

DESIGN AND DEVELOPMENT OF ANTI-INFLAMMATORY DRUG NAPROXEN SOLID DISPERSIONS AND FORMULATIONS BY FACTORIAL DESIGN APPROACH

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Abstract

Naproxen is a non-steroidal anti-inflammatory (NSAID) drug that can be used as an analgesic, anti-inflammatory, and antipyretic. Objectives: The study's major goal was to improve the drug's solubility and dissolution rate, as well as its oral bioavailability. Methods: Physical mixture, kneading process, and solvent evaporation method were used to make Naproxen solid dispersions (SDs). Using a two-level factorial design and three independent components, X₁: β -Cyclodextrin, X₂: Kolliphor p-188, and X₃: PVPK-30 and designed by a Design expert (DOE). The formulation was studied by flow parameters, physical characteristics, Fourier-transform infrared spectroscopy, and comparative investigations with commercially available Naprosyn and F₂. Major Results: In vitro performance of solid dispersions SD's was favorable (100% drug release 20 minutes), compared to a pure drug, where 100 percent drug release takes 80 minutes. The FTIR spectra of pure drug and combinations with excipients were having no chemical interaction. The F₄<F₈<F₇<F₁<F₆<F₅<F₃<F₂ depicts the order of released various formulations. The release profiles of F₂ and the Naprosyn tablet are similar. These findings suggest that a new naproxen tablet formulation, including the β -Cyclodextrin: Kolliphor - p188 complex, could be a viable alternative for improving oral bioavailability.

Keywords: Design Expert; In Vitro; Naprosyn; Naproxen; Solid Dispersion

Introduction

The naproxen is an NSAID that is used to treat rheumatoid arthritis and osteoarthritis over time, is classified as BCS Class II. The literature reported naproxen plus sumatriptan, treatment of acute migraine attacks in adults (Law *et al.*, 2013) are reported, the solubility of 15.9 mg/L (at 25°C), log p 3.18, creation of rapid dissolving tablets of naproxen sodium using super disintegrants had

an excellent dissolution profile was reported (Sharma *et al.*, 2013; Jeevanandham *et al.*, 2010; Chenguang *et al.*, 2018), and hydrophilic matrix materials such as HPMC were used to sustained release tablets (Harun *et al.*, 2009; Lavyna and Rao, 2015; Rao *et al.*, 2016; Srinivasa and Vijayaratana, 2017; Bhavyasri and Taraka, 2018; Vijaya and Srinivasa, 2018) are reported. The topical

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administration, the micro emulsions were evaluated as delivery (ÜstündağOkur *et al.*, 2014), time-dependent and pH-sensitive press-coated tablets with hydroxypropyl cellulose or Eudragits (Pawar *et al.*, 2013) improved nanostructured lipid carrier experimental design, physicochemical and structural qualities, the optimum formulation was chosen (Guilherme *et al.*, 2019), matrix tablets containing a hydrophobic polymer, such as Eudragit's have been developed and network meta-analysis has been used to the tolerability of NSAIDs and triptans reported (Brandes *et al.*, 2007; Xu *et al.*, 2016). Designing new products or improving current ones, as well as designing and developing manufacturing methods to manufacture them, are vital tasks in most industrial companies, and experimental design plays an important role in various sectors of research (Lundstedt *et al.*, 1998; Durakovic, 2017) optimization of processes, products that may be applied to a variety of formulations (Singh *et al.*, 2011) variable screening, discovery, and design reported (Aydar, 2018). The taste masking agent and super disintegrant on tablet characteristics, a three-level complete factorial design was reported (Ibrahim and Abou El-Ela, 2017). The design was used to effect of varying drug release behavior from both lipophilic and hydrophilic products (Furlanetto *et al.*, 2006), and experimental designs were used to find the effects of variables during the preparation (Yang *et al.*, 2014; Sammour *et al.*, 2006), 3² factorial design was used to investigate the effect of the amount of camphor and super disintegrant during the preparation NP, (Montgomery, 1999) and DoE and quality by design (QbD) as applicable to drug delivery development employing a more scientific approach, factorial design, optimizations was reported uses design various formulations and optimizations are reported (Chowdary and Rao, 2011; Chowdary and Rajeswararao, 2015; Ch and Chowdary, 2016; Teja and Damodharan, 2018). The research on cyclodextrin, and griseofulvin nanosponges for oral bioavailability reported (Omar *et al.*, 2020), determined the impact for anticancer drug delivery, development of rosuvastatin calcium solubility improvement, and other hydrophobic moieties was effective, utilization of cellulose/cyclodextrin as platforms for materials use pharmaceutical applications and biopharmaceutical consideration (Ramarao *et al.*, 2016) with an emphasis on delivery also discussed (Gidwani and Vyas, 2015; Cova and Murtinho, 2018), gel with the Lidocaine better sustained release behavior, according to the release profiles reported (Abou-Okeil, 2018). The complex, keeps the quality of citrus fruit inoculated with *G. citri-aurantii* and decreases deterioration reported (Dou *et al.*, 2018). An inclusion complexation technique considerably

