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Review Article

Tofacitinib Citrate Delivery Through Pharmaceutical Formulations For Divergent Therapeutic Treatments

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ABSTRACT

The aim of article is to provide prompt and brief information on all available types of formulations of tofacitinib citrate. Tofacitinib in the form of tofacitinib citrate belongs to a new class of therapies called Janus kinase (JAK) inhibitors. Tofacitinib citrate is a medication used to treat rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. Tofacitinib is available in the form of a tablet, an extended-release tablet and as an oral solution. Janus kinase inhibitors (JAKi) belong to a new class of oral targeted disease-modifying drugs which have recently revolutionized the therapeutic panorama of rheumatoid arthritis (RA) and other immune-mediated diseases, placing alongside or even replacing conventional and biological drugs. This article elaborates on the information related to patents of tofacitinib citrate for its formulation. A survey data for the marketed formulations of tofacitinib citrate is tabulated. Based on this it is estimated that very less type of formulations pertaining to conventional formulations as tablet or gel is only available in the market. Hence, there is an immediate demand for different type of tofacitinib formulations needed for treatment of extensive cases of arthritis or vitiligo. An extensive literature survey is done on pharmaceutical formulations of tofacitinib citrate. Based on obtained data it was found these researched and developed formulations can be focused and further initiations can be done to make these formulations marketable. Wholesome, this article assists the reader to quickly grab information on marketed formulations and researched formulations of tofacitinib citrate.

Keywords: Tofacitinib citrate, Janus kinase inhibitors, Rheumatoid arthritis, Psoriatic arthritis, Ulcerative colitis, Vitiligo.

INTRODUCTION

Janus kinase inhibitors (JAKi) represent a new class of oral drugs counteracting the activation of JAKs, which are cytosolic enzymes presiding over many biologic functions, including the activation of the inflammatory cascade in immune cells. Due to their central role in the immune response and their association with several cytokine receptors, the inhibition of JAKs appeared to be a promising strategy in autoimmune diseases. To date, some oral JAKi have already been licensed for the treatment of rheumatoid arthritis and other immune-mediated diseases such as tofacitinib, baricitinib, upadacitinib, peficitinib, filgotinib, ruxolitinib, etc. [1].

Tofacitinib is food and drug administration (FDA) approved for the treatment of moderate to severe rheumatoid arthritis (RA), psoriatic arthritis (PA), and ankylosing spondylitis, ulcerative colitis (UC), polyarticular course juvenile idiopathic arthritis (pcJIA). It is also employed for the treatment of ulcerative colitis, vitiligo, psoriasis, alopecia areata, atopic dermatitis, lichen planus, and lupus erythematosus [2-6]. It is a second-generation selective Janus kinase (JAK) inhibitor targeting the JAK1 enzyme. Pubchem directory indicates molecular formula of tofacitinib citrate is $C_{22}H_{28}N_6O_8$ and molecular weight is 504.5 g/mol. Chemical name of tofacitinib citrate is 2-hydroxypropane-1,2,3-tricarboxylic acid;3-[(3*R*,4*R*)-4-methyl-3-[methyl(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile.

The chemical structure of Tofacitinib citrate is represented in Fig. 1. Clinical Pharmacology indicates tofacitinib is an orally bioavailable, small-molecule inhibitor of the JAK family, JAK1, JAK2, JAK3, and Tyk2, that competitively binds the active site of the adenosine triphosphate kinase domain, resulting in the prevention of phosphorylation and subsequent activation of the signal transducers and activators of transcription (STATs) [7]. The intracellular Janus kinases natural role is to phosphorylate the signal transducers and activators of transcription (STATs) enzymes which further influence gene expression and impact hematopoiesis and immune cell function. The JAK-STAT signaling pathway plays a major role in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis. Similar to other JAK inhibitors, tofacitinib blocks the phosphorylation and intracellular activation of signal transducers and activators of transcription, further diminishing their inflammatory effects (Fig. 2). JAKi are characterized by a novel mechanism of action, consisting of the intracellular interruption of the JAK-STAT pathway crucially involved in the immune response [8]. Anna *et al.* presented a summary

