CONTROLLED RELEASE FORMULATION OF TOFACITINIB CITRATE TABLETS EVALUATED USING QUALITY BY DESIGN (QBD) APPROACH

Abstract

The purpose of the study is to develop and optimize Tofacitinib citrate matrix tablets with controlled release excipients using the quality-by-design (QbD) approach. Product development initiated based on the physicochemical properties of the drug, the reference product characterization, QTPP (Quality Target Product Profile) and the CQAs (Critical Quality Attributes). Formula optimization of Hypromellose (Methocel K100 premium LV CR), Polyethylene Oxide (SentryPolyox WSR N80 LEO) and Magnesium Stearate was done in combination as formulation variables.The conventional monolithic controlled release matrix tablets with full factorial design of experiment (DOE) with three center points was studied.and dissolution was considered as CQA using Design- expert12 software. Hypromellose with higher viscosity grade provides controlled release pattern by maintaining the integrity and prevent faster drug release at acidic pH condition. Due to the nonionic nature of the polymer, drug release from the polymer matrices is pH independent. Present monolithic controlled release matrix system the extensive degradation of Tofacitinib Citrate in the acidic condition can be avoided with desired in-vitro drug release.

Key words: Quality-by-design, Design of experiment, Controlled release, Dissolution, Matrix system

INTRODUCTION

Novel drug delivery system is now a days a challenging technology base drug delivery system in pharmaceutical research. Controlled release drug delivery system is one of the suitable platforms for drug design related to safety and efficacy of patients. In controlled release dosage form the drug release maintained in a constant rate with maintaining therapeutic levels in plasma. It reduces the dosing frequency and minimize the adverse effect.[1]

Formulation containing hydrophilic matrix polymer is most convenient for development of dosage form. Depending on the viscosity grade of the polymer the drug release can be maintained in pre-determined rate. On contact with the aqueous media, the polymer getting hydrate and formation of gel layer via diffusion or erosion of the gel layer resulting drug release with respect to time.[2]

Quality by Design is the modern scientific and systematic approach for pharmaceutical development and manufacturing of drug product. The aim of the pharmaceutical development is to achieve the desired quality considering safety and efficacy of the drug product.[3]. The development begins with the initial risk assessment to identify high risk, medium risk and low risk during development. High Risk is unacceptable, further investigation is needed to reduce the risk. Medium Risk is acceptable,

further investigation may be needed in order to reduce the risk and Low risk is broadly acceptable risk, no further investigation is needed. Quality by Design approach gives clear understanding on process parameters and material attributes which impacts on critical quality attributes (CQA), safety and efficacy of the drug product during its lifecycle. Quality by Design (QbD) approach develops a robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product. Design of Experiments helps to build the Design space for Formulation, Process variables and desired response was evaluated by design expert software v 12. [4,5,6,7]

The present study focuses on Tofacitinib citrate controlled release tablets indicated for the treatment with moderately to severely active rheumatoid arthritis which is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2) JAK pathway blocks signaling through the common γ -chain-containing receptors for multiple proinflammatory cytokines. The pharmacokinetic profile of tofacitinib citrate characterized by rapid absorption and elimination with time to maximum plasma concentration (T_{max}) 0.5 -1 hour and terminal half-life (t1/2) 3-4.5 hours.[8,9,10].

Tofacitinib citrate is categorized as BCS Class- III (Low permeable – High soluble) drug[11]. pH dependent solubility of drug substance observed in saturation solubility study. Highest solubility was observed in 0.1N hydrochloric acid and solubility gradually decreases with increase in pH. Hence, controlled release formulations of Tofacitinib citrate tablets were developed using the release controlling polymer Polyethylene oxide, Hypromellose (Methocel K100premium LV CR) in core tablets and Ethyl cellulose, Hydroxy propyl cellulose (Klucel LF) in coating composition to get desirable drug release throughout the gastrointestinal tract.[12,13,14]

MATERIALS AND METHODS

2.1 Materials

Tofacitinib citrate was gifted from Aurobindo Pharma Limited, India., Microcrystalline cellulose was gifted from Crest cellulose Private Ltd., Hypromellose and Ethyl cellulose was gifted from Coloron asia pacific Pvt. Ltd. Polyethylene oxide was gifted from Dow chemical company. Hydroxypropyl cellulose was gifted from Ashland, Butylated hydroxytoluene was gifted from Merck, Colloidal silicon dioxide was gifted from Evonik Industries, magnesium stearate was gifted from crest cellulose private Ltd.

2.2. Manufacturing Method

The present study design focus on conventional monolithic controlled release matrix tablets with Polyethylene oxide, Hypromellose (Methocel K100premium LV CR) in core tablets and Ethyl cellulose, Hydroxy propyl cellulose (Klucel LF) in coating composition. The formulation was

manufactured with wet granulation technique with high shear rapid mixture granulator and non-aqueous solvent was used as granulating fluid.

2.3. Method of Analysis

Drug product method of analysis not available in USP monograph. Hence, dissolution method was adopted in following in-house developed method.

2.4. Dissolution Method

Buffer solution Preparation: Dissolve 68g of potassium dihydrogen orthophosphate and 8.9g of sodium hydroxide pellets in 10 liters of water and mix well. pH maintains at 6.8±0.05 with 0.2N sodium hydroxide.

Mobile phase buffer preparation: Add 1ml of trifluoro acetic acid into 1000ml of milliq water.

Mobile phase preparation: Mix the buffer with acetonitrile in the ratio of 80:20v/v

Instrumentation: A high performance liquid chromatographic system with waters 2695 separation module used for analysis.

Chromatographic conditions for HPLC:

Column	:	Kromasil 100-5 C18(150mm x 4.6mm),5µ
Pump mode	:	Isocratic
Flow rate	:	1.0mL/minute
Detection	:	UV,292 nm
Injection Volume	:	60µL
Columnoven temperature	:	40°C
Run time	:	10 minutes

2.5. Assay Method

Chromatographic conditions: The HPLC is equipped with a Kromasil 100-5 C18(150mm x 4.6mm),5µ column ,Isocratic pump mode, 1.0mL/minute flow rate, UV,292 nm detection, injection volume-60µL, Temperature-35°C, Run time-15 minutes.

EXPERIMENTAL DESIGN

Preformulation study helps in understanding the physico-chemical properties of the drug substance like solubility, stability, compatibility and solid-state characteristics followed by drug excipient compatibility studies. Tofacitinib drug substance and suitable excipients with different concentration was evaluated by Differential scanning calorimetry followed by physical evaluation.

3.1 Hygroscopicity Studies of Tofacitinib citrate drug substance:

The Hygroscopicity study was performed for Tofacitinib drug substance, by subjecting it to 80% RHcondition for 24 hrs and determining the percent mass change. The results are tabulated in Table No 1.

Maximum weight increases in hygroscopicity study was 0.102% at 80% RH from 3 samples analysis. Hence, observed weight gain below 2% indicates that Tofacitinib product is non hygroscopic in nature.

Table 1: Hygroscopicity study of Tofacitinib drug substance.

w_1(g)	w_2(g)	w_3(g)	% weight change	Hygroscopicity
5.532	18.241	23.859	0.086	Non hygroscopic
5.614	20.342	26.053	0.097	Non hygroscopic
6.216	21.329	27.667	0.122	Non hygroscopic

W_1: Sample weight, W_2: Petridis weight with Sample, W_3: Petridis weight with Sample after 24 hours in 80% RH.

