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Original Article

# DESIGN, DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING TABLETS OF TOFACITINIB CITRATE

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**ABSTRACT**

**Objective:** This study aims to Formulate Mouth Dissolving Tablets (MDTs) of Tofacitinib Citrate with the increase in bioavailability and patient compliance.

**Methods**: Mouth Dissolving Tablets (MDTs) of Tofacitinib Citrate were developed by full factorial design at $3^2$levelsand prepared by direct compression method using super integrants like sodium starch glycolate, Ludiflash. The tablets were compressed into compacts on a 10 station tablet machine. The bulk drug was characterised by determining, MP, Solubility, pH and FTIR spectra.

**Results:** The weight variation, hardness and diameter, thickness, friability, drug content, wetting time, *in vitro* disintegration time and *in vitro* dissolution studies, and stability study, tablet thickness, weight variation and drug content post compression parameters remained consistent and reproducible. All the formulations showed, almost 100 percent of drug release within 75 min. Formulations F1, F2 and F3 were prepared with 5 mg of SSG and 20 mg, 30 mg, and 40 mg Ludiflash which shows % release of drug in the order of F1<F2<F3. Formulations F4, F5 and F6 were prepared with 10 mg of SSG and 20 mg, 30 mg, and 40 mg Ludiflash which shows % release of drug in the order of F4<F5<F6. Formulations F7, F8 and F9 were prepared with 15 mg of SSG and 20 mg, 30 mg, and 40 mg Ludiflash which shows % release of drug in the order of F7<F8<F9.

**Conclusion**: It is concluded that the amount of superdisintegrants decreases disintegration time of tablets, decreases wetting time, increases the cumulative % drug release causes better absorption.

**Keywords**: Mouth dissolving tablets (MDTs), Tofacitinib citrate, Sodium starch glycolate (SSG), Ludiflash, Factorial design, Bioavailability and bioequivalence (BABE)


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## INTRODUCTION

Mouth Dissolving Tablets (MDTs) dissolve or disintegrate in saliva and are swallowed without the need of water. MDTs offer an advantage over the 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, 2]. It also applies to people who are ill in bed, in traveling, and also those who are busy, especially those who have no access to water dissolves in the oral cavity within 15-3 min [3]. The demand for the development of Mouth Dissolving Tablets (MDTs) has hugely increased as it has better compliance in patients [4]. Mouth Dissolving Tablets are appreciated by a significant sector of populations, particularly those who have difficulty to swallowing. 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 [5]. MDTs with good taste and flavor increase the acceptability of bitter drugs by various groups of the population [4, 5]. 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 [6, 7]. Tofacitinib citrate is a Janus kinase JAK1/JAK3 inhibitor class [8]. It is currently developed by Pfizer for treating severe active rheumatoid arthritis in adult patients [9]. It is used for the treatment of severe active rheumatoid arthritis in adult patients, Ulcerative colitis, Psoriatic arthritis [10]. 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 [11]. Tofacitinib citrate is a citrate salt obtained by combining equimolar amounts of tofacitinib and citric acid. Tofacitinib act as a non-specific protein-tyrosine kinase inhibitor and an antirheumatic drug [12]. Also used to treat Atopic dermatitis, solid organ malignancy, and lymphoma in rheumatoid arthritis patients. The aim of this study to prepare mouth dissolving tablets of Tofacitinib Citrate used to treat certain types of arthritis [13].

## MATERIALS AND METHODS

### Material

Tofacitinib citrate gift sample was obtained from Formulation Development and Research Centre of Excellence, Unichem Laboratories Ltd., Goa-4035011, India. Sodium Starch Glycolate (SSG), Magnesium Stearate, Talc, Lactose was purchased from Mumbai, India [14]. The Tofacitinib citrate (Chemical Formula: C22H28N6O8) has 74% oral absorption produces absolute bioavailability, with peak plasma concentration (T max) achieved in 0.5-1 hour. The volume of distribution (Vd) = 87L after intravenous administration and has 40% protein binding, mostly bound to albumin. Distribution is equal between red blood cells and plasma half-life ~3h [15, 16].

### Preparation of ludiflash

Ludiflash is a simple mixture of 90 % w/w of Mannitol, 5% w/w of Crospovidone, and 5% w/w of polyvinyl acetate was blended in a double cone blender and was kept in an oven for 2 h drying. Active pharmaceutical ingredients lubricant and other ingredients were added in the above Ludiflash excipients which Produce high Porosity tablets and having quick penetration Power [17].