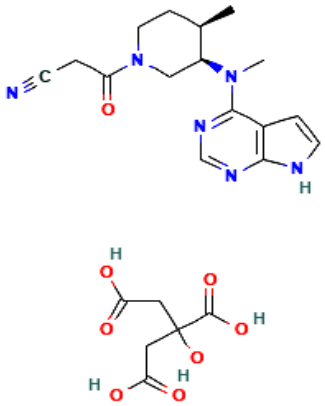

Fig. 1: Chemical structure of tofacitinib citrate

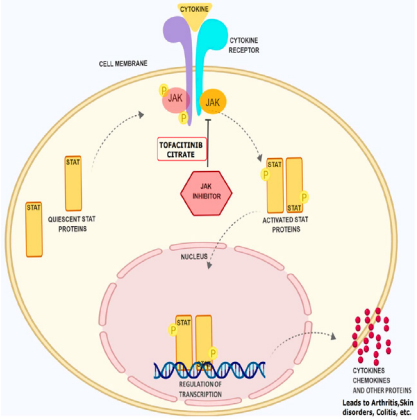

Fig. 2: Mechanism of action of tofacitinib citrate [2]

on clinical investigations of topical JAK inhibitors in dermatology [9]. William *et al.* showcased the information based on the efficiency of JAK inhibitors as topic delivery in various diseases based on proven clinical information [10]. Chovatiya *et al.* briefed on JAK inhibitors in the treatment of atopic dermatitis [11, 12].

Tofacitinib citrate is approved for medical use in the United States with an indication "to treat adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate." The FDA approved tofacitinib citrate for the treatment of adult patients in the U.S. with moderately to severely active ulcerative colitis [13].

Tofacitinib Citrate Patented Formulation

Tofacitinib is being developed as an immediate oral release tablet form with doses ranging from 5 mg to 10 mg. Tofacitinib, as the citrate salt of tofacitinib, is approved in the US under the brand XELJANZ. Approved 5 and 10 mg tofacitinib citrate tablets - XELJANZ and 11 mg tofacitinib citrate extended release tablets- XELJANZ XR through oral administration. Employed for treatment of rheumatoid arthritis as monotherapy, in combination with methotrexate for psoriatic arthritis, and for ulcerative colitis.

EP patent

Oral sustained release compositions of tofacitinib for the treatment of anti-inflammatory and auto-immune diseases, and especially Rheumatoid Arthritis. sustained release dosage form (10 to 22 mg), and when added to a test medium comprising 900 mL of 0.05M pH 6.8 potassium phosphate buffer at 37°C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, dissolves not more than 30% of the drug in 1-hour, and not less than 35% and not more than 75% of the drug in 2.5 hours and not less than 75% of the tofacitinib in 5 hours [14,15].

Table 1: Marketed formulations of tofacitinib citrate

Brand name	*Formulation*	*Dose*	*Company name*
XELJANZ	Tablets	5 and 10 mg	Pfizer
XELJANZ XR	Extended release tablets	5 and 11 mg	Pfizer
XELJANZ	Oral solution (Recently approved)	1 mg/mL	Pfizer
TOFAJAK	Tablets	5 mg	Cipla Ltd
BETRECEP	Film coated tablets	5 mg	Pfizer
JAKNAT	Tablets	5 mg	Manufactured by MSN Laboratories Pvt. Ltd. Marketed by Natco Pharma Ltd
TOFASIG	Tablets	5 mg	Signature Phytochemical Industries
TNIB	Tablets	5 mg	Microlabs Limited
TOFADOZ	Tablets	5 mg	MSN Laboratories Pvt. Ltd.
TFCT-NIB	Tablets	5 mg	Manufactured by MSN Laboratories Pvt. Ltd. Marketed by Ipca Laboratories Ltd.
TOFATAS	Ointment	2% W/W, 10 mg	Intas Pharmaceuticals Limited
TOFANAC	Gel	2% W/W	Cynak Life Sciences
Tcitib	Gel	2% W/W	Sky Impex
TOFARUS	Gel	2% W/W	Cyrus Remedies

