: Results of pre-compression studies for F1-F9

S. No.	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Bulk Density	0.61±1.348	0.56±0.675	0.65±0.746	0.52±0.463	0.62±0.257	0.68±0.876	0.57±0.624	0.58±0.632	0.54±0.532
2	Tapped Density	0.64±1.876	0.59±0.765	0.68±0.534	0.54±0.634	0.60±0.256	0.58±0.723	0.61±0.258	0.63±0.862	0.58±0.634
3	% Carr's Index	7.82±1.985	7.56±0.934	7.94±0.632	7.84±1.876	8.16±0.258	9.32±0.752	6.06±0.634	7.34±1.752	7.36±0.534
4	Hausner's Ratio	1.085±0.463	1.094±0.824	1.078±0.258	1.080±0.534	1.104±0.253	1.124±0.972	1.061±0.258	1.076±0.797	1.073±0.634
5	Angle of Repose	22.43±0.573	21.53±5.362	22.42±0.642	22.54±0.642	22.76±0.862	22.58±0.952	22.63±0.632	23.15±0.634	23.16±0.642

Values are expressed as mean±SD (n = 3).

Result of post-compression parameters

Table 6: Physical and mechanical properties of various film-forming polymers

F. code	Tack test	Thickness (mm) ±SD	Weight variation (mg)	Folding endurance	pH	% Moisture loss	% Moisture absorption	Swelling index	Disintegration time (sec)
F1	Non-tacky	0.07±0.015	59.395±1.044	100-120	6.7±0.10	9.47±0.49	8.77±0.25	44%±2.08	61.027±2.94
F2	Non-tacky	0.08±0.005	54.924±1.593	120-130	6.1±0.20	9.39±0.42	9.45±0.44	47.7%±1.51	38.549±2.65
F3	Non-tacky	0.09±0.005	54.924±2.449	120-150	6.2±0.26	8.42±0.33	10.89±0.75	50.2%±2.23	37.550±2.00
F4	Non-tacky	0.11±0.011	54.982±1.417	140-180	6.3±0.10	8.38±0.37	11.64±0.36	60.4%±3.68	37.669±1.00
F5	Non-tacky	0.11±0.004	55.05±2.080	150-190	6.6±0.11	7.15±0.48	12.65±0.27	69.8%±2.35	37.81±1.63
F6	Non-tacky	0.13±0.005	55.102±1.445	150-200	7±0.10	6.85±0.71	12.97±0.40	75.2%±3.87	37.915±2.16
F7	Non-tacky	0.16±0.005	54.738±2.056	200-220	7.4±0.10	6.45±0.46	13.83±0.76	81.1%±2.42	37.169±1.41
F8	Non-tacky	0.17±0.005	54.666±1.504	210-230	7.5±0.32	4.82±0.26	15.19±0.43	86.3%±4.44	37.015±2.94
F9	Slightly tacky	0.19±0.005	54.571±1.673	220-250	7.5±0.25	3.69±0.27	15.60±0.35	93.7%±1.41	36.818±2.08

Values are expressed as mean±SD (n = 3).

Table 7: Drug content and tensile strength of films

Formulation code	Drug content	Tensile strength (kg/mm²)
F1	95.954±1.18	0.469±0.05
F2	99.035±1.13	0.460±0.03
F3	99.035±1.37	0.460±0.06
F4	99.028±1.18	0.461±0.02
F5	99.02±1.17	0.461±0.01
F6	99.014±0.79	0.462±0.04
F7	99.058±1.61	0.459±0.07
F8	99.067±0.46	0.459±0.14
F9	99.079±1.18	0.458±0.09

Values are expressed as mean±SD (n = 3).

Table 8: % cumulative drug release

Time (min)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	17.4±0.65	24.2±0.59	28.6±0.38	12.8±0.62	19.3±0.09	23.4±0.78	11.8±0.47	15.2±0.75	17.3±0.92
2	52.6±0.45	58.4±0.87	64.2±0.98	46.2±0.87	48.5±0.76	57.6±0.39	32.4±0.68	40.6±0.29	49.7±0.53
3	61.2±0.56	66.6±0.98	76.4±0.52	57.3±0.87	59.4±0.27	68.4±0.73	49.8±0.82	51.9±0.35	61.2±0.25
4	75.6±0.36	84.4±0.67	87.3±0.94	68.4±0.34	77.2±0.84	81.2±0.38	57.9±0.53	69.8±0.86	72.8±0.48
5	82.4±0.38	92.3±0.39	96.8±0.84	77.2±0.57	86.9±0.33	91.3±0.91	68.8±0.42	80.2±0.28	84.6±0.47

