FORMULATION AND DEVELOPMENT OF PROPRANOLOL HCl IMMEDIATE RELEASE TABLET THROUGH QUALITY BY DESIGN (QbD) APPROACH

M.R BHALEKAR [a], SONALI BHARMAL [b]

Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, India.

Abstract :

The pharmaceutical quality by design (QbD) and describe how it can be used to ensure pharmaceutical quality .Quality cannot be tested into products but quality should be built in by design.The objective of the present study was to design and develop a formulation for immediate release tablet of propranolol hydrochloride using quality by design principles. The potentially high-risk formulation and process variables. Risk assessment technique was used to determine Critical quality attributes (CQA) and which studies were necessary to achieve product and process understanding to develop a control strategy. Risk assessments done The development of Generic Propranolol Hydrochloride , 10 mg. Brand Ciplar Tablet, 10 mg is summarized in this research. The immediate release (IR) tablet indicated for the relief of moderate to severe physiological symptoms. We used Quality by Design (QbD) to develop Propranolol Hydrochloride IR tablets.

The quality target product profile (QTPP) of IR tablet were identified risk assessment was carried out by prior Knowledge and experience to define the critically of factors based on their impact by Ishikawa fishbone diagram. A 2^3 full factorial design (FFD) was employed to study the effect of critical factors on various attributes of the IR tablet.

Keywords: Propranolol hydrochloride IR tablet , Quality by Design , Risk assessments ,full factorial design.

1.INTRODUCTION :

Quality by design (QbD) in formulation development has been recommended by the Food and Drug Administration (FDA) and pharmaceutical industry. FDA's stress on implementation of (QbD) began with the ideology that only increased testing does not improve product quality but it must be built into the product and this requires understanding of formulation and manufacturing process variables and their influence on product quality.[2] Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[3]

The process involves designing and developing formulations and manufacturing processes to ensure a predefined quality. Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8 (8), Pharmaceutical Development, along with ICH Q9 (9), Quality Risk Management, and ICH Q10 (10), Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality.[4,5,6,7] Design of experiments (DOE), risk assessment, and

process analytical technology (PAT) are tools that may be used in the QbD process when appropriate and are not mandatory.

Present study describes Development of Propranolol HCl immediate release tablet form to using Quality by Design approach.

2.MATERIALS AND METHODS

2.1 Materials

Propranolol Hydrochloride was obtained as gift sample from Alkem Labs, Raigad, India. Marketed tablets Ciplar 10mg was purchased from local shop Pune. Solvents used were of analytical grade. All other chemicals were procured from local sources and were of analytical grade.

2.2 Disintegration Test

The tablets disintegration test was performed to check the disintegrating time of tablets in 900 ml of distilled water at 37 ˚C in DT apparatus (Veego).

2.3 Drug Release

The dissolution method recommended in the FDA dissolution methods database for propranolol advices use of 900 mL of distilled water using USP apparatus 1 (paddle) at 100 rpm. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C and the drug concentration was determined using UV spectroscopy at a wavelength of 290nm.

Additionally multimedia dissolution study separately in dissolution media 0.1M HCl and phosphate buffer pH 6.8 was done.[10]

3.CHARACTERISATION OF PROPRANOLOL HCL

3.1 Development of solid oral dosage form using Quality by design approach:

The tablets were manufactured by a direct compression method. The formulation ingredients were chosen based on literature survey.[15] The ingredients decided were MCC (diluent), lactose (diluent) and starch (disintegrant).

3.2 Risk Assessment of Drug Substance Attributes:

A risk assessment of the drug substance attributes such as solid state, particle size, hygroscopicity, solubility, flow properties was performed to evaluate the impact that each attribute could have on the drug product Critical Quality Attributes (CQA).

3.3 Risk Assessment of the Formulation Variables:

In this initial risk assessment for formulation development, the detailed manufacturing process not been established . Thus, risks will be rated assuming that for each formulation attribute that schanged, an optimized manufacturing process was established.

