Development of Colon Targeting Tablet of a JAK Inhibitor to Combat Chronic Ulcerative Colitis: A Novel Approach for Local Drug Delivery

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ABSTRACT

Background: Tofacitinib, a pan-Janus kinase (JAK) inhibitor, initially used for the treatment of rheumatoid arthritis, was later found to have robust efficacy in Phase 2 and Phase 3 ulcerative colitis clinical trials. It had been approved by FDA for its use in the treatment of moderate to severe ulcerative colitis, in 2018. **Objectives:** The main objective of the present work was to develop a 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. **Methods:** The core tablets of tofacitinib were prepared by wet granulation method containing sodium carboxymethyl cellulose (CMC) as rate controlling polymer. Formulation variables used in the matrix system and pH dependent coating were optimized. **Results:** Negligible drug release was obtained in 0.1 N HCl and 6.4 pH phosphate buffer media, where as in 7.2 pH phosphate buffer media, the drug release increased up to $94.2 \pm 2.0\%$. Minimum concentration of sodium CMC was 11% (w/w) to ensure 6 h's extended release of drug from the matrix tablet. While, the minimum functional coating percentage, was found to be 13% in order to obtain an adequate lag time. **Conclusion:** The study showed that, the lag time of the drug release was highly affected by the coating percentage of Eudragit S 100 and product temperature during coating. After the lag time, extended drug release was observed, and rate of drug release was found to be depended on the concentrations of sodium CMC used in the core tablet. The final colon targeted formulation showed no change in either its physical appearance, drug content or in dissolution pattern even after three months of storage at $40 \pm 2°C/75 \pm 5\%$ RH.

Key words: Colon targeted matrix tablet, Controlled release, Lag period, Ulcerative colitis, Tofacitinib, JAK inhibitor, Immunosuppressant.

INTRODUCTION

Ulcerative Colitis (UC) is a chronic idiopathic inflammatory bowel disease characterized by chronic gastrointestinal inflammation that can affect any part of colon, but commonly rectum. Moreover, sometimes the inflammation further extends towards the proximal part of colon in contiguous fashion. Bloody diarrhea, urgency and tenesmus are the most noticed symptoms of ulcerative colitis. The etiology of ulcerative colitis is complex; the exact reason of its cause is still not clear; however, it is contemplated to be associated with host epigenetic, genetic, dysregulation of immune system and other environmental factors.[1-4] There has been a dramatic increase in inflammatory bowel diseases over the past several years and approximately one third of the patients of ulcerative colitis have to undergo operative treatments. If the patients of ulcerative colitis are not diagnosed and treated timely, the risk of development of colorectal cancer increases.[1-4]

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Colon targeted drug delivery trough oral route is gaining high importance, because it is used either to treat the local diseases of colon such as ulcerative colitis, Crohn's disease, colorectal cancer and so on, or for the delivery of drugs that degrade in upper GIT, e.g., proteins and peptides.[5] Various approaches have been used for colon targeted drug delivery through oral route, which include pH, time, microbial degradation dependent drug deliveries, prodrug approaches and others.[6] The problems associated with solely time or pH dependent drug delivery system are that sometime they show premature drug release or release of drug at inaccurate site(s) that can be overcome by using hybrid techniques. Combination of time dependent and pH dependent approaches can result in development of such a formulation that can prevent the drug release in upper gastrointestinal tract guaranteeing complete sustained drug release to colon after administrating matrix tablets through oral route.[7] There are large numbers of polymers that can be used in the preparation of matrix tablets, such as sodium CMC, hydroxyl propyl methyl cellulose, and polyethylene glycol and many others. Selection of polymers depends on the physiochemical properties of the drug.[8]

Conventionally available treatments for ulcerative colitis use cyclosporine, 5-aminosalisalic acid, immunomodulators, glucocorticoids and mesalamine. These agents have been neither effective, nor safe, because some of these are associated with serious and toxic side effects like osteoporosis, muscle wasting, neuropsychiatric disorders and others.[9] Other better options, such as tumor necrosis factor (TNF-α) inhibitors, have high safety and long term efficacy data, but the main drawbacks established with these biologicals are loss of responses due to the formation of antibody and the high cost associated with long term therapy (add reference). Reportedly, 33% patients are unable to respond to TNF blockers and another one third of the patients have been reported with loss of response over time.[10,11] Consequently, a new, most efficient, long lasting and safe option is a need of the day for the treatment of ulcerative colitis which will target the Janus kinases (JAK) / signal transducer and transcription (JAK / STAT) signaling pathways. Thus, the oral application of the colon targeted drug delivery system containing the pan-JAK inhibitor, tofacitinib, will meet most of the criteria required so far to fulfill the requirement for effective treatment of UC. Tofacitinib has been approved by FDA in 2018 to treat moderate to severely active UC. In various clinical studies, patients suffering from moderate to severely active UC, have been treated with this small molecule, tofacitinib, as reported in the phase 2 clinical trials data by Sandborn *et al*. and Feagan.[12,13]

The objective of the research work was the development of colon targeted matrix tablet of tofacitinib intended for delivery of drug specifically to the colon, by appropriately combining the use of rate controlling polymer sodium CMC in core with a pH sensitive coating of Eudragit® S100 and to optimize the matrix formulation and process parameters of coating. The rate of drug release was controlled to reduce the dosing frequency, to prevent dose dumping and to demonstrate its site specificity. pH dependent solubility of tofacitinib led to variation in drug release *in vivo* from the conventional tofacitinib tablets, because the tablets moved throughout GIT having different pH segments and showed difference in release which cause fluctuations in drug absorption from the upper GIT. Thus, functional coating of the tablet was supposed resolve this problem by protecting the exposure of core tablet to different pH segments of the GIT. Site specific delivery of tofacitinib to the affected area would also improve the pharmacological and therapeutic responses. Tofacitinib had shown immunosuppressant activity upon systemic exposure; hence, various side effects were observed upon systemic exposure during clinical trials. However, the proposed novel formulation would provide localized colonic delivery of tofacitinib and thereby, would avoid systemic side effects.

MATERIALS AND METHODS

Materials

All the ingredients necessary for the study, namely, tofacitinib citrate, microcrystalline cellulose 101, lactose, hydroxypropyl cellulose-L, sodium carboxymethyl cellulose, magnesium stearate, Eudragit® S100, triethyl citrate, talc, isopropyl alcohol and simethicone USP (100%) had been gifted by Sun Pharmaceutical Industries Limited, Gurugram, India, All other reagents and solvents used, were of analytical grades and pharmacopoeial standards. JMP-SAS™ version 14 was used for the design of experiments and data analysis.