Solubility study of Tofacitinib citrate:

Saturation solubility of Tofacitinib citrate drug substance was carried out in the pH range of 1.2 to 7.5 and the results are tabulated below Table No 2

Table 2: pH solubility profile of Tofacitinib citrate

Solvent	pH observed after addition of drug (after 24 Hr.)	Solubility (mg/ml)	Dose/Solubility ratio(mL)*
0.1N Hcl	1.02	7.013	1.426
pH 4.5 Acetate Buffer	4.43	0.910	11.099
Purified water	5.75	2.732	3.660
pH 6.8 Phosphate Buffer	6.65	0.225	44.44
pH 4.5 Phosphate Buffer	7.35	0.144	69.44

$$*\text{Dose/Solubility} = \frac{\text{Highest Dose[mg]}}{\text{Saturation Concentration[mg/ml]}} \leq 250 \text{ mL}$$

Solid state characterization:

Tofacitinib citrate drug substance used in the present study exhibits crystalline form. Tofacitinib citrate drug substance have been analyzed by X-Ray powder diffraction the 2-Theta value presented in Table No-3.The diffractogram presented in Figure No-1

Table 3: Theta value of crystalline form of Tofacitinib citrate.

S. No.	1	2	3	4	5	6	7
2 -Theta value	5.84	14.91	16.10	16.28	20.35	21.18	27.05

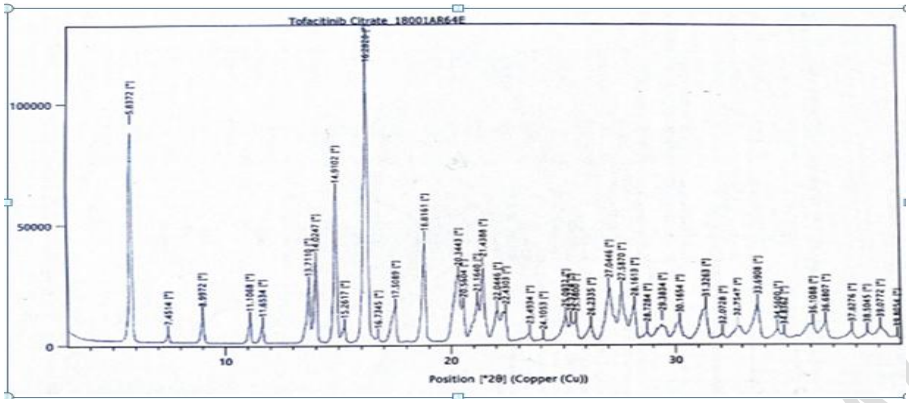


Fig. 1: XRD data of Tofacitinib drug substance

Formulation design experiments

Quality by Design (QbD)

Quality by design is a scientific basis Pharmaceutical development begins with a predefined goal that provides more clarity on product and process quality. It includes the profile of the quality target product, the critical quality attribute, the critical process parameters, and the control strategy. Current study, concentration of hydrophilic polymer in core tablets and pore-forming hydrophobic polymer has a direct impact on the critical quality attribute.

The goal is defined early in development based on the properties of the drug substance. From start to finish, the result of developing a formulation and manufacturing process with an acceptable control strategy that ensures drug performance. Physical and chemical property that are within specific limit or range to make it within design space. From the QTPP the CQA was identified based on risk assessment those are outside the acceptable range for that attribute.

Table 4: Quality target product profile (QTPP)

Identification of QTPP	Target
Dosage form	Oral Tablets
Dosage design	Monolithic controlled release dosage form
Administration route	Oral
Stability	Ensure impurity levels as per ICH and stable polymorphism
Physical attributes	To maintain as per quality standard
Identification	Should be consistent prior to development
Dissolution	Percentage drug release as per specific requirements.
Degradation Product	Specified and unspecified impurity should be within limits
Polymorphism	Should be consistent during manufacturing process and storage
Differential scanning calorimetry (DSC)	Should be consistent during manufacturing process and storage

Table 5: Critical quality attributes (CQA)

Quality attributes of Drug product		Target	Critical/ Noncritical	Justification
Physical attributes	Appearance	Color,size and shape	Noncritical	It can't be corelate Tablet Color, size and shape to patient safety
	Odor	Odor of tablet	Noncritical	As the drug and excipients does not have odor. It can't be corelate Tablet odor to patient safety
	Size	Easy to Swallow	Noncritical	Smaller size of the tablets designed for patient compliance and acceptance.
	Friability	It should not more than 1% w/w	Noncritical	It is not directly link to patient safety. It gives strengths to quality of product.
	Hardness	4-8 kp	Critical	Compression force and formulation components impact hardness.
Identification		Original form of Drug substance	Critical	Formulation and process variability may unlikely impact on Identity.
Related substance		Any unspecified Impurity: NMT 0.2%w/w Total Impurity: NMT 1.0%w/w	Critical	Input materials of drug substance, excipients and process parameters impacts degradation product.
Assay		95%-105%	Critical	Input materials of drug substance, excipients and process parameters impacts assay of product.
Dissolution		2 Hrs- 25-35% 4 hrs- 40-60%	Critical	Input materials of drug substance, excipients and

Quality attributes of Drug product	Target	Critical/ Noncritical	Justification
	6 Hrs-60-75% 8 Hrs- NLT 80 %		process parameters impacts assay of product.
Polymorphism	Consistent throughout development	Critical	polymorphism should be retained during manufacturing process and storage.

At the initial stage of QbD development, material attributes that impact the quality of the product was identified through risk assessment process and categorized the risk. Based on the risk analysis formulation factors are evaluated through experiments to understand the resultant response through design of experiment process.

Formulation factor impacted the quality are:

- In put material of drug product and selected excipients.
- Critical process parameters for Manufacturing process.
- Control strategy with range and limits.

Initial Risk assessment of formulation variables impact on Drug product CQA:

An initial risk assessment was evaluated based on the prior knowledge of drug substance and the excipients used in the manufacturing of dosage form and that formulation variable have high risk on affecting drug product CQA. The results of initial risk assessment are represented in below table and the justification of the risk prioritization is presented. Each formulation variable that has a high risk to impact the drug product CQAs is further evaluated in subsequent risk assessments to determines which formulation variables need to be studied to reduce the risk.

Table 6: Initial Risk assessment of formulation Variables

Drug product CQAs	**Formulation Variables**		
	Microcrystalline Cellulose Level	Hypromellose Level	Polyethylene Oxide Level
Assay	Low	Low	Low
Dissolution	Low	High	High
Related substance	Low	Low	Low

Drug product CQAs	**Formulation Variables**		
	Magnesium stearate	**Colloidal silicon dioxide Level**	**Butylated Hydroxy Toluene Level**

Assay	Low	Low	Low
Dissolution	Medium	Low	Low
Related substance	Low	Low	Low

Low	Low risk is accepted. No further investigation is required
Medium	Medium risk is also acceptable. If required further investigation needed to reduce the risk.
High	High risk is unacceptable. Further investigation is required to reduce the risk from high to low

Table 7: Justification for the Initial Risk assessment of formulation Variables

Formulation Variables	Drug product CQAs	Justification
Microcrystalline Cellulose Level	Assay	Microcrystalline Cellulose is used as diluent/filler .It improves the flow property of the blend. Hence it will not impact the assay of finish product . So, the risk is low.
	Dissolution	Microcrystalline Cellulose is used as diluent/filler .It improves the flow property of the blend. Hence it will not impact the dissolution of finish product . So, the risk is low.
	Related substance	Microcrystalline Cellulose is used as diluent/filler in intragranular stage. It improves the flow property of the blend and improve the bulk density of the blend. Hence it will not impact the Related substance of finish product . So, the risk is low.
Hypromellose (Methocel K100 premium LV CR) Level	Assay	Hypromellose (Methocel K100 premium LV CR) is used as release retardant hydrophilic polymer .It has good binding properties. Hence it will not impact the assay of finish product . So, the risk is low.
	Dissolution	Hypromellose (Methocel K100 premium LV CR) is used as release retardant hydrophilic polymer .It has good binding properties. Hence it will impact the dissolution of finish product . So, the risk is High.
	Related substance	Hypromellose (Methocel K100 premium LV CR) is used as release retardant hydrophilic polymer .It has

