Journal of Medicinal and Chemical Sciences 6 (2023) 2218-2227

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Tofacitinib in Pharmaceutical Solid Dosage from Dissolution Study: Development and Validation of RP-HPLC Method

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ARTICLE INFO

Article history

Receive: 2023-01-13
Received in revised: 2023-03-07
Accepted: 2023-04-17
Manuscript ID: JMCS-2303-1983
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Mehrdad Hamidi

DOI:10.26655/JMCHEMSCI.2023.9.26

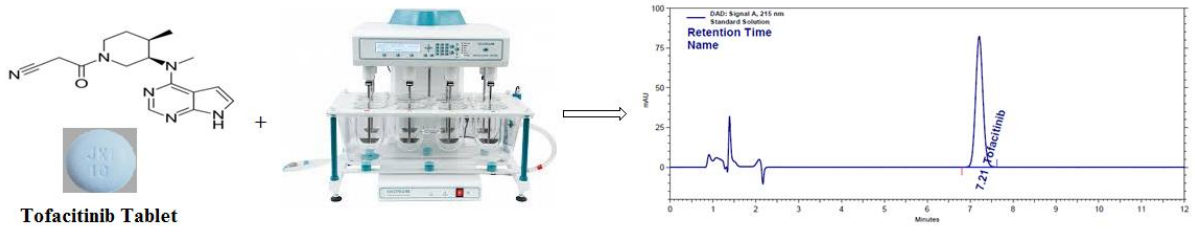
KEYWORDS

Tofacitinib
Liquid-chromatography
Dissolution and Validation

ABSTRACT

A simple, sensitive, precise, and accurate reversed phase high performance liquid chromatographic (RP-HPLC) method has been developed for the dissolution study of Tofacitinib in Tofacitinib tablets dosage form. The mobile phase for the method was made by combining ortho phosphoric acid and acetonitrile in an 85:15 v/v ratio in a triethylamine buffer with a pH of 3.5. Using a stationary phase column, the separation was accomplished. Waters X-Bridge shield RP-18 (150 × 4.6 mm, 5), column temperature and sample temperature were both kept at ambient levels, and the injection volume and runtime were 20 µL and 12 minutes, respectively. The UV detection occurred at 215 nm, and the flow rate was 1.0 mL/min. Tofacitinib's retention period was shown to be 7.2 minutes. ICH guidelines were followed in the method's validation. The accuracy, reproducibility, and consistency of the suggested procedure were discovered.

GRAPHICAL ABSTRACT



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Introduction

Tofacitinib is chemically known as 3-[(3R,4R)-4-methyl-3- [methyl (7H-Pyrrolo [2, pyrimidine-4yl) amino] piperidin-1-yl]-3-oxopropanenitrile. It is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis [1]. Cytokines work within a complex regulatory network in RA, signalling through different intracellular kinase pathways to modulate the recruitment, activation, and function of immune cells and other leukocytes [2-6]. Several research works elucidated the safety and efficacy of Tofacitinib drug [7-14]. The chemical structure of Tofacitinib was displayed in Figure 1.

The research review demonstrates that not one of the major pharmacopoeias such as USP, EP, JP, and BP reported any LC methods. Only a limited number of techniques have been published too far for the tofacitinib assessment in pharmaceutical dosage forms employing RP-HPLC methods [15–17] and HPTLC [18].

According to a research review, there is no such straightforward RP-HPLC method for analysing tofacitinib's solubility in pharmaceutical dosage forms. Therefore, we attempted to create a straightforward HPLC method for tofacitinib in the dose form of tofacitinib tablets. According to the ICH guidelines, a straightforward HPLC approach is described in the current work for the dissolution investigation of tofacitinib in tofacitinib tablet dosage form [19, 20].

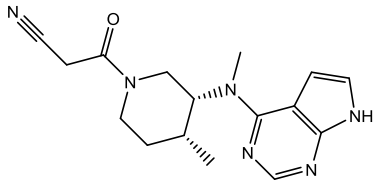

Figure 1: Chemical structure of Tofacitinib

Materials and Methods

Chemicals and reagents

Working standard for tofacitinib (Clearsynth, Hyderabad, India), the mentioned formulation was acquired on the neighbourhood market. Hydrochloric acid and orthophosphoric acid (Merck, Bombay, India), acetonitrile (J.T. Baker, USA), triethylamine, and ultra-pure water (Milli-Q system, Millipore, Bedford, MA, USA) were utilized in this stduy. In addition, analytical and HPLC-grade chemicals and solvents were used in this investigation.