Methods

Preparation of calibration curve of tofacitinib citrate

The stock solution (100 µg/mL) of tofacitinib citrate was prepared in 0.1 N HCl and sonicated for 10 min. Using the stock solution, serial dilutions of different concentrations were prepared to get 5, 10, 15, 20, 25 µg/mL concentrations. The absorbance of prepared dilutions against blank was measured at 289 nm using UV spectrophotometer and to validate the data obtained, the preparation of the calibration curve was performed

in triplicate. The same procedure was followed for preparation of calibration curves in pH 6.4 and pH 7.2 phosphate buffer solutions and in distilled water. The absorbance of prepared dilutions against blank was measured at 287 nm, 287 nm and 288 nm in pH 6.4 phosphate buffer solution, pH 7.2 phosphate buffer solutions and distilled water, respectively.[14]

Pre-formulation studies

The following properties were evaluated during the pre-formulation studies:

Physical characterization

Physical properties of tofacitinib citrate were evaluated on its appearance, color, odor, melting point, solubility and drug identification.

Drug and excipients compatibility study

Physical compatibility of the drug with other excipients was tested in order to identify if there was any drug-excipients incompatibility. Drug alone and its physical mixture (1:1) were kept for a period of four weeks at three different condition, viz, 25±2°C/60±5% RH, 40±2°C/75 ±5%RH open, 40±2°C/75±5% RH closed and observed for any change in the physical appearance. FTIR absorption spectra of pure drug and its physical mixture with other ingredients were taken at room temperature using KBr press pellet technique. Pellets were prepared by applying 5-7 tons pressure. IR spectra of tofacitinib citrate alone, tofacitinib citrate with sodium CMC and physical mixture of tofacitinib citrate with all other excipients were recorded using FTIR-500 Fourier Transform Infrared Spectroscopy (Perkin Elmer, Japan).[15]

Micromeritic properties of blends

The following micromeritic properties were studied:[16]

- **Determination of bulk density**
  Weighed quantity of the blend was transferred into a graduated cylinder to measure the volume occupied by the blend and then the bulk density of the blend was calculated using the following formula.
  Bulk density = Mass of powder / Volume of powder

- **Determination of tapped density**
  Tapped density of the blend was measured using USP type 1 apparatus. Weighed quantity of the blend was transferred into a graduated cylinder. The cylinder was fixed in tapped densitometer holder, tapped for 10, 500 and 1250 times and observed up to not more than 1 ml difference after tapping 500 and 1250 times. The tapped volume was observed after 1250 tapping and calculated the tapped density using the following formula.
  Tapped density = Mass of powder / Tapped volume

- **Carr's index**
  Carr's index or compressibility index, measuring the tendency of a blend to be compressed, was calculated using the tapped density and bulk density values using the mentioned formula.
  Carr's index = [(tapped density-bulk density) / tapped density] × 100

- **Hausner's ratio**
  Hausner's ratio is the ratio of tapped density to bulk density. It is the number that is correlated to the flow ability of a powder or granular material. It was calculated by the formula.
  Hausner's ratio = Tapped density / Bulk density

- **Angle of repose**
  Angle of repose was determined by the funnel method. A funnel was fixed in a burette stand at 2.4 cm height from the base. Then the blend was poured onto the funnel and allowed to form a pile. Surface diameter and height of the heap were measured. The same procedure was repeated three times and the average of three observations was taken and placed in the given equation to calculate the angle of repose of the blend.
  Tan (α) = height / 0.5 base

Preparation and optimization of core tablets

Controlled release matrix tablets of tofacitinib citrate were prepared according to the design generated by the software JMP™ version 14, using wet granulation method.

A full factorial design 2^3 was used to study the quantitative aspects of the effects and relationships among various formulation variables of the core tablet. Design with a total of 8 experimental runs and 2 additional center points was selected to optimize the various formulation parameters at two levels (low and high, coded as –1 and +1) as shown in Table 1. In this design microcrystalline cellulose (X1) used as disintegrate, hydroxyl propyl cellulose-L (X2) used as binder and sodium CMC (X3) used as release rate controlling polymer were taken as independent variables and their effect was studied on drug release (%) at 1 h (Y1), at 3 h (Y2) and at 6 h (Y3) which were taken as dependent variables (Table 2). Batch F9 was considered as a center point with a reproducible batch F9 rep. The dissolution response of all the batches were statistically analyzed and obtained the composition of a final core batch, described in Table 16.

All ingredients were weighed accurately and sifted separately through #30 ASTM sieve. Tofacitinib citrate, microcrystalline cellulose and lactose were co-shifted through #30 ASTM sieve and mixed for 10 min. The mixed blends were granulated using binder solution of hydroxyl propyl cellulose (HPC). The prepared granules were dried at 60°C for 2 h in a hot air oven and checked for the moisture content to be not more than 1%. These dried granules were passed through #40 ASTM sieve to get uniform sizes and mixed with sodium carboxy methyl cellulose for 10 min. Magnesium stearate was added to lubricate the blend and continue mixing for another 10 mins in the same poly bag. Flow properties of blend were determined prior to compression. Lubricated blends were compressed into tablets (Table 2) using Cadmach 16 station tablet press machine with 6 mm round concave punches. Weight variation, thickness, hardness, friability and *in vitro* dissolution studies were performed for the core tablets. Enteric coatings were performed on the optimized batch.

Preparation of coating media

Accurately weighed quantity of talc and Eudragit® S100 were shifted through ASTM 60# sieve separately. Accurately weighed quantity of isopropyl alcohol (IPA) was collected in a stainless steel container and Eudragit® S100 was slowly added to it by continuously stirring and the dispersion was continuously stirred further for 1 hr. Talc was separately dispersed in water for 30 min in high speed colloidal mill to get a homogenous dispersion and then simethicone USP (100%) was added in this dispersion to avoid foaming. The dispersion of talc was added to the dispersion of isopropyl alcohol under continuous stirring for about 30 min, followed by the addition of triethyl citrate to it to stabilize the dispersion. The prepared dispersion was passed through ASTM 60# sieve and the dispersion was kept under stirring at slow speed throughout the coating process.

