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

Abstract

The goal of the project is to use the quality-by-design (QbD) method to create and optimise Tofacitinib citrate matrix tablets with controlled release excipients. The drug's physicochemical parameters, reference product characterisation, QTPP (Quality Target Product Profile), and CQAs were used to start product development (Critical Quality Attributes). Hypromellose (Methocel K100 premium LV CR), Polyethylene Oxide (SentryPolyox WSR N80 LEO), and Magnesium Stearate were used as formulation variables and were optimised together. The complete factorial design of experiment (DOE) with three centre points was used to investigate traditional monolithic controlled release matrix tablets. Using Design-expert12 programme, dissolution was assessed as CQA. At acidic pH, hypromellose with a higher viscosity grade provides a regulated release pattern by retaining the integrity of the medication and preventing rapid drug release. 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

In pharmaceutical research, a novel drug delivery system is presently a demanding technology-based drug delivery system. One of the most ideal platforms for medication design linked to patient safety and efficacy is the controlled release drug delivery system. The medicine is released at a steady pace in a controlled release dose form, allowing therapeutic plasma levels to be maintained. It lowers the frequency of dose and lessens the risk of side effects. [1]

The easiest way to construct a dosage form is to use a formulation that contains a hydrophilic matrix polymer. The medication release rate can be maintained at a predetermined pace depending on the viscosity grade of the polymer. When the polymer comes into contact with aqueous solutions, it hydrates and forms a gel layer via diffusion or erosion, resulting in drug release. [2]

The present scientific and methodical approach to pharmaceutical development and manufacture is known as Quality by Design. The goal of pharmaceutical development is to obtain the required quality while considering the drug's safety and efficacy. [3]. During development, the initial risk assessment determines if the project is high risk, medium risk, or low risk. High risk is unacceptable; further research is required to lower the risk. Medium Risk is tolerable; nevertheless, additional

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inquiry may be required to lower the risk and improve the situation. Low risk is a danger that can be tolerated by most people; no more inquiry is required. The Quality by Design technique provides a thorough knowledge of the process parameters and material properties that have an influence on the pharma product's critical quality attributes (CQA), safety, and efficacy during its development. The Quality by Design (QbD) method creates a stable formulation and manufacturing process, as well as an appropriate control system, to assure the drug's performance. Design of Experiments aids in the creation of the Design space for Formulation, as well as the evaluation of process factors and desired responses using design expert software version 12. [4,5,6,7]

The current study focuses on Tofacitinib citrate controlled release tablets, an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis that is recommended for the treatment of moderately to severely active rheumatoid arthritis (RA). JAK enzymes pair to transmit cytokine signalling (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Many proinflammatory cytokines (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2) signal through common -chain-containing receptors, which is suppressed by the JAK pathway. Tofacitinib citrate has a quick absorption and elimination profile, with a time to maximum plasma concentration (Tmax) of 0.5-1 hour and a terminal half-life (t1/2) of 3-4.5 hours. [8,9,10].

Tofacitinib citrate is classified as a BCS Class III medication (low permeability, high soluble)[11]. In a saturation solubility investigation, drug ingredient solubility was found to be pH dependant. The highest solubility was found in 0.1N hydrochloric acid, and solubility diminishes as pH rises. Tofacitinib citrate tablets with controlled release formulations were created employing the release regulating polymer Polyethylene oxide, Hypromellose (Methocel K100premium LV CR) in the core tablets and Ethyl cellulose, Hydroxy propyl cellulose (Klucel LF) in the coating composition and 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 K100 premium 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 68 g of potassium dihydrogen orthophosphate and 8.9 g 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 1 ml of trifluoro acetic acid into 1000 ml 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 (150 mm x 4.6 mm),5µ column ,Isocratic pump mode, 1.0 mL/minute flow rate, UV, 292 nm detection, injection volume-60 µL, Temperature-35°C, Run time-15 minutes.

EXPERIMENTAL DESIGN

Preformulation studies aid in the knowledge of the drug substance's physico-chemical properties such as solubility, stability, compatibility, and solid-state characteristics, which are followed by drug excipient compatibility studies. Differential scanning calorimetry and physical examination were used to assess the tofacitinib drug substance and appropriate excipients at various concentrations.

