Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

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Formulation and Evaluation of Tofacitinib Nanosponges Incorportaed Tablet

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Cite this paper as: Gourav Thakur, Dr. Sachin Kumar, (2025) Formulation and Evaluation of Tofacitinib Nanosponges Incorportaed Tablet. *Journal of Neonatal Surgery*, 14 (32s), 2846-2854.

ABSTRACT

The present study aims on the formulated and analyze of a novel oral tablet formulation incorporating tofacitinib-loaded nanosponges aimed at enhancing solubility, bioavailability, and sustained drug release. Tofacitinib, a Janus kinase (JAK) inhibitor, is limited by poor aqueous solubility and rapid systemic clearance. To address these challenges, by using emulsion solvent diffusion method nano-sponges were develop with various polymers including Eudragit RL 30, Poloxamer 188, and ethyl cellulose. Among twelve formulations (T1–T12), formulation T3 was optimized based on particle size (127.4 nm), zeta potential (–25.4 mV), and highest entrapment efficiency (88.43%), polydispersity index (0.303). The optimized nanosponge (T3) was further compressed into tablets using direct compression. The tablet formulations (NT1–NT4) underwent pre-compression and post-compression evaluations including Carr's index, angle of repose, content uniformity, hardness, friability, and in vitro dissolution. NT3 demonstrated excellent flowability, robust mechanical properties, and the highest drug release profile, reaching 90.12% over 12 hours, indicating a sustained release pattern. These findings suggest that nanosponge-incorporated tablets provide a promising platform for increased the performance of drug and patient compliant of tofacitinib in the treatment of autoimmune diseases.

Keywords: *Tofacitinib, Nanosponges, Tablets, Emulsion Solvent Diffusion,*

1. INTRODUCTION

Nanotechnology has introduced novel drug delivery systems, among which nanosponges are highly promising due to their ability to encapsulate and protect drugs, enhance solubility, and provide sustained release. Nanosponges are porous particles formed via crosslinking polymers, capable of encapsulating both hydrophilic and hydrophobic drugs. Tofacitinib, a JAK inhibitor, used for autoimmune diseases such as RA, PsA, and UC, suffers from low solubility and bioavailability. Incorporating tofacitinib into nanosponges, followed by tablet formulation, offers potential benefits including enhanced stability, targeted delivery, and patient compliance.[1,2,3]

2. MATERIALS AND METHODS

2.1 Materials

Tofacitinib, Eudragit RL 30, Poloxamer 188, Ethyl Cellulose, PVA, and other excipients were sourced from reliable suppliers. Instruments included FTIR, UV-Visible spectrophotometer, SEM, Zetasizer, and dissolution apparatus.

2.2 Preformulation Studies Organoleptic properties, melting point (201°C), solubility profile (soluble in DMSO, slightly soluble in water), and FTIR spectra confirmed identity and compatibility with polymers. UV-Vis analysis showed λmax at 288 nm. Calibration curve was linear in the range of 0–10 µg/mL with $R^2 = 0.9815$.

2.3 Method of preparation of tofacitinib loaded nanosponge

The emulsion solvent diffusion system is generally used for tofacitinib-loaded nanosponges preparation. This method involves two distinct phases: an aqueous phase containing polyvinyl alcohol (PVA) and an organic phase comprising Tofacitinib along with Eudragit S100. Initially, Tofacitinib and Eudragit S100 are dissolved in an suitable organic solvent.

The resulting organic solution is then gradually introduced into the aqueous phase under continuous stirring for at least two hours. The formed nanosponges are subsequently isolated through filtration, thoroughly washed, and dried either at ambient conditions or in a vacuum oven set at 40 °C for 24 hours [4]

Table 1: Composition of tofacitinib loaded nanosponges.

Code	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Tofacitinib (mg)	20	20	20	20	20	20	20	20	20	20	20	20
Poloxamer 188 (mg)	60	120	180	240	-	-	-	-	-	-	-	-
Ethyl cellulose (mg)	-	-	-	-	60	120	180	240	-	-	-	-
Eudragit RL 30 (mg)	-	-	-	-	-	-	-	-	60	120	180	240
PVA (%W/V)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Dichloromethane (ml)	18	18	18	18	18	18	18	18	18	18	18	18
Distilled water (ml)	100	100	100	100	100	100	100	100	100	100	100	100

2.4 Characterization of Tofacitinib-Loaded Nanosponges

2.4.1 Particle Size and Polydispersity Index (PDI):[5]

Particle size and PDI were measured using a Zetasizer Nano ZS at room temperature with a 633 nm laser and 90° scattering angle, indicating uniform particle distribution.

