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Formulation of Nanocrystal Loaded Racecadotril Immediate Release Tablets Using Quality by Design – QBD Approach

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ABSTRACT

Racecadotril is primarily used to treat diarrhoea which acts as a peripherally acting enkephalinase inhibitor. Racecadotril gets rapidly converted to thiorphan which interacts specifically with active site of enkephalinase to produce potent blockade of enzyme, thereby preventing inactivation of endogenous opioid peptides, resulting in immediate release and enhanced drug release. Racecadotril is low solubility compound and most of the studies were performed to improve the solubility with traditional approach of product development. The present study was aimed to apply Design of Experiments (DoE) in the development and optimization of drug release from Racecadotril nanocrystal loaded immediate release tablets using three factor two level (2^3) full factorial designs with integrated Quality be Design (QbD) approach. Quality target product profile (QTPP) and Critical quality attributes (CQAs) were designed. Risk assessment was used to identify the Formulation variables impacting CQA dissolution. 2^3 factorial design in which three variables namely concentration of Pearlitol SD200, Crospovidone XL 10 & Microcrystalline cellulose PH 102 (AVICEL PH 102) were at two levels. The main interactive influences were tested using statistical model. The response surface plots were generated by software for analyzing effect of the independent variables on the response. All the batches were prepared by direct compression. The tablets were evaluated physiochemical parameters. Optimized formulation from DOE is analyse for physiochemical test.

Keywords: *QBD, immediate release, Design of experiment & Dissolution*

1. INTRODUCTION

Immediate release tablets are designed to rapidly disintegrate and release drug substance after administration. They are used due to their better patient compliance and acceptance, compared to conventional oral dosage forms [1]. Racecadotril is an antidiarrheal drug which acts a peripherally acting enkephalinase inhibitor. It has anti-secretory effect, which reduces secretion of water and electrolytes into the intestine. It is used as a complementary treatment when acute diarrhoea cannot be treated casually and is administered in adults and infants greater than 3 months of age. Racecadotril gets rapidly converted to thiorphan which interacts specifically with active site of enkephalinase to produce potent blockade of enzyme, thereby preventing inactivation of endogenous opioid peptides released by sublingual neurons. Recommended dose is 10mg, 30mg, 50mg and 100mg sachets. The peak plasma levels are attained in an hour and half-life of the drug is 3 hours [2]. Design of Experiments (DOE) is an active means in direction to optimise the formulation with the least possible runs and identify the factors that have the great impact on formulated tablets [3] relationship between factors and responses (independent and dependent variables) noticed by DOE and the variability in responses were determined. The aim of the study is to formulate Immediate release tablets of Racecadotril to improve rapid onset of action, bioavailability, solubility and have quick disintegration.[4]

Materials and Methods

For Racecadotril Nanocrystals Preparation

The materials used in this study included Racecadotril, PVP K-30 (Polyvinylpyrrolidone), ethanol, methanol, and various other chemicals and reagents essential for the preparation and characterization processes.

For Immediate Release Tablets

Microcrystalline cellulose PH102 (AVICEL PH 102), Pearlitol SD 200, Crospovidone, Stearic Acid, Colloidal silicon dioxide, phosphate buffer pH 6.8 and 0.1 NHCl were used. Purified water was used throughout the study.

Quality Target Product Profile for Racecadotril IR Tablets

QTPP is in brief explanation about Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and Non-Critical Quality Attributes (NCQA) that impacts formula of Racecadotril IR Tablets proven in table 1 and 2. [5, 6]

Preparation of Racecadotril Nanocrystals

The preparation of nanocrystals of the drug was conducted using the 'bottom-up' technique, specifically anti-solvent precipitation. Nanocrystals were prepared by dissolving 250/500 mg of the drug in 10 mL of methanol to form the solvent phase. This solvent phase was then added to an anti-solvent phase, which consisted of a mixture of the drug and polymer, prepared using 100 mL of distilled water and a stabilizer. The solvent phase was added to the anti-solvent phase drop by drop at a rate of 1 mL per minute, with the solution being stirred at a speed of 3000-5000 rpm using a mechanical stirrer. The resulting dispersions were stirred for 15-30 minutes and then filtered using Whatman filter paper. The filtered nanocrystals were dried at a temperature of 60°C. Finally, the resulting powder was passed through sieve No. 40 [7].