Formulation Variables	Drug product CQAs	Justification
		good binding properties. During drying process required amount of moisture was kept to avoid gelling and swelling nature of the blend . Hence it will not impact the Related substance of finish product . So, the risk is Low.
Polyethylene Oxide (sentryPolyox WSR N80 LEO) Level	Assay	PolyethyleneOxide(sentryPolyox WSR N80 LEO) is used as release retardant hydrophilic polymer .It has good binding properties. Hence it will not impact the assay of finish product . So, the risk is low.
	Dissolution	Polyethylene Oxide(sentryPolyox WSR N80 LEO) is used as release retardant hydrophilic polymer .It has good binding properties. Hence it will impact the dissolution of finish product . So, the risk is High.
	Related substance	Polyethylene Oxide(sentryPolyox WSR N80 LEO) is used as release retardant hydrophilic polymer .It undergo oxidation properties. So,Butylated Hydroxy Toluenedded in formulation as antioxidant.During drying process required amount of moisture was kept to avoid gelling and swelling nature of the blend . Hence it will impact the related substance of finish product . So, the risk is low.
Magnesium stearate	Assay	Magnesium stearate is used as lubricant. Hence, it will impact the assay of finish product . So, the risk is low.
	Dissolution	Magnesium stearate is used as lubricant. It has the higher surface area and lipophilic in nature. Hence, it may impact the dissolution of finish product . So, the risk is medium.
	Related substance	Magnesium stearate is used as lubricant. Hence, it will impact the related substance of finish product . So, the risk is low.
Colloidal silicon dioxide Level	Assay	Colloidal silicon dioxide is used as glidant. Colloidal silicon dioxide has smaller particles and larger

Formulation Variables	Drug product CQAs	Justification
		surface area which improves the flow property of the blend. It is used as adsorbent which adsorb the surface moisture from the blend and tablets. Hence it will not impact the assay of finish product . So, the risk is low.
	Dissolution	Colloidal silicon dioxide is insoluble in water.It doesn't have any binding properties. Hence it will not impact the dissolution of finish product . So, the risk is low.
	Related substance	Colloidal silicon dioxide absorb moisture. Hence it will not impact the Related substance of finish product . So, the risk is low.
Butylated Hydroxy Toluene Level	Assay	Butylated Hydroxy Toluene is used as an antioxidant and prevent oxidation during storage. It is unlikely impact the assay. Hence the risk is Low.
	Dissolution	Butylated Hydroxy Toluene is used as an antioxidant and prevent oxidation during storage. Butylated Hydroxy Toluene is not release controlling polymer. It is unlikely impact the dissolution. Hence the risk is Low.
	Related substance	Butylated Hydroxy Toluene is used as an antioxidant and prevent oxidation of Polyethylene Oxide . It improves the stability of the drug product as well. It is unlikely impact the Related substance. Hence the risk is Low.

Formulation and Development

Formulation Development of Tofacitinib citrate Tablets were designed as controlled release drug delivery based on literature data and preformulation study. Controlled release hydrophilic excipients were selected based on target drug release profile. Calculated amount of Tofacitinib citrate drug substance and Hypromellose (Methocel K100 premium LV CR) was co sifted through ASTM 30 mesh (600 micron screen). Remaining material of intra granular portion like Microcrystalline Cellulose (Avicel PH 101), Polyethylene Oxide (sentryPolyox WSR N80 LEO) and Colloidal silicon

dioxide sifted through ASTM 25 mesh (710-micron screen).All the sifted materials again pass-through ASTM 25 mesh (710-micron screen) for uniform homogeneity of blend. Butylated Hydroxy Toluene dissolved in Isopropyl Alcohol for preparation of granulating fluid. The dry mix blend was granulated with the non-aqueous granulating fluid in a high shear mixer granulator with impeller slow and chopper slow speed over a period of three minutes. The wet mass was dried through Fluid bed processor at inlet temperature 45℃±5℃ for a period of 1 hours to get desired moisture content value not more than 3%w/w by using IR moisture analyser. The dried granules were co milled through 0.8mm screen. Extragranular Microcrystalline Cellulose (Avicel PH 102) was passed through ASTM 40mesh (425-micron screen) and blending with dried granules in low shear cone blender for a period of 10 minutes. Magnesium Stearate was screened through ASTM 60mesh (250-micron screen) and mix with the above blend then lubricate for a period of 3 minutes. Lubricated blend was compressed in to tablet with suitable punches. To prevent the dose dumping of tablets functional coating dispersion was prepared by dissolvingEthylcellulose (Ethocel 4 cP STD. Primium) and Hydroxypropyl cellulose (Klucel- LF) in hydroalcoholic solvent along with Triethyl Citrate as plasticizer and Talc as anti-adherent. The core tablets were coated with the above functional coating dispersion. Unit composition of the formulation trails are given in Table 8. Initially prototype formulation was designed and then design of experiment (DoE) was conducted with selected factor and response was evaluated in Table 8.

Table 8: Unit composition of prototype controlled release formulation

Ingredients	Quantity per unit(mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tofacitinib Citrate*¥	17.77	17.77	17.77	17.77	17.77	17.77	17.77	17.77	17.77
Microcrystalline Cellulose (Avicel PH 101)#	89.27	84.27	79.27	74.27	69.27	69.27	66.27	62.27	64.27
Hypromellose (Methocel K100 premium LV CR)	5.00	10.00	15.00	15.00	18.00	17.00	18.00	20.00	20.00
Polyethylene Oxide(sentryPolyox WSR N80 LEO)	－－	－－	－－	5.00	7.00	8.00	10.00	12.00	10.00
Colloidal silicon dioxide	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00

Butylated Hydroxy Toluene	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Extragranular									
Microcrystalline Cellulose (Avicel PH 102)	38.96	38.96	38.96	38.96	38.96	38.96	38.96	38.96	38.96
Magnesium Stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Core Tablet Weight	**163.00**	**163.00**	**163.00**	**163.00**	**163.00**	**163.00**	**163.00**	**163.00**	**163.00**
Functional Coating									
Ethylcellulose(Ethocel 4 cP STD. Primium)	4.20	4.20	4.20	4.20	4.20	4.20	4.20	4.20	4.20
Hydroxypropyl cellulose(Klucel- LF)	1.74	1.74	1.74	1.74	1.74	1.74	1.74	1.74	1.74
Triethyl Citrate	0.59	0.59	0.59	0.59	0.59	0.59	0.59	0.59	0.59
Talc	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.47
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight	**170.00**	**170.00**	**170.00**	**170.00**	**170.00**	**170.00**	**170.00**	**170.00**	**170.00**

* Tofacitinib 11mg (equivalent to Tofacitinib citrate 17.77 mg)

¥ This quantity is based on 100%w/w assay (on anhydrous basis and solvent free basis)and nil water content.

$$\text{Quantity (mg/Tab)} = \text{Label Claim} \times \frac{100}{\%w/w \text{ assay (on anhydrous basis and solvent free basis)}} \times \frac{100}{100-(\%w/w \text{ water content}+\%w/w \text{ solvent content})}$$