### Method (Direct compression)

In this process, all ingredients were accurately weighed and passed through Sieve No.180 then mixed to form powder blend and then compressed using 6 mm flat punch on Tablet press 10 station

compression machine. The hardness of the tablets was maintained at 2-3 Kg/cm2. Tablet weight was maintained at 75 mg [18, 19].

**Characterization of tofacitinib citrate**

**Determination of λmax**

For assurance of λmax stock solution Tofacitinib Citrate (conc. 1000µg/ml) in 0.1 N HCl were prepared. 1 ml of the stock arrangement was additionally weakened to 100 ml. Coming about arrangements were examined in the range of 400 to 200 nm utilizing methanol as a clear with the assistance of a UV-visible spectrophotometer [20]. Normal triplicate readings were taken.

Calibration curve of tofacitinib citrate in ph 6.8 phosphate buffer

A stock solution of Tofacitinib Citrate was prepared by dissolving 100 mg of Tofacitinib Citrate in 100 ml of phosphate buffer pH 6.8, to obtain 1 mg/ml solution and from which 1 ml was withdrawn and diluted up to 100 ml with pH 6.8 Phosphate buffer to produce 10 ug/ml of solution. 10 ug/ml solution was scanned for wavelength at which maximum absorbance occurs λmax in a U. V. Spectrophotometer (Jasco V-630, Japan) between 200-400 nm. The λmax was found at 287 nm for Tofacitinib Citrate solution in phosphate buffer pH 6.8 and the same study was carried out in 0.1 N HCl, which shows maximum absorbance at 287 nm. Normal triplicate readings were taken [21].

**The partition coefficient of the drug**

Log P [22], was estimated utilizing a separating funnel by shaking equivalent volumes of oil and watery stage.

**Melting point identification**

The Melting purpose of Tofacitinib Citrate was resolved to utilize the open capillary technique [23].

**Formulation of a mouth dissolving tablet**

The mouth dissolving tablets of Tofacitinib Citrate was prepared by using $3^2$ full factorial design [24, 25].

**Table 1: Formulae of tofacitinib citrate orally disintegrating tablets**

| S. No. | Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Tofacitinib Citrate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 2. | Sodium Starch Glycolate | 5 | 5 | 5 | 10 | 10 | 10 | 15 | 15 | 15 |
| 3. | Ludiflash | 20 | 30 | 40 | 20 | 30 | 40 | 20 | 30 | 40 |
| 4. | Mag. Stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 5. | Talc | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| 6. | Lactose | q. s. | q. s. | q. s | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. |

**Pre-compression parameters of a powder blend**

**Evaluation of pre-compression parameters**

**The angle of repose**

The frictional forces in a loose powder can be measured by the angle of repose. It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane [26].

$$\theta = \tan^{-1}(h/r)$$

Where θ is the angle of repose "h" is the height in cms, "r" is the radius in cms.

**Bulk density**

A Bulk density is determined by pouring pre sieved (180 mesh) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight. The average weight of triplicate readings was computed [26].

$$\text{Bulk Density} = \frac{\text{Mass of powder (M)}}{\text{Bulk volume of the powder (V)}}$$

**Tapped density**

It is the ratio of the mass of granules to the volume of the granules after it is expressed by gm/cc [27].

$$\text{Tapped Density} = \frac{\text{Weight of powder (W)}}{\text{Tapped volume of the powder (V)}}$$

**Carr's index**

Carr's Index was measured for the property of a powder to be compressed; as such, they are measured for the relative importance of inter particulate interactions. The average of Triplicate (three) readings was noted down [27].

$$\text{Carr}'\text{s index}(\%) = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

**Hausner's ratio**

This is the ratio of the poured density to the tapped density [28].

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

**Post-compression parameters**

**Evaluation of post-compression parameters**

**Thickness and diameter**

The thickness of individual tablets was measured with a micrometer which permits accurate measurement and provides information on the variation between tablets [29].

**Hardness**

Tablet hardness is also called crushing strength of a tablet. It may be due to poor flow properties of the powder, moisture content of the powder. Monsanto hardness tester was used to check the hardness of the tablets [30].