3.4 DOE (Design of Experiments) Formulation

The goal of formulation development was to lower the risk posed by material attributes (MA) such as concentration of MCC:lactose ratio in diluent and concentration of starch (disintegrant) of formulation to the CQA. A 2 factor 3-level full factorial design was used to explore the interaction within these variables if any. This study also sought to establish the robustness of the proposed formulation so that slight variations should not affect product quality.

Table 1 contains factor combination and the levels chosen along with the responses and acceptable ranges as per analysis. Table 11 describes formulation runs of optimization trial.

Table 1: Design of experiments for formulation development

Variables		Levels		
		+1	0	-1
A	MCC : Lactose ratio	51	42.5	34
B	Disintegrant (Starch)	15	12.5	10
Responses		Goal	Acceptable Ranges as per RLD	
Y1	Dissolution at 30 min (%)	Maximize	>98%	
Y2	Disintegration time (min)	Minimize	< 2min 45 secs	
Y3	Friability	Minimize	<1%	

3.5 Evaluation of powder blend:

The powder was evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio according to standard tests as mentioned in literature.[7][17]

3.6 Formulation of Tablets:

Tablets were prepared by direct compression method using standard 6 mm concave punches on rotary tablet compression machine (Rimek Mini Press II MT). All the product and process variables like mixing time and compression force, were kept constant and within permissible limits which were later optimized in the manufacturing process development section.

3.7 Evaluation of core tablets:

Evaluation of core tablets was done for the dimensions, weight variation, hardness, and friability by the standard methods mentioned in literature.[13]

3.8 In Vitro Dissolution Studies:

In vitro dissolution studies of Propranolol Hydrochloride tablets , was performed as per section 2.3 mentioned above.

3.9 Updated Risk Assessment of the Formulation Variables

Ideally after conducting the DOE and optimizing the formulation updated risk assessment is conducted based upon formulation development study shown in Table 13.

4.DESIGN SPACE

A design space was given which states that if the factors or variables which when operated in the range given in design space the desired outcome is achieved.

5.MANUFACTURING PROCESS DEVELOPMENT

Initial Risk Assessment of Manufacturing Process

In this initial risk assessment for manufacturing process development, the detailed manufacturing process was not established. Thus, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process was to be established.

5.1 DOE (Design of Experiments) Formulation

The experimental design for the manufacturing process of tablets consisted of 2 processes i.e. blending and Compression. In this case optimisation of only blending operation was performed and the compression force was fixed. A (22) factorial design was implemented to evaluate the effect of blending process on the formulation. The variables selected based upon the initial risk assessment were blend RPM and blend time and the response selected was content uniformity as it was identified as CQA.

Table 2: Design of experiments for formulation development

Variables		Levels	
		-1	+1
A	Blend RPM	30	60
B	Blend Time (min)	5	10
Responses		Goal	Acceptable Ranges
Y1	Assay	Maximize	>95%
Y2	Tablet content uniformity (% RSD)	Minimize % RSD	<5%

6.Evaluation of Tablet blend:

6.1 Assay :

Powder equivalent to 20 mg of Propranolol Hydrochloride was taken in 20ml of distil water for 10 minutes . Add 50ml of methanol in a 100ml volumetric flask, shake for a further 10 minutes. Add sufficient methanol and the volume was made up to 100ml. The solution was filtered by using Whatman filter paper 0.45µm and absorbance was read at 290nm.

6.2 Content Uniformity

Drug content uniformity was determined by dissolving the tablets in ethyl alcohol and filtering with Whatman filter paper (0.45 m). The filtrate was evaporated and the drug residue dissolved in 100 ml phosphate buffer pH 6.8. The 5 ml solution was then diluted with phosphate buffer pH 6.8 up to 20 ml, filtered through Whatman filter paper, and analyzed at 290 nm using a UV range(200-400nm). The mean percent drug content was calculated and % RSD was found out.

6.3 Updated Risk Assessment

Updated risk assessment was carried out based upon the findings of the formulation development.

7. CONTROL STRATEGY :

The ranges of critical parameters must be constrained to a multidimensional design space or fixed at values of all parameters known to be acceptable. The control strategy for Generic propranolol hydrochloride Tablets, 10 mg, is built upon the outcome of extensive product and process understanding studies and is depicted in Table 18.