Physical characteristic of lubricated blend parameters

Physical characteristic of the blend gives idea about the flow properties of the blend. Bulk density (gm/ml) determined by weight of the blend /volume of the blend. Tapped density (gm/ml) was determined by a measuring cylinder of 100ml capacity with initially weighted blend samples was slowly poured in to the 10mm cylinder then kept in to a densitometer (electro lab Tapped density apparatus).Initial volume of the lubricated blend was noted and tapped the cylinder for 500 times ,noted the final volume. Continue tapping in to 750 times ,noted the final volume. Tapped the cylinder for 1250 times ,noted the final volume.[15]

TD= Initial weight (gm)/ Tapped final volume(ml)

Hauser's Ratio was determined by using following formula,

HR = Tapped density(m/v)/ Bulk density(m/v) X 100

%Carr's index was determined by using following formula,

% CI= Tapped density(m/v)- Bulk density(m/v)/ Tapped density(m/v) x 100

Angle of repose was determined by using following formula,

tan θ = Cone height / Heap radius

Tofacitinib citrate lubricated blend was pass through a funnel with a maximum height level which is placed vertically and measured the maximum possible angle between the cone height(h) of powder blend and the heap radius (r).

Table 9: Physical characterization data of lubricated Blend

Batch No:	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Bulk density(gm/ml)	0.624	0.612	0.621	0.615	0.627	0.623	0.624	0.614	0.624
Tapped density((gm/ml)	0.765	0.761	0.753	0.768	0.761	0.762	0.766	0.759	0.758
Compressibility Index(%)	18.431	19.580	17.530	19.922	17.608	18.241	18.538	19.104	17.678
Hausner's ratio	1.226	1.243	1.213	1.249	1.214	1.223	1.228	1.236	1.215

Compression of Tofacitinib citrate lubricated blend

Tablets were compressed by using Eliza Press compression machine with 6x3mm capsule shape punches. Tablet was compressed with the optimum hardness range and optimum machine speed. All the prototype formulation blend was compressed and evaluated. Physical defect of the tablets like sticking , picking , capping, cracking and other undesirable characteristics were inspected. 20 tablets were selected randomly, the uniformity weight of tablets and the average weight of the tablets were noted. Thickness(mm)and hardness (KP) of 20 tablets of each batch was determined using digital vernier calipers. Initial weight 10 tablets were taken its was recorded and were placed in Roche friabilator rotated for 100 revolutions at 25 rpm and then de-dusted and reweighed. The percentage friability was calculated using the following formula,

Percentage friability (%) = {(A1-B1)/B1} × 100

where, A1 = Initial weight of tablets, B1 = Final weight of tablets after 100 revolutions

Tablets physical properties was represented in Tables no 10.

Table 10: Physical properties of compressed tablets data

Core Tablets parameters/B.No:	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Average weight(mg)	162	163	162	162	163	161	162	162	161
Uniformity weight(mg), min-Max)	158-165	160-164	161-167	160-164	161-168	160-165	163-167	161-165	160-167

Hardness(kp), Min- Max	6.2-8.2	6.5-7.9	6.7-8.1	7.2-8.6	6.7-8.3	6.1-8.5	6.4-8.3	7.3-8.4	6.9-8.5
Thickness(mm), Min-Max	3.75-3.84	3.75-3.81	3.74-3.85	3.73-3.90	3.75-3.85	3.76-3.86	3.74-3.81	3.75-3.86	3.76-3.85
Friability(%)	0.06	0.03	0.02	0.01	0.02	0.02	0.03	0.07	0.05

Coating of Tofacitinib citrate controlled release Tablets

Tablets were coated by using Ganson coating machine 6" coating pan. The physical properties of the tablets like hardness, thickness, was evaluated. All coating machine parameters like spray rate, atomization air pressure, inlet temperature, bed temperature, exhaust temperature, pan speed was evaluated. Coated Tablets physical properties was represented in Tables no 11.

Table 11: Physical properties of coated tablets data

Coated Tablets parameters/B.No:	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Average weight(mg)	170	170	171	170	169	170	170	170	171
Uniformity weight(mg), min-Max)	164-173	168-175	167-176	168-176	165-173	167-177	167-175	166-174	167-176
Thickness(mm), Min-Max	3.80-3.84	3.81-3.83	3.82-3.92	3.83-3.97	3.85-3.95	3.86-3.96	3.84-3.91	3.85-3.96	3.86-3.95

Dissolution study

Dissolution study of tofacitinib citrate controlled release tablets was performed by using USP type-II (Paddle) apparatus , Phosphate Buffer, pH 6.8 as dissolution medium at 50 rpm, volume 900ml. The apparatus was maintained temperature at 37°C ± 0.5°C. At the regular time of intervals (2,4,6 and 8hours) samples was withdrawn and replaced with fresh Phosphate Buffer, pH 6.8 media. Cumulative % drug release was analyzed by HPLC.

Swelling index study of Tofacitinib citrate controlled release Tablets

Swelling index of Tofacitinib citrate controlled release Tablets was determined at temperature 37 ± 0.5°C in pH 4.5 Phosphate buffer over a period of 12 hours. One tablet from each formulation was kept in a petri dish containing 50 ml of buffer solution. Weight of individual tablets was taken initially for swelling study (M1). Aliquot was discarded form the petri dish after 12 hours then blot the swelled tablets in tissue paper and recorded the final weight (M2) and final weight of the tablets taken after 12 hours(M2). Swelling index was calculated using following formula,

Swelling index = (M2 - M1) × 100/M2,

where M_1 is the initial weight of tablet and M_2 is the weight of hydrated tablet.[16]

Result and Discussion

Drug dissolution and Defining design space

Dissolution of Prototype evaluated from F1 to F9. Based on the initial risk assessment and the preliminary feasibility study, a design of experiment with full factorial design was performed for Tofacitinib citrate tablets formulation. Drug release profile in Phosphate Buffer, pH 6.8 at time interval 2hours, 4 hours, 6hours and 8hours were identified as a CQA of the formulation F7 composition.

Optimization of Hypromellose (Methocel K100 premium LV CR),Polyethylene Oxide (sentryPolyox WSR N80 LEO) and Magnesium Stearate levels in mg.

Based on the initial risk assessment, 2^3full factorial design of experiment (DOE) with three center points was studied and from the results of the formulation trails using Design- expert12 software was performed to optimize Hypromellose (Methocel K100 premium LV CR), Polyethylene Oxide (SentryPolyox WSR N80 LEO) and Magnesium Stearate in combination as formulation variables.Drug release at different time points was considered as response. This study also sought to establish the robustness of the proposed formulation.

Table 12: 2^3factorial design to study Hypromellose (Methocel K100 premium LV CR),Polyethylene Oxide (sentryPolyox WSR N80 LEO) and Magnesium Stearate levels in combination.