Instrumentation

For analysis, an Agilent 1260 high-performance liquid Chromatographic system with an auto sampler and PDA detector was deployed. OpenLab software was utilized to record the data. We adopted a pH metre (Thermo Orion Model), Bandelin ultrasonic bath, dissolution (Make: Electro lab), and an analytical balance (Mettler Toledo Model).

Chromatographic conditions

Waters X-Bridge shield RP-18 (150 × 4.6 mm, 5) was subjected to chromatographic analysis. The mobile phase was composed of acetonitrile and pH 3.5 triethylamine buffer in an 85:15 v/v ratio. The injection volume was 20 µL, the flow rate was 1.0 mL/min, the column oven and sampler cooler temperatures were ambient, and detection was carried out at 215 nm using a photodiode array detector (PDA).

Preparation of buffer solution

1.0 mL of triethylamine was transferred into 1000 mL of water sonicated to dissolve and mixed well, and then pH was adjusted to 3.5 with ortho phosphoric acid solution. After that, it was filtered through 0.45 µm membrane filter.

Preparation of mobile phase

An 85:15 (% volume/volume) mixture of pH 3.5 Triethylamine buffer solution and acetonitrile were produced, which was well mixed and sonicated to remove gas.

Dissolution conditions

The dissolution system (n=6) and dissolution USP apparatus Type - I were used to conduct the dissolution test for the tofacitinib formulation (Basket). 0.1N Hydrochloric acid was the medium. Dissolution media was poured into a 900 mL container, the bath was kept at 37 °C, and the basket's speed was set at 100 RPM. The sample was taken out in aliquots and filtered

using a 0.45 m PVDF membrane filter for 30 minutes.

Preparation of dissolution medium (0.1 N Hydrochloric acid)

8.9 mL of concentrated Hydrochloric acid was transferred into 1000 mL volumetric flask, containing 500 mL of water, made up to the volume with water and mixed well.

Preparation of diluent

The dissolution medium (0.1 N Hydrochloric acid) was used as a diluent.

Preparation of standard solution

Tofacitinib working standard was accurately weighed and deposited into a 100 mL volumetric flask, and then 50 mL of diluent was added, the contents were sonicated for two minutes to dissolve them, and the remaining diluent was used to make up the volume. The solution was further diluted by adding 4 mL to a 100 mL volumetric flask, making up the volume with the diluent, and thoroughly mixing it (the volume of the standard solution contains 11.2/g of tofacitinib).

Preparation of test solution

In each of six dissolution tubes, which contain 900 mL of dissolving medium that has been adjusted to 37 °C ± 0.5 °C, one tablet was put and there should be no air bubbles on the tablet's surface before starting the device. At the allotted time, 15 mL of the sample solution was removed from each dissolution vessel, the sample was kept at least 1 cm from the vessel wall and in a region that is halfway between the medium's surface and the top of the revolving paddle. Next, it was filtered through a 0.45 m PVDF syringe filter; the first 2 mL of filtrate were then discarded and the remaining solution was injected straight into an HPLC column. Tofacitinib was present in the sample solution at a concentration of 11.1 g/mL.

Preparation of placebo solution

900 mL of dissolution media that has been equilibrated to 37±0.5 °C has been placed in each of the six dissolving vessels after being precisely weighed and divided into placebo powder (equal to 10 mg of tofacitinib). There should be no air bubbles on the tablet's surface before starting the device. After the allotted time has passed, 15 mL of sample solution from each dissolving vessel should be collected. Samples should be taken out of areas that are at least 1 cm from the vessel wall and halfway between the medium's surface and the top of the revolving paddle, and then it was filtered through a 0.45 m PVDF syringe filter and the first 2 mL of filtrate were discarded. Thereafter, the remaining solution was injected straight into an HPLC column.

Method development

The maximum UV absorbance (max) of tofacitinib drug material was demonstrated at 215 nm when its standard solution of 10 g/mL was scanned between 200 and 400 nm.