8. RESULTS AND DISCUSSION :

8.1 Analysis :

Clinical Pharmacology

CIPLAR 10 mg contains Propranolol Hydrochloride is the hydrochloride form of Propranolol a synthetic beta-adrenergic receptor blocker with antianginal, antiarrhythmic, and antihypertensive properties. Propranolol competitively antagonizes beta-adrenergic receptors, thereby inhibiting beta-adrenergic reactions, such as vasodilation, and negative chronotropic and inotropic effects.

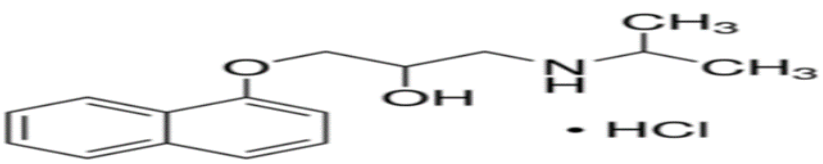


Fig 1: Structure of propranolol hydrochloride

Its empirical formula is C16H21NO2•HCl , representing a molecular weight of the free base of 360.31. Propranolol hcl is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C. CIPLAR 10 mg Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265

mg or 14.53 mg of the Propranolol , respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, starch and magnesium stearate. [9]

8.2 Mechanism of action:

propranolol is nonselective beta-Adrenergic Blocking agent propranolol inhibits response to adrenergic stimuli by competitively blocking beta-adrenergic receptors within the myocardium and within bronchial and vascular smooth muscle. Only the I-isomer of propranolol has substantial beta-adrenergic blocking activity propranolol has no intrinsic sympathomimetic activity.

8.3 Pharmacokinetics :

Propranolol hydrochloride is completely absorbed following oral administration. The mean oral absolute bioavailability of the CIPLAR Tablet is about 26%, and mean peak plasma concentrations (Cmax) are reached in approximately 2-3 hours (T max). The presence of a Hypertension , migraine headache, Angina, did not appear to affect the absorption or pharmacokinetics of Propranolol. Food has no significant effect on the bioavailability of Propranolol but delays the time to reach peak concentration by an hour. The plasma half-life of Propranolol in males and females averages 2-3 hours. Propranolol is minimally bound (90%) to plasma proteins.

9.Physiochemical Characterization

The physicochemical characterization of the RLD tablet is summarized in Table 3.

Table 3: Physicochemical characterization of the RLD

Test	Result
Description	White coloured tablets
Batch No.	SB30052
Expiry date	MAY 21
Strength (mg)	10 mg
Average weight (mg)	100 mg
Coating	No Coating
Diameter (mm)	6.5 mm
Thickness (mm)	2.29 mm

Hardness (kP)	5-6
Disintegration time (secs)	97
Disintegration observation	Rapidly disintegrates into fine powder
Assay (% w/w of label claim)	99.3% w/v

9.1 Drug Release

The cumulative % drug release at 30 min was 100.04% determined using UV spectroscopy at a wavelength of 290 nm. Usually the rate limiting process for absorption of a BCS Class I compound like Propranolol is permeation and not the solubility.