Factors: Formulation variables			**Levels(%)**		
			-1	0	+1
A:Hypromellose (Methocel K100 premium LV CR)			14.00	17.50	21.00
B:Polyethylene Oxide(sentryPolyox WSR N80 LEO)			8.00	10.00	12.00
C:Magnesium Stearate			1.00	1.50	2.00
Responses		Goal	Acceptance Ranges		
Y1	Dissolution at 2Hrs	Range	Between 25-35%		
Y2	Dissolution at 4Hrs	Range	Between 40-60%		
Y3	Dissolution at 6Hrs	Range	Between 60-75%		
Y4	Dissolution at 8Hrs	Range	Not Less Than 80%		

Table 13: Formulation variables and response in different time interval

Factor 1	**Factor 2**	**Factor 3**	**Respons e 1**	**Respons e 2**	**Respons e 3**	**Respons e 4**
A:Hypromellos e (Methocel K100 premium LV CR)	B:Polyethylene Oxide(sentryPolyo x WSR N80 LEO)	C:Magnesiu m Stearate	Dissolution in 2 Hours	Dissolution in 4 Hours	Dissolution in 6 Hours	Dissolution in 8 Hours

mg	mg	mg	Between 25-35%	Between 40-60%	Between 60-75%	Not Less Than 80%
21	12	1	31	43	63	93
21	12	2	27	40	62	88
21	8	1	32	52	63	98
14	8	2	31	44	61	97
14	12	1	34	45	74	96
17.5	10	1.5	33	51	68	97
17.5	10	1.5	34	53	67	97
14	8	1	35	60	75	98
14	12	2	33	55	71	95
21	8	2	31	54	67	93
17.5	10	1.5	34	52	69	96

ANOVA for selected factorial model:

Response 1: Dissolution in 2 Hours

Table 14: Statistical evaluation of Formulation variables and response 1

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	41.5	5	8.3	49.8	0.0011	significant
A-Hypromellose (Methocel K100 premium LV CR)	18	1	18	108	0.0005	--
B-Polyethylene Oxide(sentryPolyox WSR N80 LEO)	2	1	2	12	0.0257	
C-Magnesium Stearate	12.5	1	12.5	75	0.001	--
AB	4.5	1	4.5	27	0.0065	--
ABC	4.5	1	4.5	27	0.0065	--
Curvature	8.02	1	8.02	48.09	0.0023	--
Residual	0.6667	4	0.1667	--	--	--
Lack of Fit	0	2	0	0	1	not significant
Pure Error	0.6667	2	0.3333	--	--	--
Cor Total	50.18	10		--	--	--

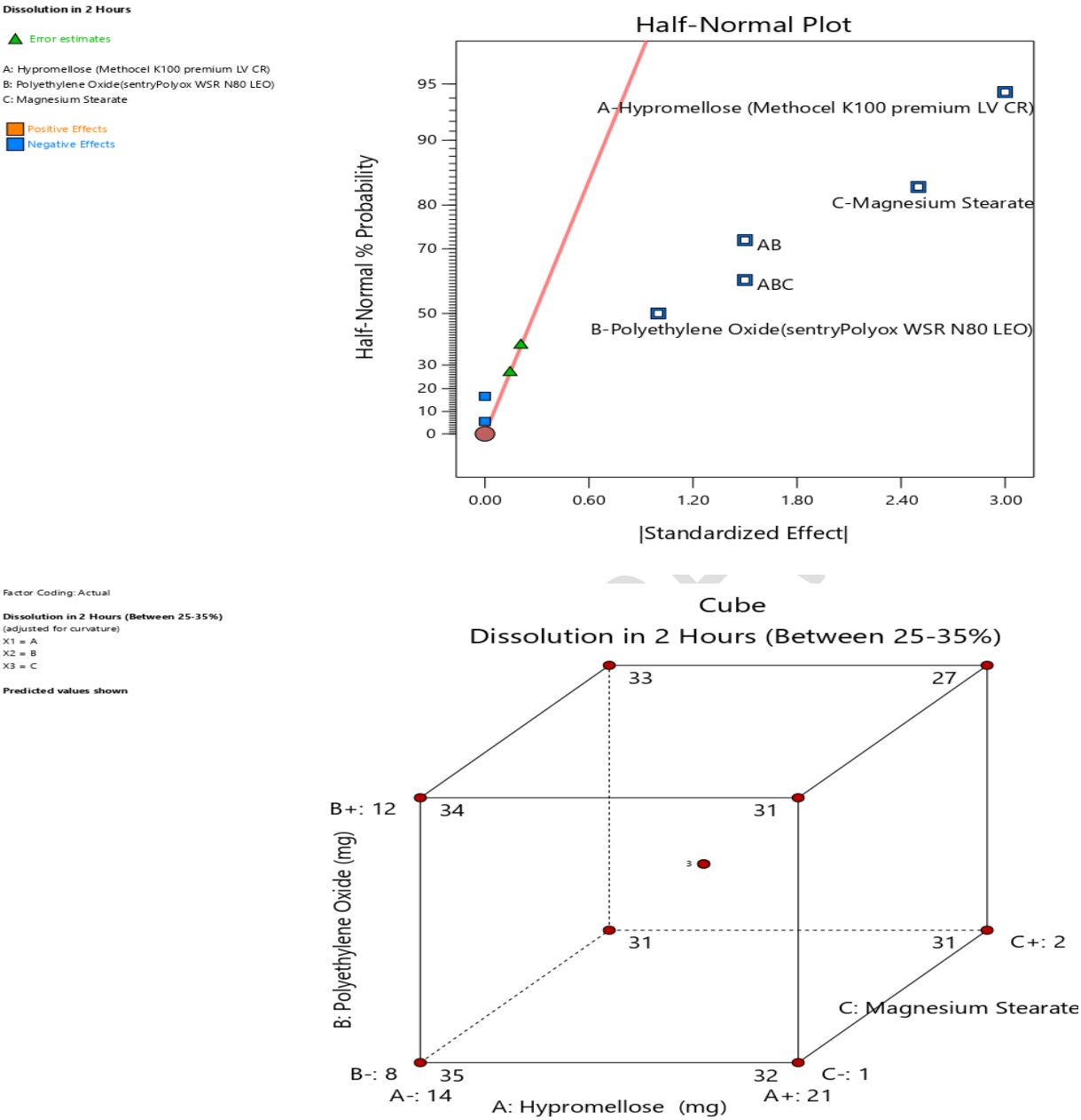


Fig. 2,3. Model F (2 hours dissolution)

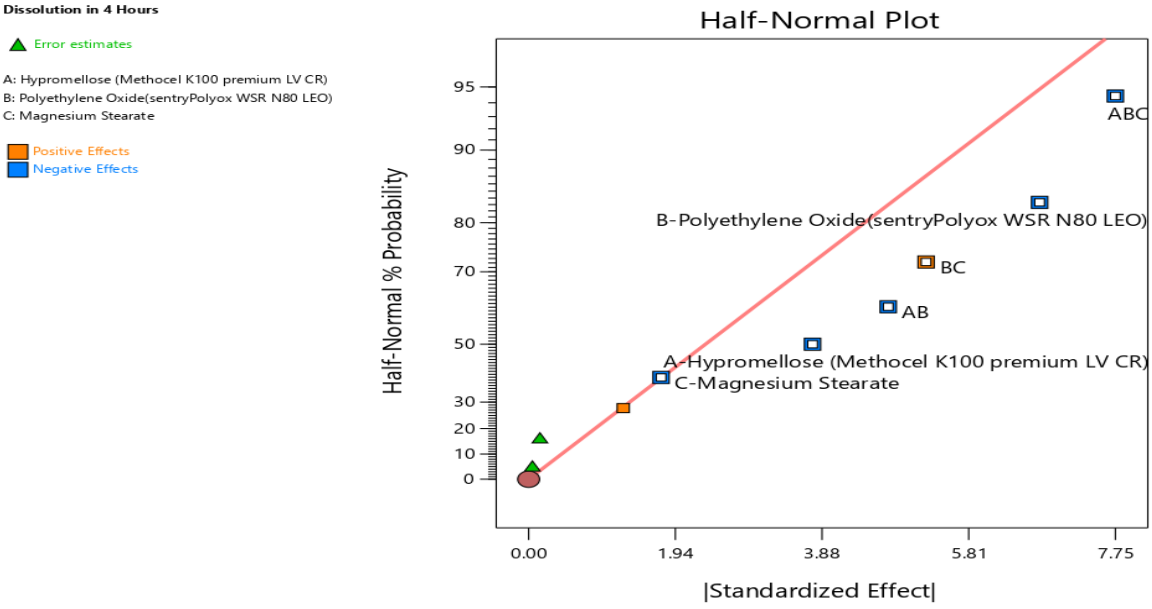
The Model F-value of 49.80 implies the model is significant. There is only a 0.11% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, AB, ABC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The Lack of Fit F-value of 0.00 implies the Lack of Fit is not significant relative to the pure error. There is a 100.00% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good.