2.4.2 Zeta Potential: [6]

Zeta potential was assessed to determine surface charge and colloidal stability, with ±25 mV considered the threshold for stability.

2.4.3 Entrapment Efficiency (%EE): [7]

%EE was evaluated by ultracentrifugation followed by UV spectrophotometric analysis of the free drug in the supernatant, indicating efficient drug loading.

2.4.4 Scanning Electron Microscopy (SEM): [8]

SEM analysis revealed the surface morphology of the nanosponges, showing porous and spherical structures after gold coating and imaging under vacuum at 10 kV.

Table 2: Nano sponges formulation composition.

Formulation Code	Tofacitinib nano-sponges (mg)	Ethyl cellulose	HPMC	Crospovidone	Mg stearate
NT1	200	40	-	58	2
NT2	200	50	-	48	2
NT3	200	-	40	58	2
NT4	200	-	50	48	2

2.5 Evaluation of Tofacitinib-Loaded Nanosponge Tablets

2.5.1 Pre-compression Parameters:

Before the compression of Tofacitinib-loaded nanosponge tablets, the granule blend was evaluated for key pre-compression parameters to ensure suitable flow and compressibility characteristics. Bulk density and tapped density were determined by measuring the volume occupied by 25 g of granules before and after tapping, respectively. These values helped in assessing the packing ability of the powder. Flowability was further analyzed using Carr's Index, which is calculated based on the difference between the bulk and tapped densities, indicating the compressibility of the blend. Hausner's ratio, derived from

the same densities, was used to evaluate the powder's cohesiveness and tendency to densify under mechanical stress. Additionally, the angle of repose was measured using the fixed funnel method, which provides an estimate of the granules' flow behavior by analyzing the slope formed by a pile of powder. These pre-compression evaluations are critical for ensuring that the blend possesses the necessary characteristics for uniform die filling and smooth tableting.

2.5.2 Post-compression Parameters:

After compression, the tablets were subjected to a range of post-compression tests to assess their physical integrity, content uniformity, and drug release performance. Weight variation was determined by individually weighing 20 tablets from each batch and calculating the percentage deviation from the mean weight, ensuring dosage consistency. Friability was assessed using a friabilator by rotating the tablets for 100 cycles and calculating the percentage of weight loss, which indicates the tablet's resistance to mechanical stress.

Tablet hardness was evaluated using a Monsanto hardness tester on six randomly selected tablets to determine their ability to withstand handling and transport. Thickness was measured using a vernier caliper to ensure dimensional uniformity. For drug content analysis, ten tablets were powdered and a portion equivalent to 20 mg of tofacitinib was analyzed spectrophotometrically at 288 nm to confirm proper drug loading. Lastly, in-vitro drug release was conducted using a USP Type II dissolution apparatus in phosphate buffer (pH 6.8) at 37 ± 0.5 °C and 100 rpm for 12 hours, and the percentage of drug released over time was measured using UV spectrophotometry. These post-compression evaluations ensure the final tablets are uniform, stable, and capable of delivering the drug effectively.

3. RESULTS

3.1 Pre-formulation studies

3.1.1 Organoleptic properties

Organoleptic evaluation revealed that the tofacitinib is off white powder; Slight sweeter taste and odourless odor (refer in Table 5.1).

Table 3: Properties of Tofacitinib.