Enteric coating of core tablets

Enteric coating was performed for the optimized matrix batch (f10) resulting from the design of experiment software. Coating was performed using Gansons coating machine by keeping inlet temperature at 35-40°C, outlet temperature at 30-35°C, bed temperature, 30°C, pan RPM of 10, atomization at 2 bar and spray rate of 10 g/min. Quantities of isopropyl alcohol and water were taken based on 10% w/w solid content of coating dispersion by keeping the ratio of IPA and water as 90:10. Coating was performed using the formula given in Table 3.

Optimization of coating process parameters

A 2^2 design was used to study the effects and relationships among various coating process parameter variables of the coated tablets (Tables 4, 5). The two-level factorial designs were the simplest form of orthogonal design, commonly employed for screening and factor influence

Table 1: Levels of Independent Variables for Core Tablet.

Independent Variable	High Level (+1)	Low Level (−1)
X1	30	10
X2	4	0
X3	11	5

Table 3: Composition of Coating Formula.

Ingredients	Quantity (g)
Isopropyl alcohol	810
Water	90
Eudragit® S100	70
Triethyl citrate	10
Talc	20

Table 2: Composition of Core Tablet Optimization Batches.

Batch Code	Tofacitinib Citrate (mg)	Lactose (mg)	Microcrystalline Cellulose (mg)	Hydroxy Propyl Cellulose-L (mg)	Sodium CMC (mg)	Magnesium Stearate (mg)
F1	16.25	66.75	10	0	5	2
F2	16.25	60.75	10	0	11	2
F3	16.25	46.75	30	0	5	2
F4	16.25	40.75	30	0	11	2
F5	16.25	62.75	10	4	5	2
F6	16.25	56.75	10	4	11	2
F7	16.25	42.75	30	4	5	2
F8	16.25	36.75	30	4	11	2
F9*	16.25	51.75	20	2	8	2
F9*rep	16.25	51.75	20	2	8	2

studies. The 2^2 design with a total of 4 experimental runs and 3 additional centre points was selected to optimize the various coating process parameters at two levels (low and high, coded as –1 and +1). *In vitro* drug release of all the batches were performed to study the impact of the process parameters on drug release and the final formulation for colon targeted drug delivery was selected on the basis of dissolution responses.

In this design product temperature (T) and % weight build up (W) were taken as independent variables and their effects were studied on drug release (%) at 1 h (Z1), 3 h (Z2) and 6 h (Z3), which were taken as dependent variables (Table 17).

Post-compression studies

The post compression studies on the prepared tablets included valuation of the following parameters:

Shape and appearance

Shape and appearance of the tablets were observed physically and color of the tablet was observed in sun light.

Hardness

Hardness of the tablets was tested using 8M bench top tablet hardness apparatus (Schlesinger® Pharmatron). The tablets were placed between two platens, one of which moved to apply sufficient force to the tablet to cause fracture. Loading occurred across the diameter of the tablets (sometimes referred to as diametric loading) and fracture occurred in that plane at a particular force applied, as was with conventional, round (circular cross-section) tablets; readings were recorded. The same procedure was followed for ten tablets from each batch and average values were calculated.

Table 4: Levels of Independent Variables of Coating Process Parameter.

Independent Variable	Higher Level (+1)	Lower level (−1)
Temperature	32	28
Weight build up	19	13

Table 5: Process Parameter Batches.

Batch Code	Product Temperature (°C)	% Weight Build Up
Coat f5 A	32°C	7%
Coat f5 B	32°C	19%
Coat f5 C	28°C	7%
Coat f5 D	28°C	19%
Coat f5 E*	30°C	13%
Coat f5 E*rep1	30°C	13%
Coat f5E*rep2	30°C	13%

Thickness

Crown thickness of 10 tablets from each batch using Vernier caliper was determined and calculated the average thickness.

Weight variation

Individual weights of 20 tablets from each batch were measured using electronic weighing balance and average weights were calculated. Then individual tablet weights were compared with the average weight and finally, the standard deviations were calculated. According to IP / BP, pharmacopoeial percentage weight variation limit is ±7.5% for 80-250 mg tablet weights.[17]

Friability

Friability test was performed using Roche friabilator according to USP guidelines. Accurately weighed 6.5g tablets were placed in the drum, it was rotated 100 times and then the tablets were collected. After removal of the loose dust, if any, the tablets were accurately reweighed and then friability was calculated in terms of % weight loss using the formula.

Friability = [(Initial weight-Final weight)/Initial weight] × 100

In general, a maximum weight loss not more than 1% is acceptable.[18]

Content uniformity

Drug content uniformity was evaluated for each batch of tablets. From each batch, five tablets were weighed and powdered. Accurately weighed powder equivalent to 16.25 mg tofacitinib citrate were taken in a 100 ml volumetric flask, dissolved in 0.1N HCl and sonicated for 20 min. Then the solution was filtered and aliquots of the filtrate were diluted and analyzed using UV spectrophotometer at 289 nm against the blank. The same procedure was repeated in triplicate and the average value was calculated.[19]

In vitro dissolution studies

In vitro dissolution study was performed using dissolution apparatus USP-Type 2 at 37±0.5°C with stirring rate of 100 rpm. To mimic the transition time from mouth to colon, dissolution for coated tablets was performed in sequential media, initially 2 h in 750 mL of 0.1N HCl, then for 1 h in 950 ml of pH 6.4 phosphate buffer (stage 1) and finally, for 6 h in 960 mL of pH 7.2 phosphate buffer (stage 2). 10 mL of aliquot was withdrawn at predetermined time point and replaced the volume with fresh media. The samples were analyzed at 289 nm in acidic media and 287 nm in basic media by a UV spectrophotometer (UV-1800 Shimadzu

Spectrophotometer, Japan) and the amount of drug present in the samples were calculated.[20]

Stability studies

Stability studies were performed for the final formulation at $40\pm2°C/75\pm5\%$ RH for 3 months and the tablets were evaluated for change in appearance, thickness, hardness, weight, assay and *in vitro* drug release.[6,21]

RESULTS AND DISCUSSION

Linear equations of calibration curve (Table 6)

Pre-formulation studies

The pre-formulation studies included the evaluation of the following parameters:

Physical characterization of drug

The observed physical characteristics of the drug under study have been recorded in Table 7.

Drug identification

UV spectra (Figure 1) of tofacitinib citrate showed the maximum absorbance at 289 nm which was in range with the USP specifications.