boosted the in-vitro antibacterial and antibiofilm investigation of the Etoposide drug as a sensible microorganism (Arumugam *et al.*, 2019). In simulated physiological fluids, the inclusion complexes showed an increase in solubility (Saidman *et al.*, 2019). The formulation, which contained 18 percent Poloxamer 407, 5% (Kolliphor p-188) P 188, and 0.4 percent HPMC, was improved and displayed outstanding gelling ability at $31.7 \pm 0.1^\circ\text{C}$ reported (Deshkar and Palve, 2019), atorvastatin-P188 solid dispersions could be a promising way to improve oral bioavailability (Dong *et al.*, 2018), P188 and P407, two poloxamers, were systematically tested for their applicability as alternative tablet lubricants. Both poloxamers have an acceptable lubricating efficiency without compromising tabletability or in vitro drug release. As a result, more research into the usage of P188 and P407 as alternative tablet lubricants is warranted reported (Dun *et al.*, 2020), treatment of leishmaniasis, buparvaquone, a veterinary medication, was synthesized as nanostructured lipid carriers reported (Monteiro *et al.*, 2017), in situ gel formulations based on a combination of poloxamer 407 and poloxamer 188 for long-term ocular ketorolac reported (Fathalla *et al.*, 2017) reported. The goal of this study was to make naproxen SDs using physical mixtures, the Kneading process, and solvent evaporation. The investigation of formulations with many parameters such as flow parameters, physical features, Fourier-transform infrared spectroscopy (FTIR), and comparative examinations with commercially available tablets (Naprosyn) and F2. The DOE was used to analysis of variance (ANOVA), 3D surface plots, counterplots, optimization, and desirability (Ramarao and Laxmi, 2023).

Materials and Methods

Naproxen was a gift sample by Divis Laboratories Ltd, β -cyclodextrin was a purchased sample from Balaji Drugs, Polyvinyl Pyrrolidone K30 from Loba Chemie Pvt. Ltd., Kolliphor P-188 was A Gift sample from IMCD India Pvt.Ltd, Mumbai; Sodium starch glycolate (SSG)from Oxford Laboratory, Mumbai; Lactose Monohydrate, magnesium stearate, and Talc from Loba Chemie Pvt. Ltd.

Design of SDs

Solid dispersion by the physical mixture

A physical mixture having equal weighed ratios of drug and polymers HPMC: PVP K30 i.e., (1:0.5:0.5) and (1:1.5:1.5) in a mortar, the resulting mixture was sieved by #22, denoted as PM1 and PM2.

SDs by solvent evaporation

SD's of Naproxen with β -cyclodextrin and Kolliphor P-188 with weight ratios of (1:0.5:0.5), (1:1:1), denoted as SD1 (1:0.5:0.5), SD2 (1:1:1), respectively. Add dichloromethane drop by drop to the drug in the mortar, triturate well, later the solvent was evaporated under room conditions, and the resulting residue dried by using a hot air oven for 1 hour, the product was stored in a desiccator overnight, ground in a mortar, and pass-through sieve no. #22 until further studies.

Tablets Preparation

Table 1, shows the composition of various factors such as the drug, polymers, and other excipients. The required quantity of a drug, β -cyclodextrin (X1) higher (+) (100 mg) lower (-) (50mg), Kolliphor P-188(X2) higher (+) (5mg) lower (-) (2.5mg), PVP K30(X3) higher (+) (3 percent) lower (-) (1.5 percent), Lactose (diluent), Sodium Starch Glycolate (super disintegrant) were weighed accurately and thoroughly mixed using a mortar and After thoroughly mixing the lubricant Talc and Magnesium Stearate, the powder was passed through sieve no. 16 and blended and using a single-punch tablet compression method.