S. No.	Properties	Result
1.	Colour	Off White powder
2.	Physical form	Powder
3.	Odor	Odourless
4.	Taste	Slight sweeter

3.1.2 Melting point analysis

Table 4: Data of melting point of tofacitinib

Observed melting point				Reported Melting Point
MP 1	MP2	MP3	Mean °C	(°C)
201	202	200	201	200-202 ºC

3.1.3 Solubility study

Table 5: Data of solubility in different solvents medium

Solvents	Concentration (mg/ml)
DMSO	92.6
Ethanol	0.31
Water	2.61
Propylene glycol	8.72

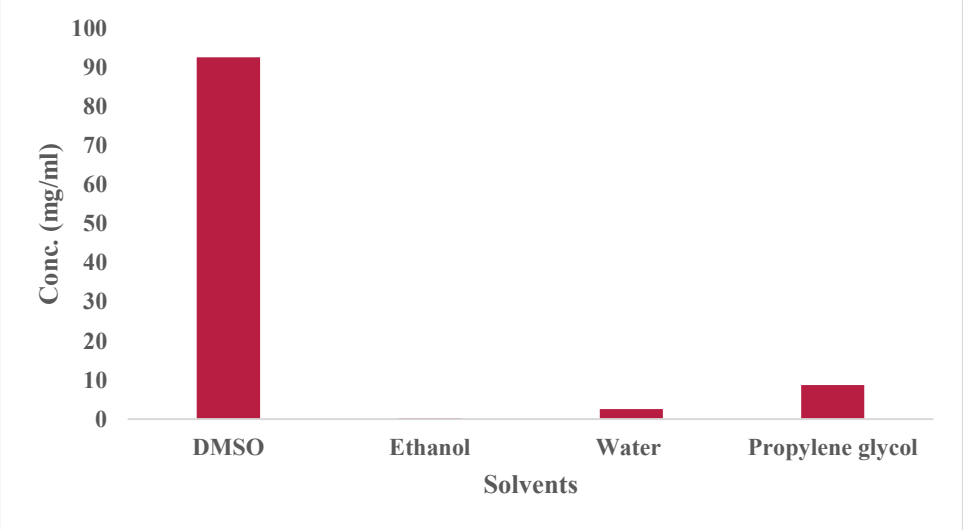

Figure 1: Solubility studies of tofacitinib in different solvents.

3.1.4 FTIR study:

The FTIR spectrum of tofacitinib, Eudragit S100, PVA is shown in Graph 1, 2, 3 the peak positions for important functional groups**.** Determining the medications' purity required a thorough analysis of their peak positions according to standards for several functional groups.

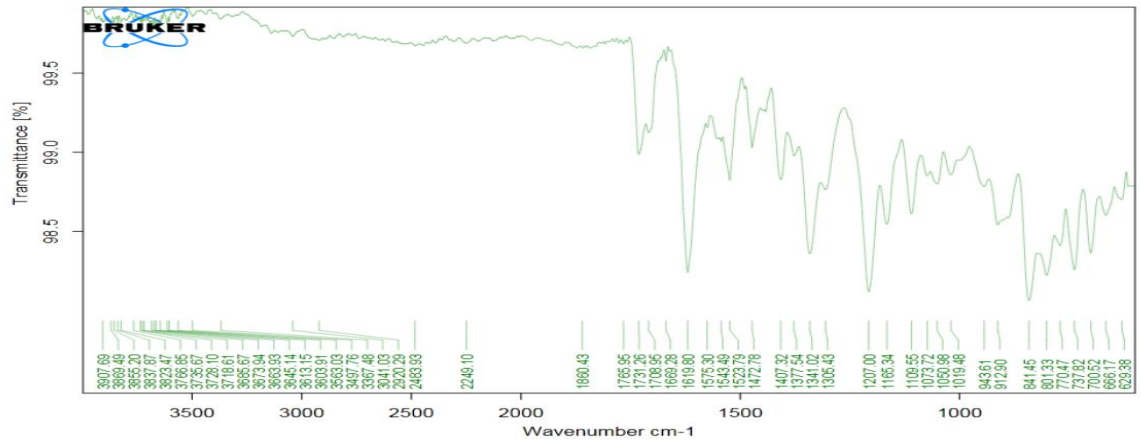

Figure 2: FT-IR spectrum of Tofacitinib.