Table 2: Evaluation observations of tofacitinib citrate-mouth dissolving tablets

S. No	*Parameter*	*Observation*
1.	Thickness	2.02 ± 0.13 to 2.313 ± 0.45 mm
2.	Hardness	2.24 ± 0.01 to 2.67 ± 0.005 kg/cm^2
3.	Friability	Less than 1% w/w
4.	Disintegration time (in sec)	F1 = 59.6 ; F2 = 51 ; F3 = 44 ; F4 = 46.5 ; F5 = 45.7; F6 = 41.25 ; F7 = 40.; F8 = 37 ; F9 = 29.75
5.	Wetting time (in sec)	F1 = 56.08; F2 = 50.74 ; F3 = 43.68; F4 = 45.47; F5 = 44.32; F6 = 37.32; F7 = 40.92; F8 = 29.61; F9 = 27.89
6.	In-vitro drug release	F1 to F9 Almost 100 percent of drug release within 75 min. Cumulative %Drug release F1 = 84.7320% in 75 minutes. F2 = 95.8531% in 75 minutes. F3 = 101.9082% in 75 minutes. F4 = 96.71 % in 75 minutes. F5 = 100% in 75 minutes. F6 = 106% in 75 minutes. F7 = 91.87% in 60 minutes. F8 = 99.84% in 60 minutes. F9 = 100% in 30 minutes.
7.	Stability	Passed at varying temperature and humidity upto 90 days. Dissolution profiles were matched.

Table 3: Evaluation observations of tofacitinib citrate - floating tablets

S. No	*Parameter*	*Observation Range for F1–F19*
1.	Weight variation	Passed, 298–302 ± 1.4–1.8 mg
2.	Hardness	Passed
3.	Thickness	Passed
4.	Tablet friability	All less than 1%
5.	Drug content	99.4–100.4%
6.	In vitro buoyancy studies	Floating time within 1 minute. upto 12 hours.
7.	Swelling index	Good swelling capacity
8.	In Vitro Dissolution Studies	F1-F5 does not give release up to 12 hours and release observed up to 8 hr only. F6-F10 give the sustained effect up to 10 hours. F11-F19 gives release up to 12 hours. Finally batch F18 (combination of 2 polymers-50 mg Carbopol 934 and 50 mg Polyox N-60k) gives maximum %drug release 99.7% in 12 hours.
9.	Drug Release Kinetic Study	R^2 value Zero order model = 0.932 First order model = 0.730 Higuchi model = 0.984 Korsmeyer-Peppas model = 0.527 Hixon Crowell model = 0.910
10.	Stability Study	Formulation F18 found to be stable at 40°C/75% RH condition

Tofacitinib Citrate Marketed Formulations

Though this drug is approved by FDA and few other countries, but still under processing for approval in other countries. Very less formulations are available in the market manufactured by one to three countries as tabulated below under Table 1. Based on obtained from Google surfing it is found that these available tablet formulations are mostly only for treatment of rheumatoid arthritis and other type of arthritis. XELJANZ oral solution is a recently approved formulation administered to juvenile patients. Topical gel or ointment employed for treatment of arthritis or vitiligo or psoriasis or alopecia areata or atopic dermatitis. Overall based on these marketed formulations, it was found that very few formulations are manufactured. Common side effects include diarrhea, headache, and high blood pressure. Serious side effects may include infections, cancer, and pulmonary embolism.