*Data represent mean±SD, n=3

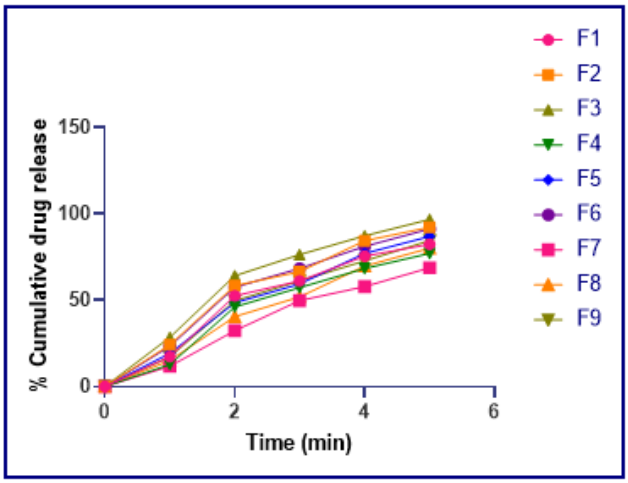

Fig. 4: Cumulative % drug release from the formulations F1-F9

FT-IR studies

FT-IR tests were carried out on the following samples, such as Tofacitinib Citrate and Pure drug+Excipient, in order to explore the structural composition of the drug and excipients in the form of functional group frequencies and their reproducibility in excipient mixtures and formulations. Fig. 5 and 6 shows typical FT-IR spectra of the material mentioned above. When compared to Tofacitinib

Citrate+excipient, which shows infrared absorption at 3753.76; 3537.77; 3098.08; 1671.98; 1455.99; 1926.54; 2727.82, pure Tofacitinib Citrate showed high infrared absorption at 3784.62; 3136.65; 3375.78; 2265.95; 1617.98; 1725.98, 832.13 cm^{-1}. Another finding was that the IR spectra of Tofacitinib Citrate+Excipient did not contain any new peak, indicating that there was no strong interaction and no incompatibility between the excipients in the formulation.

DSC studies

Due to drug entrapment in the lipid, the melting point of Tofacitinib Citrate (pure drug) was 214.22 °C (fig. 7), possibly due to the presence of excipients. Because the drug was encased in lipid, the melting point of mixture of Pure drug+Excipient in 212.49 °C (fig. 8).