Characterization of the tablets

All tablets were evaluated for hardness; Monsanto hardness tester was used to determine the hardness of the tablet. Friability was determined using a Friability Tester (FT 1020), which was used to weigh 20 tablets before placing them in a friability. Disintegration time, Lab India Tablet Disintegrating Tester (DT, 1000) was used. Dissolution study, dissolution rate of Naproxen from tablets was determined using a USP Type II (LAB INDIA, DS 8000) with phosphate buffer pH6.8, stirrer speed of 50 rpm; 5ml was withdrawn

at 10, 20, 30, 40, 50, and 60 min. A UV-Vis Spectrophotometer was used to analyze the samples at 231nm (ELICO Double beam SL 210). The dissolution of each prepared tablet was replicated four times (n=4).

Comparative Studies

The comparative studies of optimized formulation F2 with the marketed product (Naprosyn) (Naproxen uncoated tablet containing 250mg of Naproxen manufactured by "RPG LIFE SCIENCES LIMITED, Gujarat, India). Batch no: 01N20043, Mfg. date: 05/2020, Mfg. Lic no: G/599, Exp date: 04/2024.

Data Analysis

Using DOE are subjected to ANOVA (Analysis of variance) (Ch and Chowdary, 2016), 3D Surface plots, Counter plots, and Desirability (Tarakaramarao and Somireddy, 2022; Somireddy and Ch, 2022) reported.

Results and Discussion

Dissolution behavior of different solid dispersions

The in vitro performance of solid dispersions up to the drug-polymer ratio of the drug: β -cyclodextrin: Kolliphor P188 (1:0.5:0.5) was considered favorable. The solid dispersion extends the naproxen release time to more than 30 minutes. The dissolution behavior of a pure drug in the presence of various carriers HPMC: PVP K30, i.e., (1:0.5:0.5), (1:1.5:1.5) (PM1, PM2), (1:1) (K1) and drug: β -cyclodextrin: Kolliphor P188 (1:0.5:0.5), (1:1:1) (SD1, SD2) shown in Figure 1.

Table 1. Experimental Design - 2³ Factorial Designs

Factor	High(+)	Low(-)	Optimized
X ₁ ; β -Cyclodextrin (mg)	100	50	75
X ₂ ; Kolliphor P-188 (mg)	5	2.5	3.75
X ₃ ; PVP K30 (%)	3	1.5	2.25

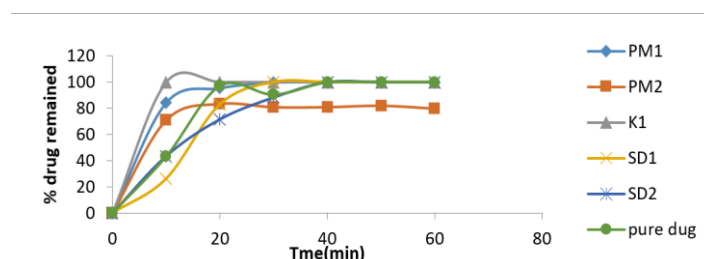


Figure 1. Dissolution profiles of Naproxen pure drug and its solid Dispersion

Flowability and Compressibility

The flow properties of a prepared blend were investigated using an angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index are shown in 0.300 to 0.380 gm/cc, 0.354 to 0.439 gm/cc, angle of repose 10 to 15, Carr's index 10 to 17%, and Hausner's ratio 1.25. The above characteristics of the prepared blend show excellent to good flow properties and are appropriate for direct compression (Reshma and Rao, 2017), Table 2, displays the flow properties.

Drug - excipients compatibilities

The FTIR spectrum of Naproxen showed characteristic peaks observed at 1681 cm⁻¹, 1629 cm⁻¹, 1174 cm⁻¹, 1156 cm⁻¹, 1027 cm⁻¹, 924 cm⁻¹, 895 cm⁻¹, 854 cm⁻¹ (Due to C-C Stretch), 1452 cm⁻¹, 1392 cm⁻¹ (Due to C-H Bending in a plane), 895 cm⁻¹, 854 cm⁻¹, 793 cm⁻¹, 673 cm⁻¹, 642 cm⁻¹ (Due to C-H Rocking), 1452 cm⁻¹, 1392 cm⁻¹, 1225 cm⁻¹ (Due to O-H Bending), 1725 cm⁻¹, 1681 cm⁻¹, 1629 cm⁻¹ (Due to C=O Stretch), 1225 cm⁻¹, 1174 cm⁻¹, 1156 cm⁻¹, 1027 cm⁻¹, 924 cm⁻¹ (Due to C-O Stretch), confirming the drug structure was shown in Figure 2 and Figure 3.