Mobile phase made up of various solvent compositions were tested to achieve the best separation to produce a suitable and reliable HPLC method for the tofacitinib assessment in the dosage form of tofacitinib tablets. It was attempted using a mobile phase composed of Triethylamine buffer, pH-adjusted to 3.5, Acetonitrile in the ratios of 50:50, 65:35, 75:25, and 85:15 % v/v. When tofacitinib was injected, increased retention times and unsatisfactory peak tailing were seen, and the tofacitinib peak was not properly eluted in the ratios of 50:50 % v/v and 65:35 % v/v. The peak form was good for the following trial, but there was some small tailing. The mobile phase is 75:25 v/v. The mobile phase for the subsequent attempt is composed of 85:15 % v/v. Tofacitinib was eluted to produce a nice peak and meet the requirements for system appropriateness. Figure 2 depicts the chromatogram for the Tofacitinib standard. Table 1 presents the method's results for system appropriateness.

Results and Discussion

Specificity: Blank and placebo interference

The blank, placebo solution, standard, and sample solution were prepared and analysed as per method. Blank and placebo were injected in the above mentioned chromatographic conditions

and the blank and placebo chromatograms were recorded. Chromatogram of blank solution in Figure 3 showed no peak at the retention time of Tofacitinib peak. This indicates that the blank solution used in standard and sample preparation do not interfere in estimation of Tofacitinib in Tofacitinib tablets formulation. Similarly, chromatogram of placebo solution in Figure 4 showed no peaks at the retention time of Tofacitinib peak. This indicates that the placebo used in sample preparation do not interfere in estimation of Tofacitinib in Tofacitinib tablets formulation (Figure 5). The observations are listed in Table 2.

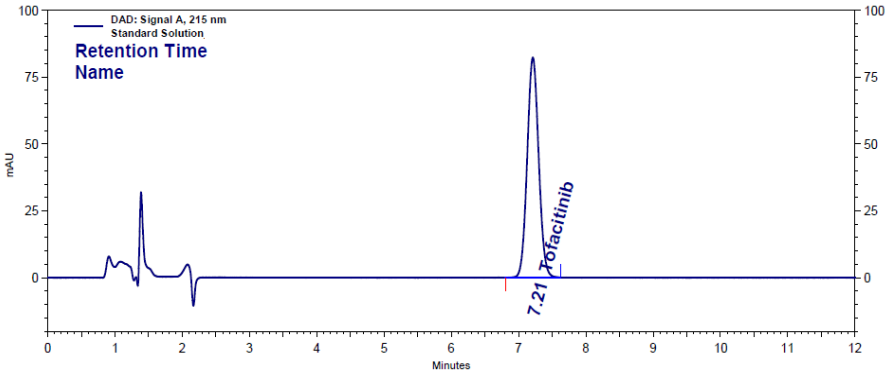

Figure 2: Typical chromatogram standard

Table 1: System suitability results

S.No.	System suitability parameters	Tofacitinib
1	Retention time	7.21
2	Tailing factor	1.10
3	Theoretical plates	7610
4	% RSD of six replicate standard solution	0.07