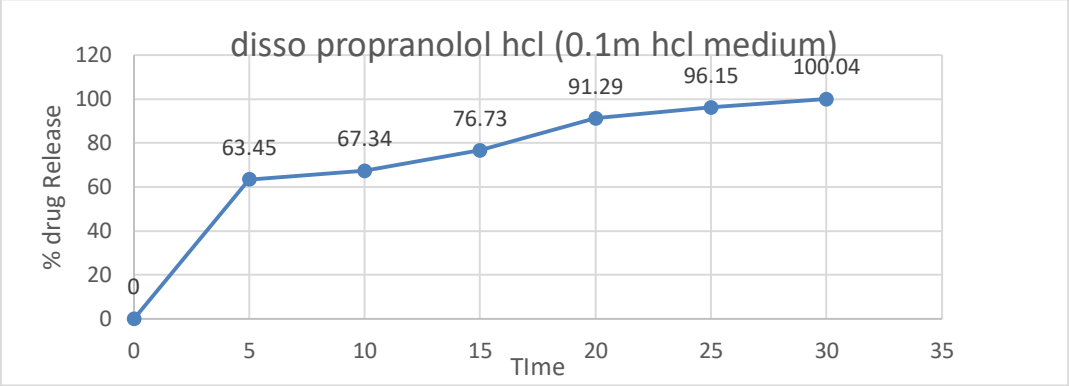


Fig 2: Percent release from RLD

9.2 Disintegration Test

The disintegration for water soluble drug is potential indicator of bioavailability, DT for RLD was found to be 97 secs which is well below the Pharmacopoeia limits (15 min).

9.3 Quality Target Product Profile for tablet

Based on the clinical and pharmacokinetic (PK) characteristics as well as the in vitro dissolution and physicochemical characteristics of the RLD, a quality target product profile (QTPP) was defined for Generic Propranolol hydrochloride Tablets, 10 mg in Table 4.

Table 4: QTPP profiling for tablet

QTPP Elements	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design	Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration	Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength	10 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics	Immediate release enabling Tmax in 2 to 3 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability	At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes Identification Assay Content Uniformity Dissolution Degradation Products Residual Solvents Water Content Microbial Limits	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).
Container closure system	Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Alternative methods of administration	None	None are listed in the RLD label.

Table 4 summarizes the quality attributes of generic Propranolol Hydrochloride tablets and indicates which attributes were classified as drug product critical quality attributes (CQA). For this product, assay, content uniformity (CU) and dissolution are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, are investigated and discussed in detail in subsequent formulation and process development studies.

On the other hand, in Table 5, CQAs including identity, residual solvents and microbial limits which are unlikely to be impacted by formulation and/or process variables are not discussed in detail. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy.

Table 5: CQA'S for generic tablet

Quality Attributes of Drug Product		Target	CQA?	Justification
Physical Attributes	Appearance	Colour and shape acceptable to the patient. No visual tablet defects observed.	No	Colour, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odour	No unpleasant odour	No	In general, a noticeable odour is not directly linked to safety and efficacy, but odour can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odour. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the Propranolol hydrochloride tablet.
	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.
Identification		Positive for Propranolol Hydrochloride	Yes	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus,

			assay will be evaluated throughout product and process development.
Content Uniformity (CU)	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution	NLT 80% at 30 minutes in 900 mL of distilled water using USP apparatus 1 at 100 rpm	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.

9.4 Multimedia Dissolution

Different dissolution media Distilled water (DW), 0.1M HCl and phosphate buffer (PB) pH 6.8) were used to determine the effect of dissolution medium on release.

As shown in Figure RLD tablets exhibited a very rapid dissolution in dissolution media of different composition and showed no sensitivity to medium pH.

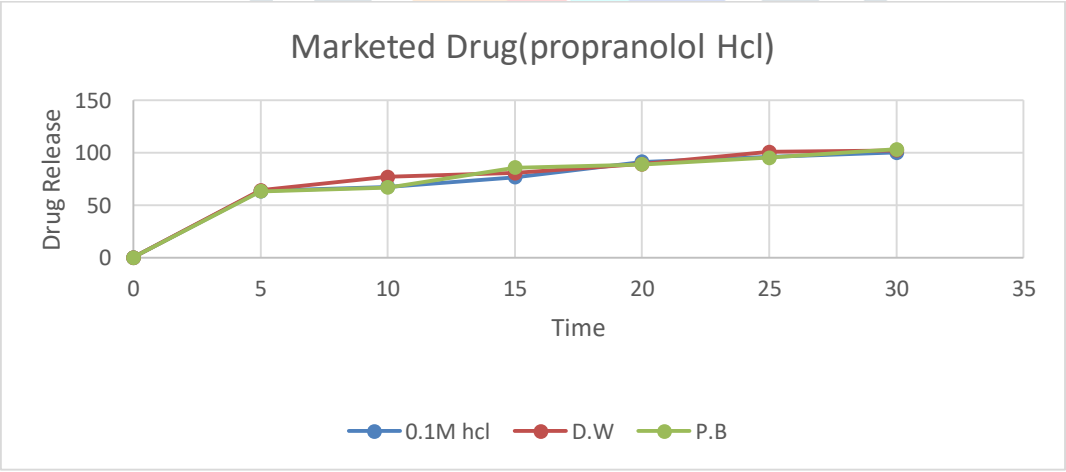


Fig 3: % Release of propranolol hydrochloride in different dissolution media

Table 6: Cumulative drug release at 30 min in different pH media.