Tablet properties

The prepared tablets' properties are shown in Table 3. The hardness between 4 and 4.5 kg/cm², corresponds to the increased hardness-relevant binding properties of naproxen tablets. The percentage of weight loss of no more than 1%. All of the formulation tablets disintegrated within a short period. F1 is 6 min 30 sec., F2 is 5 min 39 sec., F3 is 4 min 53 sec., F4 is 4 min 45 sec., F5 is 5 min 15 sec., F6 is 6 min., F7 is 5 min 30 sec., and F8 is 6 min 30 sec. The disintegration time of all prepared tablets ranges from 4 minutes 45 seconds to 6 minutes. The F1 and F8 formulations with low levels of β -cyclodextrin, Kolliphor P188, PVP K30, and higher levels of β -cyclodextrin, Kolliphor P188, PVP K30 had the highest disintegration. Table 4 shows the effect of β -cyclodextrin, Kolliphor P188, and PVP K30 concentrations on tablet disintegration time. The higher the concentration of three polymers and the lower the concentration of three polymers, the longer the disintegration time. The drug content of all prepared tablets ranges between 95 and 98 percent. The above quality control parameters of the prepared tablets meet the official IP specification for uncoated tablets.

Table 2. Experimental Design - 2³ Factorial Designs

S.no	Formulations	Bulk density (gr/cc)	True density (gr/cc)	The angle of repose(°)	Carr's Index	Hausner's ratio
1	F1	0.370	0.439	13.02	10.51	1.18
2	F2	0.342	0.419	13.780	12.63	1.22
3	F3	0.300	0.371	14.371	17.32	1.23
4	F4	0.355	0.354	10.187	10.11	0.99
5	F5	0.380	0.415	11.119	13.26	1.09
6	F6	0.315	0.372	12.410	10.98	1.18
7	F7	0.342	0.400	11.321	14.28	1.16
8	F8	0.310	0.384	12.167	15.43	1.23

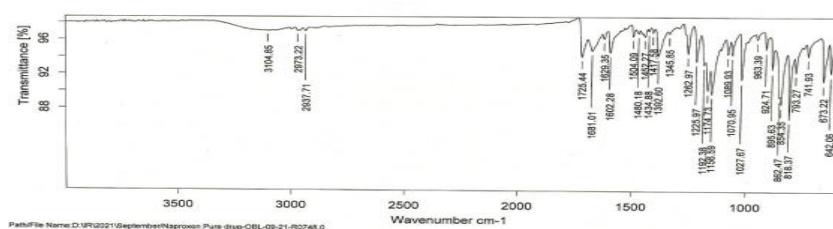


Figure 2. FTIR Spectrum of Naproxen

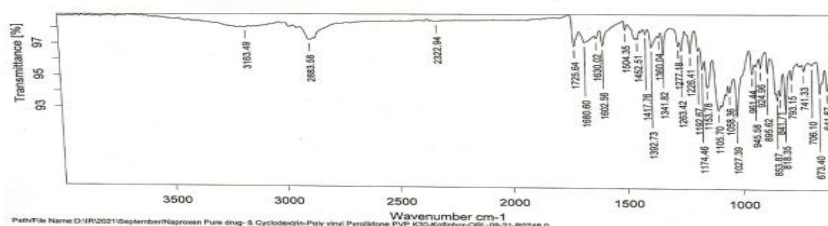


Figure 3. FTIR Spectrum of optimized formula

Dissolution

The F1 formulation provides complete drug release in 20 minutes, and the F2 formulation, which contains 100mg β -cyclodextrin, 2.5 mg Kolliphor, and 1.5 percent PVP K30, performs significantly better in terms of dissolution and complete drug release in 20 minutes. The F3 formulation, which contains 50mg β -cyclodextrin, 5mg Kolliphor, and 1.5 percent PVP K30, performs significantly better in terms of dissolution. The F3 formulation provides complete drug release in 20 minutes. The F4 formulation provides complete drug release in 30 minutes. The F5 formulation provides complete drug release in 20 minutes. The F6 formulation

provides complete drug release in 20 minutes. The F7 formulation provides complete drug release in 30 minutes. The F8 formulation provides complete drug release in 30 minutes. The increasing order of drug dissolution in various formulations is depicted as $F4 < F8 < F7 < F1 < F6 < F5 < F3 < F2$, as shown in Figure 4 and Figure 5.

