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QUALITY-BY-DESIGN-BASED DEVELOPMENT AND OPTIMIZATION OF WURSTER-COATED INDOMETHACIN EXTENDED-RELEASE PELLETS FOR MULTIPLE UNIT PELLET SYSTEM (MUPS) CAPSULES: IN VITRO CHARACTERIZATION AND COMPARATIVE DISSOLUTION EVALUATION

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ABSTRACT:
Objective: the objective of the present investigation was to develop and optimize indomethacin extended-release pellets for encapsulation into a multiple unit pellet system (MUPS) using a quality-by-design (QbD) approach. Extended-release pellets were prepared by Wurster fluid-bed coating employing ethyl cellulose as the rate-controlling polymer, with povidone and talc as formulation auxiliaries, to achieve a robust and reproducible sustained-release dosage form.
Methods: An optimisation approach grounded in QbD and utilizing response surface methodology (RSM) was applied to analyse the effects of significant formulation variables on drug release characteristics. The independent factors for indomethacin release consisted of ethyl cellulose, povidone, and talc content. The formulations were meticulously characterized for their micromeritic properties, friability, drug content, and in vitro release performance and short term accelerated stability study.
Results: The optimized indomethacin ER pellets filled into hard gelatin capsule (HGC) displayed a controlled release for a duration of 12 hours, effectively minimizing the initial burst and allowing for once-daily administration. The optimized indomethacin ER pellets exhibited controlled release over 12 hours (97% at 12h), with dissolution comparable ($f2 = 85$, $f1 = 3$) to the marketed product (Indocap SR Tablets 75mg), meeting USP specifications in pH 6.2 phosphate buffer. The formulation demonstrated acceptable micromeritic properties (Carr's Index: 10.84) and stability under accelerated conditions (60±2°C for 28 days). Future investigations may include in vivo pharmacokinetic studies and stability assessments according to ICH guidelines to further confirm clinical importance and commercial viability. The f2 metric of dissolution data between test and reference product was found to be 85%, which shows similarity between test and reference products. Statistical analyses and response surface plots identified the content of ethyl cellulose of 8 mg per capsule, was found to be most critical material attribute for in vitro release of indomethacin.
Conclusion: At 12 hours, the cumulative drug release reached 92–100%, fulfilling the sustained-release profile objectives. ANOVA confirmed a statistical significance ($p = 0.0194$). Factor effect screening demonstrated that ethyl cellulose (Factor A) exerted a statistically significant influence ($p = 0.0065$), whereas povidone K30 and talc exhibited negligible contributions.

KEYWORDS: Indomethacin, NSAIDs, Ethyl Cellulose, Wurster coating, Multiple Unit Pellet System, Quality by Design.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are acknowledged for their pain-relieving and anti-inflammatory properties, accounting for approximately 8% of prescriptions worldwide, with a higher prevalence among individuals aged 65 and above. Furthermore, there has been an increase in over-the-counter use, with 26% exceeding the recommended dose and many undisclosed to medical professionals [1,2]. NSAIDs are a drug class FDA-approved for use as antipyretic, anti-inflammatory, and analgesic agents [3] used to treat pain, fever, and other inflammatory processes. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and are used as opioid-sparing agents in certain acute trauma cases [4–6]. The main mechanism of action of NSAIDs is inhibition of the cyclooxygenase (COX) enzyme. Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins [7]. Importantly, because COX-1 is the primary mediator of gastric mucosal integrity and COX-2 is mainly involved in inflammation, COX-2-selective NSAIDs may provide anti-inflammatory relief without

compromising gastric mucosal integrity [8]. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. To deliver the recommended total dose, these subunits are encapsulated or compressed into a tablet [9]. Multi-particulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. Recently, much emphasis has been laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits, such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [10,11].

To prepare the formulation, a bottom spray coating (wurster coating) process was chosen for the sugar sphere drug layering process that yields the controlled release drug product because this process is commercially acceptable and results in highly uniform coating of particulates as compared to extrusion spheronization or centrifugal coating granulation process.

A statistical approach i.e., response surface methodology (RSM) is chosen for optimising the coating dispersion composition to achieve drug release which is comparable to that of marketed formulation. Ethyl cellulose was selected as the rate-controlling polymer due to its established safety profile, excellent film-forming properties, and ability to provide pH-independent sustained release through its hydrophobic nature. Povidone K30 was incorporated as a binder to improve drug loading efficiency and ensure uniform adhesion of the drug-polymer layer to the sugar spheres, while talc served as an anti-tacking agent to prevent pellet agglomeration during the coating process. Moreover, investigated the compatibility of drug with excipients, and compared the drug release profile of optimized formulation with a marketed product.

MATERIALS AND METHOS

Materials

Indomethacin was selected as model drug for the development of extended-release (ER) pellet formulation. It was generously supplied as gift samples by Jubilant Generics Ltd., Roorkee, India.

The marketed product of Indomethacin sustained release capsules 75mg (Indocap SR capsules/ B.No. JSR-281), manufactured by Jagsonpal Pharmaceuticals Limited was procured from a local chemist's shop. Excipients were selected based on their intended use and their functionality. Sugar Spheres (Pharm-A-Sphere 30-35 mesh) were used as base for drug-polymer layering. Ethyl cellulose 4 cps was used as the primary release-retardant polymer, Povidone K30 was used as a binder, Talc used as an anti-tacking and glidant agent. Other processing aids included are isopropyl alcohol and purified water as solvents. All other reagents were analytical grade from standard suppliers.

METHODS

Calibration Curve of Indomethacin

A standard stock solution of indomethacin was prepared by accurately dissolving 100 mg of the drug in 100 mL of methanol to obtain a concentration of 1 mg/mL. An aliquot of 5 mL of this stock solution was subsequently diluted to 100 ml with phosphate buffer (pH 6.2) to yield a working standard solution containing 50 µg/mL of indomethacin. The absorption spectrum of the drug was recorded over the wavelength range of 200-800 nm using a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan) to determine the wavelength of maximum absorbance (λmax). Based on the obtained spectrum, indomethacin exhibited maximum absorbance at 319 nm, which was selected for quantitative analysis.

A series of standard solutions with concentrations ranging from 5 to 50 µg/mL were prepared by appropriate dilution of the working standard solution using phosphate buffer (pH 6.2) as the diluent. The absorbance of each solution was measured at 319 nm against the corresponding blank. A calibration curve was constructed by plotting absorbance versus concentration, and the linear regression equation along with the correlation coefficient (R^2) was determined to assess the linearity of the analytical method.

Melting Point Determination

The melting characteristics of indomethacin were examined by the capillary tube method employing a melting point apparatus (Jyoti Scientific Laboratories, Gwalior, India). The filled capillary tube was subjected to gradual heating, and the sample was observed for phase transition. The temperatures at the onset and completion of melting were noted, and the resulting melting range was compared with literature-reported values as a preliminary confirmation of drug identity and purity.

FTIR

FTIR spectroscopy was employed to investigate the compatibility between indomethacin and the excipients used in the formulation. The spectra of pure indomethacin and optimized ER pellets were recorded using an FTIR spectrophotometer (FTIR-8400S, Shimadzu, Japan) by the potassium bromide (KBr) pellet method. Approximately 2-5 mg of sample was mixed with spectroscopic-grade KBr (1:100 ratio), finely triturated, and compressed into pellets under a pressure of about 9 tons/in². The obtained spectra were analyzed for characteristic functional group peaks and compared to evaluate potential drug-excipient interactions and structural changes resulting from the formulation process.

Drug-Excipients Compatibility Study

The compatibility of drug and polymers under experimental conditions is an important prerequisite before formulation to confirm that the drug does not react with the polymers and other excipients under experimental conditions. Hence, preformulation investigations were executed to recognize the characteristics of the drug and to assess suitable excipients. The selected excipients are sugar spheres, ethyl cellulose, povidone, talc and isopropyl alcohol. Indomethacin was mixed with individual and mixture of all excipients at specific ratio and filled into glass vials in duplicate. One set of vials were closed with a rubber closure, sealed, and kept in an oven at 60±5°C for 4 weeks. Similarly, 2nd set of vials were closed with a rubber closure that was punctured with a needle to make it permeable to external temperature and humidity and then kept at controlled room temperature (20 -25°C) & relative humidity (NMT 60%) for 4 weeks. Samples were visually checked periodically up to 4 weeks and compared with the control samples kept in separate vials under sealed condition. In addition, vials containing API and a mixture of all excipients in a 1:10 ratio was checked for FTIR study by taking the powder content after 4 weeks of study.

Formulation development of MUPS Capsules

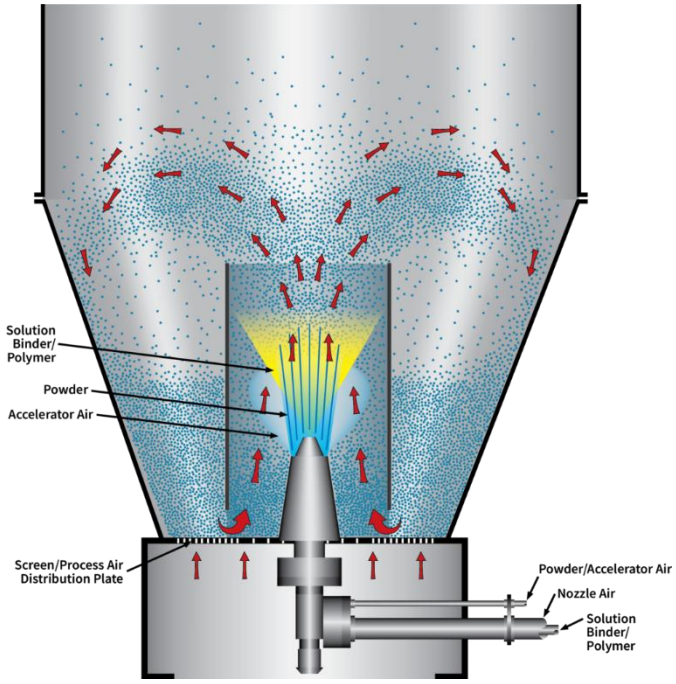
Indomethacin ER pellets were prepared by Wurster coating process using bottom-spray fluid bed processor (Make-ACG Pam Pharma, Model GPCG 1.1), involving sequential steps of preheating, drug-polymer layering, drying and lubrication, as per the formula listed in Table 1. The input quantity (mg/capsule) of selected formulation variables i.e., ethyl cellulose, povidone and talc were varied as per design of experiments (DoE) plan mentioned in table 6. A Box-Behnken design was selected as it requires fewer runs than a full factorial design while still allowing estimation of quadratic and interaction effects. The 15-run design provided adequate degrees of freedom for model fitting and residual analysis.