3.1 Tofacitinib citrate drug ingredient hygroscopicity studies:

Tofacitinib medicinal material was studied for hygroscopicity by exposing it to an 80 percent RH environment for 24 hours and calculating the percent mass change. Table 1 summarises the findings. The maximum weight gain in the hygroscopicity testing was 0.102 percent at 80 percent RH based on

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three samples. As a result, a weight increase of less than 2% suggests that the Tofacitinib product is non-hygroscopic.

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 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

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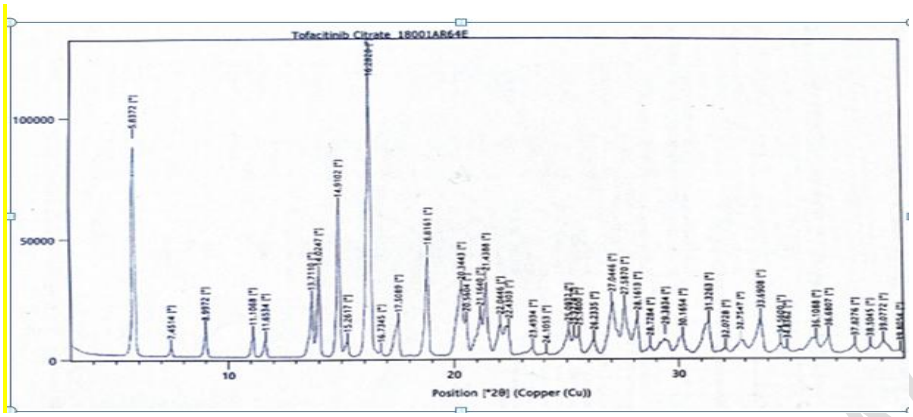

Fig. 1: XRD data of Tofacitinib drug substance

Formulation design experiments

Quality by Design (QbD)

Designing for quality requires a scientific foundation. Pharmaceutical development starts with a purpose in mind, which helps to clarify product and process quality. The quality goal product profile, the critical quality characteristic, the critical process parameters, and the control plan are all included. According to the current research, the amount of hydrophilic polymer in core tablets and the amount of pore-forming hydrophobic polymer has a direct effect on the important quality characteristic.

Early in the development process, the aim is established based on the qualities of the drug ingredient. The outcome of creating a formulation and manufacturing process with an appropriate control plan that assures medication performance from start to end. Physical and chemical properties that are within a certain limit or range, allowing it to fit into the 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

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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 correlate 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 correlate 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% 6 Hrs-60-75% 8 Hrs- NLT 80 %	Critical	Input materials of drug substance, excipients and 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.

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- 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 determine 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 improves 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	Assay	Hypromellose (Methocel K100 premium LV CR) is used as release retardant hydrophilic polymer .It has good

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Formulation Variables	Drug product CQAs	Justification
premium LV CR) Level		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 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	Polyethylene Oxide (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 under go oxidation properties. So, Butylated Hydroxy Toluene added 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 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 absorbs moisture. Hence it will not impact the Related substance of finish product. So, the risk is low.
Butylated Hydroxy	Assay	Butylated Hydroxy Toluene is used as an antioxidant and prevents oxidation during storage. It is unlikely impact the

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Formulation Variables	Drug product CQAs	Justification
Toluene Level		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