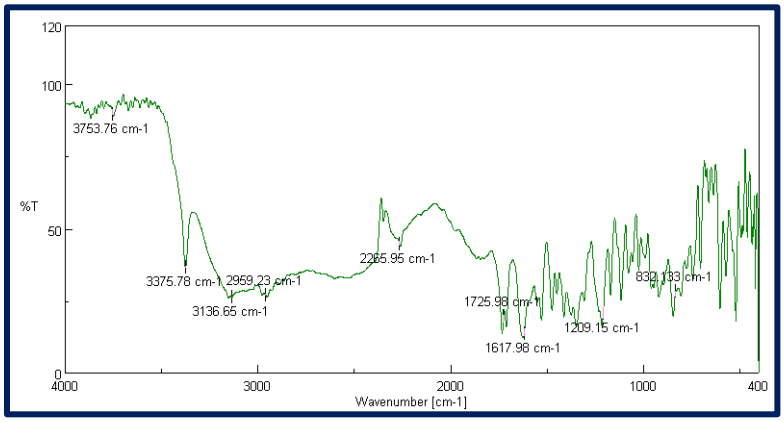

Fig. 5: FTIR of pure drug to facitinib citrate

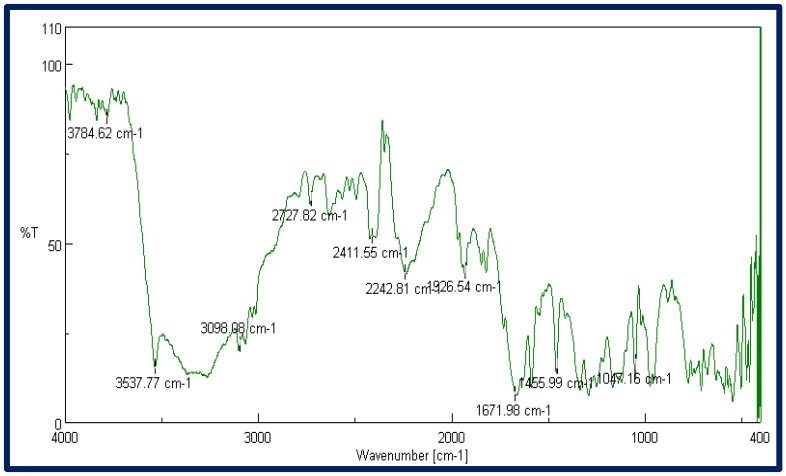

Fig. 6: FTIR of pure drug and excipients

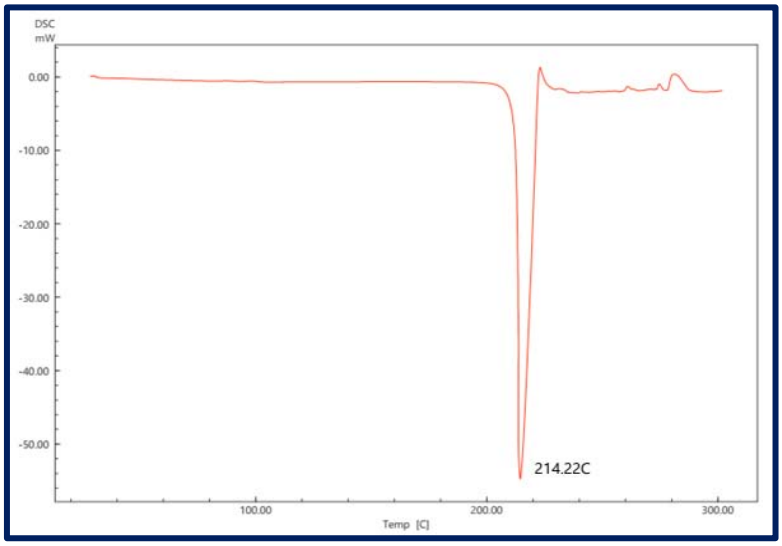

Fig. 7: DSC of pure drug to facitinib citrate

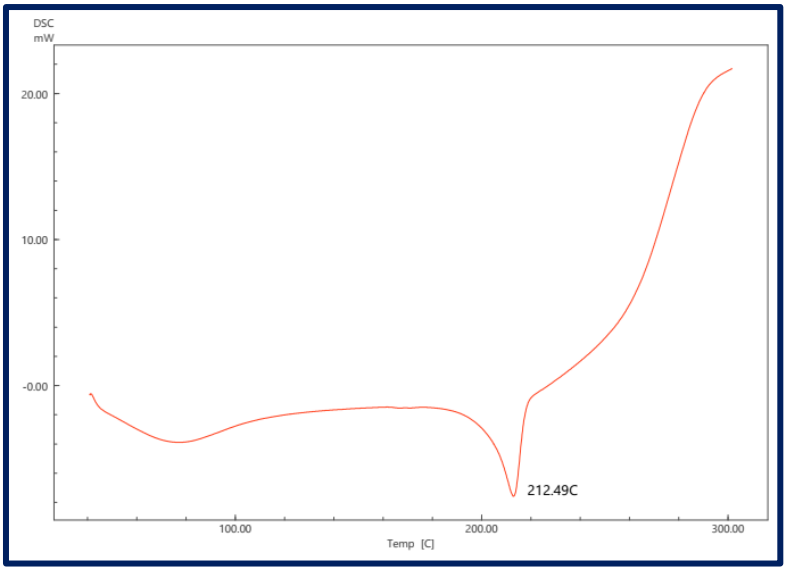

Fig. 8: DSC of pure drug and excipients

Accelerated stability studies of optimize batch F3 and F6

Table 9: Accelerated stability studies of F3

Parameter	Appearance	Tensile strength (kg/mm2)	Disintegration time (sec)	Drug content
Initial	Transparent and both surfaces smooth	0.472±0.06	39±2.1	98.59%
After 10 d	Transparent and both surfaces smooth	0.468±0.04	41±1.9	98.25%
After 20 d	Transparent and both surfaces smooth	0.456±0.07	40±1.7	97.97%
After 30 d	Transparent and both surfaces smooth	0.459±0.05	42±2.2	97.69%
After 40 d	Transparent and both surfaces smooth	0.457±0.04	40.8±1.3	97.35%
After 50 d	Transparent and both surfaces smooth	0.444±0.05	41.6±1.9	97.34%
After 60 d	Transparent and both surfaces smooth	0.440±0.08	43.2±1.8	97.33%

Values are expressed as mean±SD (n = 3).

Table 10: Accelerated stability studies of F6

Parameter	Appearance	Tensile strength (kg/mm2)	Disintegration time (sec)	Drug content
Initial	Transparent and both surfaces smooth	0.555±0.04	51.6±2.16	97.40±0.79
After 10 d	Transparent and both surfaces smooth	0.548±0.03	51.8±3.11	97.15±1.19
After 20 d	Transparent and both surfaces smooth	0.541±0.06	51.0±2.21	97.04±0.33
After 30 d	Transparent and both surfaces smooth	0.539±0.05	53.2±1.16	96.97±0.92
After 40 d	Transparent and both surfaces smooth	0.538±0.04	54.7±1.23	96.85±1.85
After 50 d	Transparent and both surfaces smooth	0.535±0.04	54.1±2.14	96.70±0.54
After 60 d	Transparent and both surfaces smooth	0.534±0.04	55.6±1.18	96.19±1.65

Values are expressed as mean±SD (n = 3).