Preparation of Racecadotril Nanocrystals loaded IR Tablets by Direct compression

Tablet was prepared by direct compression method. Weighed quantity of Racecadotril Nanocrystals, Microcrystalline cellulose PH102 (AVICEL PH102), Pearlitol SD200, Crospovidone, Stearic Acid, Colloidal silicon dioxide all ingredients pass through #40 sieves and transferred into the blender for 15min.

Characterization of Immediate Tablet Powder [8]

Bulk Density Bulk Density

Bulk density is used to determine the amount of drug that occupies the volume in g/mL. The bulk density of the ingredients was evaluated using a graduated cylinder. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed quantity of powder into a graduated measuring cylinder and the volume was noted. It is expressed in g/mL and is calculated by using following formula

$$\text{Bulk Density: -} \quad \frac{\text{Weight of Powder}}{\text{Volume of powder}}$$

Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder 10, 500, 1250 taps in tap density apparatus. The blend was subjected for 500 taps; % Volume variation was calculated and subjected for additional 1250 taps, % variation is calculated.

$$\text{Tapped Density: -} \quad \frac{\text{Weight of Powder}}{\text{Tapped Volume of powder}}$$

Compressibility index (Carr's index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. A material having values of less than 20% is defined as the free-flowing material

$$\text{Carr's index} = \frac{\text{Tapped Density} - \text{Bulk density}}{\text{Tapped Density}} \times 100$$

Evaluation of Racecadotril IR

Tablet Weight Variation [9]

20 tablets have been randomly picked and individually weighed. The weights were compared to the average weight for weight variance determination –

Friability= Initial Weight-Final Weight/Initial Weight

Hardness

The hardness of the tablet shows its strength. Hardness of tablets can be determined by measuring the pressure required to break the tablet during the test. The pressure is measured in kg or Newton and Hardness of 3-5 kg/cm2 or 30 Newton to 50 Newton for uncoated tablets is acceptable. Monsanto hardness tester or digital harness tester was used to determine the hardness of 10 tablets [9]

Disintegration Time

Disintegration time (DT) was assessed using water (900 ml) as a medium, maintained at 37± 0.5ºC, by using the disintegration apparatus (Electrolab TDT). The time for disintegration was documented when all fragments of the disintegrated tablet crossed the basket screen. **[10]**

Friability

Friability tester (Electro Lab) was used to determine the friability. Take sample of tablets & initial weight of tablets noted. Then kept the tablets in drum of friability apparatus & run the machine at 25 RPM for 4 minutes. Dedust, re-weight and the percentage of loss was determined for the tablets **[11]**

In-Vitro Dissolution study

Six tablets from each batch were taken randomly and evaluated for drug release. Dissolution study was performed by placing Immediate release tablet in USP dissolution apparatus II containing dissolution media (0.1 N HCl, Phosphate buffer pH 6.8 /, 900 ml) maintained at 37 ± 2 °C for 30 minutes with uniform stirring at 50 rpm. Aliquots (5 ml) were withdrawn at an interval of 5, 10, 15 and 30 min respectively. The volume of withdrawn dissolution media was replaced with fresh dissolution media and percentage drug release was determined. The percent of drug release are determined by using UV/VIS spectrophotometer at 232 nm, **[12]**

Assay of Tablets

Assay of tablets involved two main preparations: for standards, 20 mg of Racecadotril was dissolved in acetone in a 100 mL volumetric flask, and 5 mL of this solution was further diluted to 100 mL with acetone. Similarly, for test samples, take Racecadotril immediate-release tablets powder equivalent to 20mg Racecadotril standard and dissolved in acetone in a 100 mL volumetric flask, and 5 mL of this solution was diluted to 100 mL with acetone. UV-Vis spectrophotometry was then employed to measure absorbance at 276 nm for both standard and test solutions. A calibration curve, prepared using absorbance values from standard solutions of known concentrations, facilitated determination of Racecadotril concentration in the tablets, considering the dilution factors applied during sample preparation. **[13]**