Table 1: Composition of Indomethacin MUPS Capsules

Name of Ingredient/ Brand Name	**Vendor**	**Std. Quantity (mg/capsule)**	**Quantity per batch (g)**
			Batch size: 2000 Capsules
Stage 1: Drug-Polymer Layering			
Sugar Spheres (Pharm-A-Sphere 30-35 mesh)	Hanns G. Werner	179.20	@358.40
Indomethacin (Micronized)	FIS Spa	75.00	*180.00
Ethyl cellulose (Ethocel 4 cps Std. Prem.)	Colorcon	0.80	*1.92
Povidone (Kollidon K-30)	BASF	15.00	*36.00
Talc (Talc Luzenac Pharma)	Luzenac Pharma	2.00	*4.80
Isopropyl Alcohol	Finar	q. s.	*623.28
Purified Water	-	q. s.	*267.12
Wt. of ER pellets		272.00	544.00
Stage 2: Capsule Filling			
Wt. of ER pellets	-	272.00	544.00
HGC Shell (Size '2') – No.s	Associated Capsules	1.00	2000.00

**Contains 20% overages to compensate the loss during spraying step*
$ Quantity varies between different formulation(s) as per DoE protocol

@ Used as filler to compensate the weight change of the capsule
q.s.: quantity sufficient



As per DoE plan, required quantity of drug and all excipients were weighed using precision weighing balance. Isopropyl alcohol and purified water in a 7:3 ratio are mixed in stainless steel container and addition of Ethyl cellulose under continuous stirring (stirring time: 30 min) followed by addition of Povidone and stirred to get clear solution (stirring time: 30 min). Then drug and talc were dispersed in the above polymer solution and stirred further to get uniform dispersion (stirring time: 30min) followed by sifting of dispersion through 80# mesh screen.

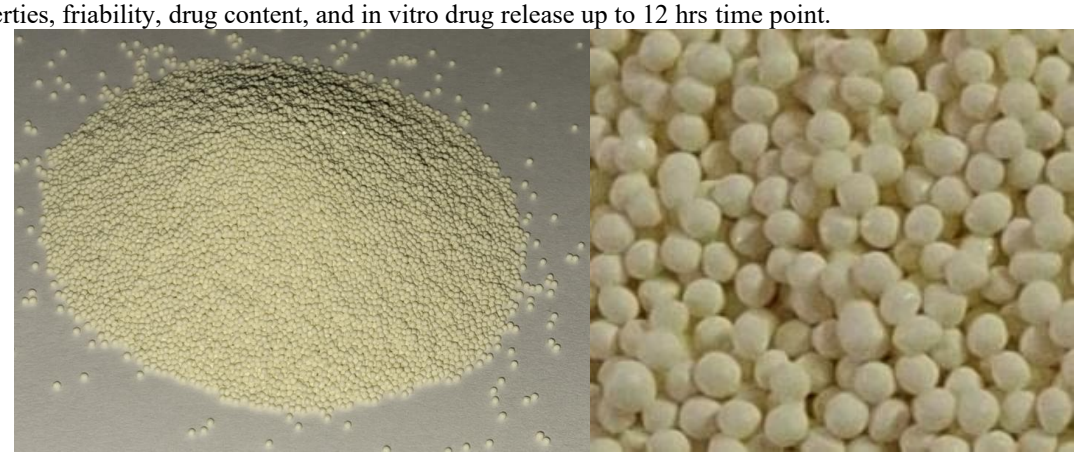
Sugar Spheres added to the product container of Fluid Bed Processor (GPGC 1.1) with bottom spray attachment and preheated the material till the bed temperature achieved between 30-35°C. Then drug-polymer dispersion was sprayed onto preheated/ fluidized sugar spheres using the process parameters listed in Table 2 to achieve the target weight gain of 50.0 ±2% w/w. To ensure uniform drug-polymer layering on the pellets, the height of the Wurster column was carefully adjusted during the spraying step to maintain optimal fluidization of the pellets/ prevents both agglomeration (from over wetting) and coating loss (from poor draft). Drug-layered pellets were finally dried at inlet temperature of 50-60ºC for 30min as part of the curing process. The coated pellets were weighed accurately and blended in double cone blender for 3 minutes to uphold the coating's integrity and then filled into size 2 empty hard gelatin capsules (HGC) by manually. Each capsule was checked for fill integrity and uniformity in weight using a precision analytical balance.

Table 2: Critical process parameters (CPPs) used in GPCG 1.1 to prepare Indomethacin ER pellets

CPPs	**Observations**
Number of Guns	01
Nozzle tip diameter (mm)	1.0
Filter bag pore size (µ)	10
Air distribution plate type	C
Column height (mm)	10-15
Inlet Air Temperature (ºC)	30-46
Exhaust Temperature(ºC)	25-35
Product Temperature(ºC)	30-35 (target 32)
Inlet Air Flow (CFM)	50-100
Atomization Pressure (bar)	1.0-1.2
Spray Rate (gm/minute)	2-14
Inlet air RH (%)	25-35
Drying temperature(ºC)	50-60

Drying Time (Minute)	30 min
LOD (at 105°C in 2 minutes).	Not More Than 3.0%

To impart extended-release properties and to achieve desired drug release profile, the multiple composition was developed by varying the concentration of ethyl cellulose, povidone and talc in the coating dispersion according to the experimental design. Talc was incorporated during the coating process also to minimize pellet agglomeration and improve processability. The resulting coated pellets were evaluated for micromeritic properties, friability, drug content, and in vitro drug release up to 12 hrs time point.



Optimization by design of experiments (DoE)

QbD based strategy was adopted for the optimisation of indomethacin ER pellets. Response surface methodology (RSM) was employed using Design-Expert® software to study the effect of formulation variables on drug release behaviour.

For indomethacin ER pellets, a Box–Behnken design was applied with three independent variables: concentration of ethyl cellulose (Factor A), povidone K30 (Factor B), and talc (Factor C). The dependent responses were percentage drug release at 1 hour (R1), 2 hours (R2), 4 hours (R3), and 12 hours (R4). The goal was to minimise burst release while achieving sustained release at least up to 12 hours. Experimental data were fitted to linear, interaction (2FI), and quadratic models. Model adequacy was evaluated using ANOVA, adjusted and predicted R^2 values, and lack-of-fit tests. Perturbation plots and 3D response surface plots were generated to visualise factor influences and interactions. Finally, a numerical optimisation based on a desirability function was performed to identify the optimal formulation space, ensuring robust performance of indomethacin ER pellets.

Drug Content

The final formulation selected based on DoE study outcome was subjected to assay testing before and end of stability study. Diluent was prepared by mixing Phosphoric acid and water in a 1:99 ratio to make a 100 mL solution. 10 capsules were randomly selected. The contents were emptied, weighed and powdered in mortar and pestle. Transferred a portion of the powder, nominally equivalent to 75 mg of indomethacin, to a 100-mL volumetric flask, added 40 mL of diluent, and shacked for 1 hour. About 40 mL of acetonitrile was added and sonicated for 15 minutes, then diluted to volume up to the mark with acetonitrile followed by centrifugation. Diluted 10 mL of filtrate up to the mark in 250 mL volumetric flask with phosphate buffer pH 6.2 to obtain a 30µg/mL concentration and measured the absorbance using a UV Spectroscopy at λmax = 319 nm. Absorbance is plotted on a standard curve to calculate the quantity of drug or assay, considering the respective dilution factor.

Micromeritics Properties

Bulk and tapped densities were determined to evaluate the flow behaviour of indomethacin ER pellets. Bulk density was determined by weighing accurately 10g (M) of prepared Indomethacin ER Pellets, and transferred them into a 100 mL measuring cylinder without tapping during transfer. The volume (V) occupied by the drug was measured. Bulk density (ρ_b) was measured by using the formula:

$$\rho_b = \frac{M}{V}$$

Where, M = mass of the pellets

V = untapped volume

Tapped density was determined by weighing accurately 10g of indomethacin ER pellets into a graduated cylinder. The volume occupied by the pellets was recorded. The cylinder was then subjected to 1250 manual taps from a height of approximately 3 cm, and the final volume (V_f) was measured. Tapped density (ρ_T) is calculated by the following formula:

$$\rho_T = \frac{M}{V_f}$$

Where, M = mass of the blend

V_f = final tapped volume

Furthermore, the compressibility index, determined from bulk and tapped density data, characterizes the pellet properties. Carr's compressibility index was calculated as follows

Carr's index = [Tapped density - Bulk density/Tapped density] X 100

Friability Testing

In Multiple Unit Pellet System (MUPS) formulations the friability is critical quality attribute, as it allows pellets to withstand the external forces without fracturing or damaging their functional polymer coatings during unit operations like fluidized bed drying, blending, encapsulation and packing. Ideally, the friability of the pellets should be maintained at less than 1.0% (often less than 0.5%) to prevent premature drug release and ensure uniform therapeutic delivery. Hence, using a Roche friabilator, the friability of Indomethacin ER pellets of optimized test batch was measured. A sample of approx. 6.5g was weighed, rotated at a speed of 25 rpm for 4 minutes (100 revolutions), dedusted, and then reweighed. The percentage of weight loss was computed.