Model Dependent

Table. 4 shows the dissolution parameters $t_{1/2}$, t_{90} , DE_{30} , PD_{10} , PD_{15} , MDT, and Dissolution rate constant (K1) are significant (Tarakaramarao *et al.*, 2020).

Table 3. Physical properties of prepared Naproxen Tablet Formulations

S.no	Formulations	Hardness (Kg/cm ²)	Friability (%)	Disintegration time (min .sec)	Drug content (%)
1	F1	4.3	0.534	6.30	97.30
2	F2	4.2	0.539	5.39	96.18
3	F3	4.0	0.612	4.53	95.97
4	F4	4.1	0.722	4.45	97.58
5	F5	4.2	0.598	5.15	95.13
6	F6	4.4	0.552	6.00	98.190
7	F7	4.2	0.618	5.30	97.178
8	F8	4.3	0.702	6.30	96.973

Table 4. Dissolution parameters of prepared Naproxen tablet Formulation

Formulation	DE10 (%)	DE30 (%)	PD10 (%)	PD15 (%)	$t_{1/2}$ (min)	T90 (min)	MDT	K1 (min-1)	Zero order (r)	First order(r)
F1	32.3	38.2	64.6	84.5	7	16	14.363	0.1038	0.986	0.996
F2	35.93	59.186	71.86	87	4	14	19.987	0.1268	0.969	0.998
F3	35.92	59.506	71.84	87	8	14	20.08	0.1268	0.969	0.997
F4	25.11	61.453	50.22	66	10	25	19.635	0.0787	0.981	0.999
F5	34.87	40.622	69.74	87	2	15	4.0639	0.1197	0.974	0.998
F6	33.01	40.613	66.02	86.5	5	16	14.1037	0.1080	0.983	0.996
F7	24.26	39.913	48.52	67.5	10	19	14.175	0.0944	0.981	0.995
F8	28.36	38.673	56.72	69	12	22.5	2.959	0.0660	0.966	0.997

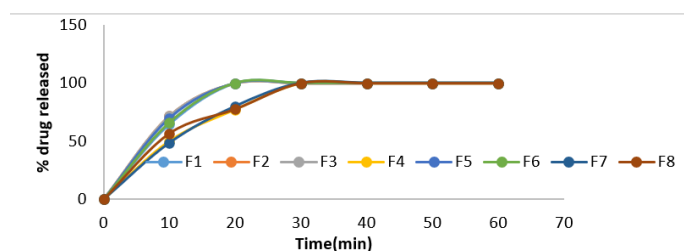


Figure 4. Mean Dissolution profile of Naproxen tablet formulation Prepared F1-F8

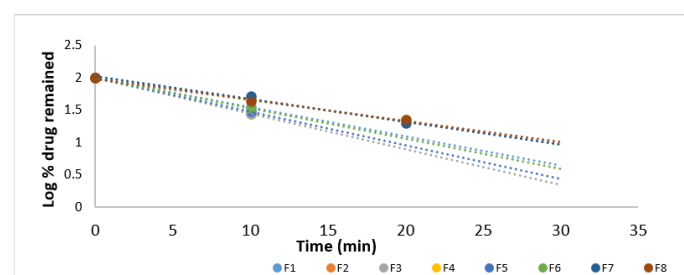


Figure 5. First-order Dissolution profile of Naproxen tablet formulation Prepared F1-F8

Comparative Studies

The value of F1 was found to be less than 15 (4.689), indicating that the two curves are identical or equivalent, F2 was found to be greater than 50 (97.461).