Based on literature data and a preformulation research, tofacitinib citrate Tablets were developed as a controlled release drug delivery system. Controlled release hydrophilic excipients were chosen depending on the release characteristics of the target medication. Tofacitinib citrate drug substance and Hypromellose (Methocel K100 premium LV CR) were processed together with an ASTM 30 mesh sieve (600 micron screen). The remaining intra-granular material, such as Microcrystalline Cellulose (Avicel PH 101), Polyethylene Oxide (sentryPolyox WSR N80 LEO), and Colloidal Silicon Dioxide, was sorted using an ASTM 25 mesh screen (710-micron screen). For consistent mix homogeneity, all sifted ingredients are passed through an ASTM 25 mesh (710-micron screen). For the manufacture of granulating fluid, butylated hydroxy toluene was dissolved in isopropyl alcohol. Over the course of three minutes, the dry mix blend was granulated with the non-aqueous granulating fluid in a high shear mixer granulator with impeller slow and chopper slow speeds. Using an IR moisture analyser, the wet mass was dried in a Fluid bed processor at inlet temperature 45°C-5°C for 1 hour to achieve the target moisture content value of less than 3% w/w. Through a 0.8mm screen, the dry granules were co milled. Extragranular Microcrystalline Cellulose (Avicel PH 102) was blended with dried granules in a low shear cone blender for 10 minutes after passing through an ASTM 40mesh (425-micron screen). Magnesium Stearate was screened using an ASTM 60 mesh (250 micron screen) before being mixed with the aforesaid mixture and lubricated for 3 minutes. With the use of appropriate punches, the lubricated mix was crushed into a tablet. To avoid dosage dumping, a functional coating dispersion was made by dissolving ethylcellulose (Ethocel 4 cP STD. Primium) and hydroxypropyl cellulose (Klucel- LF) in a hydroalcoholic solvent with Triethyl Citrate as a plasticizer and Talc as an anti-adherent. The aforesaid functional coating dispersion was applied to the core tablets. Table 8 shows the unit composition of the formulation trails. The prototype formulation was created first, followed by a design of experiment (DoE) using the specified component, and the response was analysed in Table 8.

Table 8: Unit composition of prototype controlled release formulation

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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

The flow qualities of the mix are determined by the physical characteristics of the blend. Bulk density (gm/ml) is calculated as the weight of the blend divided by the volume of the mix. A 100ml measuring cylinder with originally weighted blend samples was progressively emptied into a 10mm cylinder and stored in a densitometer to estimate its density (gm/ml) (electro lab Tapped density

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apparatus). The initial volume of the lubricated mix was recorded, and the ultimate volume was calculated by tapping the cylinder 500 times. Continue punching in for a total of 750 times, taking note of the final volume. I tapped the cylinder 1250 times and recorded the 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

Eliza Press compression machine with 6x3mm capsule form punches was used to compress the tablets. The ideal hardness range and machine speed were used to compress the tablet. The prototype formulation mix was compressed and tested in its entirety. The tablets were examined for physical defects such as sticking, picking, capping, cracking, and other undesirable qualities. Twenty pills were chosen at random, and the uniformity weight and average weight of the tablets were recorded. Digital vernier callipers were used to measure the thickness (mm) and hardness (KP) of 20 tablets from each batch. The initial weight of 10 pills was recorded, and they were then placed in a Roche friabilator and spun for 100 revolutions at 25 rpm before being de-dusted and reweighed. The following formula was used to compute the % friability:

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

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

Tablets physical properties were represented in Tables 10.

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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, were 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 were represented in Tables 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,

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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 2 hours, 4 hours, 6 hours and 8 hours 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- expert 12 software was performed to optimize Hypromellose (Methocel K100 premium LV CR), Polyethylene Oxide (Sentry Polyox 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 (sentry Polyox 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

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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		--	--	--