DISCUSSION

3^2 Factorial Design in Design expert program with Polynomial Quadratic Model and Multiple Linear Regression approach was used to optimize formulation and process parameters for Film formulation, as shown in table 3. The quadratic model suggests a P value of 0.0001 in the sum of squares. Selected the highest-order polynomial with significant additional terms and no aliasing. The chosen model has a minor lack of fit, as evidenced by the P-value of 0.0001 obtained from the Lack of Fit test. The Model F-value of 4.580 indicates that the model is statistically significant. An F-value of this magnitude has a 0.01% chance of occurring due to noise. Model terms with P-values less than 0.05 are significant.

The Adjusted R^2 of 0.9841 is reasonably close to the Predicted R^2 of 0.9897; that is, the difference is less than 0.2. When all other factors are maintained constant, the coefficient estimate provides the expected change in response per unit change in factor value. In an orthogonal design, the intercept is the overall average response of all the runs. The coefficients are modifications based on the factor settings around that average.

The high levels of the factors are coded as+1 and the low levels of the factors are coded as-1 by default. By comparing the factor coefficients, the coded equation can be used to determine the relative impact of the components. It was discovered from the data that there was a good association between Weight Variation (R^2 = 0.9841), It determines whether there is an increase in polymer concentration (when using ANOVA) It exhibits P<0.0001. It could be because of the influence of lower concentration and higher plasticizer concentrations. P-value = 0.0001 was calculated using ANOVA [36].

Mouth-dissolving films containing Tofacitinib citrate were prepared by casting method. Films of HPMC and Glycerin (low viscosity) was prepared with an objective to dissolve the film in the mouth. 45% w/w and 50% w/w of polymer concentration were exhibited desired mouth dissolving time and other film parameters.

All the batches were evaluated for thickness using digital vernier caliper. As the formulation contains different concentration of polymer, hence the thickness of the film was found in the range of 0.07 to 0.19 mm. The thickness increases with the increase in the concentration of polymer. Folding endurance was found to vary between 95.7 to 105.4-fold indicates that the film has good flexibility. The formulation with high concentration of polymer has low value of folding endurance because after specific increase in the concentration of the polymer decrease in folding endurance is observed due to film thickness. More thickness lower will be folding endurance [37].

Disintegration time was found to vary between 25 to 35 second film prepared with the HPMC F3 and F6 containing 45% w/w and 50% w/w of polymer concentration had shown fast disintegration as compared to other concentrations. Drug content was evaluated and it varied in the range of 95.954±1.18 to 99.079±1.18. drug content was found to be low for F1 formulation i.e., 93.15±1.05 and more for F3 and F6 formulation i.e., 99.035±1.37 and 99.014±0.79. As per the USP the drug content was found to be in the range of 85-115%.

The surface pH of all the selected formulation was ranging between 6.1 to 7.5; since surface pH of the film was found to be around neutral pH, there will not be any kind of irritation to the oral mucosal cavity. The moisture loss of all the selected formulation was measured. Out of all the selected formulation the film with F3 and F6 containing 45% w/w and 50% w/w of polymer concentration showed the lowest % moisture loss than other formulation and hence it is more stable than other. Accelerated stability also shows that F3 and F6 formulation, there is no any significant change in the physical appearance, disintegration time, drug release, drug content compared with the initial data from the two-month stability data.

CONCLUSION

The present study revealed that the MDFs of Tofacitinib could be successfully prepared by solvent casting technique with the intention of obtaining better therapeutic efficiency with increasing bioavailability and improving patient compliance. From among different polymers screened HPMC 5cps showed minimum *in vitro* disintegration time and maximum tensile strength compared to other polymers. Hence, it selects for the preparation of films of the drug. Further, it was concluded that amongst all the different formulations, formulation F3 and F6 containing 45% w/w and 50% w/w of polymer concentration, respectively, were found to be having satisfactory physicochemical and mechanical properties. Also, the stability study of these two optimized formulation confirmed the longer shelf life of MDFs. Hence, the present study confirms the enormous potential of MDFs for improving patient convenience and compliance by hastening the onset of action and circumventing hepatic first-pass metabolism, especially in pediatric and geriatric patients.

ACKNOWLEDGEMENT

We thank the department of pharmaceutical sciences for their support and providing the facility to carry the research.

AUTHORS CONTRIBUTIONS

All the authors have equally contributed to this manuscript.

CONFLICT OF INTERESTS

Authors of this publication declare no conflict of interest.

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