Compatibility study

In compatibility studies, no change was observed even after four weeks in the physical appearance. Drug interactions with other excipients were studied using FT-IR spectroscopy and no drug interaction was observed (Figures 2 and 3). From the interpretation data (Table 8) of the spectra obtained with the drug alone
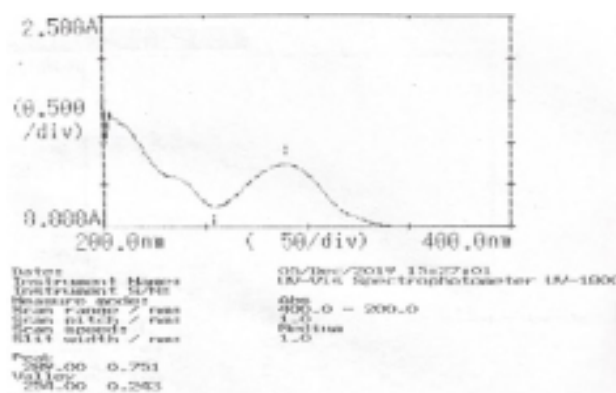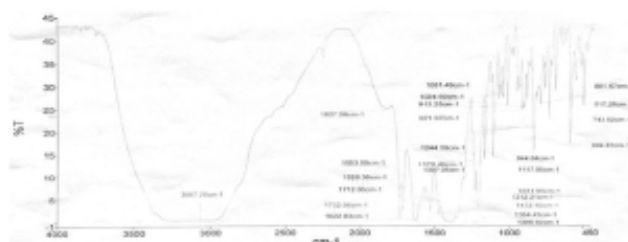

Figure 1: UV Spectra of Tofacitinib Citrate.

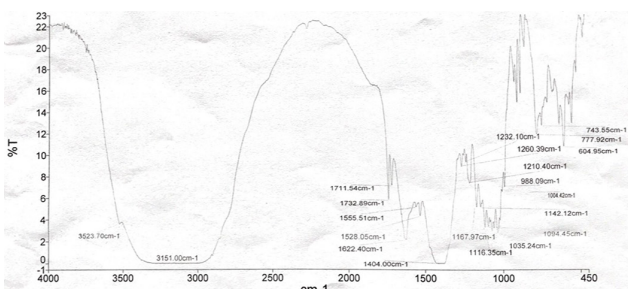**Figure 2: FT-IR Spectra of Tofacitinib Citrate.**

Figure 3: FT-IR Spectra of Physical Mixture of Tablet.

Table 6: Linear Equations in Different Media.			
Sr. No.	Media	Linear Equations	R² Value
1	Distilled water	y = 0.0298x + 0.0287	0.9999
2	0.1 N HCl	y = 0.0282x + 0.0152	0.9994
3	pH 6.40 phosphate buffer	y = 0.0348x − 0.0264	0.9959
4	pH 7.20 phosphate buffer	y = 0.0324x + 0.0267	0.9997

Table 7: Drug Characteristics.		
Description	Results	
Appearance	White to off white powder	
Odor	Odorless	
Melting point	215±2°C obtained by capillary method	
Solubility (n=3)	pH 1.2 HCl	27.14 mg/mL
	pH 6.4 phosphate buffer media	0.2640 mg/mL
	pH 7.2 phosphate buffer media	0.2044 mg/mL
	Water	3.35 mg/mL

Table 8: Interpretation of FT-IR Spectra of Tofacitinib Citrate.		
Sr. No.	Functional Groups	Wave No. Observed(cm⁻¹)
1	N-H Wagging (amines)	913
2	O-H Bend (carboxylic acid)	921
3	=CH- Bend (alkenes)	1081
4	C-N-Stretch (aliphatic amine)	1244, 1170
5	C-O-Stretch (alcohol, carboxylic acid)	1307
6	C-H (rocking)	1354, 1395
7	C-H Bend	1472
8	C=O-Stretch	1712, 1732
9	=CH-Stretch	3057.29
10	C-N-Stretch (aromatic)	1231

and its physical mixture with other ingredients, it was observed that there was no major changes in frequencies of observed functional groups which indicated that there was no chemical interaction between the drug and excipients used in the formulations.

Micromeritic properties of blends

The micromeritic properties of the prepared blends have been depicted in Table 9. From the values of the Hausner's ratio and Carr's index it was concluded that all the blends were in fair flow ability range. The angle of repose of all the blends, except F2 and F4, indicated good flow properties.

Post-compression studies

Shape and appearance

The prepared core tablets were white colored, circular in shape and with plane concave surfaces.

Table 9: Micrometric Properties of Prepared Blends.

Batch Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (Ø)
F1	0.666	0.800	1.201	16.75	34.2±0.95
F2	0.655	0.816	1.245	19.73	36.1±0.96
F3	0.677	0.833	1.230	18.72	34.6±0.92
F4	0.689	0.833	1.208	17.28	35.2±1.01
F5	0.666	0.800	1.201	16.75	32.8±1.24
F6	0.666	0.816	1.225	18.38	34.6±0.70
F7	0.689	0.833	1.209	17.28	33.3±0.75
F8	0.689	0.851	1.235	19.03	35.0±0.90
F9*	0.666	0.816	1.225	18.38	33.4±0.93
F9*rep	0.666	0.816	1.225	18.38	33.4±0.92
F10	0.654	0.798	1.220	18.04	34.5±0.91

Evaluation of core tablets

The readings of the various evaluated parameters of the prepared core tablets are recorded in Table 10.

In vitro drug release and optimization of core tablets

Drug released from the core tablets was evaluated in basic media using USP-II apparatus at 37±0.5°C with stirring rate of 100 RPM. 10 ml aliquots were taken at predetermined time point and replaced the volume with the same media to avoid calculation errors. Samples were filtered and analyzed by UV spectrophotometer at 287 nm. Batches F1 to F10 were evaluated in which batch F9 and F9 reproducible was considered as center point. F10 was formulated considering the composition suggested by the JMP software, as mentioned in Table 16. Effects of selected factors on drug release at the end of 1 h, 3 h and 6 h were visible from the variations in %DR obtained at different levels of individual factor and combination of factors. The %DR varied from 17.3 to 73.0% after 1 h, 47.5 to 96.8% after 3 h and 85.6 to 96.4% after 6 h (Table 11).