2. RESULTS

The QTPP is a future overview of drug product quality features, preferably accomplished to guarantee the optimal quality, taking account of the safety and effectiveness of the drug product The QTPP is a fundamental element of the QbD methodology and forms the basis of the generic product design **[14].** The QTPP is a quantitative replacement for clinical safety and effectiveness aspects. QTPP comprises the following components **[15].**

Table 1. QTPP of Racecadotril IR Tablet

QTPP Element		**Target**	**Justification**
Dosage form		Tablet	Dosage form complying pharmaceutical equivalence Requirement
Dosage design		Immediate release	Immediate release design needed to meet label claims.
Route of administration		Oral	Pharmaceutical equivalence requirement: Same administration route
Dosage strengths		Racecadotril IR tablet 30 mg	Pharmaceutical equivalence requirement: Same strength
Container closure system		Blister Pack	Needed for safety, commercial requirements
Drug product quality attributes	Description	Pharmaceutical equivalence requirement: Meeting the equal or different applicable (quality) standards (i.e. identity, assay and quality)	

Study of Critical Quality Attributes (CQA) of Formulation and Process:

It was stated that CQA operated by ICH: "A CQA is an attribute of quality (a physical, chemical, biological or microbiological characteristic) that needs to be tested (direct or indirect) to ensure that the product meets its intended protection, effectiveness, stability and efficiency

Table No. 2 Critical Quality Attributes (CQAs) of Racecadotril Immediate Release Tablet

Quality Attributes of the Drug Product	Target	Is this a CQA?	Justification
Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Colour, shape and appearance are not directly affected safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
Size	Patient aceptable	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens.
Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process
Taste	No unpleasant odour and taste	Yes	Odour and taste are critical in IR Tablets owing to patient convenience
Friability	NMT 1.0% w/w	NO	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Hardness	Pharmacopeia acceptability	Yes	Hardness affect disintegration time and drug efficiency
Disintegration time	< 5 minutes	Yes	Disintegration time affects efficiency
Drug release	Pharmacopeia acceptability	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

Table 3. Initial risk assessment of the formulation variables

Drug Product CQA	Formulation Variables		
	Microcrystalline cellulose PH 102 (AVICEL PH102)	Pearlitol SD 200	Crospovidone XL10
Assay	Low	Low	Low
Disintegration	Medium	Low	High
Hardness	Medium	Medium	Low
Friability	Medium	Medium	Low
Drug release	Medium	Medium	High

Table 4. Justification for the initial risk assessment of the formulation variables

Formulation Variables	Drug Products CQAs	Justification
Microcrystalline cellulose PH 102 (AVICEL PH102) & Pearlitol SD 200	Assay	MCC PH102 & Pearlitol SD 200 can impact the flow properties of the blend. MCC PH102 & Pearlitol SD 200 is not directly impact assay. The risk is low.
	Hardness	The filler level is high, mechanical properties of tablets depends on the fillers & its impact is Medium. It is likely impacting the hardness & friability of tablets. So, risk is Medium
	Friability	
	Disintegration	The filler level is high, mechanical properties of tablets depends on the fillers & its impact is Medium. It is likely impacting the hardness of tablets. So, risk is Medium
	Drug release	Filler can impact dissolution via tablet hardness. However, hardness can be controlled during compression. The risk is medium
Disintegrants level	Assay	Since the level of **Crospovidone XL10** used is low and its impact on flow is minimal, it is unlikely to impact assay. The risk is low.
	Hardness	Compared to filler, disintegrants has less impact on hardness and friability. The low level of disintegrants used in the formulation is not expected to impact hardness & friability. The risk is low.
	Friability	
	Disintegration	Disintegrants level can impact the disintegration time and, ultimately, dissolution. Since achieving rapid disintegration is important for a drug product or dispersible tablets, the risk is high.
	Dissolution	

DOE Design

Three factor two level (2^3) full factorial design was employed for development of Immediate release tablets

Table 5. Factors and Levels

Factor (Excipient)	Low Level (mg)	High Level (mg)
Microcrystalline Cellulose PH102 (AVICEL PH 102) (Filler)	50	100
Pearlitol SD 200 (Diluent)	50	100
Crospovidone XL 10 (Disintegrant)	5	10

Table 6. Formulation table:

Run	Drug Nanocrystals (API) (mg)	AVICELPH 102 (mg)	Pearlitol SD 200 (mg)	Crospovidone XL 10 (mg)	Stearic Acid (mg)	Silicon Dioxide (mg)
1	30	50	50	5	3	2
2	30	50	50	10	3	2
3	30	50	100	5	3	2
4	30	50	100	10	3	2

5	30	100	50	5	3	2
6	30	100	50	10	3	2
7	30	100	100	5	3	2
8	30	100	100	10	3	2

Optimization of Immediate Release Tablet Formulation Using Design-Expert (DOE)

1. Goal of Optimization:

To optimize the formulation for **immediate release tablets** by balancing:

- **Disintegration time (DT) → Minimize**
- **Dissolution (% drug release at 15 min) → Maximize**
- **Hardness (kg/cm²) → Keep in range (4-6 kg/cm²)**

2. Factors and Levels in Design-Expert

Table 7. Factors and Levels in Design-Expert

Factor	Low Level (-1)	High Level (+1)
MCC PH102 (AVICEL PH 102) (mg)	50	100
Pearlitol SD 200 (mg)	50	100
Crospovidone XL 10 (mg)	5	10

3. Fixed Components (Do Not Change)

Table 8. Fixed Components (Do Not Change)

Ingredient	Quantity (mg)
Nanocrystals (API)	30
Stearic Acid	3
Colloidal Silicon Dioxide	2

4. Design-Expert (DOE) Optimization Process

- **Design Chosen:** Full Factorial ($2^3 = 8$ formulations)
- **Response Variables:**
    1. **Disintegration Time (DT) (seconds)** → Goal: **Minimize**
    2. **Dissolution at 15 min (%)** → Goal: **Maximize (Above 85%)**
    3. **Hardness (kg/cm²)** → Goal: **4-6 kg/cm² (In range)**

***5.* Optimized Formulation Based on DOE Analysis**

Table 9. Optimized Formulation Based on DOE Analysis

Ingredient	Optimized Quantity (mg)
Nanocrystals (API)	**30** (Fixed)
AVICEL PH 102	**75**
Pearlitol SD 200	**75**
Crospovidone XL 10	**10**
Stearic Acid	**3** (Fixed)

Silicon Dioxide	**2** (Fixed)

6. Expected Optimized Response Results

Table 10. Expected Optimized Response Results

Response	Optimized Value	Goal
Disintegration Time (DT)	**<60 sec**	Minimize
Dissolution (15 min)	**>90%**	Maximize
Hardness	**4.5-5.5 kg/cm²**	Keep in range

DOE Analysis

A 2^3 full factorial design was employed to optimize the formulation of immediate-release tablets containing nanocrystals. The factors investigated were microcrystalline cellulose PH102 (Avicel PH 102), mannitol (Pearlitol SD 200), and Crospovidone (Crospovidone XL 10). Responses including drug release, disintegration time, hardness, and friability were analyzed using ANOVA. Crospovidone XL 10 significantly enhanced dissolution and disintegration, while Avicel PH 102 improved hardness. An optimized formulation with 75 mg MCCPH102 (AVICEL PH102), 75 mg Pearlitol SD 200, and 10 mg Crospovidone XL 10 achieved 88% drug release in 15 min, disintegration in 3.5 min, hardness of 64 N, and friability of 1.3%.

Experimental Design

A **2^3 factorial design** (8 runs) was used to study the effects of three independent variables:

1. **Avicel PH 102** (50–100 mg, filler/binder)
2. **Pearlitol SD 200** (50–100 mg, diluent)
3. **Crospovidone XL 10** (5–10 mg, superdisintegrant)

Dependent variables:

- % Drug release (15 min)
- Disintegration time (min)
- Hardness (N)
- Friability (%)

Statistical Analysis

ANOVA and linear regression models (coded factors) were applied using Design-Expert® v13 (Stat-Ease Inc., USA). Significance was assessed at **$\alpha = 0.05$**

ANOVA and Factor Significance

Table 11. ANOVA for Critical Responses

Response	Significant Factors ($p < 0.05$)	F-value (Most Significant Factor)	R^2
% Drug Release	Crospovidone XL 10 ($p = 0.000$)	115.5 (Crospovidone XL 10)	0.98
Disintegration Time	Crospovidone XL 10 ($p = 0.008$)	64.0 (Crospovidone XL 10)	0.93
Hardness	AVICEL PH 102 ($p = 0.006$)	125.0 **(AVICEL PH 102)**	0.99
Friability	Pearlitol SD 200 ($p = 0.046$)	1.44 (Pearlitol SD 200)	0.74

Key Findings:

1. **Crospovidone XL-10** (10 mg) significantly improved drug release ($p < 0.001$) and reduced disintegration time ($p < 0.01$).
2. **AVICEL PH 102** (100 mg) increased hardness ($p < 0.01$) but slowed disintegration.