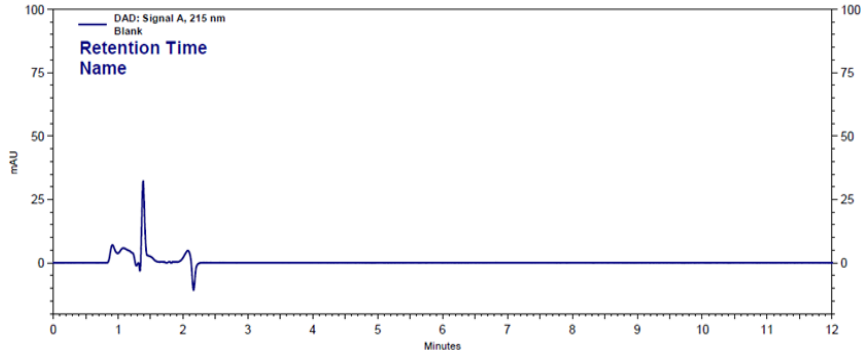

Figure 3: Typical chromatogram blank

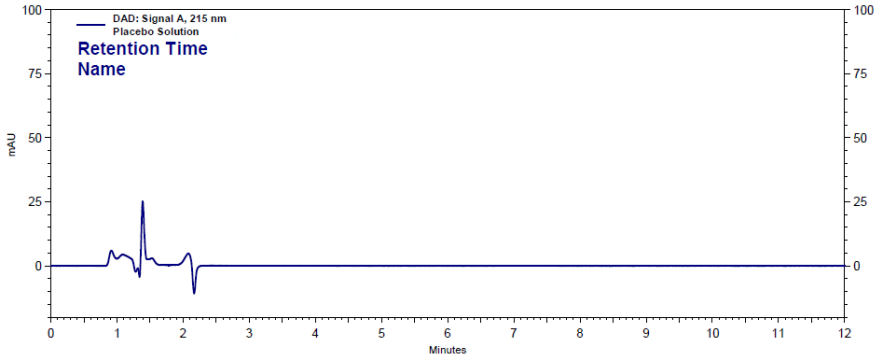

Figure 4: Typical chromatogram placebo

Table 2: Specificity results

S.No.	Name	Retention Time (min)	Blank	Placebo
1	Blank.	N.D.	N.A.	N.A.
2	Placebo soln.	N.D.	N.A.	N.A.
3	Standard soln.	7.21	No	No
4	Sample soln.	7.23	No	No

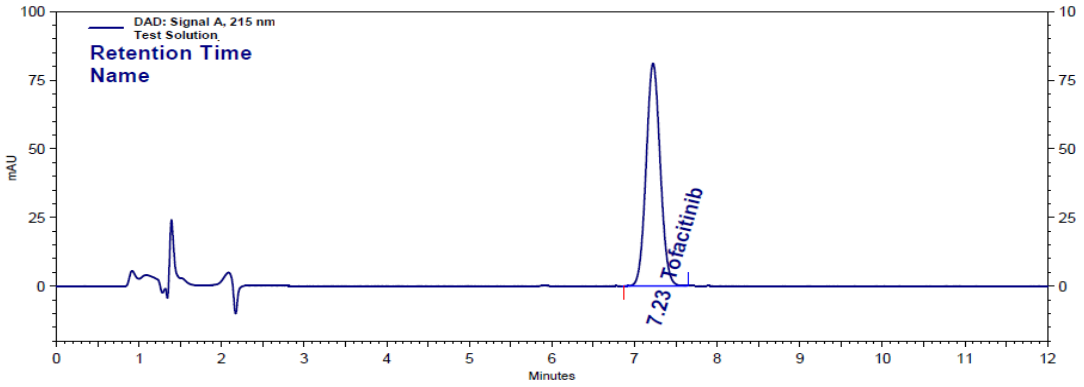

Figure 5: Typical chromatogram sample

System precision

System precision was demonstrated by preparing standard solution as per method and injected the same into HPLC system in six replicate injections of standard solution. The area of analyte peak was recorded for these standard injections. The system precision was evaluated by computing the % relative SD for the peak area of these standard readings. The observations are provided in Table 3.

The six replicate standard solutions' relative standard deviation was found to be less than the specified limit, or 0.07%.

Method precision

Method precision was demonstrated by performing dissolution for six units as per method. The % drug dissolved of each unit was quantified for the sample. The method precision was evaluated by calculate the individual, mean % drug dissolved, and % relative SD for each set of samples. The results of the precision study are listed in Table 4.

The method precision was established as mentioned in the developed method and the results are found satisfactory. The % relative SD of 6 units is 0.26%.

Intermediate precision

Intermediate precision of the method was demonstrated by carrying out method precision study in six preparations of a same sample. Representing a single batch by two different analysts on different days. These samples were prepared as per the method.