Tofacitinib Citrate Formulations Developed Through Research

Mouth dissolving tablets

Meghana *et al.* designed, developed and evaluated mouth dissolving tablets of tofacitinib citrate (dose = 5 mg). Pre-compression studies were done and reported. Tablets were prepared by direct compression method. Ludiflash mixture (90% w/w of mannitol, 5% w/w of

Table 4: Evaluation observations of tofacitinib citrate – effervescent floating tablets

S. No	*Parameter*	*Observation*
1.	Hardness	~3 kg/cm^2
2.	%Friability	0.166–0.610% from F1–F9
3.	Swelling index	42.25–48.45% from F1–F9
4.	Weight variation	Passed
5.	Floating capacity	Within one minute total floating time was more than 12 hours
6.	*In-vitro* disintegration time	~ within 15 minutes
7.	Drug content	~ 88–95 % (from F1 to F9)
8.	*In-vitro* drug release	F3 showed 96.35% release in 12 hours
9.	Drug release kinetic study	F1-F9 formulation followed the Korsmeyer-Peppas model
10.	Stability study	40 ± 2°C for 3 months of F3 found to be passed.

Table 5: Evaluation observations of tofacitinib citrate – controlled release matrix tablets

S.No	*Parameter*	*Observation*
1.	Hardness	6–8KP
2.	Friability	Less than 1%
3.	Weight variation	Passed
4.	Drug release	Upto 98% in 8 hours.

Table 6: Evaluation observations of tofacitinib citrate - colon targeting tablet

S.No	*Parameter*	*Observation*
1.	Hardness	4 Kp
2.	Friability	Less than 1%
3.	Weight Variation	Passed
4.	Content uniformity	98–99%
5.	Drug release	Upto 2 hours. 0.1 N HCl, at 3 hours. Ph 6.4 phosphate buffer and from 4th hours. to 9 hours. Ph 7.2 phosphate buffer. The %DR varied from 17.3–73.0% hours 85.6–96.4% after 6 h. F10 showed drug release in extended period over 6 hours, less than 50% drug release after 3 hours and comparatively maximum drug release after 6 hours. Thus, batch F10 (16.25 mg drug, 48.75 mg Lactose, 20 mg microcrystalline cellulose, 2 mg hydroxy propyl cellulose-L, 11 mg Sodium CMC, 2mg magnesium stearate) was considered as the optimum batch for enteric coating.
6.	Stability study	Passed. Performed for the final formulation at 40 ± 2°C/75 ± 5% RH for 3 months

Table 7: Evaluation observations of tofacitinib citrate - microneedles

S. No	*Parameter*	*Observation*
1.	The insertion test of microneedles *in-vitro*	Microneedle tips have successfully inserted into the stratum corneum of the skin and reached the dermis.
2.	The drug loading capacity	The drug content of the microneedle tips was highest in eight groups. However, when the added amount surpassed 6 mg, the drug load on the microneedle tip decreased. When the drug dosage on the microneedle tips is 6 mg, the 24 h average cumulative permeation amount per unit area is highest in four groups. Therefore, the dosage of tofacitinib was set at 6 mg. The skin penetration of the group 8 mg was minimum among the four groups.
3.	Microneedle dissolution test *in-vivo* and *in-vitro*	Microneedle tips dissolved completely within 25 seconds in an *in-vitro* dissolution experiment, within 2.5 minutes in an *in-vivo* dissolution experiment and can dissolve rapidly after being inserted into the skin. After 2.5 minutes, the tips of the microneedle can be completely dissolved.
4.	Establishment of RA model in SD rats and evaluation of treatment	Degree of joint swelling in the microneedle group was significantly less than that in the model group
5.	Pathological sections of rat skin	Compared with the arthritic rats in the control group, joint inflammation in the rats resolved faster after microneedle administration, and was totally cleared within 24 hours
6.	Pharmacokinetic experiment	The t1/2 of tofacitinib in rats in microneedle group was prolonged compared with the oral group (2.37 ± 1.70 vs. 5.33 ± 1.11 h)
7.	Western blot analysis of STAT3/p-STAT3 protein	Therapeutic effect of the microneedle was slightly better than that of oral administration

Crospovidone, and 5% w/w of polyvinyl acetate) was used. Active pharmaceutical ingredients lubricant and other ingredients were added in the above Ludiflash excipients which produce high porosity tablets. Nine formulations with varying increasing concentrations of sodium starch glycolate (SSG) were prepared and evaluated for various post-compression parameters as described in Table 2 [16].