Sr. No	Medium	Time	% Release
1	Distilled water	30 min	102.30
2	Phosphate Buffer pH 6.8	30 min	103.27
3	HCl 0.1 N	30 min	100.04

This may be accounted to the pKa of the drug (9.56) it remains unionised at all body pH according to pH partition hypothesis. Thus, it was concluded that 900 mL of 0.1 M HCl medium using USP apparatus 1 at 100 rpm can be used as dissolution medium for further analysis of the batches.

Component Analysis of Drug Product

9.4 UV visible Spectroscopy

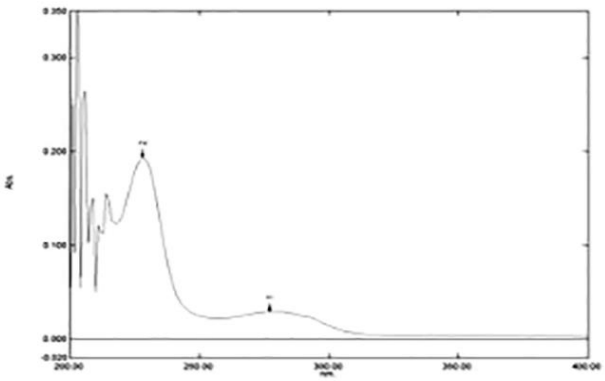


Fig 4. UV spectra of propranolol hydrochloride

The UV spectrum of Propranolol hydrochloride was obtained which showed absorption maxima at 224 nm and 290 nm.

9.5 Melting Point Determination

Melting point of the pure drug of Propranolol Hydrochloride was determined by the capillary method and was found to 163 (± 2) °C, which is very close to the reported melting point 166 °C.

9.6 Assay

Fig 4. Calibration Curve of Propranolol Hydrochloride in 0.1 M HCl

The regression equation from the calibration curve was

$y = 0.0278x + 0.005$ ($R^2 = 0.9996$) ……... [Equation 3]

the beers law was obeyed within concentration range of 5-25 µg/ml. The absorbance of filtrate from assay procedure was 0.579 which meant the percent assay is 103.23 % w/v.

9.7 Risk Assessment of Drug Substance Attributes:

Drug substance attributes are important as they directly influence the product properties and therefore it was very necessary to assess the risks associated with drug substance properties.

Table 7: Initial risk assessment for drug substance attributes

Drug Substance CQA's	Drug Substance Attributes				
	Solid State Form	PSD	Hygroscopicity	Solubility	Flow Properties
Assay	Low	Medium	Low	Low	Medium
Content Uniformity	Low	Medium	Low	Low	High
Dissolution	High	Low	Low	Low	Low

Table 8: Justification for initial risk assessment for drug substance attributes

Drug Substance Attributes	Drug Products CQAs	Justification
Solid State Form	Assay	Drug substance solid state form does not affect tablet assay and CU. The risk is low.
	Content Uniformity	
	Dissolution	Different polymorphic forms of the drug substance have different solubility and can impact tablet dissolution. The risk is high.
Particle Size Distribution (PSD)	Assay	A small particle size and a wide PSD may adversely impact blend flowability. In extreme cases, poor flowability may cause an assay failure. The risk is medium.
	Content Uniformity	Particle size distribution has a direct impact on drug substance flowability and ultimately on CU. Due to the fact that the drug substance is milled, the risk is medium .
	Dissolution	The drug substance is a BCS class I compound; therefore, PSD can affect dissolution. The risk is low.
Solubility	Assay	Solubility does not affect tablet assay and CU. The risk is low.
	Content Uniformity	
	Dissolution	Propranolol showed low (61.7 mg/L at 25 °C)) and constant solubility across physiological pH range. Drug substance solubility strongly impacts dissolution. The risk is low.
Flow Properties	Assay	Propranolol hcl has poor flow properties. In extreme cases, poor flow may impact assay. The risk is medium.
	Content Uniformity	Propranolol hcl has poor flow properties which may lead to poor tablet CU. The risk is high.
	Dissolution	The flowability of the drug substance is not related to its degradation pathway or solubility. Therefore, the risk is low .