**Friability**

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using a friabilator (Roche type) for 100 revolutions (25 rpm for 4 min.) Tablets were removed. De-dusted and weighed again. Average Triplicate readings were noted and SD was computed [31].

$$\%F = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

**Weight variation**

The 20 tablets were selected at random and weighed on a Digital balance Average of three weights was calculated from the total weight. The percentage deviations from the mean value were calculated [32].

$$\text{Weight Variation} = \left[\frac{w1 - w2}{w2}\right] \times 100\%$$

Where w1 is the initial weight of the tablet

w2 is the average weight of the tablet

**Wetting time**

A petri dish containing 6 ml of 6.8 phosphate buffer was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. A small quantity of amaranth red color was put on the upper surface of the tablet. The time required for the upper surface

of the tablet to become red was noted as the wetting time of the tablet. An average of three readings was noted and Standard deviation was computed [33].

**Determination of drug content**

Ten tablets from each formulation were powdered. The powder equivalent to 5 mg of Tofacitinib citrate was weighed and dissolved in acidic buffer pH 1.2 in 100 ml standard flasks. From this, suitable dilution was prepared and the solution was analyzed at 287 nm using a UV double beam Spectrophotometer using phosphate buffer PH 6.8 as blank [34].

**Disintegration test**

One Tablet was placed in each of the 6 tubes of the disintegration tablet, and a disk was placed upon each tablet. The apparatus was maintained at (37±0.5 °C) using PH 6.8 (stimulated saliva fluid) and was operated (30 cycles/min.) The time taken for complete disintegration with no palpable mass remaining was noted. Average disintegration time and standard deviation were computed [35].

**Dissolution test**

*In–vitro* dissolution tests for all the formulations from F1-F9 were carried out by using modified dissolution apparatus [36, 37].

**RESULTS AND DISCUSSION**

**Result of pre-compression parameters**

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

**Bulk density**

The apparent bulk densities for all formulated batches were found to be in between 0.543±0.023 gm/ml and 0.586±0.028 gm/ml Bulk densities were found in acceptable limits, which indicating that the packing properties required during compression are adequate in all formulations.

**Tapped density**

The values of tapped density were found to be in between 0.586±0.028 gm/ml and 0.626±0.011 gm/ml Tap densities were found in acceptable limit, which indicating that the packing properties required during compression are adequate in all formulations.

**Percentage carr's index**

The values of percentage Carr's index range from 6.063±2.602% to 8.246±0.323%, indicating that the blends have excellent compressibility.

**Hausner's ratio**

Flow property was also insured by measuring Hausner's ratio. The values were found to be in between 1.052±0.039 to 1.1056±0.037 which indicates excellent flowing property.

**The angle of repose**

The angle of repose of all formulated batches was found to be between 21.443°±0.965 and 23.636°±4.602, which implies good free-flowing nature of blends from hopper to die cavity.

**Table 2: Result of pre-compression parameters**

| S. No. | Parameter | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Bulk Density ±SD (n=3) | 0.58±0.01 | 0.54±0.192 | 0.55±0.01 | 0.54±0.04 | 0.56±0.089 | 0.54±0.04 | 0.57±0.01 | 0.58±0.186 | 0.54±0.097 |
| 2. | Bulk Density ±SD (n=3) | 0.62±0.05 | 0.58±0.189 | 0.60±0.04 | 0.58±0.08 | 0.60±0.05 | 0.59±0.03 | 0.61±0.01 | 0.63±0.06 | 0.58±0.05 |
| 3. | Bulk Density ±SD (n=3) | 6.41±0.04 | 7.5±0.026 | 8.246±0.05 | 7.36±0.04 | 7.17±0.06 | 9.27±0.01 | 6.06±0.05 | 7.34±0.18 | 7.36±0.03 |
| 4. | Bulk Density ±SD (n=3) | 1.065±0.168 | 1.084±0.094 | 1.080±0.01 | 1.079±0.018 | 1.076±0.04 | 1.105±0.01 | 1.061±0.05 | 1.076±0.02 | 1.073±0.01 |
| 5. | Bulk Density ±SD (n=3) | 23.63±0.02 | 21.63±0.04 | 22.44±0.01 | 21.63±0.06 | 21.66±0.07 | 22.58±0.195 | 22.63±0.08 | 23.15±0.01 | 23.16±0.06 |

mean ±SD, n=3

**Result of post-compression parameters**

The mean thicknesses of all the formulations, F1 to F9 were found to be in the range of. 2.02±0.13 to 2.313±0.45 mm and the tablet mean diameter of all formulations was found to be in the range of 6.01±0.01 to 6.09±0.06 mm. This indicated that the tablet production is consistent and reproducible. The hardness was found to be between the range of 2.24±0.01 to 2.67±0.005 kg/cm$^2$, indicating that tablets have good mechanical strength.