Friability (%) = (W1 - W2) ÷ W1 × 100

Where, W1 is Initial weight (before test)

W2 is Final weight (after test)

In Vitro Drug Release Study

Dissolution testing is a critical quality attribute (CQA) that dictates formulation performance and determines how the body will absorb the drug and defines its overall bioavailability. Indomethacin ER Capsule is official in the USP (Table 3). Hence, the dissolution testing method 2 is referred to from the USP and presented below. Both dissolution profiles are generated for the prepared formulation and reference marketed product (Indocap SR Tablets 75mg) using USP official dissolution method Test 2. Similarity of dissolution profile of test and reference marketed product is checked by f2 calculation with the objective to demonstrate that test product shall perform its pharmacological action as effectively as the marketed product. Sample dilution was adjusted for each time point to ensure that the measured absorbance fell within the linear range of the calibration curve (5-50 µg/mL). The dilution factors were validated for accuracy and precision

Table 3: Dissolution Method Applied- USP Test 2 [12]

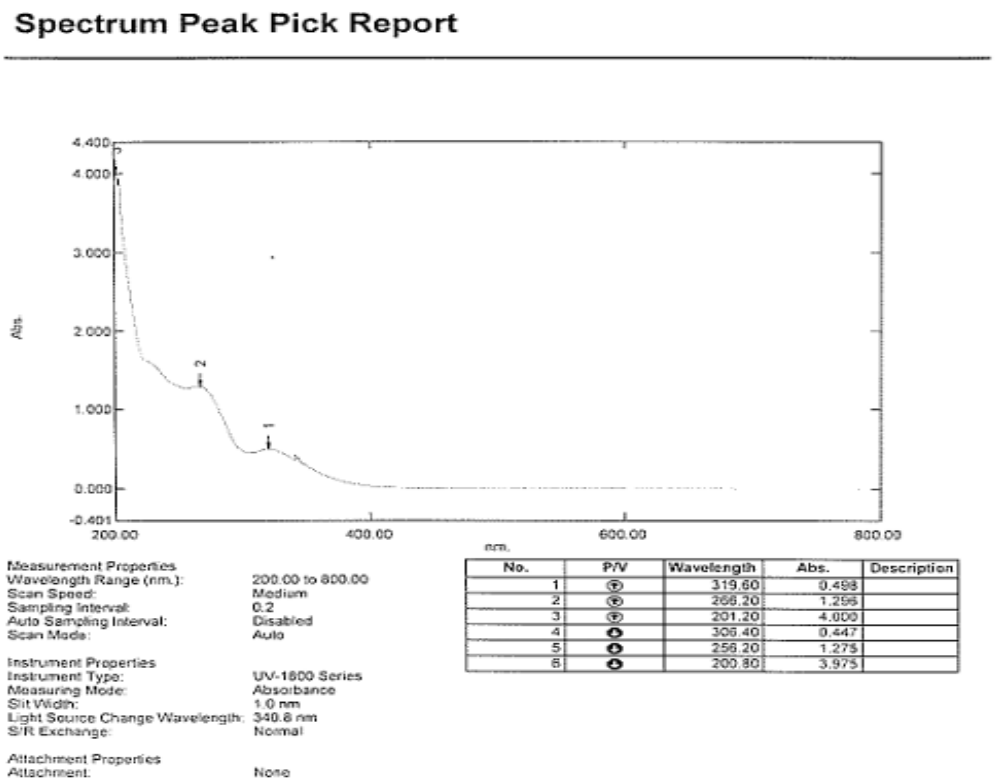
Dissolution Parameters	**Observations**
Medium / Volume	pH 6.2 phosphate buffer/ 900 mL
Apparatus / Make	Type 1 (Basket) / Lab India
Time points	1, 2, 4, 12 hrs.
Instrument used / Make & model	UV Spectrophotometer / Shimadzu UV-1280
Sample solution preparation and testing	One capsule in each of 6 baskets was dropped. Lowered the baskets in dissolution vessel and run dissolution as per above parameters. 10mL of aliquot withdrawn from each vessel at predetermined time intervals. Sample dilution was adjusted for each time point to ensure that the measured absorbance fell within the linear range of the calibration curve (5-50 µg/mL). The dilution factors were validated for accuracy and precision.
Specification limit as per USP Test 2 monograph is followed	Time (h) Amount dissolved 1hr 12-32% 2hr 27-52% 4hr 50-80% 12hr NLT 80%

RESULT AND DISCUSSION

Calibration Curve of Indomethacin

Wavelength of maximum absorbance (λmax) of Indomethacin was found to be 319 nm as shown in Fig. 1a. The calibration curves of Indomethacin were prepared in phosphate buffer (pH 6.2) using the UV spectrophotometric method. The statistical analysis of the calibration curves showed good linearity, with the correlation coefficient

close to 1 (i.e., 0.9997), as shown in Fig 1b. It shows that the drug is following Beer's Lambert law in the concentration range of 5-50 µg/mL



- The observed λ_{max} was 319.60 nm.

Fig. 1.a. Absorption maxima (λmax) of Indomethacin

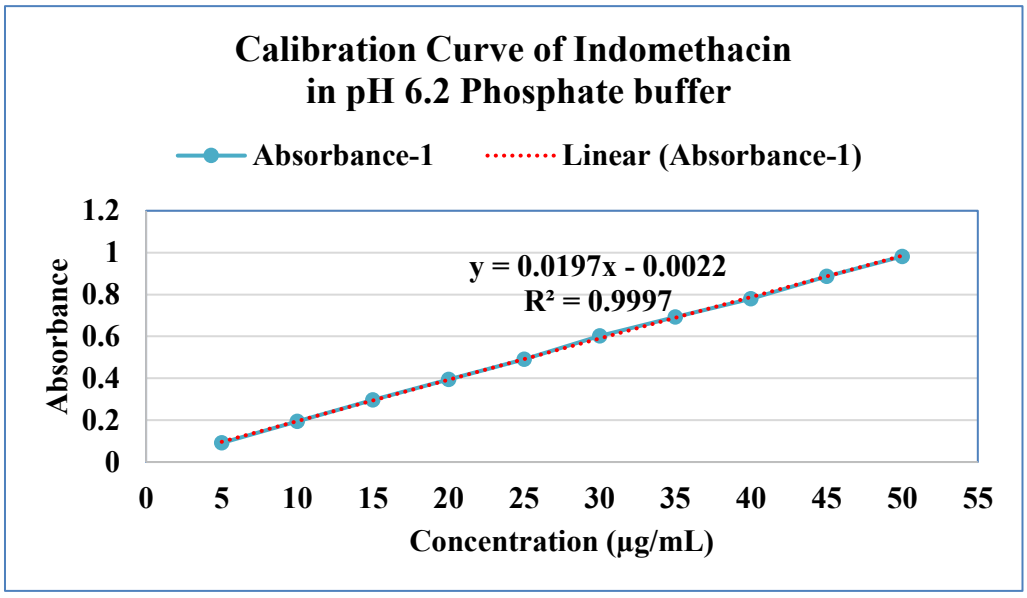


Fig. 1.b. Standard Curve of Indomethacin in Phosphate Buffer pH 6.2

Melting point determination

The melting point of Indomethacin was found in the range of 151ºC in accordance with the standard specified in the reference [13].

FTIR

The FTIR spectra of indomethacin API sample were analysed, revealing the characteristic peaks corresponding to C=C stretching at 1455.2 cm^{-1}, C=O stretching at 1692 cm^{-1}, and C–H stretching at 3022 cm^{-1} (Fig. 2a). These peaks were compared with the reference spectrum (Fig. 2d) [14] and found to be consistent, thereby confirming the identity of the drug.

Since ethyl cellulose has lower concentration (0.8 mg) in the formulation, the FTIR peaks were absent in the formulation. However, PVP K 30 has characterized peaks at 1691 cm^{-1} (lactam carbonyl stretching), 2966 cm^{-1} (aliphatic stretching), 1454 cm^{-1} (CH2 bending), 1311cm^{-1} (CN stretching) and 1066 cm^{-1} (C-C stretching). It was difficult to differentiate between C=C stretching of Indomethacin and CH2 bending of PVPK 30. Although the FTIR spectra of the physical mixture showed slight peak broadening (indicative of physical interactions such as hydrogen bonding), the absence of new peaks or significant peak shifts confirmed chemical compatibility between indomethacin and the excipients (Fig. 2b). Furthermore, similar characteristic peaks were observed in the indomethacin ER pellets, indicating compatibility of the drug with the excipients (Fig. 2c) throughout the manufacturing process.