ANOVA for selected factorial model:

Response 2: Dissolution in 4 Hours

Table 15: Statistical evaluation of Formulation variables and response 2

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	345.75	6	57.63	33.73	0.0076	significant
A-Hypromellose (Methocel K100 premium LV CR)	28.13	1	28.13	16.46	0.027	--
B-Polyethylene Oxide(sentryPolyox WSR N80 LEO)	91.13	1	91.13	53.34	0.0053	--
C-Magnesium Stearate	6.13	1	6.13	3.59	0.1546	--
AB	45.12	1	45.12	26.41	0.0143	--
BC	55.13	1	55.13	32.27	0.0108	--
ABC	120.13	1	120.13	70.32	0.0036	--
Curvature	18.03	1	18.03	10.56	0.0475	--
Residual	5.13	3	1.71	--	--	--
Lack of Fit	3.13	1	3.13	3.13	0.2191	not significant
Pure Error	2	2	1	--	--	--



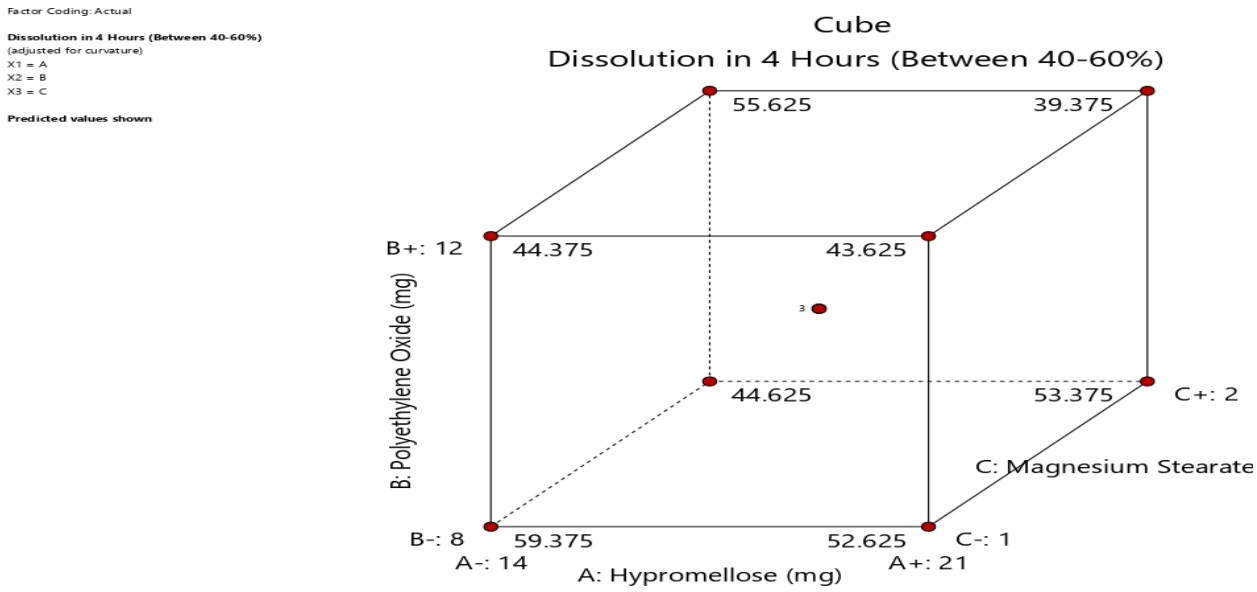


Fig.4,5. Model F (4 hours dissolution)

The Model F-value of 33.73 implies the model is significant. There is only a 0.76% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, BC, ABC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The Lack of Fit F-value of 3.13 implies the Lack of Fit is not significant relative to the pure error. There is a 21.91% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good.

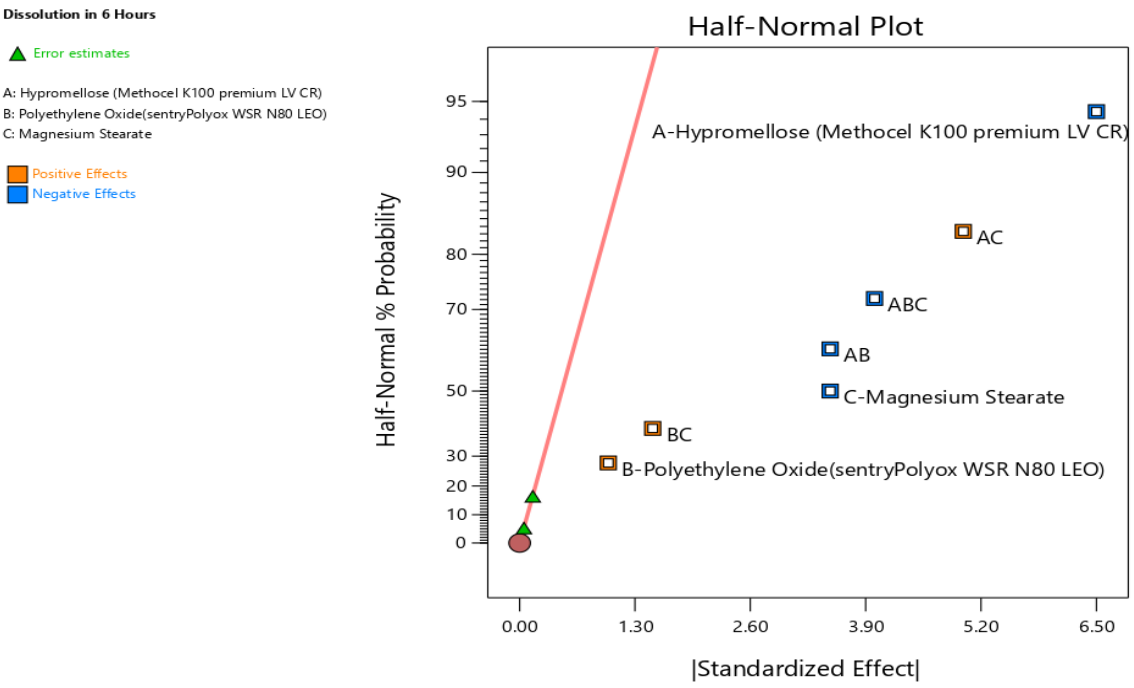
ANOVA for selected factorial model:

Response 3: Dissolution in 6 Hours

Table 16: Statistical evaluation of Formulation variables and response 3

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	222	7	31.71	31.71	0.0309	significant
A-Hypromellose (Methocel K100 premium LV CR)	84.5	1	84.5	84.5	0.0116	--
B-Polyethylene Oxide(sentryPolyox WSR N80 LEO)	2	1	2	2	0.2929	--
C-Magnesium Stearate	24.5	1	24.5	24.5	0.0385	--
AB	24.5	1	24.5	24.5	0.0385	--
AC	50	1	50	50	0.0194	--
BC	4.5	1	4.5	4.5	0.1679	--
ABC	32	1	32	32	0.0299	--