All the batches of all the formulation tablets were found to pass the weight variation test as the friability is less than 1 % w/w. The formulations F1, F2, and F3 were prepared with 5 mg of SSG and 20 mg, 30 mg, and 40 mg Ludiflash, respectively. F1, F2, and F3 showed disintegration times of 59.6, 51and 44 sec respectively and wetting times of 56.08, 50.74, and 43.68 sec respectively. The formulations F4, F5, and F6 were prepared with 10 mg of SSG and 20 mg, 30 mg, and 40 mg Ludiflash, respectively. F4, F5, and F6 showed disintegration times of 46.5, 45.7, and 41.25 sec respectively, and wetting times of 45.47, 44.32, 37.32 sec, respectively. The formulations F7, F8, and F9 were prepared 15 mg of SSG and 20 mg, 30 mg, and 40 mg Ludiflash, respectively. F7, F8, and F9 showed disintegration times of 40.5,37 and 29.75 sec. Respectively and wetting times of 40.92, 29.61, and 27.89 sec respectively. The results suggest that as the content of Ludiflash is increasing the disintegration time and wetting time of tablets decrease.

**Table 3: Result of post-compression parameters**

| S. No. | Batch code | Thickness (mm)±SD (n=3) | Diameter (mm)±SD (n=3) | Hardness (kg/cm$^2$)±SD (n=3) | Weight variation±SD (n=3) | Friability %±SD (n=3) | Disintegration time (sec)±SD (n=3) |
|---|---|---|---|---|---|---|---|
| 1. | F1 | 2.18±0.001 | 6.053 ±0.066 | 2.24±0.01 | 74.933±0.125 | 0.778±0.102 | 59.56±0.087 |
| 2. | F2 | 2.096 ±0.098 | 6.052 ±0.055 | 2.675±0.005 | 75.283±1.113 | 0.444±0.280 | 51±0.092 |
| 3. | F3 | 2.050 ±0.120 | 6.056 ±0.055 | 2.57±0.02 | 75.766±0.577 | 0.416±0.295 | 44±0.148 |
| 4. | F4 | 2.313 ±0.452 | 6.01±0.011 | 2.463±0.005 | 75.8±0.507 | 0.770±0.169 | 48±0.092 |
| 5. | F5 | 2.09±0.084 | 6.05±0.060 | 2.523±0.005 | 73.4±1.732 | 0.636±0.048 | 45.7±0.01 |
| 6. | F6 | 2.04±0.113 | 6.053 ±0.064 | 2.39±0.01 | 75.75±0.409 | 0.572±0.268 | 46.5±0.06 |
| 7. | F7 | 2.02±0.13 | 6.081 ±0.111 | 2.343±0.015 | 74.65±1.125 | 0.402±0.244 | 40.5±0.102 |
| 8. | F8 | 2.262 ±0.620 | 6.059 ±0.070 | 2.523±0.015 | 75.3167±1.284 | 0.772±0.154 | 37±0.068 |
| 9. | F9 | 2.15±0.049 | 6.097 ±0.066 | 2.33±0.01 | 74.616 ±0.288 | 0.536±0.068 | 29.75±0.048 |

Mean±SD, n=3

**Result of *in vitro* drug release data of formulation F1-F3**

***In vitro* drug release data of formulation F1 (n=3)**

The F1 formulation, containing 5 mg of SSG and 20 mg of Ludiflash, was found to release nearly 17% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 75 min if could release 84% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

***In vitro* drug release data of formulation F2 (n=3)**

The F2 formulation, containing 5 mg of SSG and 30 mg of Ludiflash was found to release nearly 18.23% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 75 min if could release 95.85% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

***In vitro* drug release data of formulation F3 (n=3)**

The F3 formulation, containing 5 mg of SSG and 40 mg of Ludiflash was found to release nearly 22.90% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 60 min it could release 84.58% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

In the above discussion of F1, F2 and F3 containing 5 mg of SSG and varying amounts of Ludifash 20 mg,30 mg, and 40 mg, respectively, the release rate constant was found to increase in the following order F3>F2>F1 and the disintegration time was found to be F3<F2<F3.