Data Analysis

Four responses were chosen for statistical optimization and fitted to specific models: Y1 (PD15), Y2 (PD10), Y3 (MDT), and Y4 (DE30). Responses PD15 (Y1), A model with a statistically significant (Reshma and Rao, 2017) $p < 0.0119$ is shown in Table 5. The model equation PD15 = $+1.03977 - 5.55000 X_2$. The negative sign for coefficient X2 indicates that as the concentration of Kolliphor P188 increases, the percent drug dissolves in 15 minutes decreases, or the R^2 value for PD15 is 0.5671, indicating a good correlation between independent and dependent variables. Response PD10 (Y2): The PD10 is a statistically significant result of $p < 0.0481$, shown in Table 5. The model equation can determine PD10 = $+82.71045 - 4.49200X_2$. The negative sign for coefficient X2 indicates that as the concentration of Kolliphor P188 increases, the percent drug dissolves in 10 minutes

decreases; the R^2 value for PD10 is 0.4044, indicating a good correlation between independent and dependent variables. The formulation variables were investigated and optimized to ensure that the process was as quick as possible. The disintegration of tablets and medication release (Mostafa *et al.*, 2020) reported. Response MDT (Y3), The MDT yielded a statistically significant result of $p < 0.0160$. Table 5, the model equation can determine MDT. $Y_3 = -6.10991 + 0.42984X_1 + 8.63080X_2 - 2.58447X_3 - 0.10931X_1X_2$. The positive sign for X1 and X2 indicates that as the concentration of β -cyclodextrin and Kolliphor P188 increases, so does the dissolution time. The negative sign for coefficient X3 indicates that as PVP K30 concentration decreases, the percent drug dissolve decreases, and dissolution time increases. MDT has an R^2 value of 0.8798, indicating a strong correlation between independent and dependent variables. Response DE30 (Y4, analysis of variance DE30 produced a model with a statistically significant $p < 0.0154$ shown in Table.5. The model equation can be DE30 = $+73.22960 - 3.90113X_3$, a negative sign for coefficient X3 indicates that increasing the concentration of PVP K30 reduces drug efficiency

Table 5. Analysis of variance of Dependent variables (Responses)

Percentage Drug Dissolved in 15 min (PD15)						
Source	Sum of square	Df	Mean square	F value	P value	Remarks
Model	385.03	1	385.03	10.48	0.0119	Significant
B-kolliphor P 188	385.03	1	385.03	10.48	0.0119	
Curvature	249.21	1	249.21	6.78	0.0314	
Residual	293.94	8	36.74			
Lack of fit	293.94	6	48.99			
Pure error	0.000	2	0.000			
Cor Total	928.18	10				
Percentage Drug Dissolved in 10 min (PD10)						
Model	252.23	1	252.23	5.43	0.0481	Significant
B-kolliphor P 188	252.23	1	252.23	5.43	0.0481	
Curvature	344.19	1	344.19	7.41	0.0261	
Residual	371.46	8	46.43			
Lack of fit	371.46	6	61.91			
Pure error	0.000	2	0.000			
Cor Total	967.87	10				
Mean Dissolution Time (MDT)						
Model	285.53	4	71.38	9.15	0.0160	Significant
A-Beta CD	1.99	1	1.99	0.25	0.6353	
B-kolliphor P 188	2.34	1	2.34	0.30	0.6075	
C-PVP K30	187.86	1	187.86	24.07	0.0044	
AB	93.35	1	93.35	11.96	0.0181	
Curvature	6.06	1	6.06	0.78	0.4185	
Residual	39.02	5	7.80			
Lack of fit	39.02	3	13.01			
Pure error	0.000	2	0.000			
Cor Total	330.61	10				
Dissolution Efficiency (DE30)						
Model	428.03	1	428.03	9.42	0.0154	Significant
C-PVP K30	428.03	1	428.03	9.42	0.0154	
Curvature	473.53	1	473.53	10.42	0.0121	
Residual	363.39	8	45.42			
Lack of fit	363.39	6	60.57			
Pure error	0.000	2	0.000			
Cor Total	1264.95	10				