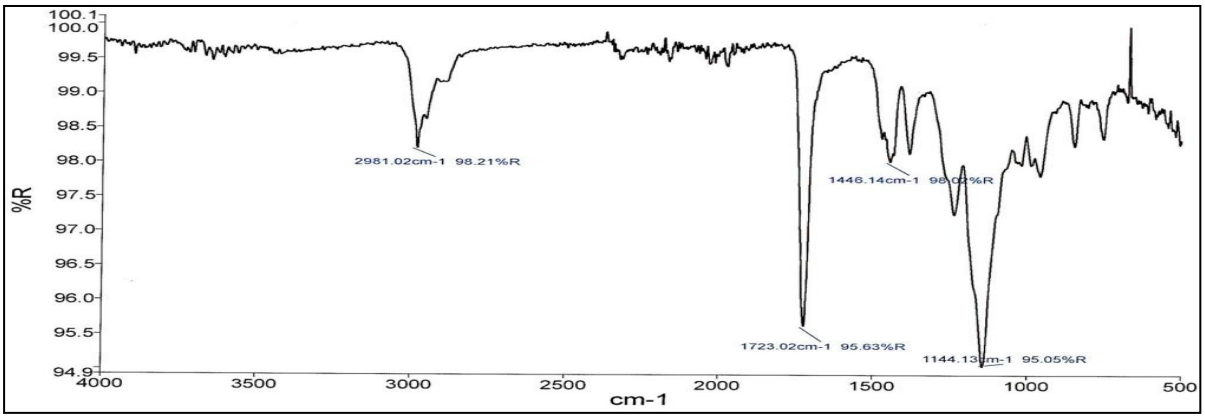

Figure 3: FT-IR spectrum of Eudragit S100.

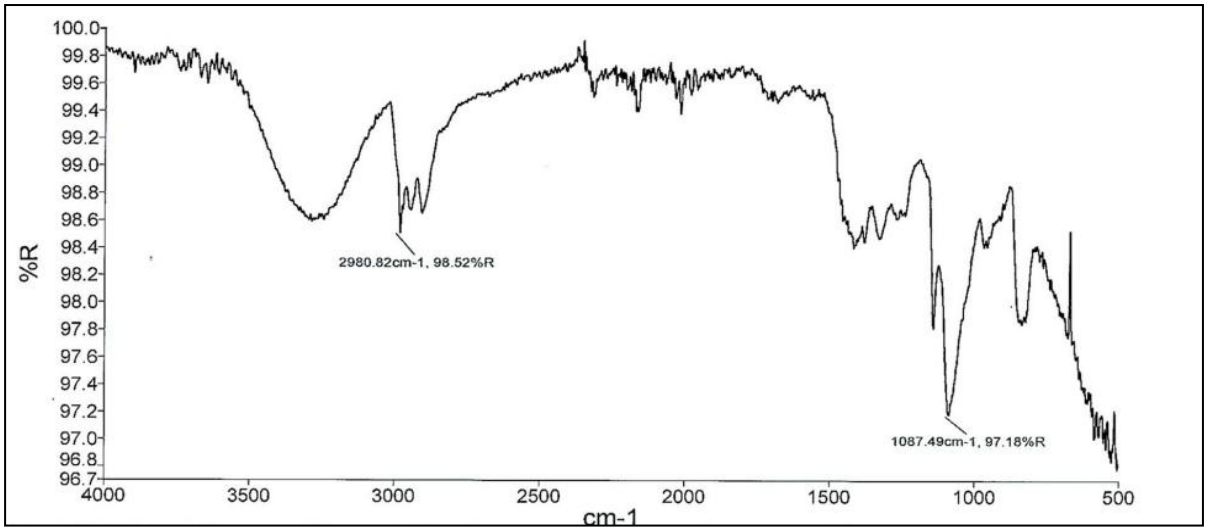

Figure 4: FT-IR spectrum of PVA.

3.2 Preparation of calibration curve and determination of λ_{max}

Table 6: Calibration curve data of tofacitinib in water at 288 nm

Conc.	Abs.
0	0
2	0.282
4	0.444
6	0.696
8	0.816
10	0.956

3.3 Characterization of Tofacitinib loaded nanosponge

3.3.1 Particle size analysis

The formulations T1 to T12 were found to have mean vesicular diameters of 127.4 nm and 243.6 nm, respectively. The T3 formulation had the lowest vesicular diameter of 127.4 nm shown in below figure.