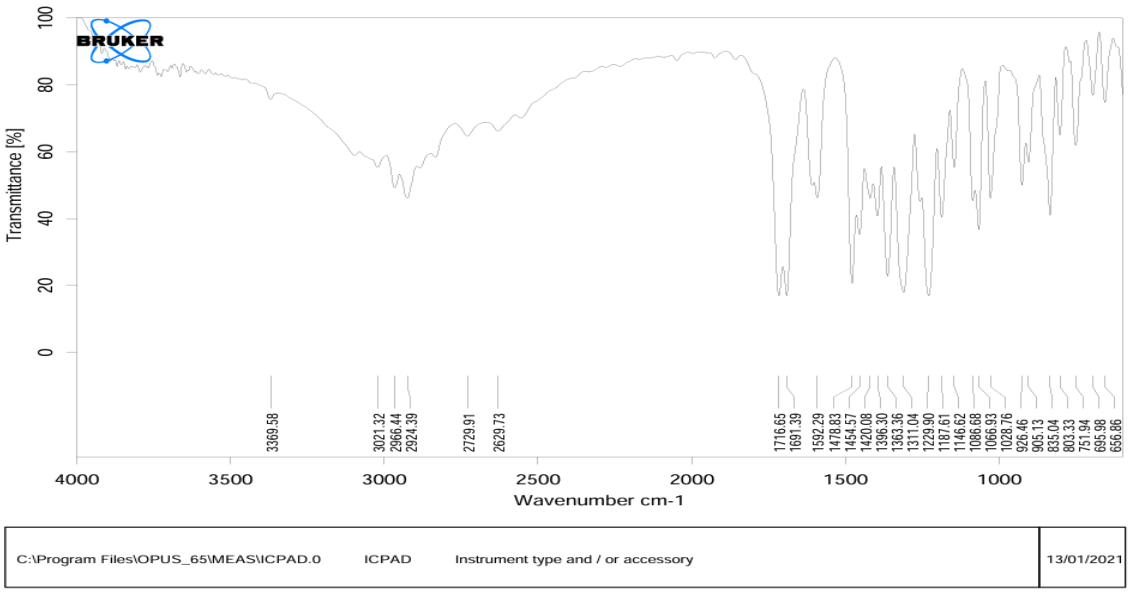


Fig. 2.a. FTIR spectra of Indomethacin API

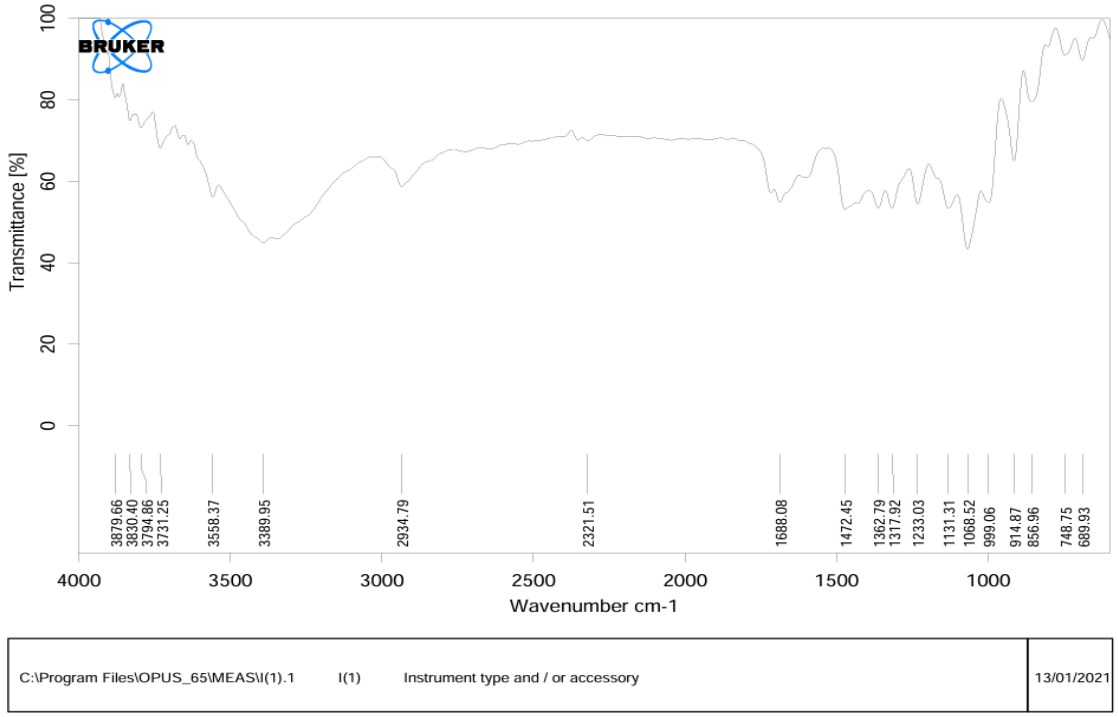


Fig. 2.b. FTIR spectra of physical mixture of the drug & excipients after 4 weeks at 60±5°C

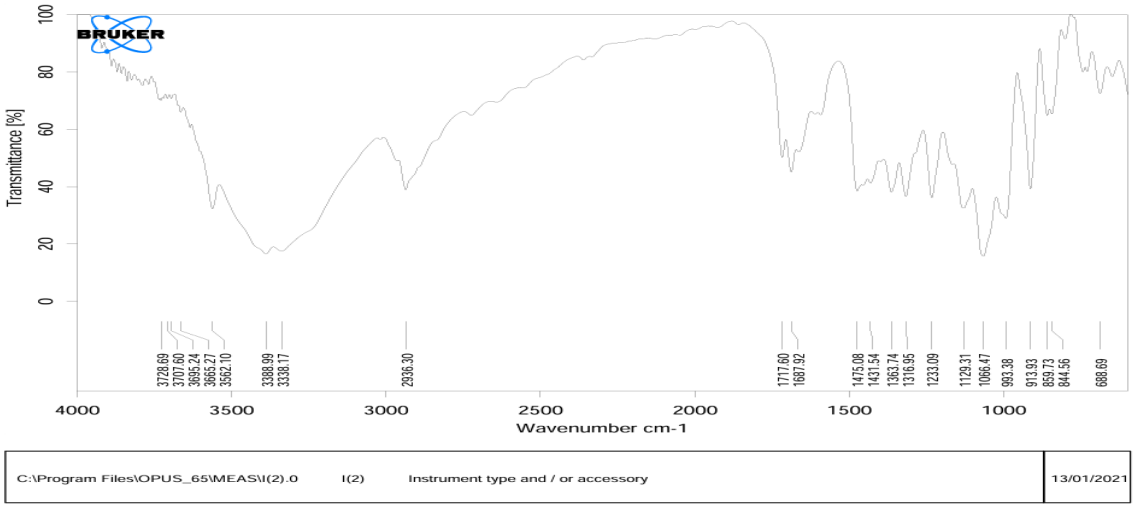


Fig. 2.c. FTIR spectra of Indomethacin ER pellets

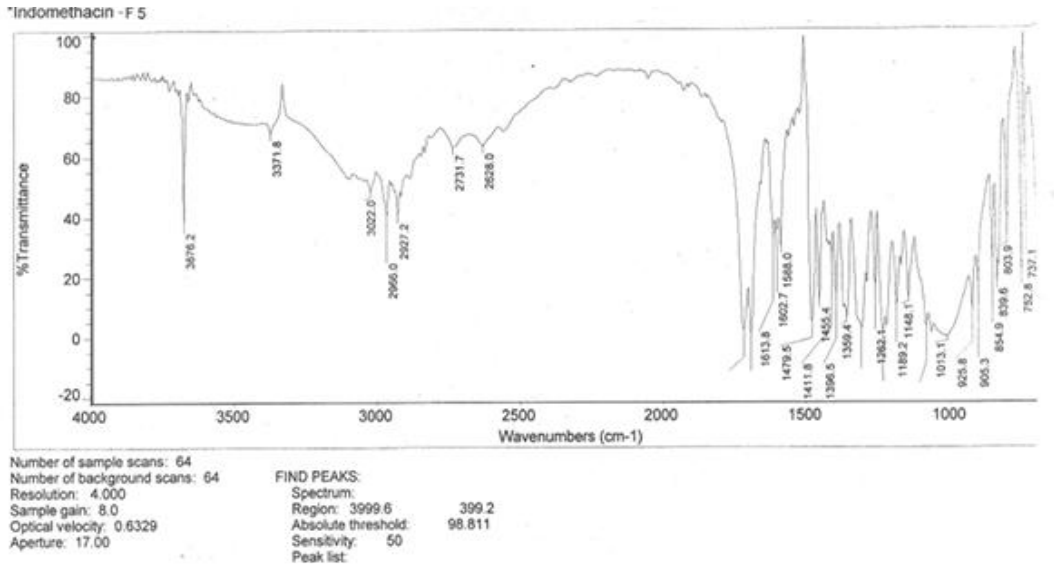


Fig. 2.d. FTIR spectra of Reference FT-IR Spectrum of Indomethacin [14]

Drug- Excipient Compatibility Study

The drug-excipient study was evaluated using Indomethacin, which was mixed with excipients at the ratios listed in Table 5 and stored in duplicate vials at different conditions. No significant characteristic changes were observed by visual inspection. Further one vial prepared with API and mixture of all excipients in 1:10 ratio and kept in oven at 60±5°C kept for 4 weeks was checked for FTIR study by taking the powder content after 4 weeks of study, and there is no significant change in characteristic peak of API found in the drug-excipient mixture stored at 60±5°C for 4 weeks indicating good compatibility of selected excipient with indomethacin (Fig. 2b).

Table 5: Drug-excipient compatibility study- visual observations

Excipients (E)	**Drug: Excipient Ratio**	**Vials with punctured rubber closure/cap kept at controlled room temperature (20 -25°C) & relative humidity (NMT 60%)**			**Vials with rubber closure/cap kept in oven at 60±5°C**		
		1 week	**2 weeks**	**4 weeks**	**1 week**	**2 weeks**	**4 weeks**
Sugar Spheres (Pharm-A-Sphere 30-35 mesh)	1:10	No color change	No color change	No color change	No color change	No color change	No color change
Ethyl cellulose (Ethocel 4 cps Std. Prem.)	1:10	No color change	No color change	No color change	No color change	No color change	No color change

Povidone (Kollidon K-30)	1:10	No color change	No color change	No color change	No color change	No color change	No color change
Talc (Talc Luzenac Pharma)	1:5	No color change	No color change	No color change	No color change	No color change	No color change

Formulation Optimization

A response surface methodology (RSM) was employed to optimise the formulation of indomethacin ER pellets. The independent variables selected were; content (%w/w) of ethyl cellulose (Factor A), povidone K30 (Factor B), and talc (Factor C). The design matrix with coded and actual values, along with the corresponding dissolution responses at 1, 2, 4, and 12 hours, is shown in Table 6. The primary objective was to achieve sustained indomethacin release over 12 hours by systematically evaluating the effects of these formulation variables.

Table 6. Design matrix with formulation variables used and corresponding experimental runs

B.Code	Std	Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
			A: Ethyl cellulose	B: Povidone K30	C: Talc	Dissolution at 1 hr	Dissolution at 2 hrs	Dissolution at 4 hrs	Dissolution at 12 hrs
			%w/w	%w/w	%w/w	% Mean±SD (n=6)	% Mean±SD (n=6)	% Mean±SD (n=6)	% Mean±SD (n=6)
IERP-01	1	14	0.25	4.51	0.74	22.0±4.9	33.0±4.5	56.0±3.8	94.0±3.7
IERP-02	2	13	0.33	4.51	0.74	24.0±1.6	37.0±1.1	55.0±1.0	98.0±0.9
IERP-03	3	8	0.25	6.51	0.74	23.0±2.0	30.0±2.2	52.0±6.0	92.0±2.5
IERP-04	4	4	0.33	6.51	0.74	23.0±1.2	34.0±1.0	56.0±0.6	97.0±1.7
IERP-05	5	11	0.25	5.51	0.64	25.0±3.0	33.0±2.5	55.0±2.1	97.0±5.0
IERP-06	6	1	0.33	5.51	0.64	23.0±0.9	36.0±1.3	61.0±6.5	100.0±2.5
IERP-07	7	10	0.25	5.51	0.84	23.0±5.0	32.0±5.6	59.0±1.9	96.0±5.7
IERP-08	8	3	0.33	5.51	0.84	22.0±3.3	36.0±1.2	55.0±5.1	98.3±0.8
IERP-09	9	2	0.29	4.51	0.64	25.0±1.6	32.0±2.0	61.0±1.9	98.0±1.9
IERP-10	10	7	0.29	6.51	0.64	26.0±1.9	35.5±2.2	59.0±2.5	96.0±2.5
IERP-11	11	12	0.29	4.51	0.84	21.0±1.6	35.0±2.7	58.0±2.0	97.0±1.9
IERP-12	12	5	0.29	6.51	0.84	24.0±2.1	36.0±2.0	56.0±3.0	95.0±1.1
IERP-13	13	6	0.29	5.51	0.74	25.0±1.1	35.0±1.6	56.0±1.7	97.0±3.5
IERP-14	14	9	0.29	5.51	0.74	24.0±1.5	34.0±1.9	56.0±1.9	99.0±2.1
IERP-15	15	15	0.29	5.51	0.74	24.0±1.7	35.0±2.1	56.0±2.4	96.0±2.3

Response 1: Dissolution at 1 Hour

The drug release at 1 hour ranged between 21–25% across different formulations (Table 6). Fit summary results (Table 7) suggested that the linear model was most suitable for this response, as it provided the best balance of statistical adequacy ($p = 0.0224$) and non-significant lack of fit ($p = 0.2507$). ANOVA (Table 8) revealed that talc (Factor C) had a significant influence ($p = 0.0059$), while ethyl cellulose (A) and Povidone K30 (B) showed no major effects. The influence of ethyl cellulose at 1 h was not significant, this is probably due to the

hydrophobic of ethyl cellulose and predominantly influenced by pore former rather than the concentration of ethyl cellulose.