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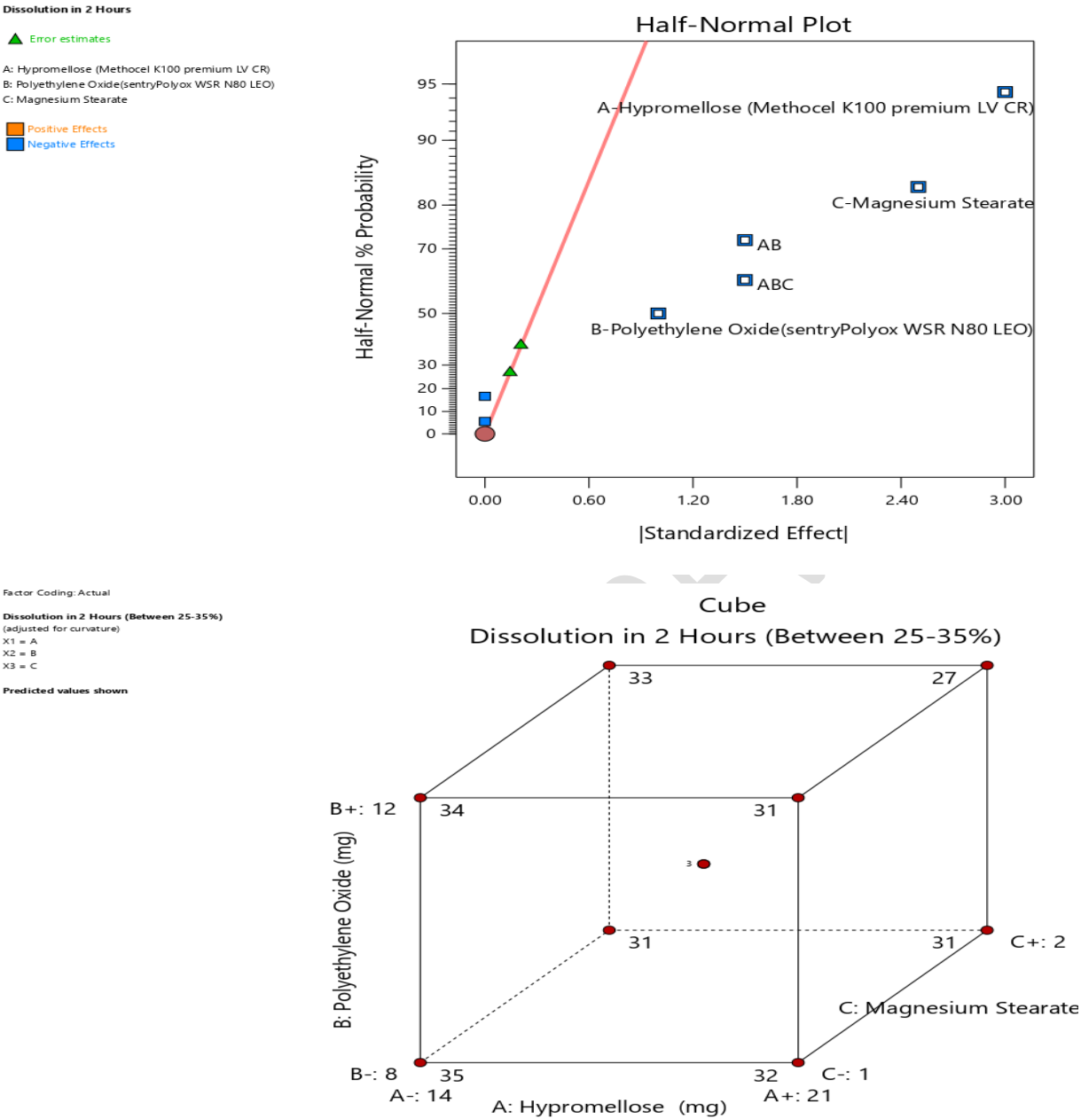


Fig. 2: Model F (2 hours dissolution)

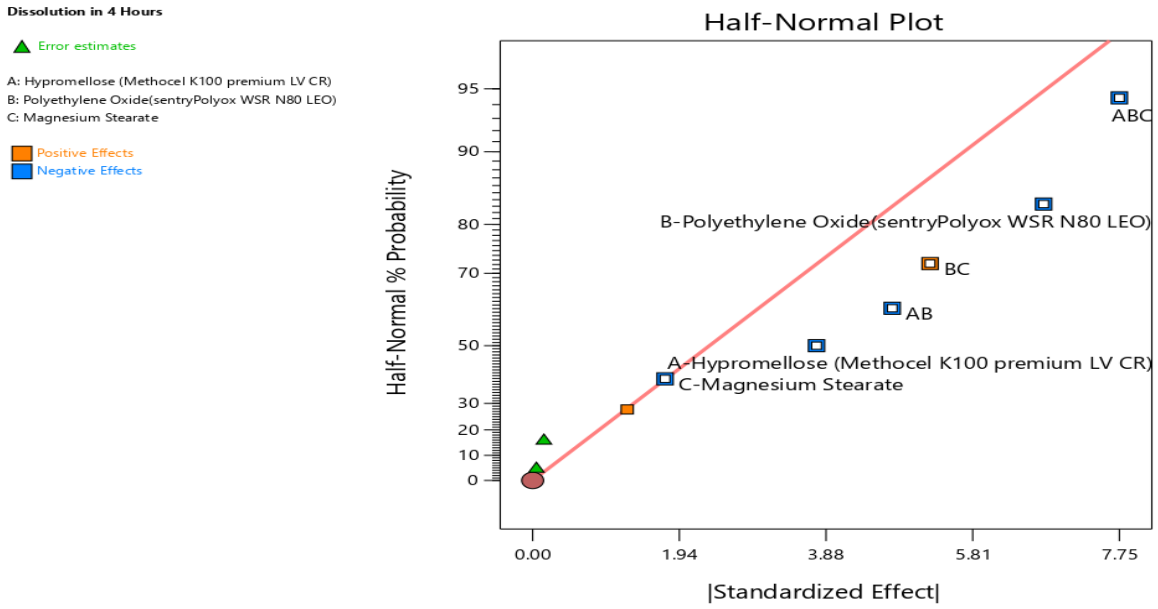
The Model F-value of 49.80 implies the model is significant. There is only a 0.11% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, AB, ABC are significant model terms. Values greater than 0.1000 indicate 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	--	--	--