Obtained data of dependent variables were subjected to multiple regression analysis using JMP SAS software. The equation 1 (mathematical model) obtained for %DR at 1 h is summarized below:

$$Y1 = 86.280833333 + -1.3815 \cdot X1 + 0.39125 \cdot X2 + (X1-2) \cdot \{(X2-20) \cdot 0.039375\} + -6.829166667 \cdot X3 + (X1-2) \cdot \{(X3-8) \cdot 0.5895833333\} + (X2-20) \cdot \{(X3-8) \cdot -0.137916667\} + (X1-2) \cdot \{(X2-20) \cdot \{(X3-8) \cdot -0.00520833)\}.$$

The equation 2 (mathematical model) obtained for %DR at 3 h is summarized below:

Table 10: Evaluation of Core Tablets.

Batch Code	Thickness* (mm)	Weight Variation§ (mg)	Hardness* (Kp)	Content Uniformity€ (%)	Friability (%)
F1	3.17±0.017	100.08±0.53	4.04±0.017	98.8±1.13	0.90
F2	3.21±0.024	100.46±0.75	4.25±0.24	99.1±1.10	0.92
F3	3.22±0.023	99.92±0.78	4.40±0.15	98.0±1.60	0.92
F4	3.24±0.044	100.49±0.37	4.45±0.18	98.6±1.36	0.91
F5	3.17±0.018	99.71±0.42	4.15±0.10	98.5±1.25	0.90
F6	3.24±0.014	100.29±0.27	4.58±0.11	99.7±1.20	0.92
F7	3.20±0.020	99.27±0.42	4.43±0.21	98.0±1.34	0.76
F8	3.24±0.014	100.48±0.83	4.51±0.22	99.9±1.40	0.75
F9*	3.24±0.018	99.94±0.71	4.50±0.23	99.2±1.12	0.62
F9*rep	3.24±0.016	99.99±0.21	4.48±0.15	99.7±1.15	0.63
F10	3.21±0.037	100.04±0.58	4.33±0.18	99.0±1.50	0.76

*(All values represent mean± SD, §n=20, *n=6, €n=3)*

Y2=125.71833333 +0.2625·X1+ 0.185·X2+(X1-2)· {(X2-20)·-0.0025}+ -7.166666667 ·X3+(X1-2)· {(X3-8)·-0.00833333}+(X2-20)·{(X3-8)· 0.05083333333}+(X1-2)·{(X2-20)· {(X3-8)·0.0195833333)}.

The equation 3 (mathematical model) obtained for %DR at 6 h is summarized below:

Y3=98.212 +-0.46875·X1+ 0.04125·X2+ (X1-2)· {(X2-20)·- 0.060625}+ -0.9125·X3+(X1-20)·{(X3-8)· -0.09375}+(X2-20)·{(X3-8)·-0.01625}+(X1-2)· {(X2-20)·{(X3-8)·0.021875)}.

From the equations, it is clearly evident that sodium CMC is controlling the drug release (as evident by coefficient value of -6.82916667), whereas, MCC is increasing the drug release (co-efficient = +0.39125), as observed at end of 1 h, where, HPC-L = X1, MCC = X2, sodium CMC = X3 and Y1, Y2 and Y3 represent dissolution responses after 1, 3 and 6 h, respectively.

As evident from Tables 12-15 and equations 1, 2 and 3, the interaction terms (X1X2, X1X3, X2X3) between the two variables are statistically not significant ($p > 0.05$).

Similarly, as observed the *p* values are 0.0380, 0.0079, 0.0338, respectively ($p < 0.05$) for sodium CMC, indicating that it provides statistically significant difference for the model developed for drug release at the end of 1 h, 3 h and 6 h.

Formulations having higher concentrations of sodium CMC in matrix showed more retardation of drug release in comparison to less concentration of sodium CMC. Although f2, f4, f6, f8 and f10 formulations had shown extended drug release, however, only the formulation f10 showed drug release in extended period over 6 h, less than 50% drug release after 3 h and comparatively maximum drug release after 6 h. Thus, batch f10 (composition shown in Table 16) was considered as the optimum batch for enteric coating.

From Figure 4, it is evident that *R²* values for the selected model at 1, 3 and 6 h are 0.93, 0.98 and 0.96, respectively. The results of the statistical analysis suggest close correlation between actual and predicted values. The *R²* values indicate how close the data are fitted to the regression lines. Here, *R²* value indicates a better fit. However, RMSE values observed are 11.625, 5.4449 and

Table 11: Drug Release from Core Tablets.						
	% Drug Release from the Core Tablet					
Batch Code	1 h	2 h	3 h3hrs	4 h4hrs	5 h5hrs	6 h6hrs
F1	59.1±4.4	92.1±3.1	93.2±1.1	92.8±0.1	91.5±0.5	91.5±2.2
F2	18.7±0.4	27.6±4.6	49.6±8.5	65.0±12.2	80.5±14.5	88.8±4.3
F3	73.0±2.6	90.6±3.6	96.3±1.6	96.4±2.1	95.6±1.1	96.4±1.8
F4	17.3±1.5	38.5±5.0	54.1±3.1	71.9±6.7	85.2±4.2	90.4±1.9
F5	44.3±1.8	92.0±2.0	96.8±2.2	95.6±1.6	95.0±1.7	95.8±0.9
F6	19.3±3.1	33.2±9.5	48.3±11.0	63.8±14.0	79.0±9.5	85.6±7.1
F7	62.6±0.4	87.0±11.9	95.0±3.0	92.7±12.2	96.5±1.1	90.6±10.5
F8	19.8±0.5	39.2±6.2	57.3±9	73.8±11.2	84.4±9.6	87.6±8.0
F9*	24.3±0.3	38.2±7.8	67.4±7.4	83.5±5.3	89.4±1.6	89.2±1.7
F9*rep	28.7±4.0	49.5±9.5	68.1±11.4	82.4±8.3	90.9±3.9	92.1±2.4
F10	20.5±0.5	33.5±3.1	47.5±9.2	75.5±6.2	87.3±2.4	89.9±0.5

(All values are expressed as mean±SD)

Table 12: Analysis of variance for Core Table.						
Responses	Sources	Degree of Freedom	Sum of Squares	Mean Square	F Ratio	Prob>F
Y1 (% drug release 1 h)	Model Error Corrected total	7 2 9	3784.2188 270.2902 4054.5090	540.603 135.145	4.0002	0.2145
Y2 (% drug release 3 h)	Model Error Corrected total	6 3 9	3746.2300 70.3390 3816.5690	624.372 23.446	26.6298	0.0107
Y3 (% drug release 6 h)	Model Error Corrected total	7 2 9	98.31875 4.26125 102.58000	14.0455 2.1306	6.5922	0.1380

Table 13: Parameter Estimates after 1 h for Core Tablet.