Table 7. Fit summary of different polynomial models for Response 1 (% drug release at 1 hr).

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0224	0.2507	0.4495	0.1526	Suggested
2FI	0.4738	0.2303	0.4372	-0.3805	
Quadratic	0.4281	0.2012	0.4589	-1.7224	
Cubic	0.2012		0.8119		Aliased

Table 8. ANOVA for quadratic model describing Response 1 (% drug release at 1 hr).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	14.08	3	4.69	4.81	0.0224	significant
A-Ethyl cellulose	0.1513	1	0.1513	0.1550	0.7013	
B-Povidone K30	2.64	1	2.64	2.71	0.1279	
C-Talc	11.28	1	11.28	11.56	0.0059	
Residual	10.73	11	0.9756			
Lack of Fit	10.07	9	1.12	3.36	0.2507	not significant
Pure Error	0.6667	2	0.3333			
Cor Total	24.81	14				

Model and perturbation plots (Fig. 3) confirmed that talc content strongly affected the early release by modifying pellet surface properties. The 3D response surface plots (Fig. 4) further illustrated that increasing talc levels enhanced drug release at 1 hr, whereas variations in EC and PVP had minimal effects. Ethyl cellulose played a minor role in suppressing burst release, but talc concentration was the dominant factor influencing initial drug diffusion.

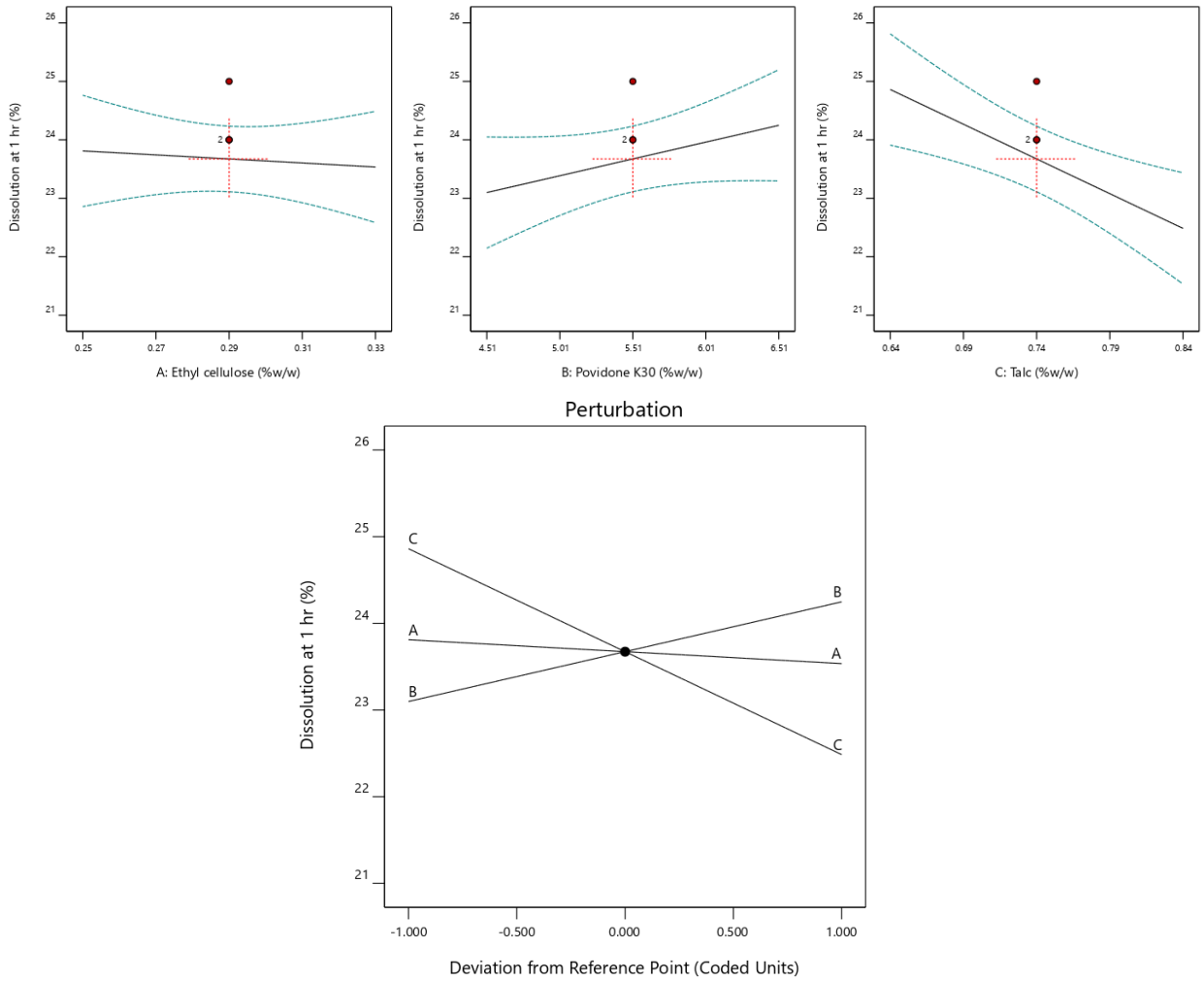


Fig. 3. Model graphs and perturbation plots showing the effect of formulation variables on Response 1 (dissolution at 1 hr).

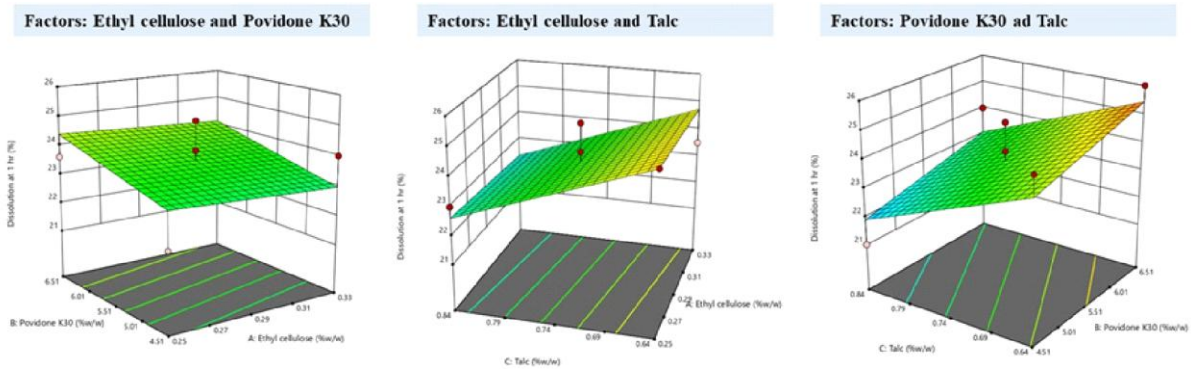


Fig. 4. 3D surface response plots illustrating the influence of formulation variables on % drug release at 1 hr.

Response 2: Dissolution at 2 Hours

Drug release at 2 hours ranged from 32–37%. The fit summary (Table 9) suggested that a linear model adequately described the data, with ANOVA (Table 10) confirming the model significance ($p = 0.0209$). Among factors, ethyl cellulose (Factor A) exerted the strongest effect ($p = 0.0031$), while Povidone K30 and talc showed no significant contribution.

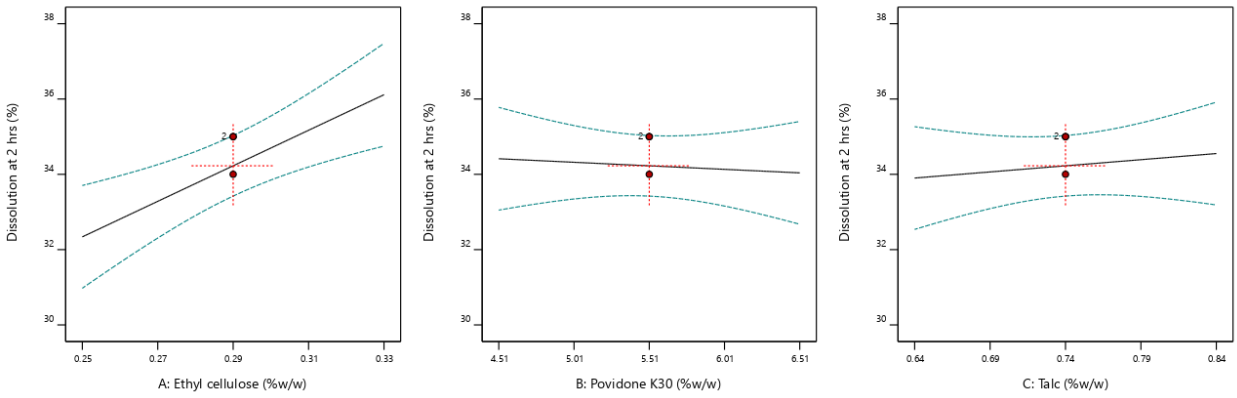
Table 9. Fit summary of different polynomial models for Response 2 (% drug release at 2 hrs).

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0209	0.1290	0.4568	0.1099	Suggested
2FI	0.8717	0.0953	0.3128	-0.9903	
Quadratic	0.8069	0.0583	0.0808	-4.0753	
Cubic	0.0583		0.9097		Aliased

Table 10. ANOVA for quadratic model describing Response 2 (% drug release at 2 hrs).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	29.63	3	9.88	4.92	0.0209	significant
A-Ethyl cellulose	28.50	1	28.50	14.21	0.0031	
B-Povidone K30	0.2813	1	0.2813	0.1402	0.7152	
C-Talc	0.8450	1	0.8450	0.4213	0.5296	
Residual	22.06	11	2.01			
Lack of Fit	21.40	9	2.38	7.13	0.1290	not significant
Pure Error	0.6667	2	0.3333			
Cor Total	51.69	14				

Model graphs (Fig. 5) showed that increasing ethyl cellulose content consistently reduced the dissolution at 2 hours, indicating its dominant role in controlling early-to-mid release. 3D surface plots (Fig. 6) demonstrated that higher ethyl cellulose concentrations produced slower release, whereas lower levels allowed faster diffusion. Thus, at this stage, EC was identified as the key rate-controlling polymer, while the effects of PVP and talc were negligible.