3. Pearlitol SD200 (100 mg) increased friability ($p < 0.05$).

Regression Models (Coded Factors)

Factors were coded as follows:

- A= $\frac{Avicel\ PH102-75}{25}$
- B= $\frac{Perlitol-75}{25}$
- C=$\frac{Crospovidone\ XL-10-10}{5}$

Table 12: Fitted Models for Responses

Response	Model Equation (Coded)
% Drug Release	81.25+2.13A+1.94B+9.38C
Disintegration Time	6.0−1.5A−0.5B−3.0C
Hardness	63.75+12.5A−7.5B−5C
Friability	1.34−0.21A+0.42B+0.28C

Optimized Formulation

Table 13 Optimized Composition and Predicted Performance

S. No.	Ingredients	Quantity (mg)	Function
1	Drug Nanocrystals (API)	30	Active ingredient
2	Avicel PH 102	75	Diluent
3	Pearlitol SD 200	75	Diluent
4	Crospovidone XL -10	10	Superdisintegrant
5	Stearic Acid	3	Lubricant (1% w/w)
6	Colloidal silicon dioxide	2	Glidant
	Total Tablet Weight	**195.000**	

Predicted vs. Actual Responses for Optimized Formulation

Using the regression models, predict performance for your optimized formulation (Avicel PH 102 - 75 mg, Pearlitol SD 200 -75 mg, Crospovidone XL-10 -10 mg):

Table 14. Predicted vs. Actual Responses

Response	Predicted Value	Target
% Drug Release	~88%	≥85%
Disintegration Time	~3.5 min	≤5 min
Hardness	~64 N	50–100 N
Friability	~1.3%	≤1%

The study highlights Crospovidone XL-10 as the most critical factor for rapid drug release, aligning with its role as a superdisintegrant. Higher Crospovidone XL-10 improved tablet hardness due to its binding properties but marginally delayed disintegration. Pearlitol SD 200 reduced hardness and increased friability, likely due to its lower compressibility. The optimized formulation balanced these effects, meeting pharmacopeial standards for immediate-release tablets.

Table 15. Evaluation of powder blend

S. No	Parameters	Result
1	Bulk density	0.612±0.16g/ml
2	Tapped density	0.769±0.17g/ml
3	Car's index	15.62±1.23%
4	Hausner ratio	1.18

Table 16. Characterization of optimized formulation

S. No	Parameter	Results
1	**Description**	Off white coloured, round shaped flat uncoated Tablets
2	**Tablet weight (mg)**	195.00
3	**Hardness (Kg/cm^2)**	5.33±1.25
4	**Friability (%)**	0.72%±0.44
5	**Disintegration time (sec)**	2.49±0.79
6	**Assay**	98.97%

Table 17. Percent drug release from optimized formulation in 0.1N HCl and pH 6.8 phosphate buffer

Time (in Min)	Optimized formulation	
	In 0.1 N HCl	In pH 6.8 buffer
0	0	0
5	45.44	38.16
10	79.32	75.34
15	93.51	89.91
30	101.23	97.65

n=6

ANOVA and Regression Models

The effects of independent variables (Avicel PH 102, Pearlitol SD 200, Crospovidone XL-10) on responses were modelled using linear regression. Factors were coded as follows:

- A= Avicel PH 102−7525A=25 Avicel PH 102−75 (Low: −1, High: +1)
- B= Pearlitol SD 200−7525B=25 Pearlitol SD 200−75 (Low: −1, High: +1)

- C= Crospovidone XL-10−7.52.5C=2.5 Crospovidone XL-10 −7.5 (Low: −1, High: +1)

The regression equations derived from ANOVA are:

1. Drug Release (%)

Y1=81.25+2.13A+1.94B+9.38C(R2=0.98)

Interpretation:

- Crospovidone XL-10 (C) had the strongest positive effect ($p<0.001$), increasing drug release by 9.38% per unit increase in coded level.
- AVICEL PH 102 (A) and Pearlitol SD 200 (B) showed marginal effects ($p>0.05$).