Curvature	2.18	1	2.18	2.18	0.2777	not significant
Pure Error	2	2	1	--	--	--
Cor Total	226.18	10	--	--	--	--



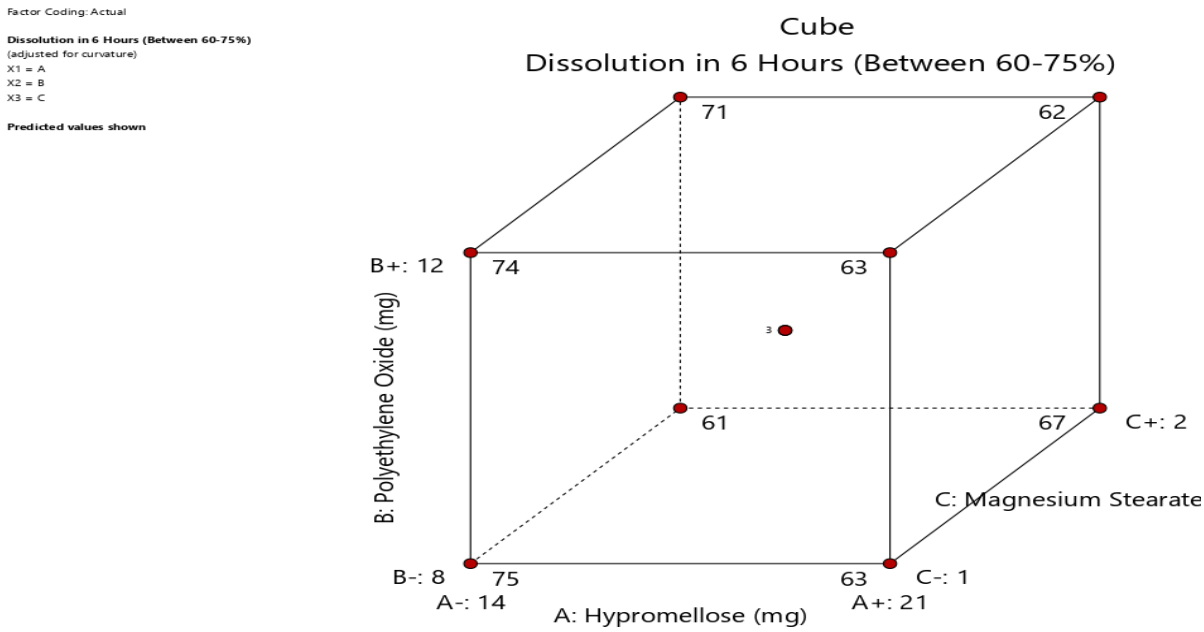


Fig. 6,7. Model F (6 hours dissolution)

The Model F-value of 31.71 implies the model is significant. There is only a 3.09% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, C, AB, AC, ABC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

ANOVA for selected factorial model:

Response 4: Dissolution in 8 Hours

Table 17: Statistical evaluation of Formulation variables and response 4

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	79.5	6	13.25	59.63	0.0033	significant
A-Hypromellose (Methocel K100 premium LV CR)	24.5	1	24.5	110.25	0.0018	--
B-Polyethylene Oxide(sentryPolyox WSR N80 LEO)	24.5	1	24.5	110.25	0.0018	--
C-Magnesium Stearate	18	1	18	81	0.0029	--
AB	4.5	1	4.5	20.25	0.0205	--
AC	8	1	8	36	0.0093	--
ABC	0	1	0	0	1	--
Curvature	8.02	1	8.02	36.07	0.0092	--

Residual	0.6667	3	0.2222	--	--	--
Lack of Fit	0	1	0	0	1	not significant
Pure Error	0.6667	2	0.3333	--	--	--

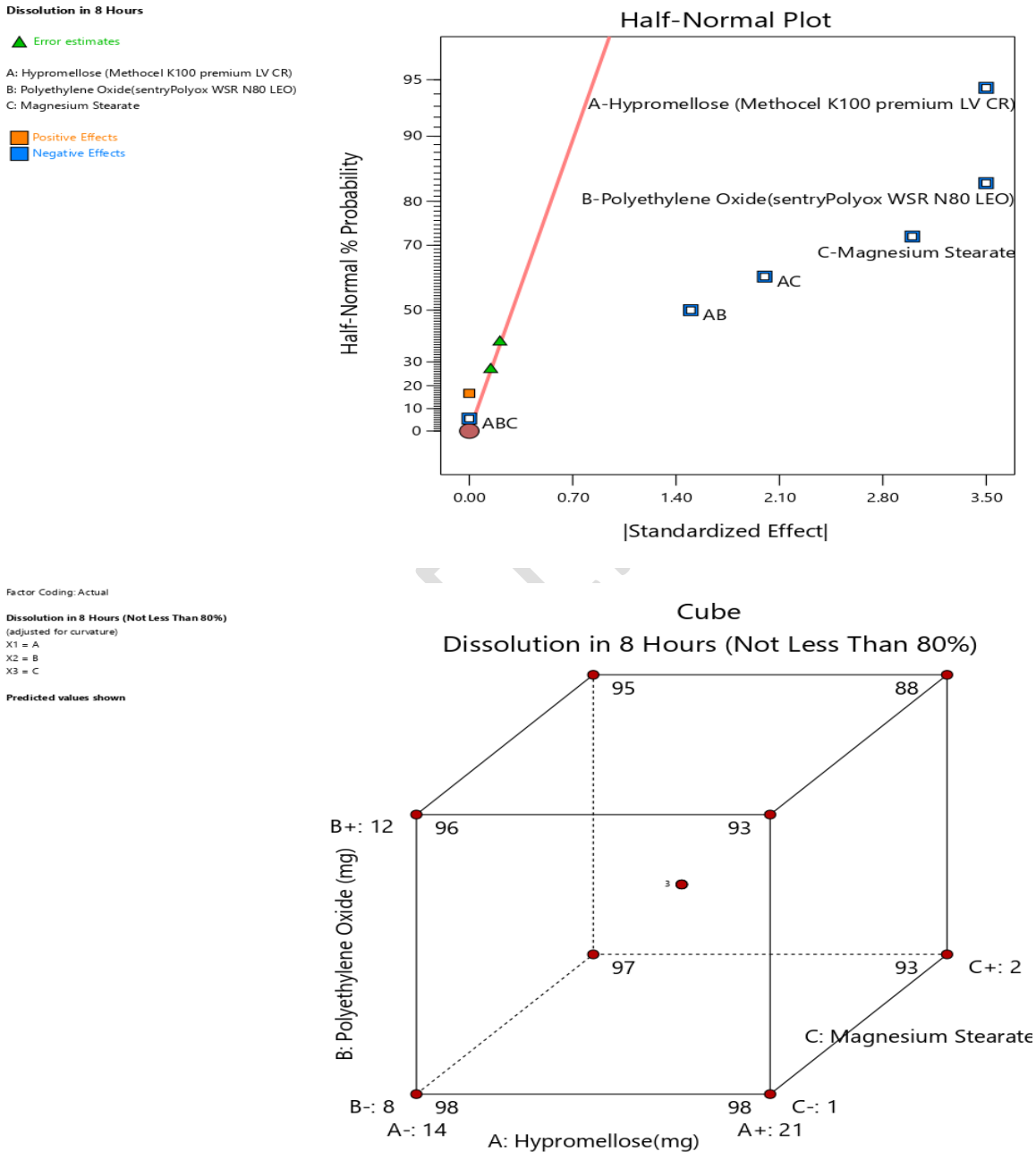


Fig. 8,9. Model F (8 hours dissolution)

The Model F-value of 59.63 implies the model is significant. There is only a 0.33% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, AB, AC is significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The Lack of Fit F-value of 0.00 implies the Lack of Fit is not significant relative to the pure error. There is a 100.00% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good. We want the model to fit.