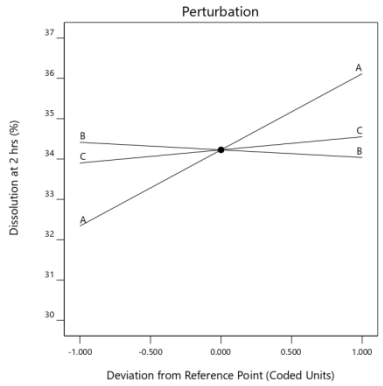


Fig. 5. Model graphs and perturbation plots showing the effect of formulation variables on Response 2 (dissolution at 2 hrs)

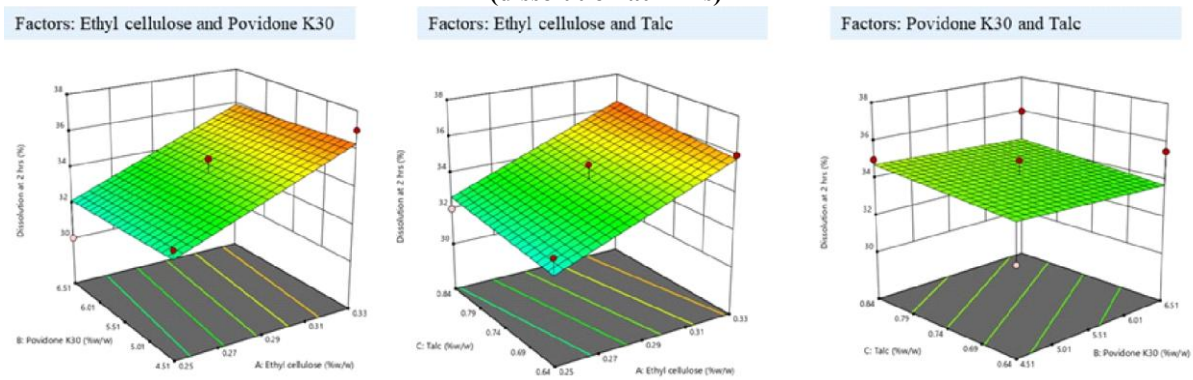


Fig. 6. 3D surface response plots depicting the influence of formulation factors on % drug release at 2 hrs.

Response 3: Dissolution at 4 Hours

At 4 hours, drug release values were in the range of 52–62% (Table 6). The quadratic model best fitted the data (Table 11), with high adjusted R^2 (0.8613), indicating reliable predictability. ANOVA (Table 12) revealed that ethyl cellulose (A) ($p = 0.0787$), Povidone K30 (B) ($p = 0.0750$), and talc (C) ($p = 0.0300$) all influenced this response, though the interaction terms (AC, A^2, and C^2) also played significant roles.

Table 11: Fit summary of different polynomial models for Response 3 (% drug release at 4 hrs).

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.4977	0.0338	-0.0344	-0.7190	
2FI	0.2483	0.0367	0.1267	-1.5667	
Quadratic	0.0061	0.1812	0.8613	0.2925	Suggested
Cubic	0.1812		0.9567		Aliased

Table 12. ANOVA for the quadratic model describing Response 3 (% drug release at 4 hrs).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	83.04	9	9.23	10.66	0.0090	significant
A-Ethyl cellulose	4.20	1	4.20	4.86	0.0787	
B-Povidone K30	4.35	1	4.35	5.03	0.0750	
C-Talc	7.80	1	7.80	9.01	0.0300	
AB	6.25	1	6.25	7.22	0.0434	
AC	21.16	1	21.16	24.45	0.0043	
BC	0.0025	1	0.0025	0.0029	0.9592	
A^2	7.37	1	7.37	8.51	0.0331	
B^2	0.0698	1	0.0698	0.0807	0.7878	
C^2	29.21	1	29.21	33.75	0.0021	
Residual	4.33	5	0.8655			
Lack of Fit	3.79	3	1.26	4.68	0.1812	not significant
Pure Error	0.5400	2	0.2700			
Cor Total	87.37	14				

Model plots (Fig. 7) showed that at this mid-phase, drug release was governed not only by EC but also by the combined effects of PVP and talc. The 3D surface plots (Fig. 8) highlighted that moderate EC with higher PVP and talc produced balanced release (~55–58%), indicating synergistic effects between polymer, binder and glidant. Thus, unlike the early phase, the significant interplay between all three factors controlled the 4-hour

dissolution behaviour. The release profile at the midpoint was complex due the factors such as erosion of solubilization of pore formers, erosion and disintegration of ethyl cellulose and drug solubility at diffusion layer thickness and core mechano-chemical strength and hence, the drug release profile fit with quadratic model.

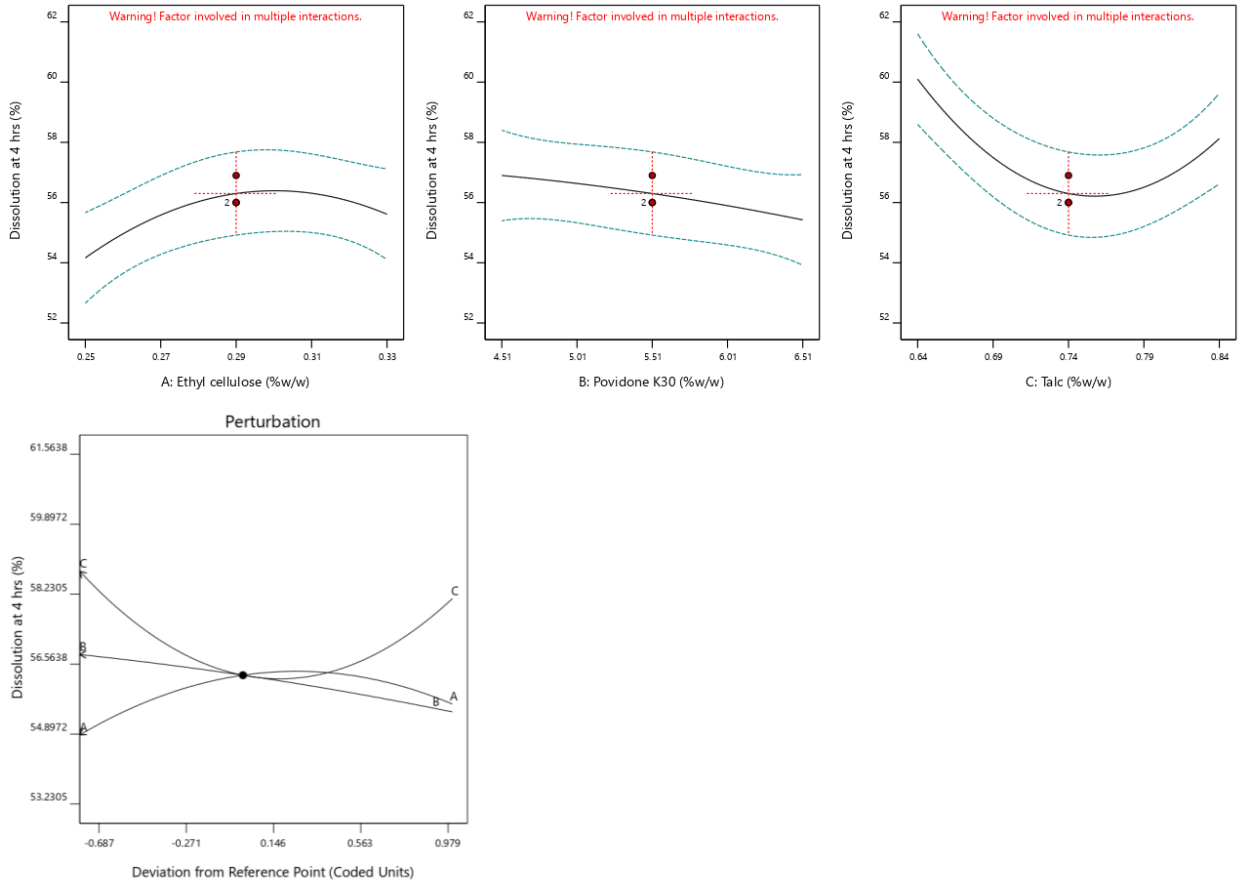


Fig. 7 Model graphs and perturbation plots showing the effect of formulation variables on Response 3 (dissolution at 4 hrs).

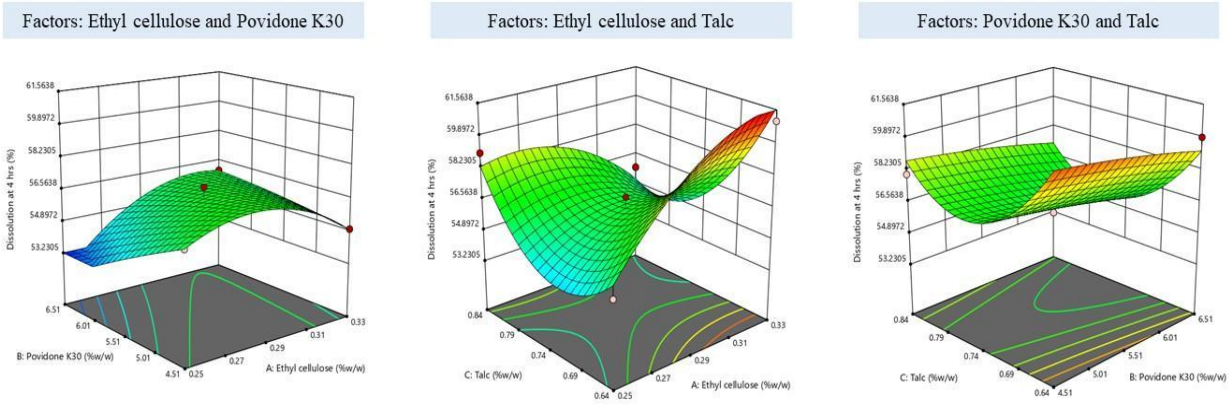


Fig. 8. 3D surface response plots illustrating the influence of formulation factors on % drug release at 4 hrs.

Response 4: Dissolution at 12 Hours

At 12 hours, drug release extended between 92–100%, achieving the sustained release target. The fit summary (Table 13) suggested a linear model, and ANOVA (Table 14) showed the model was significant ($p = 0.0194$). Among factors, ethyl cellulose (Factor A) was highly significant ($p = 0.0065$), while Povidone K30 and talc contributed minimally.