**Table 4: Result of *in vitro* drug release data of formulation F1-F3**

| S. No. | Time (min) | F1 | | F2 | | F3 | |
|---|---|---|---|---|---|---|---|
| | | Cumulative drug release (CDR)±SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) | Cumulative drug release (CDR) ±SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) | Cumulative drug release (CDR)±SD (n=3) | Cumulative drug release % (% CDR)±SD (n=3) |
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 1 | 0.100452565±0.049 | 2.5142684±0.164 | 0.095508±0.079 | 2.3945213±0.047 | 0.114784±0.094 | 2.8985802±0.083 |
| 3. | 3 | 0.256637613±0.047 | 6.4234879±0.068 | 0.225545±0.049 | 5.6547348±0.069 | 0.323433±0.045 | 8.1674946±0.026 |
| 4. | 5 | 0.455397251±0.063 | 11.398324±0.124 | 0.40067±0.84 | 10.045391±0.056 | 0.598961±0.174 | 15.125272±0.074 |
| 5. | 10 | 0.696563862±0.047 | 17.434582±0.162 | 0.727154±0.048 | 18.230805±0.092 | 0.907174±0.19 | 22.908434±0.046 |
| 6. | 15 | 1.038467985±0.074 | 25.992241±0.082 | 1.220583±0.042 | 30.601798±0.0956 | 1.467147±0.024 | 37.049171±0.076 |
| 7. | 30 | 1.500553134±0.086 | 37.557959±0.163 | 1.813912±0.086 | 45.477415±0.092 | 1.9765±0.083 | 49.91162±0.186 |
| 8. | 45 | 2.049463627±0.045 | 51.296864±0.164 | 2.48468±0.194 | 62.294536±0.179 | 2.66403±0.179 | 67.273472±0.178 |
| 9. | 60 | 2.709001006±0.049 | 67.804696±0.086 | 3.153939±0.167 | 79.073835±0.092 | 3.349547±0.086 | 84.584531±0.187 |
| 10. | 75 | 3.385300034±0.92 | 84.732061±0.176 | 3.823198±0.047 | 95.853135±0.178 | 4.035568±0.142 | 101.90829±0.168 |

*Data are expressed as mean ±SD (n=3)

**Comparative *in vitro* drug release data of formulation F1-F3**

The comparative study of dissolution profile of formulations F1, F2, and F3 was prepared with 5 mg of sodium starch glycolate and 20 mg, 30 mg, and 40 mg Ludiflash, respectively. Each of the tablets in all the formulations contains 5 mg of Tofacitinib citrate. The percentage release of drugs from F1, F2, and F3 were found to be 84.7320%, 95.8531%, and 101.9082% in75 min. Study respectively. The slope values of release data suggest that as the amount of Ludiflash increased rate of release of the drug gradually increases. The order of the above formulation was obtained in the following manner F1<F2<F3.

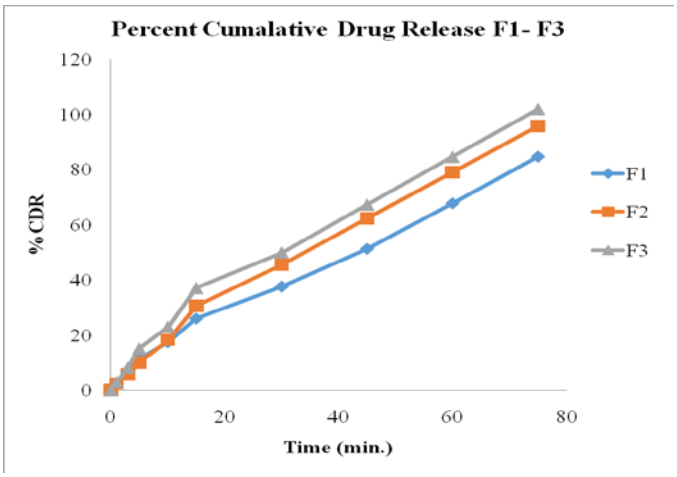


**Fig. 1: Comparative *in vitro* drug release profile of formulations F1-F3, *in vitro* drug release data of formulation F1-F3 (data represents mean±SD, n=3)**

**Result of *in vitro* drug release data of formulation F4-F6**

***In vitro* drug release data of formulation F4**

The F4 formulation, containing 10 mg of SSG and 20 mg of Ludiflash was found to release nearly 21.26% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 75 min it could release 96.71% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