Term	Estimate	Std. Error	t Ratio	Prob>|t|
Intercept	86.280833	14.76852	5.84	0.0281*
HPC-L	-1.38125	2.055063	-0.67	0.5708
MCC	0.39125	0.411013	0.95	0.4416
(HPC-L-2)*(MCC-20)	0.039375	0.205506	0.19	0.8657
Sod. CMC	-6.829167	1.370042	-4.98	0.0380*
(HPC-L-2)*(Sod. CMC-8)	0.5895833	0.685021	0.86	0.4801
(MCC-20)*(Sod. CMC-8)	-0.137917	0.137004	-1.01	0.4201
(HPC-L-2)*(MCC-20)*(Sod. CMC-8)	-0.005208	0.068502	-0.08	0.9463

Table 14: Parameter Estimates after 3 h for Core Table.

Term	Estimate	Std. Error	t Ratio	Prob>|t|
Intercept	125.71833	6.91715	18.17	0.0030*
HPC-L	0.2625	0.962532	0.27	0.8106
MCC	0.185	0.192506	0.96	0.4380
(HPC-L-2)*(MCC-20)	-0.0025	0.096253	-0.03	0.9816
Sod. CMC	-7.166667	0.641688	-11.17	0.0079*
(HPC-L-2)*(Sod. CMC-8)	-0.008333	0.320844	-0.03	0.9816
(MCC-20)*(Sod. CMC-8)	0.0508333	0.064169	0.79	0.5113
(HPC-L-2)*(MCC-20)*(Sod. CMC-8)	0.0195833	0.032084	0.61	0.6037

Table 15: Parameter Estimates after 6 h for Core Table.

Term	Estimate	Std. Error	t Ratio	Prob>|t|
Intercept	98.2125	1.854344	52.96	0.0004*
HPC-L	-0.46875	0.258035	-1.82	0.2109
MCC	0.04125	0.051607	0.80	0.5080
(HPC-L-2)*(MCC-20)	-0.060625	0.025803	-2.35	0.1432
Sod. CMC	-0.9125	0.172023	-5.30	0.0338*
(HPC-L-2)*(Sod. CMC-8)	-0.09375	0.086012	-1.09	0.3895
(MCC-20)*(Sod. CMC-8)	0.01625	0.017202	0.94	0.4446
(HPC-L-2)*(MCC-20)*(Sod. CMC-8)	0.021875	0.008601	2.54	0.1260

1.4597, at three time points. Considering the P value, the model is found to be insignificant (p>0.05) for effect of factors selected on drug release at the end of 1 and 6 h. However, borderline significant effects have been observed at the end of 3 h.

The composite desirability of 0.3742 had been obtained which predicted 37.2% chance of getting desired response using optimized values of factors (Figure 5). However, this was only for the core tablets and the prepared core tablets were also coated using functional coating which also impacted on desirability. Thus, the selected formulation fitted in the model after coating, as it produced drug release according to the desired release pattern. Selected pattern for core tablet showed 10-30% drug release in 1 h, 35-55% drug release in 3 h and not less than 80% drug release in 6 h.

As per the design of experiment, the core tablet composition was optimized and the final batch was prepared with the given concentrations (Table 16).

In vitro drug release from coating process parameters batches

Drug release from the coating process parameter batches have been mentioned below in Table 17.

Assuming negligible drug release in 0.1N HCl and in pH 6.4 phosphate buffer stage 1, the effect of selected factors on drug release at the end of 1 h, 3 h and 6h, in pH 7.2 phosphate buffer stage 2, was visible from the variation in % drug release obtained at different levels of individual factor and combination of factors.
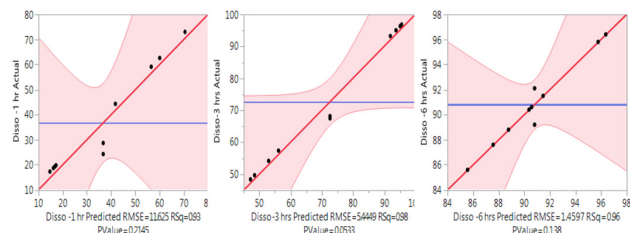

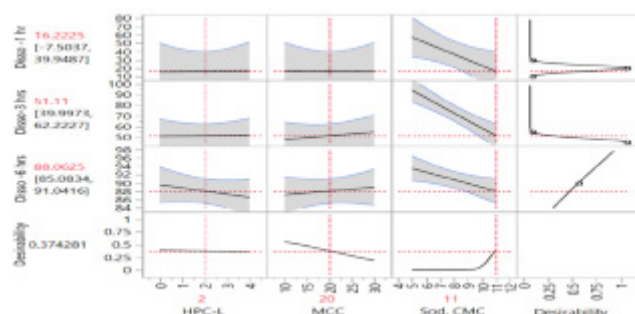**Figure 4: Dissolution Response Actual by Predictable Plots.**

Figure 5: Prediction Profiler for Core Tablets.

Table 16: Composition of F10 Batch.		
Sr. No.	Ingredients	Quantity (mg)
1	Tofacitinib citrate	16.25
2	Lactose	48.75
3	Microcryatalline cellulose	20
4	Hydroxy propyl cellulose-L	2
5	Sodium CMC	11
6	Magnesium stearate	2

Obtained data of dependent variables were subjected to multiple regression analysis using JMP SAS software. The equation, Z1 (mathematical model), obtained for % drug release at 1 h is summarized below:

$$Z1 = 5.8 + 0.15 \cdot T + -0.5 \cdot W + (T-30) \cdot \{(W-13) \cdot -0.045833333\}.$$

The equation, Z2 (mathematical model), obtained for % drug release at 3 h is summarized below:

$$Z2 = 36.389285714 + 1.825 \cdot T + -4.125 \cdot W + (T-30) \cdot \{(W-13) \cdot -0.120833333\}.$$

The equation, Z3 (mathematical model), obtained for % drug release at 6 h is summarized below:

$$Z3 = 94.366666676 + 0.15 \cdot T + -0.466666667 \cdot W + (T-30) \cdot \{(W-13) \cdot 0.0625\}$$

From the equations Z1, Z2 and Z3, it is clearly evident that percentage weights built-up are controlling the drug release (as evident by the coefficient values of -0.5, -4.125 and -0.466666667) at the end of 1 h, 3 h and 6 h respectively, whereas product temperature is increasing the drug release (co-efficient = +0.15, +1.825 and + 0.15), as observed at the end of 1 h, 3 h and 6 h, respectively. As evident from the Tables 18-21 and equations Z1, Z2 and Z3, the interaction terms (WT) between the two variables are statistically not significant ($p>0.05$). Similar to, as observed in Table 19, 20 the p value for weight build up, at the end of 1h, indicating that it provides nearly statistically significant difference and at the end of 3 h indicating that it provides statistically significant difference for the model developed for drug release at the end of 3 h.