Table 13. Fit summary of different polynomial models for Response 4 (% drug release at 12 hrs).

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0194	0.6462	0.4640	0.2226	Suggested
2FI	0.9935	0.5037	0.2704	-0.6968	

Quadratic	0.0786	0.8608	0.6676	0.2945	
Cubic	0.8608		0.3923		Aliased

Table 14. ANOVA for the quadratic model describing Response 4 (% drug release at 12 hrs).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	34.45	3	11.48	5.04	0.0194	significant
A-Ethyl cellulose	25.56	1	25.56	11.22	0.0065	
B-Povidone K30	6.13	1	6.13	2.69	0.1293	
C-Talc	2.76	1	2.76	1.21	0.2945	
Residual	25.06	11	2.28			
Lack of Fit	19.90	9	2.21	0.8557	0.6462	not significant
Pure Error	5.17	2	2.58			
Cor Total	59.51	14				

Model and perturbation plots (Fig. 9) demonstrated that increasing ethyl cellulose concentration markedly retarded drug release, confirming its role as the primary release-controlling excipient. The 3D plots (Fig. 10) further showed that high EC with low levels of PVP and talc slowed release, whereas moderate EC levels allowed complete release by 12 hours.

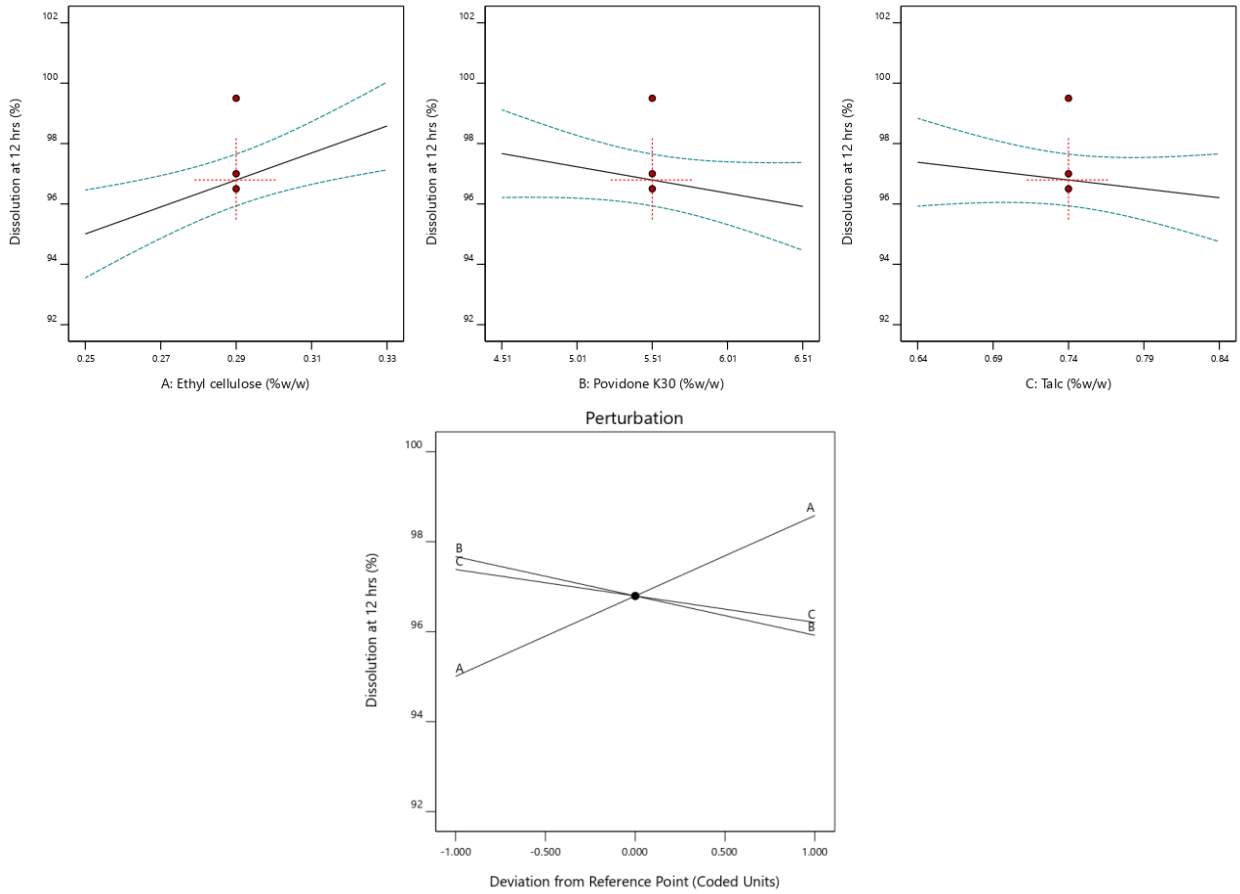


Fig. 9. Model graphs and perturbation plots showing the effect of formulation variables on Response 4 (dissolution at 12 hrs).

Overall, ethyl cellulose was identified as the dominant factor throughout the dissolution profile, talc primarily

influenced the initial burst release, and Povidone K30 contributed to binding and uniformity but had limited direct impact on release kinetics. The optimized formulation achieved a sustained-release profile aligning with once-daily therapeutic requirements.

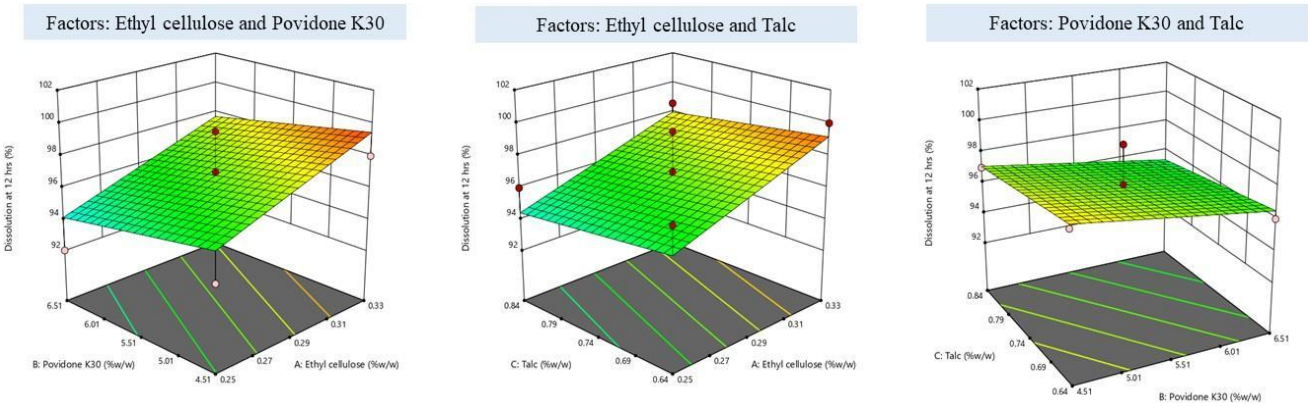


Fig. 10. 3Dsurface response plots illustrating the influence of formulation factors on % drug release at 12 hrs.

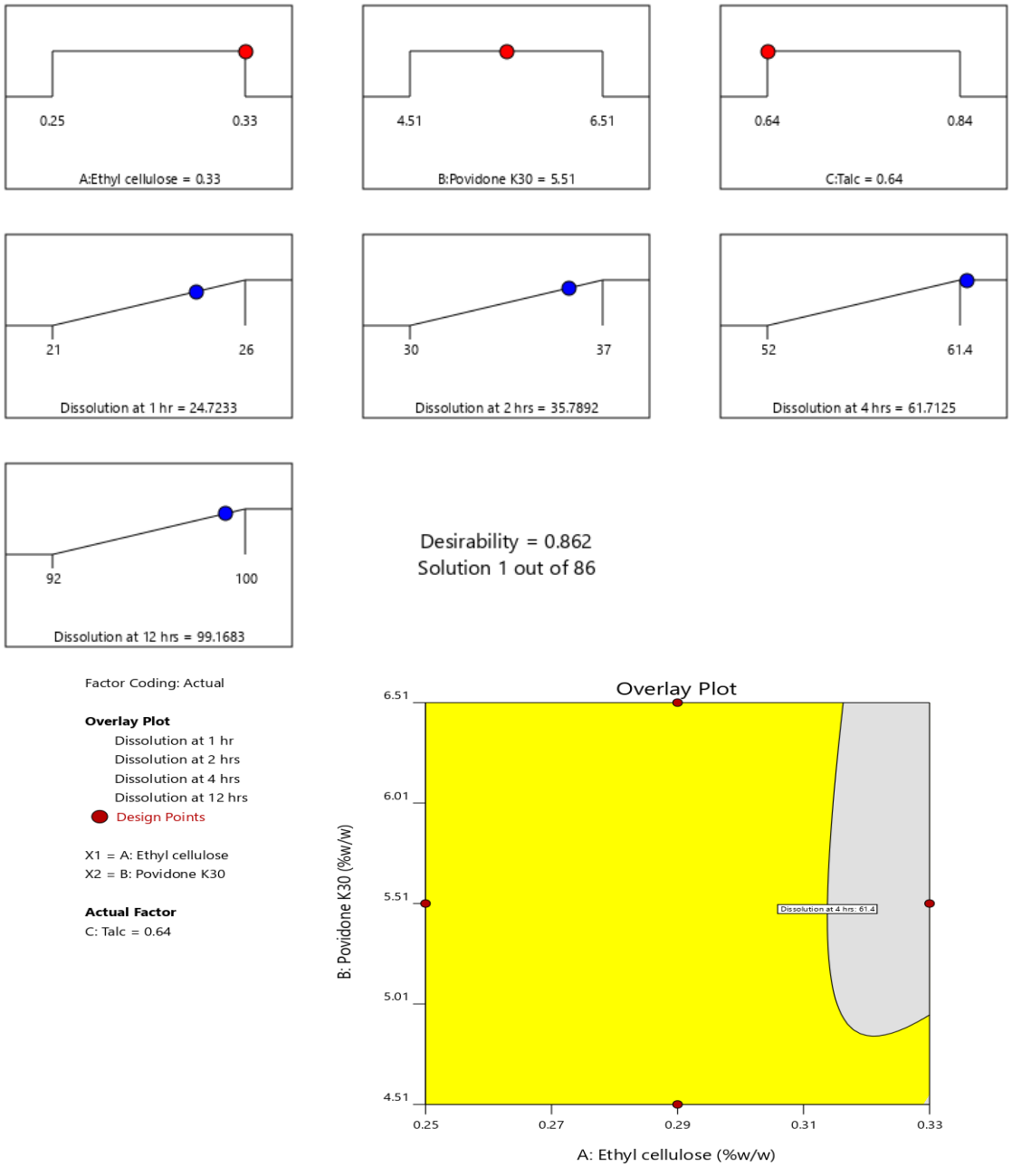


Fig. 11. Graphical optimisation (overlay plot) showing the design space for Indomethacin ER Pellets with target constraints for both responses.