Table 6. Statistical Parameters

Parameters	PD ₁₅	PD ₁₀	MDT	DE ₃₀
Std. DEV	6.06	6.81	2.79	6.74
Mean	82.23	65.87	13.21	51.29
C.V%	7.37	10.35	21.14	13.14
PRESS	522.56	660.37	277.45	646.03
-2 log-likelihood	67.36	69.93	45.14	69.69
R-Squared	0.5671	0.4044	0.8798	0.5408
Adj R-squared	0.5130	0.3300	0.7836	0.4834
Pred R-Squared	0.2304	-0.0588	0.1451	0.1837
Adeq precision	5.568	5.107	8.533	6.264
BIC	72.15	74.73	57.13	74.49
AICc	72.86	75.43	67.14	75.19

in 30 min. DE30 has an R^2 value of 0.5408 indicating a good correlation between independent and dependent variables. All response statistical parameters are shown in Table 6. Tablets that dissolve quickly in the mouth (FDTs) Rapid disintegration when placed in the mouth, as well as good mechanical strength to endure handling, packaging, and shipping, are two factors that contribute to desirable and successful FDTs reported (Solaiman *et al.*, 2016; Teja and Damodharan, 2018).

Optimization

The formulation characteristics of taste masking furosemide were optimized using a model reported (Ibrahim and Abou El-Ela, 2017). The higher the desirability value, the better the formulation and the optimized formulae can be obtained directly from the desirability function response surface plots. The desirability concern was found to be higher (0.6364) for the optimized formula, indicating the formulation's suitability. Each response is optimized with the desired target adjustment point. To obtain a product, PD15 (Y1) was set to be the target, PD10 (Y2) was set to be the target, MDT (Y3) was set to be minimized, and DE30 (Y4) was set to be minimized. Three independent variables were used to optimize the formulation per the goals of the responses, and the composition of the optimized formulation was demonstrated using a desirability function shown in Table 1 in X1, X2, and X3 were 75 mg, 3.75 mg, and 2.25%, respectively, with desirability function of 0.6364. To validate the theoretical prediction, statistical optimization was performed on the prepared optimized formulation to fulfill all of the dissolution parameters (Ch and Chowdary, 2016). The application of the most common screening designs, such as two-level full factorial, fractionate factorial design, in pharmaceutical and/or analytical Quality by QbD, implementation of Design of Experiments (DoE) in pharmaceutical and/or analytical QbD reported (Fukuda *et al.*, 2018). The DOE is a statistical tool used in the development and

optimization of various types of systems, processes, and products reported (Challa and Reshma, 2022). The statistical tools that can be used include graphic design, comparisons, screening, and optimization (Durakovic, 2017; Taraka Ramarao and Pavani, 2023) reported.

Discussion

The above characteristics of the prepared blend show excellent to good flow properties and are appropriate for direct compression, Table 2 shows the flow properties. The FTIR spectrum indicates no chemical interaction between the drug and excipients, characteristic peaks are shown in Figure 2 and Figure 3. The tablets prepared to fulfill official specifications are shown in Table 3. The combination of low polymer concentrations of β -Cyclodextrin, Kolliphor- P188, and PVP K30 has a negative effect on tablet disintegration, whereas high polymer concentrations of β -Cyclodextrin, Kolliphor- P188, and PVP K30 have a positive effect. Figure 4 and Figure 5 show formulations F2 and F3 have the fastest and most rapid drug release rate of 100 percent at 20 minutes. The formulation F2 with market tablets has a similar dissolution shown in Figure 6. Figure 7 to Figure 8 depicts the contour and 3D response surface plots, as well as the desirability and optimized plots of all formulation factors. As values for observed and close agreement with model prediction, that PD15 was found to be 100%, PD10 was found to be 69.78%, MDT was found to be 12.90%, and DE30 was found to be 56.813%. The agreement between experimental and expected outcomes revealed the validity and predictability of the model. The optimized formulation produced, respectively, PD15 of 100%, PD10 of 69.78%, MDT of 12.909%, and DE30 of 56.813%. Additionally, the percentage prediction error was used to compare the predicted and experimental values to assess the predictor's accuracy and dependability (Pathan *et al.*, 2013). The statistical Significance level for the ANOVA of

PD15, PD10, MDT, and DE30 is $p \leq 0.0119$, and significance was reported (Tarakaramarao *et al.*, 2020). The statistical optimization was done on the prepared, optimized formulation to satisfy all of the dissolution parameters to validate the theoretical

prediction (Ch and Jami, 2022; Ramarao and Gunta, 2022; Ramarao *et al.*, 2023; Tarakaramarao *et al.*, 2016) recently reported. The flowchart diagram is shown in Figure 9.