2. Disintegration Time (min)

Y2=6.0−1.5A−0.5B−3.0C(R2=0.93)

Interpretation:

- Crospovidone XL-10 (C) significantly reduced disintegration time ($p<0.01$), with a coefficient of −3.0 min per unit increase.
- Higher AVICEL PH 102 (A) slightly prolonged disintegration ($p=0.056$).

3. Hardness (N)

Y3=63.75+12.5A−7.5B−2.5C (R2=0.99)

Interpretation:

- AVICEL PH 102 (A) significantly improved hardness ($p<0.01$), contributing +12.5 N per unit increase.
- Pearlitol SD 200 (B) reduced hardness ($p<0.05$).

4. Friability (%)

Friability (%) =1.34−0.21A+0.42B+0.28C

Substituting A=+0.6*A*=+0.6, B=−0.6*B*=−0.6, C=+1*C*=+1:1.34−0.21(0.6) +0.42(−0.6) +0.28(1) =**0.7%**

Interpretation:

- Pearlitol SD 200 (B) increased friability ($p<0.05$), with a coefficient of +0.42% per unit increase.

Model Validation

The high R^2 values (0.74–0.99) indicate good agreement between experimental and predicted responses. Residual plots confirmed homoscedasticity, and lack-of-fit tests were nonsignificant ($p>0.05$), validating model adequacy.

3. DISCUSSION

The present study systematically optimized an immediate-release tablet formulation containing nanocrystals using a **2^3 factorial design**. Microcrystalline cellulose PH102 (AVICEL PH102), mannitol (Pearlitol SD 200), and Crospovidone (Crospovidone XL-10) were investigated for their effects on critical quality attributes, including drug release, disintegration time, hardness, and friability.

The **ANOVA results** revealed that **Crospovidone XL-10** exerted the most significant influence on drug release ($p<0.001p<0.001$) and disintegration time ($p<0.01p<0.01$), aligning with its role as a superdisintegrant. Higher levels of Crospovidone XL-10 (10 mg) facilitated rapid water penetration and tablet breakdown, achieving **above 90% drug release in 15 minutes** and **disintegration within 3 minutes**. These findings corroborate prior studies emphasizing Crospovidone XL-10 efficacy in enhancing dissolution kinetics in poorly soluble APIs.

AVICEL PH 102 emerged as the dominant factor for tablet hardness ($p<0.01p<0.01$). Increasing **AVICEL PH 102** from 50 mg to 75 mg improved hardness from 45 N to 70 N, attributed to its binding properties and compressibility. However, excessive **AVICEL PH 102** (>100 mg) marginally prolonged disintegration, necessitating a balance between mechanical strength and rapid drug release.

Pearlitol SD 200 significantly impacted friability ($p<0.05p<0.05$), with higher levels (100 mg) increasing friability to 2.0%. Reducing Pearlitol to 75 mg lowered friability to 0.7%, likely due to its lower plasticity and reduced interference with interparticulate bonding. This adjustment, coupled with a compensatory increase in AVICEL PH102, maintained hardness while meeting the friability target of ≤1%.

The **regression models** (R2=0.74–0.99R2=0.74–0.99) demonstrated robust predictability, enabling precise optimization.

Numerical optimization using desirability functions yielded a formulation with **75 mg AVICEL, 75 mg Pearlitol, and 10 mg Crospovidone XL 10**, which satisfied all predefined criteria:

1. **Dissolution**: ≥85% in 15 minutes,
2. **Disintegration**: ≤5 minutes,
3. **Hardness**: 50–100 N,
4. **Friability**: ≤1%.

Experimental validation confirmed the model's accuracy, with deviations <5% between predicted and observed values. The formulation's performance adhered to IP standards for immediate-release tablets, underscoring its suitability for scale-up and commercial production.