Table 3: System precision results

S.No.	No. of injections	Peak area
1	Injection – 1	2112323
2	Injection – 2	2111598
3	Injection – 3	2113767
4	Injection – 4	2113209
5	Injection – 5	2113068
6	Injection – 6	2115796
Average		2113294
STDEV		1439.5339
%RSD		0.07

Table 4: Method precision results

S.No.	No. of preparations	% Drug dissolved
1	Preparation 1	100.5
2	Preparation 2	100.8
3	Preparation 3	100.9
4	Preparation 4	100.5
5	Preparation 5	100.2
6	Preparation 6	100.8
Average		2113294
SD		1439.5339
%RSD		0.07

Table 5: Results of intermediate precision

S.No.	No. of preparations	% Drug dissolved
1	Preparation 1	100.7
2	Preparation 2	100.2
3	Preparation 3	100.3
4	Preparation 4	100.3
5	Preparation 5	100.4
6	Preparation 6	100.4
Average		2113294
SD		1439.5339
%RSD		0.07

Table 6: Comparison between method precision and intermediate precision

S.No.	Method precision	Intermediate precision
1	100.5	100.7
2	100.8	100.2
3	100.9	100.3
4	100.5	100.3
5	100.2	100.4
6	100.8	100.4
Overall Average	100.5	
Overall STDEV	0.2449	
Overall %RSD	0.24	

The method precision was evaluated by calculate the individual, mean % drug dissolved, % relative SD for each set of samples and overall mean % drug dissolved, % relative SD for both method precision and intermediate precision. The results of the precision study are presented in Tables 5 and 6.

Linearity

By creating solutions with concentrations ranging from 20% to 150% of the usual concentration level, the linearity of area for tofacitinib was demonstrated. The peak area of these solutions was recorded when they were added to the HPLC apparatus. It was done to plot concentration versus area response. The relationship between concentration and area response co-efficient of determination was assessed, as depicted in Figure 6. The observations are listed in Table 7.

Accuracy

By creating recovery samples of tofacitinib at 20%, 100%, and 150% of the intended stock sample concentration level, the test method's accuracy was put to the test. For each concentration level, the recovery samples were made in three copies. The % recovery of each sample was computed for the amount added after the afore mentioned samples were recorded.

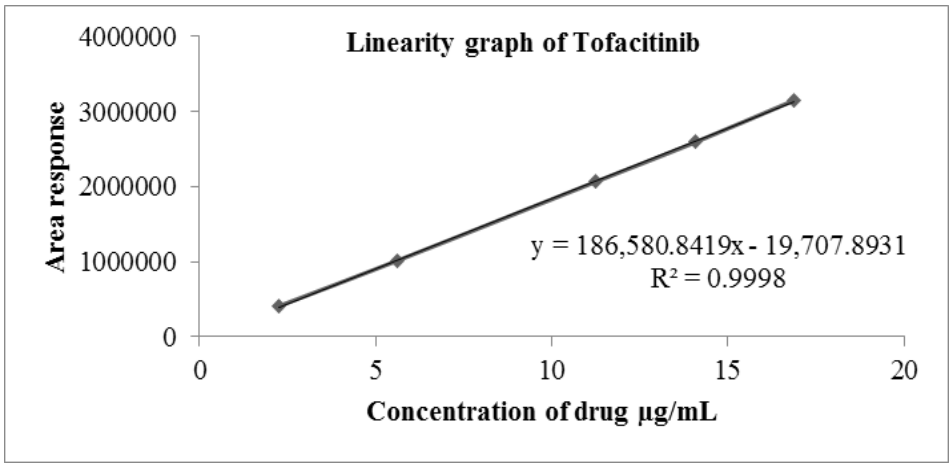

Figure 6: Linearity plot of tofacitinib

Table 7: Linearity studies of tofacitinib

S.No.	Linearity Level	Concentration(ppm)	Area Response
1	Linearity at 20 %	2.251	413821
2	Linearity at 50 %	5.6275	1021450
3	Linearity at 100 %	11.2551	2069124
4	Linearity at 120 %	14.0688	2592488
5	Linearity at 150 %	16.8826	3149479
Correlation coefficient (r^2)			0.9998
Intercept			-19707.8931
Slope			186580.8419
% Y-intercept			-0.95

Table 8: Recovery studies of tofacitinib

% Level	% Recovery	Mean % Recovery	% RSD
20 % level 1	100.3	100.4	0.15
20 % level 2	100.6		
20 % level 3	100.4		
100 % level 1	100.8	100.8	0.06
100 % level 2	100.8		
100 % level 3	100.7		
150 % level 1	100.6	100.6	0.06
150 % level 2	100.6		
150 % level 3	100.5		

By calculating the relative standard deviation of the findings of the three recovery samples, we evaluated the recovery accuracy at each level. The procedure and data collected, which are shown in Table 8, were judged to be accurate.