From Figure 6, it is evident that R^2 value for the selected model is 0.77, 0.88 and 0.45 at 1, 2 and 3 h. The results of the statistical analysis suggest close correlation between the actual and predicted values at the end of

Table 17: Drug Release from Coated Tablet Batches.								
Dissolution Media	Time (hr)	% Drug Release from the Coated Tablets						
		Coat f5 A	Coat f5 B	Coat f5 C	Coat f5 D	Coat f5 E*	Coat f5 E*rep1	Coat f5 E*rep2
0.1 N HCl	0	0.00±0.0	0.00±0.0	0.00±0.0	0.00±0.0	0.00±0.0	0.00±0.0	0.00±0.0
	2	0.4±0.5	0.2±0.1	1.4±0.7	0.4±0.2	0.3±0.3	2.6±0.1	0.2±0.1
PB pH 6.4 Stage-1	3	1.9±0.4	0.4±0.3	2.0±0.4	0.2±0.1	0.1±0.1	3.7±1.0	0.3±0.2
PB pH 7.2 Stage-2	4	7.6±0.3	0.5±0.2	5.9±1.0	1.0±0.4	3.5±0.2	1.7±1.2	6.4±0.3
	5	23.5±2.0	1.8±0.5	21.5±1.9	1.2±0.4	15.8±0.9	15.6±2.5	17.4±1.1
	6	62.0±4.1	9.6±2.1	51.8±8.1	5.2±0.7	40.3±1.5	52.4±4.9	41.3±3.5
	7	95.0±2.1	27.8±2.9	88.1±6.6	17.0±2.4	74.4±0.1	74.8±10.3	76±5.7
	8	95.3±1.7	54.0±4.5	96.7±1.7	38.4±2.7	89.6±0.4	93.7±6.2	91.5±2.0
	9	93.2±1.4	89.1±4.4	94.1±0.9	87.0±4.9	94.0±2.0	97.7±2.3	95±0.7

(All values are expressed as mean± SD)

Table 18: Analysis of Variance for Coated Tablets.						
Responses	**Sources**	**Degree of Freedom**	**Sum of Squares**	**Mean Square**	**F Ratio**	**Prob>F**
Y1 (% drug release after 1 h)	Model Error Corrected total	3 3 6	37.570000 11.270000 48.840000	12.5233 3.7567	3.3336	0.1746
Y2 (% drug release after 3 h)	Model Error Corrected total	3 3 6	2511.9500 358.7786 2870.7286	837.317 119.593	7.0014	0.0721
Y3 (% drug release after 6 h)	Model Error Corrected total	3 3 6	33.970000 40.850000 74.820000	11.3233 13.6167	0.8316	0.5585

Table 19: Parameter Estimates after 1 h for Coated Tablets.				
Term	**Estimate**	**Std Error**	**t Ratio**	**Prob>|t|**
Intercept	5.8	14.70571	0.39	0.7196
Prod. Temp	0.15	0.484553	0.31	0.7771
% Wt build up	-0.5	0.161518	-3.10	0.0535
(Prod.temp-30)*(% Wt build up-13)	-0.045833	0.080759	-0.57	0.6100

Table 20: Parameter Estimates after 3 h for Coated Tablets.				
Term	**Estimate**	**Std Error**	**t Ratio**	**Prob>|t|**
Intercept	36.389286	82.97312	0.44	0.6906
Prod. Temp	1.825	2.733963	0.67	0.5522
% Wt build up	-4.125	0.911321	-4.53	0.0202*
(Prod.temp-30)*(% Wt build up-13)	-0.120833	0.45566	-0.27	0.8080

Table 21: Parameter Estimates after 6 h for Coated Tablets.				
Term	**Estimate**	**Std Error**	**t Ratio**	**Prob>|t|**
Intercept	94.366667	27.99756	3.37	0.0434*
Prod. Temp	0.15	0.922519	0.16	0.8812
% Wt build up	-0.466667	0.307506	-1.52	0.2264
(Prod.temp-30)*(% Wt build up-13)	0.0625	0.153753	0.41	0.7116

1 and 3 h until the coating dissolve. Here, the values indicate a better fit. However, RMSE value is observed to be 1.9382, 10.936 and 3.6901.

Considering the P value the model was found to be insignificant (*p*>0.05) for effect of factors selected, on drug release at the end of 1, 3 and 6 h.

The composite desirability of the final formulation, 0.810244 as shown in Figure 7, was obtained, which predicted 81 % chance of getting desired response using optimized values of the factors.

Coating was performed using different process parameters and the effects of bed temperature and percentage weight build up had been shown in the various formulations (Coat f5 A to Coat f5 E). Lower bed temperature during coating resulted in formation of poor film leading to premature drug release, as observed in acidic stage from Coat f5 C in comparison to Coat f5 A, in which bed temperature was higher. However, in both the batches, coating percentages were same. At higher temperature, particles of dispersion melted and hard film was formed that prevented the drug release in acidic stage. Formulations Coat f5 B and Coat f5 Having 19% coating showed more drug retardation and increase in the lag time leading to incomplete drug release in buffer stage 2 (Table 17 and Figure 8). Coated at optimum bed temperature and percent weight build up, formulation Coat f5 Emet the pharmacopoeia specifications, as it hardly released drug in acid and phosphate buffer stage 1, but released maximum drug in phosphate buffer stage 2. Further, the release pattern was confirmed by observing the reproducible batches.
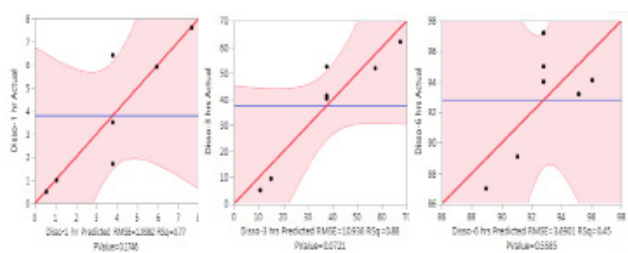
The results of the stability studies are Table 22.