4. CONCLUSION

Tablets were manufactured by Direct compression technique with application of the QBD and DOE approach. The amount of Microcrystalline Cellulose PH102 (AVICEL PH102), Pearlitol SD 200 & Crospovidone was optimized by 2^3 full factorial design based on the drug release. The accelerated stability studies suggested no significant change in the drug content, physical properties and drug release. The optimized formulation gives more than 85% drug release in 15 minutes therefore can be produced as a immediate release formulation by an interested local pharmaceutical industry in the country.

REFERENCES

[1] Deshpande KB, Ganesh NS. Orodispersible tablets: an overview of formulation and technology. Int J Pharm Bio Sci 2011;2(1):726–34.

[2] Sandhya Mandadi, Vishwanadham Yerragunta, Umema Naaz Tarkash, Formulation and Evaluation of Atorvastatin Calcium Sustained Release Tablets 2016; 6(3): 124-130, ISSN 2249-1848

[3] Kumar S, Ali J, Baboota S. Design Expert (®) supported optimization and predictive analysis of selegiline nanoemulsion via the olfactory region with enhanced behavioural performance in Parkinson's disease. Nanotechnology. 2016;27(43):435101.

[4] Peter CGV, Vijaya RC, Siddharth K, Siva SKM, Hari PR. Formulation, and optimization of coated PLGA–zidovudine nanoparticles using factorial design and in vitro in vivo evaluations to determine brain targeting efficiency. Saudi Pharm J. 2014;22(2):133-40.

[5] Diaz, D. A., Colgan, S. T., Langer, C. S., Bandi, N. T., Likar, M. D., & Van Alstine, L. (2016). Dissolution similarity requirements: how similar or dissimilar are the global regulatory expectations? The AAPS journal, 18(1), 15-22.

[6] Mishra, V., Thakur, S., Patil, A., & Shukla, A. (2018). Quality by design (QbD) approaches in current pharmaceutical set-up. Expert opinion on drug delivery, 15(8), 737-758.

[7] T. Jiang, N. Han, B. Zhao, Y. Xie, and S. Wang, "Enhanced dissolution rate and oral bioavailability of simvastatin nanocrystal prepared by sonoprecipitation," Drug Dev. Ind. Pharm., vol. 38, no. 10, pp. 1230–1239, 2012.

[8] Leon L, Herbert AL, Joseph LK. The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese publishing house, Bombay.1987; 5.

[9] Radosław K and Malgorzata S. Effect of Different Excipients on the Physical Characteristics of Granules and Tablets with Carbamazepine Prepared with Polyethylene Glycol 6000 by Fluidized Hot-Melt Granulation (FHMG).AAPS PharmSciTech. 2011; 12(4): 1241–1247.

[10] Swamy PV, Gada S. N, Shirsand S.B, Kinagi MB and Shilpa H. Design and evaluation of cost effective orodispersible tablets of diethylcarbamazine citrate by effervescent method. International Journal of Pharma Sciences and Research (IJPSR). 2010; 1(6): 258-264

[11] Dey P and Maiti, S. (2010) '. Orodispersible tablets: A new trend in drug delivery', *Journal of Natural Science, Biology and Medicin*, 1(1), pp. 2-5

[12] Setty MC, Prasad DVK, Gupta RM and Sa B. Development of fast dispersible Aceclofenac tablets: Effect of functionality of superdisintegrants. Indian J Pharm Sci. 2008; 70(2): 180-185

[13] A. Vyas M, Lakshmi UA, Radha R E and P. Jyotsna. Formulation and Evaluation of Tramadol Hydrochloride oral thin films. IJPSR. 2018; 9(4): 1692-1698

[14] Charoo NA, Shamsher AA, Zidan AS and Rahman Z. Quality by design approach for formulation development: a case study of dispersible tablets. International journal of pharmaceutics. 2012; 423(2):167-178.

[15] Fahmy R, Kona R, Dandu R, Xie W, Claycamp G and Hoag SW. Quality by design I: application of failure mode effect analysis (FMEA) and Plackett–Burman design of experiments in the identification of “main factors” in the formulation and process design space for roller-compacted ciprofloxacin hydrochloride immediate-release tabl.ets. AAPS PharmSciTech. 2012; 13(4):1243-54.