Solution stability

The standard and sample solutions for solution stability were created under a variety of circumstances, including bench top at room temperature and in a refrigerator at 2 to 8 °C. By contrasting initially prepared standard and sample solutions with recently prepared standard solutions, the stability of standard and sample solutions was ascertained. Tables 9 and 10 include tabular lists of the observations. Solution stability parameter was established, and the standard and sample solutions are stable up to 48 hours at bench top and in refrigerator (2-8 °C) conditions.

Filter validation

Filter validation for the sample solution was carried out by centrifuging one portion of the solution and filtering the remaining portion through 0.45 m PVDF and 0.45 m Nylon filters. The observations are listed in Table 11.

Filter validation parameter was established. Based on the above results and observations, 0.45 µm PVDF and 0.45 µm Nylon filterers are suitable for filtration.

Robustness

The robustness of the approach was evaluated by making small adjustments to the chromatographic and dissolving settings, such as the mobile phase ratio, buffer pH, flow rate, temperature, medium volume, and rpm. The following altered conditions each received an injection of standard solution. The observations are listed in Table 12.

Table 9: Results for solution stability of standard

Time interval	Similarity factor	
	Room Temperature	Refrigerator
Initial.	N.A.	N.A.
24 hrs.	01.01	01.01
48 hrs.	01.00	01.02

Method is robust for changes like flow rate, column oven temperature, pH variation, organic phase of mobile phase, volume of medium, and rpm.

Table 10: Results for solution stability of sample

Bench-top			Refrigerator	
Time interval	% Drug dissolved	% Recovery	% Drug dissolved	% Recovery
Initial	100.5	NA	100.5	NA
24 hrs.	100.6	100.1	100.5	100.0
48 hrs.	101.6	101.1	100.8	100.3

Table 11: Results for filter validation

S.No.	Filter details	Area Response	% Filter interference
1	Centrifuged-Sample	2015239	NA
2	0.45 µm PVDF Sample	2025309	0.50
3	0.45 µm Nylon Sample	2025173	0.49

Table 12: Results of robustness studies

Parameter		Theoretical plates	Tailing factor	% RSD
Flow variation ± 10 %	0.9 mL	6895	1.3	0.11
	1.1 mL	7892	1.0	0.07
Temperature variation ± 5 °C	20 °C	6542	1.2	0.21
	30 °C	7541	1.1	0.18
pH variation ± 0.2	3.3	6723	1.2	0.14
	3.7	7005	1.2	0.11
Mobile phase variation ± 10 %	83.5:16.5 v/v	6932	1.1	0.23
	86.5:13.5 v/v	7128	1.0	0.08
Volume of medium ± 2 %	882 mL	7214	1.3	0.17
	918 mL	7189	1.1	0.16
RPM ± 0.2	98	6987	1.0	0.11
	102	7036	1.1	0.12

Conclusion

The technique created for the precise measurement of tofacitinib in the sample after dissolution. Tofacitinib could be completely dissolved after 30 minutes when used with a USP Type-I apparatus (Basket) spinning at 100 rpm in 900 mL of 0.1N hydrochloric acid. This procedure was validated for a number of parameters in accordance with the ICH guidelines, including accuracy, precision, linearity, specificity, system suitability, solution stability, filter study, and robustness. The outcomes met the standards for acceptance. The new approach can therefore be successfully used for the routine analysis of tofacitinib in bulk and pharmaceutical dose forms because it is easy to use, precise, affordable, eco-friendly, and safe.

Acknowledgments

The authors are grateful to the Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur and Andhra Pradesh, India, for providing the facilities to carry out this research work.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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HOW TO CITE THIS ARTICLE

Narapereddy Krishna Prasad, Alladi Devi Sravanthi. Tofacitinib in Pharmaceutical Solid Dosage from Dissolution Study: Development and Validation of RP-HPLC Method. *J. Med. Chem. Sci*., 2023, 6(9) 2218-2227

DOI: https://doi.org/10.26655/JMCHEMSCI.2023.9.26

URL: http://www.jmchemsci.com/article_170264.html