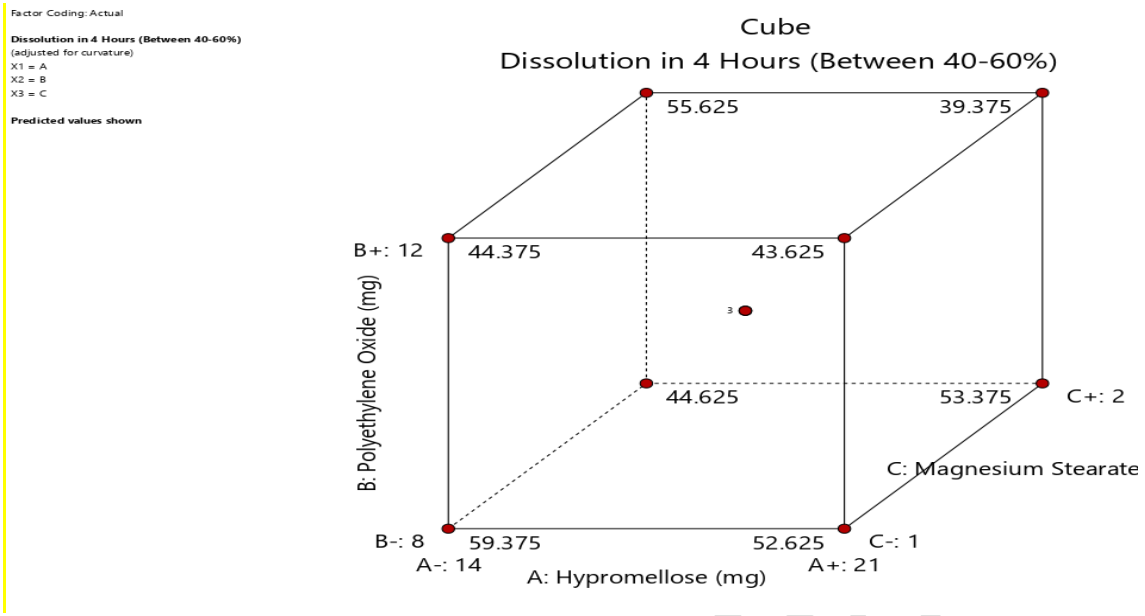


Fig. 3: Model F (4 hours dissolution)