Floating tablets

Sanjeshkumar *et al.* formulated and evaluated floating tablets of tofacitinib citrate. Pre-compression studies were done and reported. Tablets were prepared using hydroxy propylene methyl cellulose (HPMC), Polyox N-60K, Carbopol 934 P and guar gum polymers. Floating tablets were based on effervescent approach using sodium bicarbonate a gas releasing agent. Direct compression method was employed for tablets. Tablet contains a total dose of 28.6 mg for 12 hours. Sustained release dosage form and it should release 5 mg initial dose in 1st hour like conventional dosage form and remaining dose

Table 8: Evaluation observations of tofacitinib citrate - liposomes

S. No	*Parameter*	*Observation*
1.	Size	60 nm
2.	Drug release profile	In pH 7.4 phosphate buffered saline at 37°C. It was found that free drug was rapidly released, with over 80% of drug was released within the first 10 hours. In contrast, the percentage of drug released from liposome was less than 60% even after 48 hours.
3.	Viability of the cell culture	Done by MTT assay.The cell viabilities were >80% when the cells incubated with free drug or drug loaded liposome at the highest concentration of 50 μg/mL, indicating that drug or drug loaded liposome was little toxic towards HUVECs.
4.	*In-vivo* therapeutic efficiency	Drug loaded liposomes significantly relieved the paw thickness and arthritic joint scores compared to control and placebo.
5.	Pro-inflammatory cytokine expression joint tissue after therapy	Liposomes had greater anti-inflammatory activity than free drug or phosphate buffer saline.
6.	Histopathology of the ankle joints after therapy	The knee joints from drug loaded liposomes treated groups exhibited a clear interface and showed significant reduction of pathologic features, including synovial hyperplasia, lipid peroxidation in synovial cells, pannus formation, and bone erosion

will be release in remaining 11 hours. The formulation containing Polyox N-60K and Carbopol 934 P in combination was optimized as it showed drug release up to 12 hours. In 19 formulations were prepared and evaluated optimized formulation F18 was found stable during stability condition up to 1-month [17]. The results for evaluation of tablets are listed in Table 3.

Effervescent Floating Tablet as Antirheumatic Agent

Maniyar *et al.* formulated and evaluated effervescent floating tablets of Tofacitinib citrate (Dose – 20 mg). Pre-compression studies were done and reported. Compatibility studies were done and reported. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, and Carbopol 934. 9 formulations were prepared and evaluated [18]. The pre-compression evaluation parameters results are tabulated in Table 4.

Controlled Release Matrix Tablets

Satyabrata *et al*. formulated controlled release matrix tablets of tofacitinib citrate (Dose = 11 mg tofacitinib) and evaluated by QbD approach. It was formulated by employing with polyethylene oxide, hypromellose in core tablets and ethyl cellulose, hydroxy propyl cellulose in coating composition. Solid state characterization was determined by X-ray diffraction study. The formulation was manufactured with wet granulation technique with high shear rapid mixture granulator and non-aqueous solvent was used as granulating fluid. A total of 9 formulations were prepared with varying amounts of excipients. QbD approach was applied and results also evaluated by Qbd approach [19]. The post-compression tablets were evaluated and brief results are tabulated in Table 5.

Colon Targeting Tablet for Treatment of Chronic Ulcerative Colitis

Vakar *et al.* formulated and evaluated extended release matrix tablet of tofacitinib citrate (Dose = 16.25 mg). Pre-formulation studies were performed. Drug-excipient compatibility study also was performed.