Updatedrisk assessment of formulation variables impact on Drug product CQA:

The results of updated risk assessment are represented in below table and the justification of the risk prioritization is presented.

Table 18: Updated risk assessment of formulation Variables

Drug product CQAs	**Formulation Variables**		
	Microcrystalline Cellulose Level	Hypromellose Level	Polyethylene Oxide Level
Assay	Low	Low	Low
Dissolution	Low	Low*	Low*
Related substance	Low	Low	Low

Drug product CQAs	**Formulation Variables**		
	Magnesium stearate	Colloidal silicon dioxide Level	Butylated Hydroxy Toluene Level
Assay	Low	Low	Low
Dissolution	Low*	Low	Low
Related substance	Low	Low	Low

*The level of risk reduced from the initial risk assessment

Table 19: Justification for the Initial Risk assessment of formulation Variables

Formulation Variables	**Drug product CQAs**	**Justification**
Hypromellose (Methocel K100 premium LV CR) Level	Dissolution	The level of Hypromellose (Methocel K100 premium LV CR) in formulation at the range 14-21mg gives desired dissolution in predetermined rate. In this range study of hydrophilic polymerdoes not impact the product CQA. The risk is reduced from high to low.
Polyethylene Oxide (sentryPolyox WSR N80 LEO) Level	Dissolution	The level of Polyethylene Oxide (sentryPolyox WSR N80 LEO) in formulation at the range 8mg to 12mg gives desired dissolution in predetermined rate. In this range study of hydrophilic polymer does not

Formulation Variables	Drug product CQAs	Justification
		impact the product CQA. The risk is reduced from high to low.
Magnesium stearate	Dissolution	The level of Magnesium stearate in formulation at the range 1mg to 2mg gives desired dissolution in predetermined rate. In this range study of hydrophobic lubricant does not impact the product CQA. The risk is reduced from high to low.

Summary of excipients range study of formulation variables and design space

Selected formulation variable clearly indicate that observed drug release was within the selected range.Hypromellose (Methocel K100 premium LV CR) level from 14mg to 21 mg, Polyethylene Oxide(sentryPolyox WSR N80 LEO) level from 8mg to 12mg and Magnesium Stearate 1mg to 2mg have entire design space showing drug release between 25-35% in 2 hours,Between 40-60%in 4 hours, Between 60-75% in 6 hours and not less than 80% in 8 hours.

Conclusion

Quality by Design approach gives clear understanding on process parameters and material attributes which impacts on critical quality attributes (CQA), safety and efficacy of the drug product during its lifecycle. Quality by Design (QbD) approach developed a robust formulation and manufacturing process with an acceptable control strategy by Hypromellose (Methocel K100 premium LV CR), Polyethylene Oxide (SentryPolyox WSR N80 LEO) and Magnesium Stearate was done in combination as formulation variables. Drug release profile in Phosphate Buffer, pH 6.8 at time interval 2hours, 4 hours, 6hours and 8hours.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

Reference:

1. Nair, A.K., Ramana, P.V., Rao, P.V.B., Reddy, B.H., Ganthi, H.K.R. and Mallu, U.R.,“Carobomer Based Controlled Release Designs of Atorvastatin Calcium Tablets

Evaluated Using Quality by Design (QbD) Approach", American Journal of Analytical Chemistry, 8, (2017),189-209.

2. Mamatha Tirunagari et al., "Formulation and evaluation of extended release tablets of an antidepressant drug venlafaxine HCL",International journal of research in pharmaceutical sciences,9(4), (2018),1146-1153.
3. Patel H, Parmar S and Patel B, "A comprehensive review on quality by design (QbD) in pharmaceuticals, Int J Pharm Sci Rev Res" 21(1), (2013), 223-236.
4. N.P. Nadpara,R.V.Thumar, V.N.kolala and P.B. Patel, "Quality by design (QbD): A complete review",International Journal of Pharmaceutical Sciences Review and Research,17(2),(2012),20-28.
5. Sanjay Bansal,Sarwar Beg,Babita Garg, Abhay Asthana, Gyati S. Asthana, and Bhupinder Singh, "QbD-Oriented Development and Characterization of Effervescent Floating-Bioadhesive Tablets of Cefuroxime Axetil", AAPS PharmSciTech, Vol. 17, No. 5, (2016), 1086–1099.
6. Ajinkya Upasani, Sanjay Kshirsagar and Mangesh Bhalekar, "Design and optimization of sustained release matrix tablet of opipramol HCL by using quality by design approach",
7. Asian journal of pharmaceutical and clinical research, Vol 7, Issue 5, (2014),227-234.
8. Aleksandar Jankovic ,Gaurav Chaudhary and Francesco Goia, "Designing the design of experiments (DOE) – An investigation on the influence of different factorial designs on the characterization of complex systems",Energy& buildings,250,(2021),111298
9. Charles J. Malemud,"The role of the JAK/STAT signal pathway in rheumatoid arthritis", Ther Adv Musculoskelet Dis., 10(5-6), (2018),117–127
10. Manisha Lamba, Rong Wang,Tracey Fletcher, Christine Alvey, Joseph Kushner, and Thomas C. Stock,"Extended Release Once Daily Formulation of Tofacitinib: Evaluation of Pharmacokinetics Compared With Immediate Release Tofacitinib and Impact of Food", The Journal of Clinical Pharmacology ,60(2),(2020),1-12
11. RujiaXie, ChenhuiDeng,QiangWang,Keith S. Kanik,Timothy Nicholas, and Sujatha Menon, "Population pharmacokinetics of tofacitinib in patients with psoriatic arthritis", Int. Journal of Clinical Pharmacology and Therapeutics,57(9),(2019), 464–473.
12. Zhihong O'Brien and Mehran F. Moghaddam,"A Systematic Analysis of Physicochemical and ADME Properties of All Small Molecule Kinase Inhibitors Approved by US FDA from January 2001 to October 2015",current medicinal chemistry, 24(29), (2017), 3159–3184
13. Nitin Tayade, Manish Rane, Jayesh Parmar, and Ali Rajabi-Siahboomi, "Application of Quality by Design (QbD) Principles in the Formulation of Hypromellose Hydrophilic Matrix Tablets",pharma times , Vol. 46(08),(2014), 20

14. Usir S. Younis, Ernest Vallorz,Kenneth J. Addison, Julie G. Ledford and Paul B. Myrdal, "Preformulation and Evaluation of Tofacitinib as a Therapeutic Treatment for Asthma",AAPS PharmSciTech, 20(5),(2019),167.
15. Chinmaya Keshari Sahoo, Surepalli Ram Mohan Rao and Muvvala Sudhakar,"HPMC a biomedical polymer in pharmaceutical dosage forms" Journal of Chemical and Pharmaceutical Sciences,Volume 8 Issue 4,(2015), 875-881
16. AbolfazlAslani and Hajar Jahangiri, "Formulation, Characterization and Physicochemical Evaluation of Ranitidine Effervescent Tablets",3(2),(2013),315–322.
17. Gurpreet Arora, Karan Malik, Inderbir Singh,Sandeep Aroraand Vikas Rana, "Formulation and evaluation of controlled release matrix mucoadhesive tablets of domperidone using Salvia plebeian gum",Journal of Advanced Pharmaceutical Technology & Research,2(3): (2011),163–169.