***In vitro* drug release data of formulation F5**

The F5 formulation, containing 10 mg of SSG and 30 mg of Ludiflash was found to release nearly 23.76% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media

continues gradually and in 60 min it could release 83.51% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

***In vitro* drug release data of formulation F6**

The F6 formulation, containing 10 mg of SSG and 40 mg of Ludiflash was found to release nearly 25.17% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 60 min it could release 89.22% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

In the above discussion of F4, F5 and F6 containing 10 mg of SSG and varying amounts of Ludifash 20 mg,30 mgand40 mg, respectively, the release rate constant was found to increase in the following order F6>F5>F4, and the disintegration time was found to be F6<F5<F4.

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

| S. No. | Time (min) | F4 | | F5 | | F6 | |
|---|---|---|---|---|---|---|---|
| | | Cumulative drug release (CDR)±SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) | Cumulative drug release (CDR)±SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) | Cumulative drug release (CDR) ±SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) |
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 1 | 0.106403±0.094 | 2.6767364±0.054 | 0.140764±0.069 | 3.5387483±0.086 | 0.147637±0.093 | 3.6922075±0.073 |
| 3. | 3 | 0.263091±0.079 | 6.6184712±0.068 | 0.33768±0.056 | 8.4891193±0.094 | 0.338686±0.172 | 8.4701117±0.095 |
| 4. | 5 | 0.537278±0.095 | 13.516085±0.082 | 0.6117±0.163 | 15.377838±0.186 | 0.604995±0.18 | 15.13017±0.08 |
| 5. | 10 | 0.845491±0.087 | 21.269682±0.075 | 0.945391±0.195 | 23.766669±0.084 | 1.006571±0.064 | 25.173075±0.085 |
| 6. | 15 | 1.229635±0.034 | 30.933425±0.186 | 1.373952±0.026 | 34.54051±0.162 | 1.524472±0.069 | 38.125144±0.19 |
| 7. | 30 | 1.823802±0.017 | 45.880646±0.854 | 1.96175±0.048 | 49.31746±0.054 | 2.209152±0.83 | 55.248133±0.029 |
| 8. | 45 | 2.474958±0.025 | 62.26153±0.094 | 2.645592±0.182 | 66.508917±0.059 | 2.884613±0.067 | 72.140569±0.095 |
| 9. | 60 | 3.159806±0.085 | 79.489964±0.169 | 3.321891±0.059 | 83.510753±0.078 | 3.567784±0.054 | 89.225832±0.059 |
| 10. | 75 | 3.844653±0.074 | 96.718398±0.189 | 3.99886±0.087 | 100.52944±0.534 | 4.251626±0.029 | 106.32786±0.068 |

*Data are expressed as mean±SD (n=3)

**Comparative *in vitro* drug release data of formulation F4-F6**

The comparative study of dissolution profile of formulations F4, F5, and F6 was prepared with 10 mg of sodium starch glycolate and 20 mg, 30 mg, and 40 mg Ludiflash, respectively. Each of the tablets in all the formulations contains 5 mg of Tofacitinib Citrate. The basic *in vitro* data obtained were tabulated (table 9, 10, and 11); the percentage release of drugs from F4, F5, and F6 were found to be 96.71 %, 100 %, and 106 % in 75 min. Study respectively. The slope values of release data suggest that as the amount of Ludiflash increased rate of release of the drug gradually increases. The order of the above formulation was obtained in the following manner F4<F5<F6.

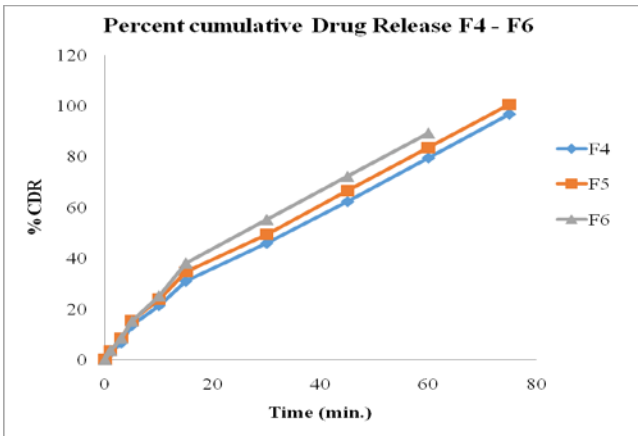


**Fig. 2: Comparative *in vitro* drug release profile of formulations F4-F6, *In vitro* drug release data of formulation F4-F6 (data represents mean±SD, n=3)**