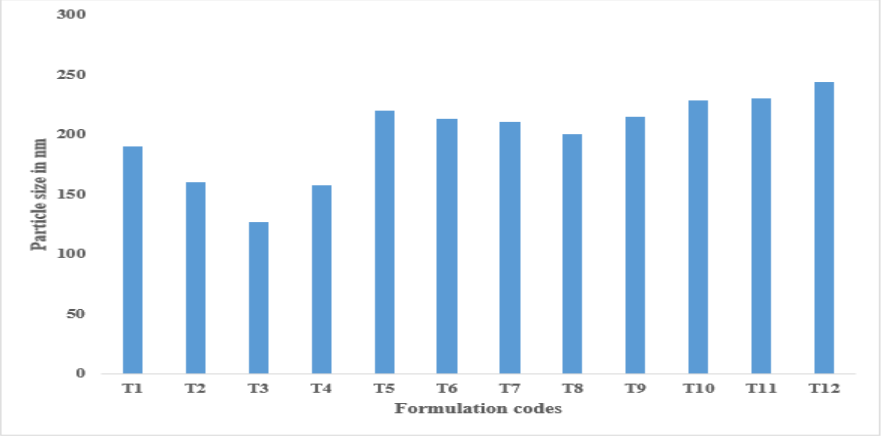

Figure 5: Particle size of various formulations (T1 to T12).

3.3.2 Polydispersity index

The Polydispersity Index (PDI) of the nanosponge to be indicating a uniform particle size distribution and narrow dispersion within the formulations. Among all the formulations T1 to T12 formulation was showing the PDI of 0.303 - 0.562. A PDI value equal to or less than suggests that the sample is mono dispersed

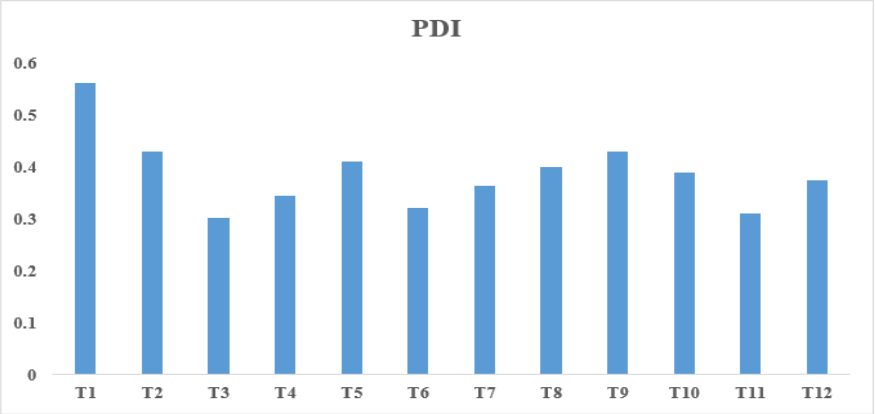

Figure 6: PDI value of T1 to T12 nanosponge formulation.

3.3.3 Zeta potential

The frequently used technique for determining the stability of colloidal dispersion is called zeta potential. Improved stability against aggregation is the outcome of increased repulsion between charged particles caused by an increase in zeta potential. According to the findings, every formulation was determined to be stable. The Zeta potential of formulation T1 to T12 had the zeta potential value of -12.4 to -25.4 among all formulations, indicating improved A higher absolute value indicates a stronger electrical charge on the surface of the nanosponge, leading to robust repulsive forces among the particles and preventing their aggregation (T3)

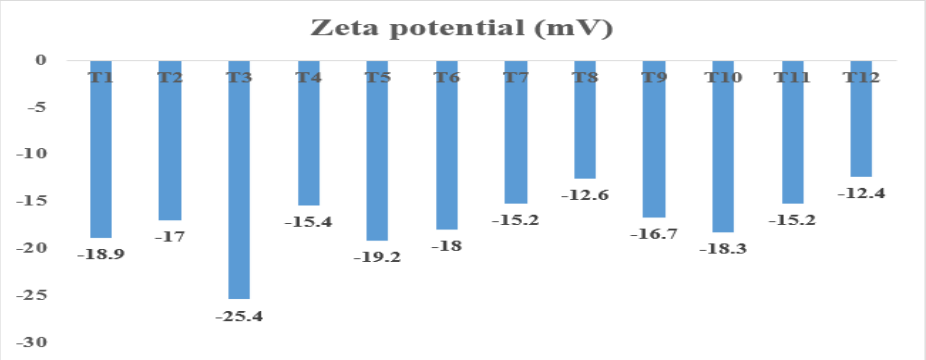

Figure 7: Zeta potential value of T1 to T12 nanosponge formulation.