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	--	--	--	--

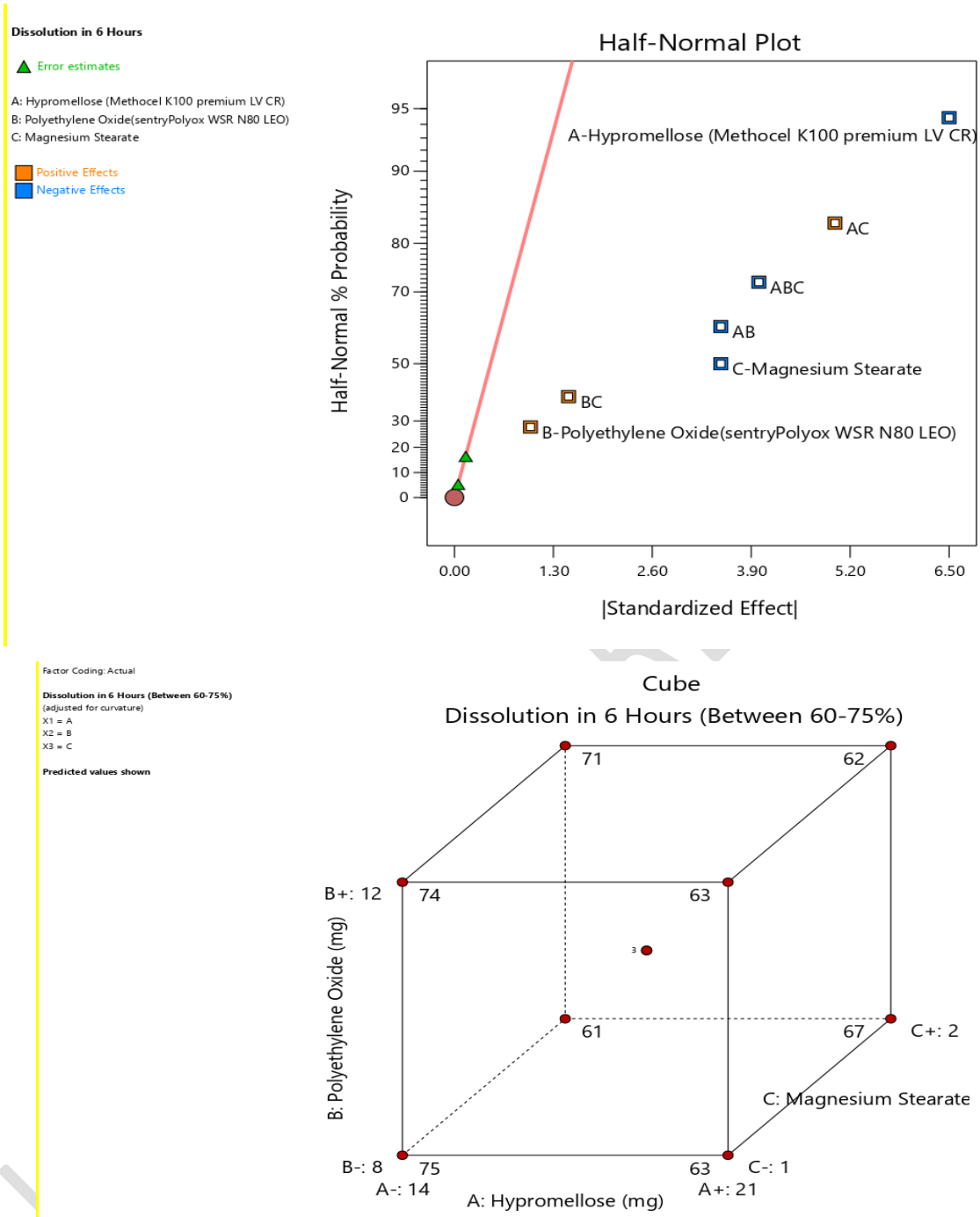


Fig. 4: Model F (6 hours dissolution)