10. Formulation development of propranolol hydrochloride immediate release tablets:

10.1 Risk Assessment of the Formulation Variables:

Initial risk assessment for formulation variables was done and listed as table 9. The effect of starch and MCC: lactose ratio on assay, content and dissolution was assessed and the level of risk associated was assigned through colour code.

Table 9: Initial risk assessment of formulation variables

Drug Product CQA's	Drug Product Attributes	
	Pregelatinized Starch	MCC/Lactose Ratio
Assay	Low	Medium
Content Uniformity	Low	High
Dissolution	High	Low

Table 10: Justification for initial risk assessment of the formulation variables

Drug Product Attributes	Drug Products CQAs	Justification
Starch	Assay	As starch is disintegrant it doesn't directly interfere with the assay or the blending of the mixture. The risk is low.
	Content Uniformity	
	Dissolution	Dissolution is directly dependent on the amount of disintegrant added and can impact tablet dissolution. The risk is high.
MCC:Lactose Ratio	Assay	MCC: Lactose ratio can affect the upto some extent as they are mostly used as filler and can displace the drug out of tablet. More than 90% of tablet composition is by this ratio and hence may affect the assay
	Content Uniformity	MCC:Lactose ratio is highly affecting the content uniformity as they constitute around 90%of the formulation and if not properly blended can affect the content of uniformity.
	Dissolution	MCC:Lactose ratio possess a low risk to dissolution as their contribution to dissolution is low and are not directly related to dissolution.

10.2 DOE (Design of Experiments) Formulation

The 2 factor 3 level as full factorial design would require 27 experiments which demands lot of time and material resources. Hence a full factorial design was chosen which gave 9 set of experiments with randomized runs. Another advantage was that this design avoids treatment combinations that are extreme in terms of region in which we are doing our experiment.

Table 11: Full factorial design & responses of the trial runs for formula optimization

		Factor 1	Factor 2	Response 1	Response 2	Response 3
Std	Run	A:Disintegrant(Starch)	B:MCC : Lactose	% Release	D.T	Friability
		%	%	%	Sec	%
8	1	12.5	51	91.29	175	0.67
6	2	15	42.5	81.58	110	0.5
2	3	12.5	34	76.72	163	0.45
3	4	15	34	80.61	97	0.44
5	5	12.5	42.5	79.64	163	0.49
9	6	15	51	86.43	189	0.69
4	7	10	42.5	85.79	158	0.4
1	8	10	34	79.31	189	0.42
7	9	10	51	99.38	170	0.56

10.3 Evaluation of Powder Blends

Powder blends from 9 trial runs were prepared as per table 11. These blends were assessed for micromeritic properties. Bulk density of powder blends was in range of 0.50 – 0.31 g/ml which indicates good compressibility, angle of repose; Hausner's ratio and Carr's index were found in range 25.2˚- 30.0˚, 1.11 - 1.25, 9.81 % - 14.48% respectively which points to good flow behaviour. (Table 12).

Evaluation of tablets for different post compression parameters such as weight variation, Hardness, thickness and friability was observed to be within the Pharmacopoeia limits (Table 12). The tablet weight varied between 195.4 – 204.5 mg which is within ±4.6% allowance, hardness of tablets of all batches in range between 5.5 to 6.5 Kg/cm2. Max friability observed was 0.69 % that is less than recommended 1%.

Table 12: Evaluation of powder blends.