**Result of *in vitro* drug release data of formulation F7-F9**

***In vitro* drug release data of formulation F7 (n =3)**

The F7 formulation, containing 15 mg of SSG and 20 mg of Ludiflash was found to release nearly 26.70% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 60 min it could release 91.87% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

***In vitro* drug release data of formulation F8**

The F8 formulation, containing 15 mg of SSG and 30 mg of Ludiflash was found to release nearly 39.039% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 60 min it could release 99.84% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

***In vitro* drug release data of formulation F9**

The F9 formulation, containing 15 mg of SSG and 40 mg of Ludiflash was found to release nearly 39.573% of the drug into dissolution fluid within the first 10 min. The drug release into dissolution media continues gradually and in 30 min it could release 100% of the drug. The raw data obtained were subjected to regression analysis and cum % of drug release was plotted against time [38, 39].

In the above discussion of F7, F8 andF9, containing 15 mg of SSG and varying amounts of Ludifash 20 mg,30 mg and40 mg, respectively, the release rate constant was found to increase in the following order F9>F8>F7, and the disintegration time was found to be F9<F8<F7.

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

| S. No. | Time (min) | F7 | | F8 | | F9 | |
|---|---|---|---|---|---|---|---|
| | | Cumulative drug release (CDR)±SD (n=3) | Cumulative drug release % (%CDR)±SD (n=3) | Cumulative drug release (CDR) ± SD (n=3) | Cumulative drug release % (%CDR)± SD (n=3) | Cumulative drug release (CDR)±SD (n=3) | Cumulative drug release % (%CDR)± SD (n=3) |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 1 | 0.149313±0.046 | 3.7341263±0.084 | 0.1556822±0.074 | 3.916434785±0.028 | 0.17378478±0.018 | 4.34614066±0.124 |
| 3. | 3 | 0.3412±0.0845 | 8.5329899±0.047 | 0.63419376±0.089 | 15.95415875±0.049 | 0.834495474±0.092 | 20.8696912±0.189 |
| 4. | 5 | 0.632987±0.092 | 15.830214±0.82 | 1.14958096±0.074 | 28.91954816±0.189 | 1.582366745±0.047 | 39.5730191±0.029 |
| 5. | 10 | 1.067751±0.079 | 26.703111±0.195 | 1.68457928±0.039 | 42.3782869±0.058 | 2.35822997±0.062 | 58.9763909±0.068 |
| 6. | 15 | 1.638116±0.058 | 40.967238±0.049 | 2.26516929±0.082 | 56.98395745±0.075 | 3.174824003±0.054 | 79.3983895±0.048 |
| 7. | 30 | 2.3176±0.045 | 57.960279±0.192 | 2.86570567±0.09 | 72.09141067±0.052 | 4.006838753±0.059 | 100.206040±0.049 |
| 8. | 45 | 2.9969±0.0783 | 74.949129±0.078 | 3.48166276±0.039 | 87.5867967 ±0.054 | - | - |
| 9. | 60 | 3.67355±0.069 | 91.870908±0.029 | 3.99537378±0.086 | 100.5100195±0.058 | - | - |

*Data are expressed as mean±SD (n=3)

**Comparative *in vitro* drug release data of formulation F7-F9**

The comparative study of dissolution profile of formulations F7, F8, and F9 was prepared with 15 mg of sodium starch glycolate and 20 mg, 30 mg, and 40 mg Ludiflash, respectively. Each of the tablets in all the formulations contain5 mg of Tofacitinib Citrate. The percentage release of drugs from F7, F8, and F9 were found to be 91.87 %, 99.84 %, and 100 % in 60, 60, and 30 min. Study respectively. The slope values of release data suggest that as the amount of Ludiflash increased rate of release of the drug gradually increased. The order of the above formulation was obtained in the following manner F4<F5<F6.