3.3.4 % Entrapment efficiency (%EE)

The %EE of all 12 formulations was assessed using a cooling ultra-centrifuge (Eltek, Mumbai). The drug entrapment efficiency ranged from 70.5 % to 88.43 %. Formulation T3 had the entrapment efficiency, with a percentage of 88.43 %.

Table 7: % Entrapment efficiency of T1 to T12 nanopsonges formulation

Formulation code	% Entrapment efficiency
T1	85.6
T2	86.2
T3	88.43

T4	87.2
T5	77.54
T6	76.1
T7	81.2
T8	79.9
T9	74.3
T10	72.1
T11	70.5
T12	75.4

3.3.5 SEM

The surface morphology of the nanosponge formulation was examined using SEM. The optimized formulation (T3) displayed a spherical architecture with uniform shape and relatively narrow particle size distribution.

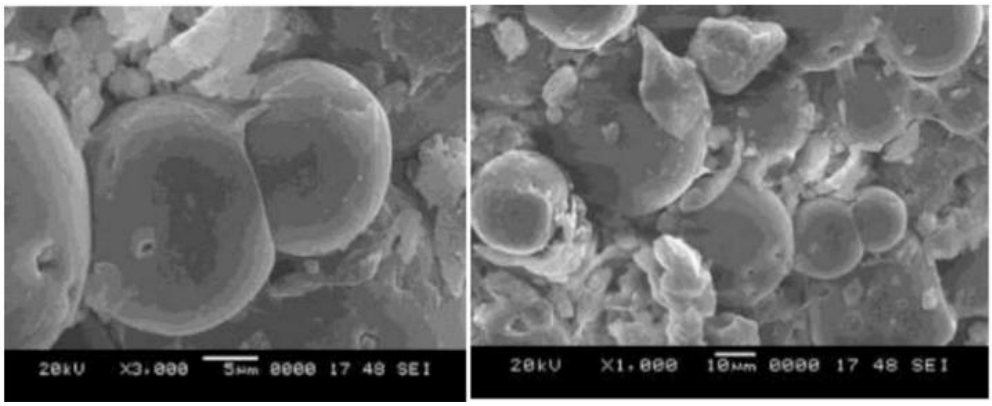

Figure 8: SEM of optimized T3 Nanosponges formulation.

3.4 Characterization of Tofacitinib incorporated tablets

3.4.1 Evaluation of pre-compression parameters

Table 8: Pre-compression testing of tablets

Formations	Bulk density (g/ml)	Tapped density (g/ml)	% Carr's index	Hausner's ratio (g/ml)	Angle of repose (g/ml)
NT1	0.44 ± 0.55	0.49 ± 0.66	10.20 ± 0.45	1.13 ± 0.85	28.76 ± 0.85
NT2	0.49 ± 0.56	0.54 ± 0.65	9.25 ± 0.43	1.10 ± 0.83	25.12 ± 0.83
NT3	0.42 ± 0.58	0.46 ± 0.62	8.69 ± 0.41	1.09 ± 0.58	24.23 ± 0.81
NT4	0.43 ± 0.61	0.48± 0.58	8.5± 0.42	1.01 ± 0.64	26.58± 0.78

3.4.2 Evaluation parameters of nanopsonges incorporated tablets

Table 9: Results of nanopsonges incorporated tablets.

Formations	Weight variation (300 ± 5%)	Hardness test	Thickness	Friability (%)	Drug content
NT1	302 ± 1.8%	3.45 ± 0.5	4.5 ± 0.8	0.18	95.12 ± 0.09

NT2	299 ± 1.7%	3.9 ± 0.3	4.3 ± 0.7	0.16	94.32 ± 0.67
NT3	300 ± 1.9%	3.2 ± 0.7	4.4 ± 0.4	0.12	96.52 ± 0.84
NT4	299 ± 0.8%	2.4 ± 1.2	4.5 ± 0.2	0.16	95.4 ± 0.32

3.5In-vitro drug release study

The *in-vitro* drug release profile of tofacitinib nanosponge-incorporated tablets was evaluated for four different formulations (NT1 to NT4) over a 12-hour period. The cumulative percentage drug release data reveals a sustained and progressive release pattern across all formulations.

Table 10: Results of % drug release study of NT1 to NT4.