Parameter F Code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's index	Hausner's Ratio	Weight variation (±5%)	Hardness ($Kg/Cm^{2)}$	Friability (%)
F1	0.44 ±0.20	20 ±0.13	25.4 ±0.14	11.1 ±0.14	1.11 ±0.12	100	6.02 ±0.11	0.42
F2	0.4 ±0.12	17 ±0.33	27.2 ±0.18	12.08 ±0.05	1.14 ±0.17	100	5.71 ±0.07	0.45
F3	0.5 ±0.12	15 ±0.24	30.2 ±0.11	13.06 ±0.14	1.21 ±0.02	100	6.26 ±0.21	0.44
F4	0.47 ±0.11	15 ±0.17	29.11 ±0.13	13.21 ±0.17	1.17 ±0.14	100	6.30 ±0.14	0.4

F5	0.41 ±0.30	16 ±0.14	28.04 ±0.12	9.81 ±0.11	1.24 ±0.08	100	6.12 ±0.15	0.49
F6	0.38 ±0.12	18 ±0.27	29.31 ±0.17	12.64 ±0.25	1.17 ±0.13	100	5.56 ±0.24	0.5
F7	0.32 ±0.15	23 ±0.05	27.08 ±0.07	13.48 ±0.34	1.13 ±0.11	100	5.6 ±0.16	0.56
F8	0.33 ±0.24	20 ±0.12	30.02 ±0.11	14.06 ±0.14	1.12 ±0.17	100	6.13 ±0.07	0.67
F9	0.370 ±0.17	20 ±0.11	29.11 ±0.13	10.21 ±0.17	1.11 ±0.02	100	6.36 ±0.21	0.69

10.4 Invitro Dissolution Studies

In vitro dissolution test was performed on the tablets and percent release was calculated. Tests revealed that all batches showed rapid disintegration and release and the goal to match the release of RLD was checked. Results showed that out of the 9 batches, F9 batch showed the highest release and much similar to the RLD release. This was confirmed by checking Similarity and Dissimilarity factor (F1 and F2 studies) with results mention in figure 8 .

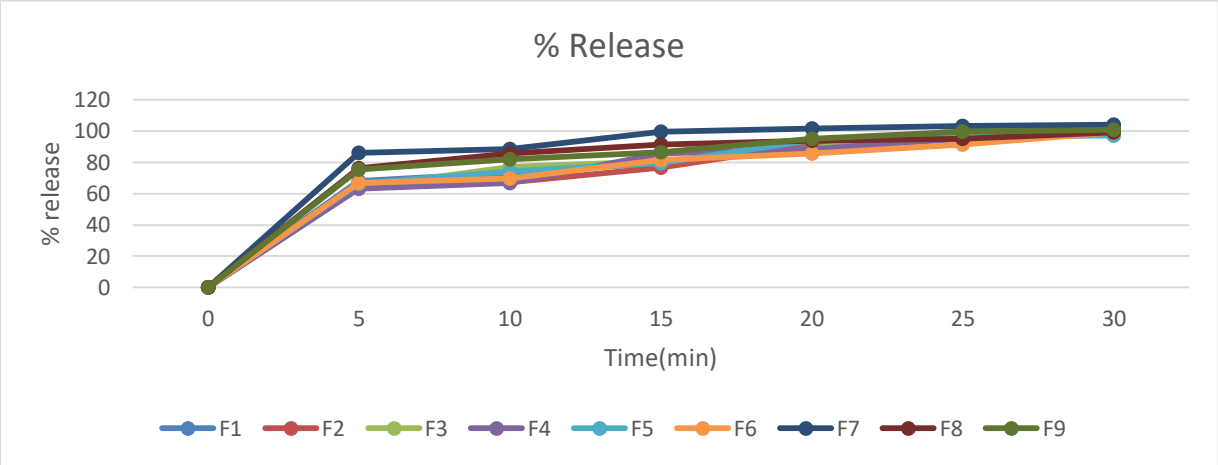


Fig 5: % Release of F1 to F9 batches

10.5 Disintegration Testing

Disintegration test was carried out on all 9 batches with distilled water as medium using the DT apparatus. All the tablets passed the DT specifications given by IP 2014 . The target was to develop a tablet with similar DT as of the RLD which was achieved by formulation batch F9 with DT 170 sec which was close to DT of RLD (200 secs).