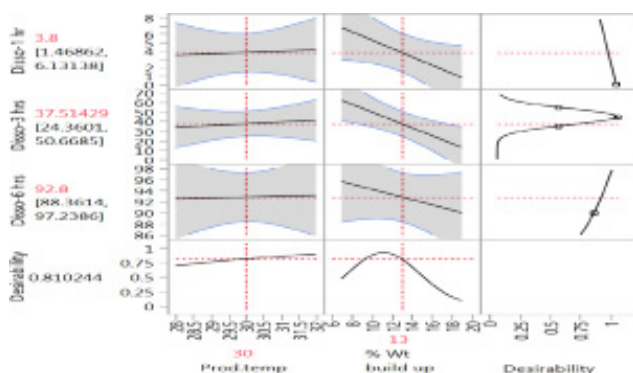**Figure 6: Dissolution Response Actual by Predictable Plots for Coated Tablets.**

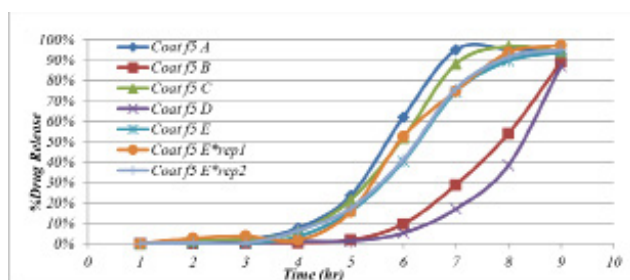**Figure 7: Prediction Profiler for Coated Tablets.**

Figure 8: Effects of Process Parameters on % Drug Release.

Table 22: Results of Stability Studies.			
Parameter	Specifications	**Test Conditions 40±2°C/75±5% RH (Accelerated)**	
		Initial	Final
Appearance	White plane surfaces; round shaped tablets	Complies	Complies
Thickness (mm)	-	3.48±0.08	3.49±0.010
Hardness (kp)	-	4.73±0.16	5.2±0.14
Weight (mg)	-	113.22 ±0.50	113.54±0.41
Assay (%)	-	98.30±1.08	97.10±1.08
Dissolution (%)	-	94.0±2.0	93.0±5.0

CONCLUSION

The present investigation has been carried out with a significant plan to develop colon specific tablet of tofacitinib. pH and time dependent matrix tablets have been prepared using sodium CMC and Eudragit® S100 coating to prevent drug release in the upper GIT and give maximum drug release in colon. Based on the results of *in vitro* drug release, 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 hr. 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 3-4 h lag time. As per the reports in literatures, in fasting stage the arrival time for smaller tablets into the colon is about 3-4 h; thus, the current formulation meets the specification of colon targeted drug delivery. On behalf of *in vitro* study current formulation is suitable for colonic delivery as negligible drug release observed in acid and phosphate buffer stage-1 followed by maximum drug release in the phosphate buffer stage 2.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST

There is no academic, financial, personal and commercial conflict of interest among the authors.

ABBREVIATIONS

JAK: Janus kinase; **STAT:** Signal transducer and transcription; **UC:** Ulcerative colitis; **FDA:** Food and drug administrative; **Kp:** Kilopound; **Sodium CMC:** Sodium carboxy methylcellulose; **GIT:** Gastro intestinal tract; **TNF:** Tumor necrosis factor; **HPC-L:** Hydroxypropyl cellulose low substitute.

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PICTORIAL ABSTRACT
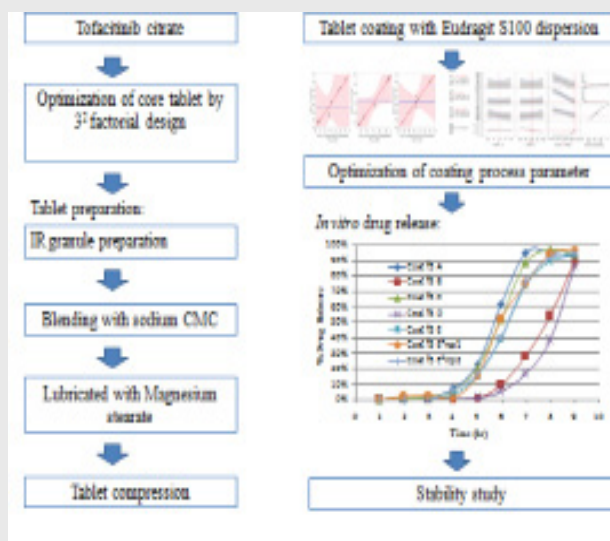
SUMMARY

Tofacitinib, the pan-Janus kinase (JAK) inhibitor, had been approved by FDA for its use in the treatment of moderate to severe ulcerative colitis, in 2018. The present work aimed to develop a new colon targeted drug delivery system for tofacitinib using combined approaches of formulating an extended release matrix tablet by wet granulation method, along with a pH sensitive polymer coating of Eudragit® S100. Formulation variables used in the latter, were optimized. Negligible drug release was obtained in 0.1 N HCl and 6.4 pH phosphate buffer media, where as in 7.2 pH phosphate buffer medium, the drug release increased up to $94.2 \pm 2.0\%$. The minimum concentration of sodium carboxymethyl cellulose (CMC) for 6 hour's extended release of drug from the matrix tablet, was observed to be 11% (w/w) and 13% was the minimum functional coating percentage for obtaining an adequate lag time. Thus it was found from the study, that the lag time of the drug release was highly affected by the coating percentage of Eudragit S 100 and product temperature during coating. The rate of drug release was found to be depended on the concentrations of sodium CMC used in the core tablet. Finally, the optimized product was found to be stable over three months of storage at $40 \pm 2°C/75 \pm 5\%$ RH.
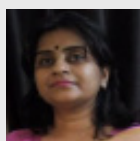
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