Confirmatory Batches of Indomethacin ER Pellets

The confirmatory batches served as model verification runs and were intentionally manufactured after completion of the DoE optimization study to independently validate the model predictions and establish process robustness under optimized conditions. Hence, following experiments were conducted.

Optimisation of Ethyl Cellulose (Polymer) Quantity (%w/w)

Batches were manufactured with different percentages of Ethyl cellulose (polymer), i.e., 0.25%, 0.29%, and 0.33% (Table 15). With 0.29% of the Ethyl cellulose quantity showing a more similar dissolution profile to the marketed formulation ((Indocap SR Tablets 75mg: B.No. JSR-281.Mfg date 2024). Hence, from a cost-effectiveness perspective and based on the DoE study, 0.29% w/w of Ethyl cellulose is selected as the optimum concentration.

Table 15: Formulation with different Ethyl cellulose (polymer) quantity (%w/w)

B.Code	**INDO-EC1**	**INDO-EC2**	**INDO-EC3**	**Marketed formulation**
Ethyl cellulose qty (%w/w)	**0.25**	**0.29**	**0.33**	
Dissolution: pH 6.2 phosphate buffer, 900 ml, USP I (basket), 75 rpm				
Time points	% Drug Released -Mean±SD (n=6)			
1 Hr (12-32%)	21.0±5.7	22.0±6.0	22.0±5.4	24.0±8.3
2 Hr (27-52%)	35.0±3.5	37.0±2.8	36.0±3.4	40.0±4.9
4 Hr (50-80%)	57.0±2.4	59.0±1.8	61.0±1.4	58.0±3.3
12 Hr (NLT 80%)	94.0±1.4	98.0±1.4	100.0±1.4	100.0±2.4

Optimisation of Binder Quantity

Batches were manufactured with different Povidone (binder) quantities, i.e., 4.51%, 5.51%, and 6.51% (Table 16). With 5.51% of povidone quantity found to have a more similar dissolution profile to the market formulation. Hence, based on the obtained dissolution and based on the DOE study, 5.51%w/w of Povidone (binder) quantity is selected as the optimum concentration. Although, release profile for all three concentrations of PVP K30 has no statistically significant difference, for process ease and manufacturing robust and reproducible batch, PVP K30 with concentration 5.51 %w/w was selected, considering the scaleup and commercial batch manufacturing robustness.

Table 16: Formulation with different percentages of Povidone (binder) quantity

B. Code	INDO-PD1	INDO-PD2	INDO-PD3	Marketed formulation
Povidone (binder) qty (%w/w)	4.51	5.51	6.51	
Dissolution: pH 6.2 phosphate buffer, 900 ml, USP I (basket), 75 rpm				
Time points	% Drug Released -Mean±SD (n=6)			
1 Hr (12-32%)	25.0±7.1	23.0±3.2	23.0±5.0	24.0±8.3
2 Hr (27-52%)	38.0±4.4	37.0±2.4	34.0±4.7	40.0±4.9
4 Hr (50-80%)	63.0±2.4	58.0±1.8	54.0±2.9	58.0±3.3
12 Hr (NLT 80%)	98.0±0.9	100.0±1.3	97.0±2.1	100.0±2.4

Optimisation of Glidant Quantity

Batches were manufactured with different talc concentrations, i.e., 0.64%, 0.74%, and 0.84% (Table 17). With 0.74% of the talc quantity showing a more similar dissolution profile to the market formulation. Hence, based on the obtained dissolution and the DOE study, 0.74% w/w talc is selected as the optimum concentration.

Table 17: Formulation with different percentages of Talc quantity

B. Code	**INDO-TC1**	**INDO-TC2**	**INDO-TC3**	**Marketed Formulation**
Talc qty (%w/w)	**0.64**	**0.74**	**0.84**	
Dissolution: pH 6.2 phosphate buffer, 900 ml, USP I (basket), 75 rpm				

Time points	% Drug Released -Mean±SD (n=6)			
1 Hr (12-32%)	22.0±5.8	23.0±3.2	25.0±3.2	24.0±8.3
2 Hr (27-52%)	36.0±3.7	39.0±1.4	34.0±2.4	40.0±4.9
4 Hr (50-80%)	61.0±1.8	57.0±0.9	60.0±1.8	58.0±3.3
12 Hr (NLT 80%)	99.0±1.4	97.0±1.3	96.0±1.4	100.0±2.4

Key process parameters (product temperature, spray rate, atomization pressure) were identified and controlled to ensure batch-to-batch consistency. The use of a 1.0 mm nozzle and 10-15 mm column height proved effective for coating 30-35 mesh sugar spheres. Future scale-up to commercial scale would require validation of the process parameters and additional studies on the impact of scale-up on pellet properties.

Composition of Optimised Formulation

Based upon the above outcome of formulation optimisation studies, the below mentioned composition was finalised and subjected for stability (short-term stress) study (Table 18)

Table 18: Composition of optimized formulation

Indomethacin MUPS capsules 75mg	
Name of Ingredient	**Std. Quantity (mg/capsule)**
Stage: Drug-Polymer Layering	
Sugar Spheres (Pharm-A-Sphere 30-35 mesh)	179.20
Indomethacin (Micronized)	75.00
Ethyl cellulose (Ethocel 4 cps Std. Prem.)	0.80
Povidone (Kollidon K-30)	15.00
Talc (Talc Luzenac Pharma)	2.00
Isopropyl Alcohol	q. s.
Purified Water	q. s.
Wt. of lubricated pellets	272.00
Stage: Capsule Filling	
Indomethacin Layered Sugar Spheres	272.00
Hard Gelatin Capsule (HGC) Shell (Size '2')	01 capsule

Micromeritics Properties & Friability

Bulk, Tapped Density, and Carr's Index, Friability of Indomethacin ER Pellets of selected formulation are mentioned in Table 19. Moreover, the flowability of both pellets were found to be good (Carr's Index values <15% indicate good flow, whereas >25% suggest poor).

Table 19: Evaluation of Indomethacin ER pellets

Parameters	**Indomethacin ER pellets**	
	Test Product	**Marketed product**
Bulk Density(gm/mL)	0.74	0.70
Tap Density (gm/mL)	0.83	0.79
Carr's Index	10.84	11.39
Friability (%)	0.2	0.3

In Vitro Drug Release Study

The dissolution profile of the optimised formulation of Indomethacin ER pellets filled in HGC was evaluated and compared with marketed product. It was found that the dissolution of optimized formulation is complies

with the USP specification limits. Moreover, the dissolution profile of optimized formulation and marketed product are statistically similar (i.e., f2 > 50%& f1<15%) as shown in Table 20. This assures that the prepared formulation may be therapeutically effective as that of marketed product.

Table 20: Dissolution profile of optimised final formulation and marketed product

B. Code	**INDO-TC1**	**Marketed Formulation (Indocap SR 75mg)**
Dissolution: pH 6.2 phosphate buffer, 900 ml, USP I (basket), 75 rpm		
Time points	% Drug Released -Mean±SD (n=6)	
1 Hr (12-32%)	23.0±3.2	24.0±8.3
2 Hr (27-52%)	39.0±1.4	40.0±4.9
4 Hr (50-80%)	57.0±0.9	58.0±3.3
12 Hr (NLT 80%)	97.0±1.3	100.0±2.4
f2 similarity factor	**85**	
f1 difference factor	**3**	

Stability Study

Short term study data is presented in below table to evaluate any change in description, assay and dissolution results on storage of developed formulation at adverse conditions of temperature (i.e.60±2°C/ 28 days).

Table 21: Stability Data of Indomethacin ER Pellets filled in HGC

Parameters	**Packing: 30 capsules per HDPE bottle (40cc) with cotton**				
	Stability storage condition:60±2°C in Hot air Oven				
	Initial	**7 days**	**14 days**	**21 days**	**28 days**
Description (*)	Complies	Complies	Complies	Complies	Complies
Assay	99.50%	97.60%	98.90%	102.10%	100.40%
% Drug Released					
1 Hr (12-32%)	23	22	19	26	25
2 Hr (27-52%)	39	43	38	44	41
4 Hr (50-80%)	57	61	56	67	59
12 Hr (NLT80%)	97	99	96	98	95

**Size 2 capsule containing white to off-white pellets*

There are no significant changes observed in description, assay and dissolution results of the developed formulation, which shows that the test product is stable at 60°C for 28 days. However, formal long-term and accelerated stability studies are required to establish the shelf life of selected formulation.

CONCLUSION

The present study successfully developed Indomethacin ER pellets by Wurster coating process with controlled parameters and optimized with different concentration of ethyl cellulose, povidone and talc through design of experiments. FTIR studies revealed no significant interaction between Indomethacin and the excipients used, indicating good drug–excipient compatibility. All prepared formulations were evaluated for various in-process and finished product CQAs including friability, micromeritic properties (Carr's Index: 10.84), drug content and in vitro drug release profile. The pellets prepared by wurster coating process showed satisfactory mechanical strength since friability values were within acceptable limits (<1%w/w), indicating good pellets integrity and handling characteristics. The optimized formulation filled in to HGC enabled precise control over % drug release up to 12 hrs and comparable to that of marketed product (f1 difference factor: 3 & f2 similarity factor: 85). The applied Response surface methodology (RSM) yielded robust models for identifying critical formulation variables and their interactions. Among the studied factors, ethyl cellulose content (0.29% w/w) played the most significant role in controlling indomethacin release up to 12 hrs. The similarity of the dissolution profile to the marketed product (f2 = 85) suggests that the formulation would likely exhibit similar in

vivo performance. However, pharmacokinetic studies would be required to establish an in vitro-in vivo correlation (IVIVC)and confirm the clinical relevance of the developed formulation and commercial viability.

Financial Assistance
None to Declare.
Conflict of Interest
None to Declare.
Author Contribution
Kailasam P contributed to the study's conceptualization, methodology development, formulation evaluation, preparation and editing of the original manuscript draft. Shailaja Pashikanti & KV Ramana Murthy were contributed significantly for co-conceptualization, investigation, and overall supervision of the work, also contributed to the review and interpretation of the results as a primary & co-guide respectively.

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