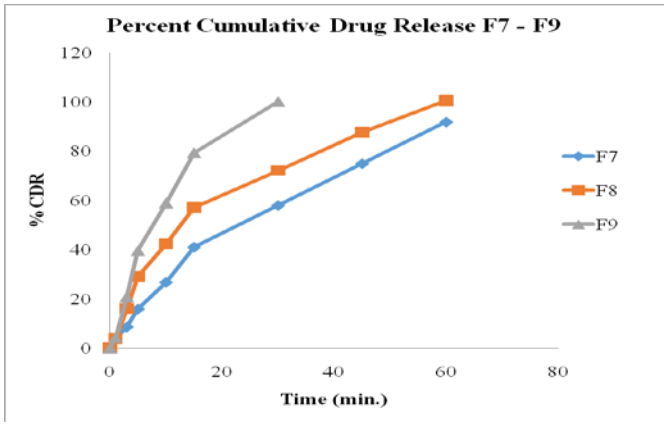


**Fig. 3: Comparative *in vitro* drug release profile of formulations F7-F9, *In vitro* drug release data of formulation F7-F9 (data represents mean±SD, n=3)**

**Result of stability studies of F9 formulation: stability studies at 40 °C/75 % RH**

The stability of Tofacitinib citrate in the fast dissolving tablets was assessed according to ICH guidelines. Arrangements were made inside a stability chamber to induce stress of temperature and humidity simultaneously and uniformly and all the tablets were kept for study [40]. A temperature of 40 ℃ and relative humidity of 75%RH were selected, and the F9 formulation was selected as a model dosage form. Nearly 50 tablets of F9 were placed inside the stability chamber so that each tablet is separated and was exposed to 40 °C/75%RH. At the end of 24 h, 30 d, 60days, and 90 d, 3 tablets were removed randomly and were subjected to dissolution. The tablets were inspected surely for any chamber [41]. The dissolution profiles were obtained and the results of these formulations were compared with the dissolution profile of the tablet which was no exposure to stress [42]. The profiles of the formulation F9 were seen to remain similar, indicated by slope, visual inspection showed that there was no apparent effect of temperature/humidity a color, odor, etc. which given in table 7.

**Table 7: Result of stability studies of F9 formulation**

| S. No. | Time (min) | Day (d) 1st | Day (d) 30th | Day (d) 60th | Day (d) 90th |
|---|---|---|---|---|---|
| | | Cumulative drug release (%CDR) ± SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) | Cumulative drug release % (%CDR) ±SD (n=3) | Cumulative drug release % (%CDR)±SD (n=3) |
| 1. | 0 | 0 | 0 | 0 | 0 |
| 2. | 1 | 4.34614±0.04 | 4.119779±0.127 | 4.351716±0.048 | 4.348949±0.097 |
| 3. | 3 | 20.84035±0.08 | 20.52177±0.076 | 20.72436±0.08 | 20.89903±0.094 |
| 4. | 5 | 39.5311±0.092 | 39.11191±0.084 | 39.22228±0.192 | 40.02293±0.079 |
| 5. | 10 | 58.96243±0.089 | 58.54463±0.057 | 58.81429±0.054 | 59.27121±0.068 |
| 6. | 15 | 79.37605±0.0492 | 78.67181±0.082 | 79.19437±0.073 | 79.68063±0.082 |
| 7. | 30 | 100.1697±0.059 | 99.506±0.067 | 99.99502±0.14 | 100.3597±0.095 |

Standard Deviation (SD) n=3, from the stability study data, it was clear that drug was stable in the optimized formulation for the study period.

Therefore it was concluded that the drug Tofacitinib Citrate formulation can retain its original potency for at least 2 y. The ICH guidelines require 6 mo of study, but because of time constraint, the results of only 3 mo study has been reported; the remaining studies would be reported elsewhere at a later time.

## CONCLUSION

The concept of formulating Mouth Dissolving Tablets of Tofacitinib Citrate using super disintegrants offers a suitable and practical of faster disintegration and dissolution characteristics. Tofacitinib Citrate was characterized by studying its absorbance, melting point, Partition coefficient and solubility in water, and various solvents and FTIR spectroscopy. The present investigation successfully formulated mouth dissolving tablets of Tofacitinib citrate with an improved drug release profile. It is concluded that the amount of Superdisintegrants decreases the disintegration time of tablets, decreases wetting time, increases the cumulative % drug release causes better absorption. The future looks bright for patients as many new drugs are being developed and now combinations of JAK inhibitors with other targeted agents are being studied in the clinic. These advances are expected to lead to further significant progress in improving patient outcomes and quality of life.

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Nil

## AUTHORS CONTRIBUTIONS

All authors have contributed equally.

## CONFLICT OF INTERESTS

The authors declared that the No conflict of interest for the given Article.

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