Table 9: Evaluation observations of tofacitinib citrate - squalenyl nanoparticles

S. No	*Parameter*	*Observation*
1.	Size, polydispersity index (PDI), zeta-potential, and pH value determination	Size = 240 nm PDI = 0.21 Zeta potential = -59.9 pH = 6.31
2.	Quantification of drug loading capacity and encapsulation efficiency	Loading capacity = 20.1 Encapsulation efficiency = 19.8
3.	*In-vitro* release study	Burst release of drug of around 40% in the first 0.25 hours followed by a continuous slow release of drug until complete.
4.	*Ex-vivo* and *In-vivo* Performance	
	Targeted follicular transport of tofacitinib in a pig ear model The therapeutic efficacy of	Results clearly demonstrated that the follicular transport was the major route for drug penetration compared to the interfollicular route. The ability of nanoparticles of tofacitinib to deliver TFB to the follicular skin was found to be good, i.e.,30.06 ± 8.32 ng/0.785 mm^2
	Tofacitinib in an allergic dermatitis mouse model	Tofacitinib loaded nanoparticles were able to reduce the ear selling by around 20% compared to drug free nanoparticles i.e, 76.20 ±5.54 μm.
5.	Stability	Exhibited good colloidal stability at storage conditions over 24 days. No visual changes were observed over the 24 days

New colonic drug delivery system for tofacitinib using combined approaches of formulating an extended release matrix tablet along with a pH sensitive polymer coating of Eudragit® S100. The core tablets of tofacitinib were prepared by wet granulation method containing

Table 10: Evaluation observations of tofacitinib citrate – hydrogel microparticles

S. No	*Parameter*	*Observation*
1.	Physical appearance	When the amount of chitosan (0.2–0.4 g) was increased, milky colored Hydrogels with soft rubbery texture were acquired. Moreover, with the increase in quantities of mucin (0.1–0.3 g) while all the other ingredients being constant (chitosan, MAA, MBA), hydrogels with light yellowish color were attained with pronounced integrity. Furthermore, by increasing the amount of MBA (0.3–0.7 g), Hydrogels with rigid texture were obtained. Likewise, there was no apparent change in color.
2.	Elemental analysis	EDX spectrum proved presence of the drug within the network from the existence of a nitrogen peak in the case of the drug-loaded hydrogel microparticles
3.	Differential scanning calorimetry and thermogravimetric analysis	The DSC thermogram of the formulation indicated heat absorption at 223.49°C, reflecting a lack of moisture content. In the TGA thermogram, initial mass loss was at 63.93°C due to the evaporation of water. Heating at elevated temperature, i.e., 293.54°C resulted in weight loss of 28.05%. It was observed that even at a temperature higher than 400°C, 45% mass of the polymeric network remained intact. Hence, the developed network was more stable
4.	X-ray diffraction analysis	Drug loaded hydrogel presented no characteristic peaks, which were evident in the diffractograms of tofacitinib at 2q = 7.54°, 21.37°, 25.64°, 31.47°, and 35.95. This concluded the change in crystallinity of the drug into an amorphous form and the incorporation of tofacitinib within the microparticles.
5.	Scanning electron microscopy	Polymeric matrix showed a glossy, highly porous, slightly cracked and moderately wavy structure. The presence of whitish spots confirms the loading of tofacitinib.
6.	Drug loading %	When the concentration of N, N'-methylenebisacrylamide was increased drug loading % declined. When the concentration of methacrylic acid was increased drug loading %increased.
7.	Equilibrium swelling studies (%)	A negligible swelling rate i.e., less than 15% was observed in pH 1.2 phosphate buffer., where as in pH 7.4 phosphate buffer profound swelling was noticed.
8.	*In-vitro* dissolution studies and release kinetics	Minimum drug release, i.e., less than 20%, was observed at pH 1.2, while there was increased drug release at pH 7.4. Drug release (%) was increased (79.88–92.31%) in formulations F1 to F3. Drug release (%) was promoted (76.92–82.63%) in formulations F4 to F6. Drug release (%) was enhanced (78–90 %) in formulations F7 to F9. The value of 'n' obtained from Korsemeyer–Peppas suggested that the drug followed super case II transport.
9.	Sol–Gel fraction	Sol fraction was reduced while an increase in gel fraction was noticed. All formulations exhibited gel fraction (%) higher than 70%, demonstrating the cross linked polymeric network's successful formation.
10.	Hydrogel microparticles size and zeta potential determination	The size of the formulated polymeric microparticles was 85 μm. Zeta potential value is was -40 mV
11.	Permeation studies	Coated microparticles depicted increased drug diffusion (83.44%) as compared to uncoated formulation (65.34%) and pure drug solution (21.56%).
12.	Anti-inflammatory studies	Formulations A and B presented a dose-dependent decrease in paw volume.
13.	Oral toxicity studies	Clinical manifestations, blood analysis and histopathological studies were done. No mortality or sign of toxicity was observed in treated groups of rabbits after oral administration of microparticles. Moreover, no physical change was seen in control as well as treated group during the 14-day observation period.