Table 6. Statistical Parameters

Parameters	PD ₁₅	PD ₁₀	MDT	DE ₃₀
Std. DEV	6.06	6.81	2.79	6.74
Mean	82.23	65.87	13.21	51.29
C.V%	7.37	10.35	21.14	13.14
PRESS	522.56	660.37	277.45	646.03
-2 log-likelihood	67.36	69.93	45.14	69.69
R-Squared	0.5671	0.4044	0.8798	0.5408
Adj R-squared	0.5130	0.3300	0.7836	0.4834
Pred R-Squared	0.2304	-0.0588	0.1451	0.1837
Adeq precision	5.568	5.107	8.533	6.264
BIC	72.15	74.73	57.13	74.49
AICc	72.86	75.43	67.14	75.19

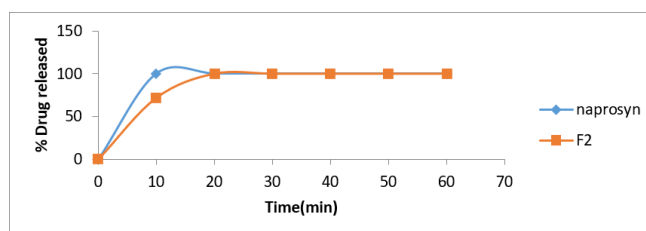


Figure 6. Comparative Dissolution profile of Naproxen marketed tablet (Naprosyn) and optimized formulation prepared F2

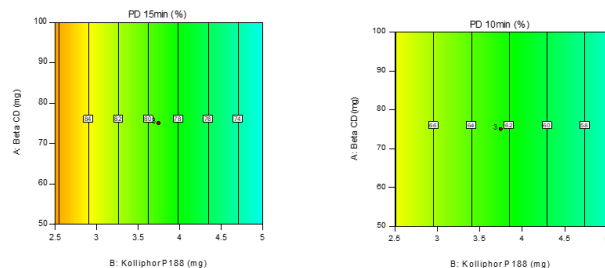


Figure 7. A. Contour plot for PD₁₅, B. Contour plot for PD₁₀

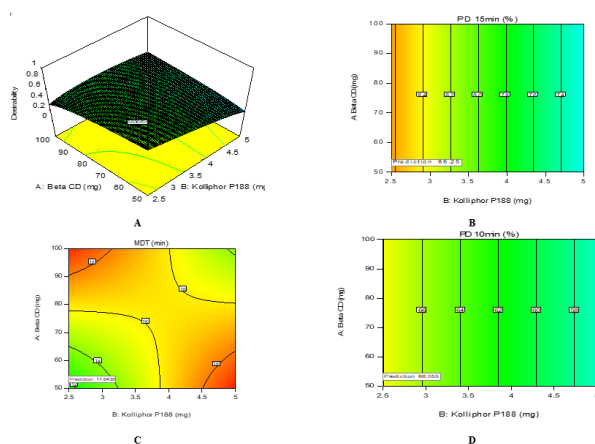


Figure 8. A. 3D Surface plot for Desirability, B. Contour plot for PD₁₅, C. Counter plot MDT, D. Counter plot PD₁₀ Optimized Formulation

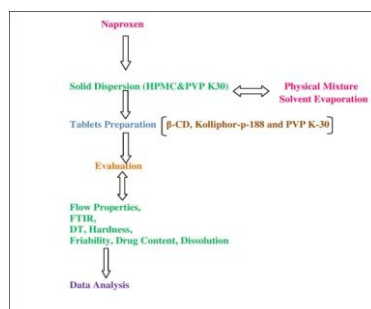


Figure 9. Flow Chart Diagram

Conclusions

When SD's with various carriers, the release was significantly improved, the blend has excellent to good flow properties and favors for direct compression. The FTIR spectrum indicates no chemical interaction between the drug and excipients. The F2 containing 100mg of drug with excipients β -cyclodextrin, 2.5mg of Kolliphor P188, 1.5 percent PVP K30 as significantly rapid dissolution in 20min performance, and the F3 formulation containing 50mg of excipients β -cyclodextrin, 5mg of Kolliphor P188, 1.5 percent PVP K30 as significantly rapid dissolution in 20min performance. $F4 < F8 < F7 < F1 < F6 < F5 < F3 < F2$ is the increasing order of drug dissolution of various formulations. The dissolution profiles of optimized formulation (F2) and market tablet (Naprosyn) are similar or identical. The methodology suggests improving bioavailability for poorly soluble drugs.

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