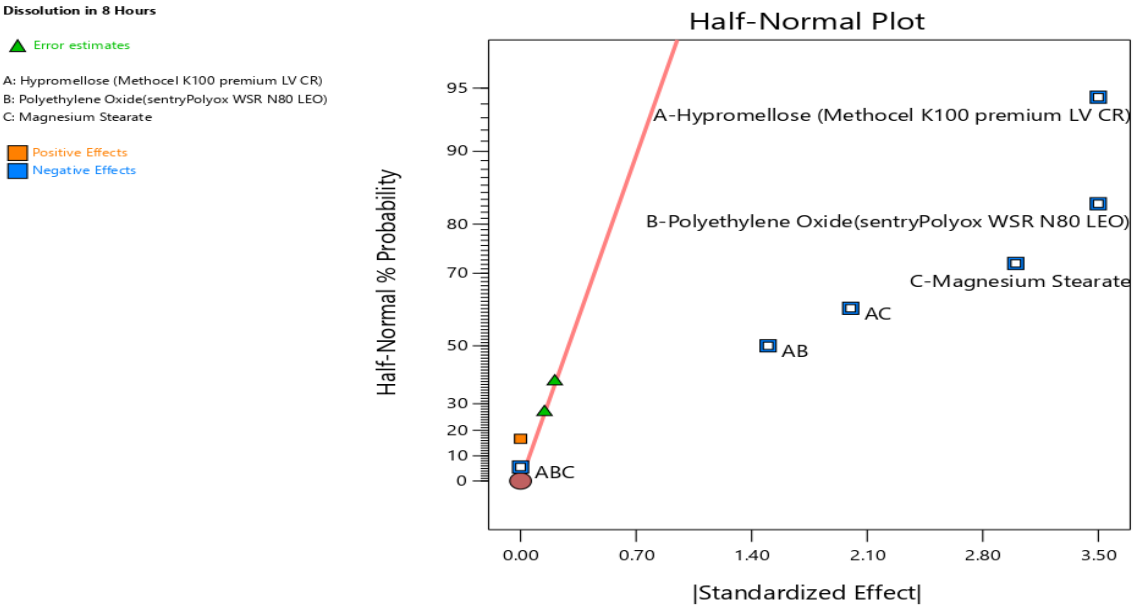
The Model F-value of 31.71 implies the model is significant. There is only a 3.09% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, C, AB, AC, ABC is significant model terms. Values greater than 0.1000 indicate 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	--	--	--



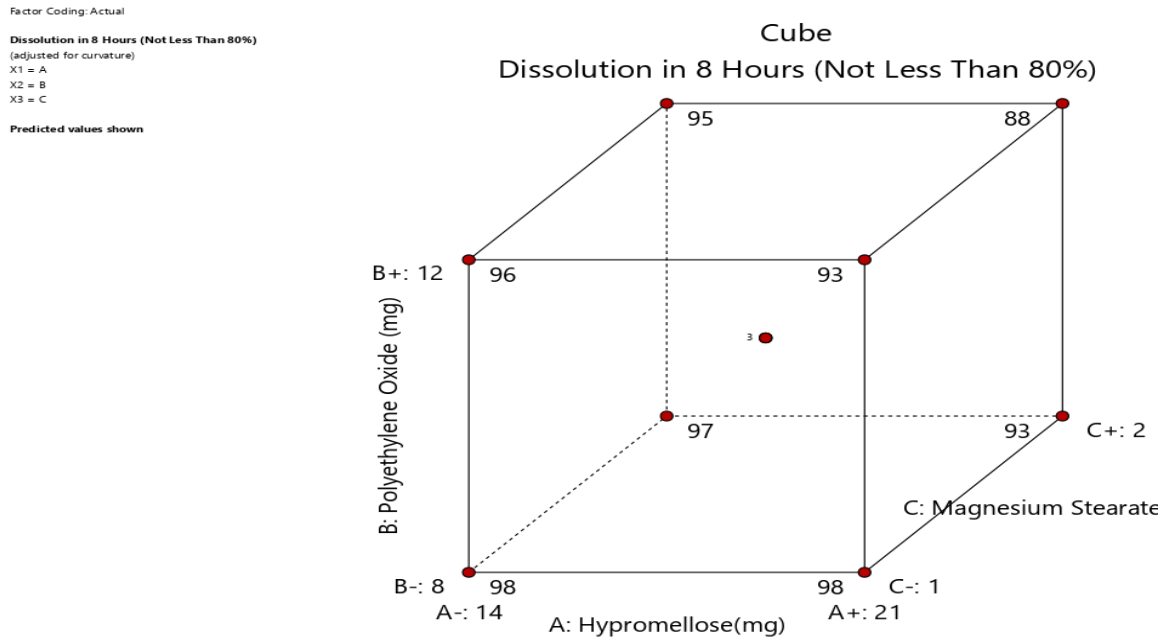


Fig. 5: Model F (8 hours dissolution)

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.

Updated risk 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 polymer does 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 (sentry Polyox 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 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 (Sentry Polyox 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 2 hours, 4 hours, 6 hours and 8 hours.

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.

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