sodium carboxy methyl cellulose (CMC) as rate controlling polymer. Other excipients involved microcrystalline cellulose, hydroxyl propyl cellulose-L, lactose, magnesium stearate, isopropyl alcohol, triethyl citrate, and talc. A total of 10 formulations were prepared. Formulation variables used in the matrix system and pH dependent coating were optimized. The post-compression tablets were evaluated and brief results are tabulated in Table 6. It has been observed that the combination of 11% sodium CMC with 20% MCC in the matrix tablets have extended the drug release up to 6 hours. The core F10 batch has been selected for the coating using 10% w/w solid content dispersion of Eudragit® S100. Coating has been performed at 30°C bed temperature and 13% weight buildup has been observed to be sufficient to get 3 to 4 hours lag time [20].

Microneedles for Treatment of Arthritis

Xiumei *et al.* prepared and evaluated tofacitinib citrate microneedles (Each contains 1-mg of tofacitinib citrate, drug testing dose 5–8 mg). Poly vinyl pyrrolidone vinyl acetate (PVPAc): 50% ethanol solution (7:3% w/w) was utilized to prepare microneedles containing tofacitinib citrate. Material component of microneedle tips contains varying concentrations of copolymer PVPAc solution and PVP-K90. Comparison of the NSAIDs ketoprofen and different dosage with these microneedles also was done [21]. Evaluation was done on certain parameters as mentioned in Table 7.

Liposomes for Treatment of Arthritis

Qiying *et al.* loaded Tofacitinib citrate into liposomes. Tofacitinib citrate was effectively loaded into the liposomes (entrapment efficiency:

Table 11: Evaluation observations of tofacitinib citrate – transferosomal gel

S. No	*Parameter*	*Observation*
1.	Homogeneity	Homogenous
2.	pH	6.6–7.0
3.	Grittiness	No grittiness
4.	Spreadability Test	1.83–3.24 gm.cm/sec.
5.	Extrudability Test	6.2–7.7
6.	Viscosity	424–610
7.	Transmission and scanning Electron Microscopy Studies	Tem depicts vesicles formed are nano-sized and unilamellar in nature. The vesicles are smaller unilamellar vesicles with a more uniform size distribution. The scanning electron micrograph seems spherical and smooth.
8.	Drug Content	83–92 %
9.	*In-vitro* Release Study	The percent cumulative drug release of optimized transferosomes, pure drug suspension, and marketed product dispersion in 24 hours was 61.20, 70.42, and 74.34 respectively. Formulation represented a burst release phase, with about 10–15% observed within 2 hours due to drug desorption and release from the transferosomes surface. However, the release of medication from optimized transferosomes was delayed beyond two hours, indicating a persistent release pattern.
10.	*Ex-Vivo* permeation study	The percent drug retention of the transferosomal gel loaded drug formulation after 24 hours was satisfactory in comparison to the marketed formulation.
11.	Stability Study	Negligible increase in particle size from 118.30.522–120.553.86 during the storage conditions (4 and 25°C). The optimized transferosomes initial % Entrapment efficiency was found to be 84.24 0.38 %. It was discovered that after 6 months of storage at 4 and 25°C, it was 81.050.625 and 79.240.45%, respectively. For six months, the optimized formulation was shown to be stable at 4 and 25°C temperatures.