Time in (hr.)	Formulation Codes			
	NT1	NT2	NT3	NT4
0	0	0	0	0
1	15.6	14.2	17.6	16.3
2	22.8	23.4	24.87	21.98
3	24.2	25.2	28.01	24.4
4	30.4	31.23	32.6	30.9
5	43.21	45.7	47.92	44.6
6	52.8	53.8	55.34	52.12
7	59.78	62.3	65.98	61.76
8	74.22	68.4	70.43	66.4
9	72.0	74.3	76.10	71.3
10	78.9	80.3	82.43	78.9
11	84.32	86.4	88.56	85.2
12	86.12	88.2	90.12	87.12

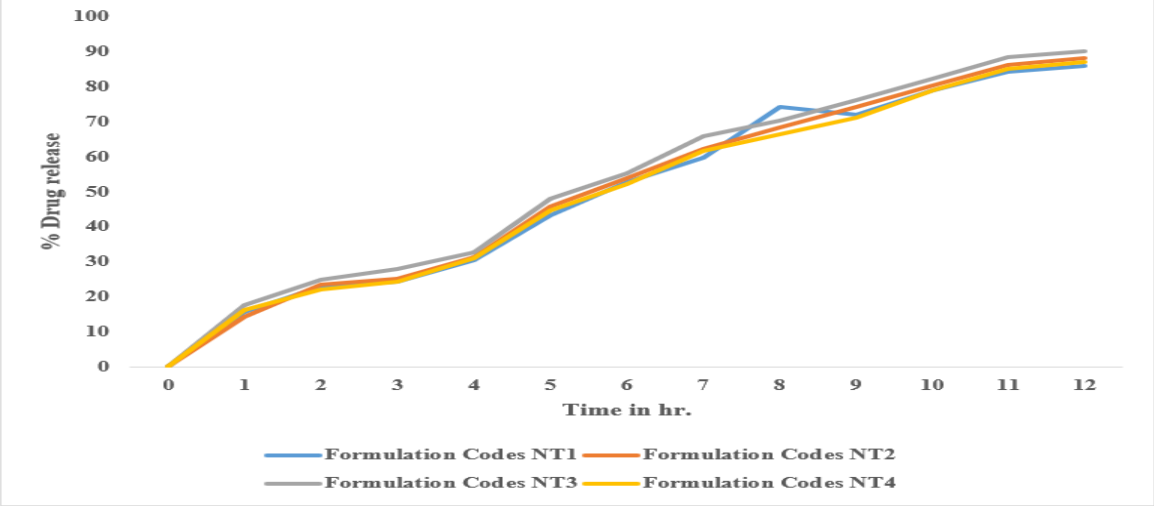

Figure 9: % drug release study of nanopsonges incorporated tablet of NT1 to NT 4 formulations.

4. CONCLUSION

The following conclusions were drawn based on the findings mentioned in "Results & Discussion" part of the present study.

The present study successfully demonstrated the formulation and evaluation of tofacitinib-loaded nanosponges incorporated into oral tablets, aiming to overcome challenges associated with poor solubility, limited bioavailability, and instability in conventional dosage forms. Among the twelve nanosponge batches, formulation T3 emerged as the optimized formulation based on its smallest particle size (127.4 nm), low polydispersity index (0.303), high zeta potential (-25.4 mV), and maximum entrapment efficiency (88.43%), indicating a stable and efficient drug delivery system. The optimized nanosponge was further compressed into tablets and evaluated for various pre- and post-compression parameters.

Pre-compression results such as bulk density, tapped density, Carr's index (8.5%–10.2%), and Hausner's ratio (1.01–1.13) revealed excellent flow properties, while post-compression analysis confirmed acceptable weight variation, sufficient hardness, low friability (<0.2%), and high drug content (94.32%–96.52%). The in vitro drug release study showed that NT3 tablets offered the most sustained and controlled drug release, achieving 90.12% cumulative release over 12 hours, which is attributed to the optimized polymer-drug ratio and nanosponge matrix structure.

Overall, the nanosponge-based tablet formulation of tofacitinib exhibited promising potential for improved oral delivery with enhanced therapeutic efficacy and patient compliance. This innovative delivery system lays the groundwork for further in vivo studies and potential clinical translation in the management of autoimmune disorders.

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