86.5}1.9%; drug loading: 2.3}0.05%) by a pH gradient method, and these molecules featured sustained drug release behaviour over 48 hours. Physico-chemical characterization was done. Intracellular accumulation of liposomes and biodistribution analyses in rheumatoid arthritis rats was also done [22]. Formulated drug loaded liposomes were evaluated as tabulated in Table 8.

Squalenyl Nanoparticles for Treatment in Inflammatory Skin Diseases

Rebekka *et al.* synthesized tofacitinib loaded squalenyl nanoparticles. Formulated free base tofacitinib and anionic squalenyl derivative (SqD)—Squalenyl hydrogen sulphate by solvent evaporation technique. Final tofacitinib loaded squalenyl nanoparticles possess concentration of 5.5 mg/mL, which contained an equivalent tofacitinib concentration of 2 mg/mL [23]. Synthesized nanoparticles were evaluated for certain parameters as tabulated in Table 9.

Hydrogel Microparticles

Rania *et al.* formulated hydrogel loaded tofacitinib citrate. The free radical polymerization technique was employed to develop mucin/chitosan copolymer methacrylic acid (MU-CHI-Co-Poly (MAA))-based hydrogel microparticles. Hydrogel microparticles were developed using different ratios of mucin, chitosan, methacrylic acid, and N, N'-methylenebisacrylamide. FTIR analysis was done [24]. The final tofacitinib citrate hydrogel gel was evaluated for various parameters as mentioned in Table 10.

Transferosomal gel for Treatment of Skin Cancer

Gayathri *et al.* formulated tofacitinib citrate loaded transferosomal gel. Pre-formulation studies and compatibility studies were performed. Formulation done by drug encapsulation in various transferosomal formulations having 100 mg drug concentrations and Carbopol-934 (0.5, 1.2 g). First step includes synthesis of transferosomes and second step included formulation of transferosomal gel. First transferosomes were prepared using phosphatydylcholine, sodium deoxycholate, tofacitinib citrate, chloroform and the methanol by solvent evaporation technique. Total 27 transferosomes were synthesized by varying excipients concentration. These synthesized transferosomes was evaluated for vesicular size determination, zeta Potential analysis, entrapment efficiency, percentage drug content, *in-vitro* drug release studies, effect of phospholipid: surfactant ratio on entrapment efficiency and drug loading, effect of vesicle composition, effect of phospholipid and surfactant ratio on the particle size and PDI, and vesicles size and PDI. The transferosomal gel was prepared by employing Carbopol, PEG-400, Isopropyl alcohol, propylene glycol and triethanolamine. By swirling transferosomes into this gel, transferosomal gel is prepared. Tofacitinib citrate, corresponding to 100 mg medication, was added to the prepared Carbopol gel transferosomes [25]. The final tofacitinib citrate transferosomal gel was evaluated for various parameters as mentioned in Table 11.

CONCLUSION

JAK inhibitors (JAKi) are emerging as a new class of drugs, which in dermatology can either be used systemically as oral drugs or locally in topical formulations. The panorama of JAKi designed for rheumatoid arthritis and is extremely innovative and dynamic. With very limited availability of tofacitinib citrate formulations based on data collected for marketed formulations. It can be said that with rising demand for tofacitinib citrate medication due to emergence and more cases for arthritis, psoriasis, vitiligo, and ulcerative colitis. Hence there is an immediate need for development and marketing of

different type of formulations of tofacitinib citrate. Based on articles obtained, for formulations of tofacitinib citrate it can be concluded that these formulations can be accessed from researchers and can be taken for further product manufacturing and marketing. So that it would be beneficial for treatment of for arthritis, psoriasis, vitiligo, and ulcerative colitis. It can be finally concluded that the article helps the readers or scientists or researchers to have a quick and brief information on formulations of tofacitinib citrate.

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CONFLICTS OF INTEREST

We declare no conflicts of interest

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