10.6 DOE Evaluation :

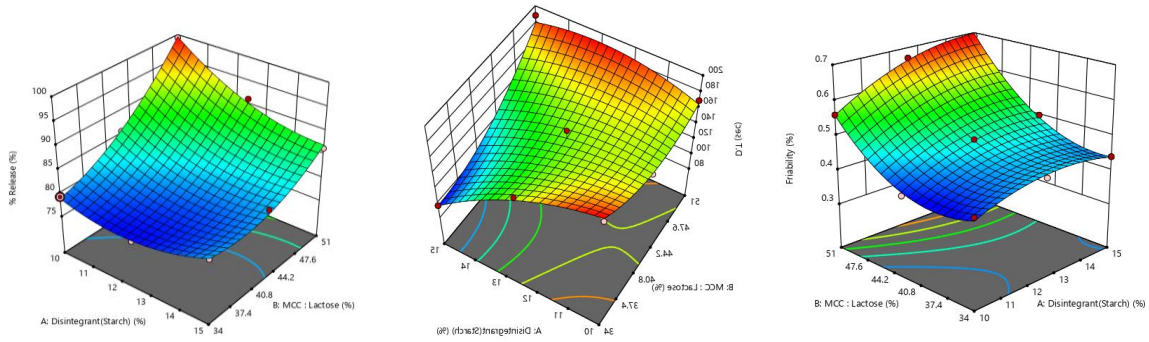


Fig 6 . Response surface curves describing effect of starch and mcc:lactose ratio on a) %Rrelease b) DT and c) Friability

Figure 6 (a) shows the response surface for the percent release which gives the equation

% Release= + 80.36 -2.64 * A+ 6.74 * B-3.56 * AB+2.97*A^2+3.29*B^2 …….... [Equation 1]

According to equation 1 there is significant increase in the disintegration time as the content of disintegrant increases while the other variables i.e. and %MCC:Lactose ratio have slightly positive impact on the % Release as MCC has some swelling property which aids disintegration.

Figure 6 (b) shows the response surface curve for the disintegration test which gives the equation

D.T = +154.11 - 19.33 * A + 15.00 * B - 26.50 * AB + 15.67 * A^2+19.33*B^2 ……...[Equation 2]

According to the equation 2 as the concentration of the MCC: lactose ratio goes on increasing there is decrease in the DT of the tablet and as the concentration of starch increases there is decrease in the DT of the tablet.

Figure 6 (c) shows the response surface curves for the friability and is denoted by

Friability = 0.4867 + 0.0417 * A + 0.1017 * B + 0.0275 * AB -0.0350 * A2 + 0.0750 * B2 …….... [Equation 3]

As per the equation 3 we can see that increasing concentration of disintegrant has positive effect on the friability and the remaining factors viz. MCC:Lactose ratio have very little positive effect on the friability. Overall the friability remains well below the USP limits of 1%.

10.7 Updated Risk Assessment of the Formulation Variables :

After optimizing the formulation variables an updated risk assessment is done to check weather all the risks are reduced and being taken care of from the initial risk assessment.

Table 13. Updated risk assessment for formulation variables

Drug Product CQA's	**Drug Product Attributes**	
	Pregelatinized Starch	MCC/Lactose Ratio
Assay	Low	Low*
Content Uniformity	Low	Low*
Dissolution	Low*	Low

* indicates the risk factors reduced to low from the initial risk assessment

10.8 DESIGN SPACE

The design space is the operational range within which if operated will give the desire outcome for the tablets. According to the above DOE studies a design space is established. Starch values should be maintained in the range of 10 – 15%, while the MCC: lactose ratio should be maintained at 34-51% if maintained within the above parameters will give a release, friability and disintegration similar to RLD.

11. MANUFACTURING PROCESS DEVELOPMENT

11.1 Initial Risk Assessment

Initial Risk Assessment here is done by Ishikawa Fish Bone Diagram. Fish bone diagram gives an overall view of the all manufacturing processes and gives an idea about the risks associated with it.

Table 14: Initial risk assessment for process parameters for

Drug Product CQA's	Drug Product Attributes	
	Blending	Compression force
Assay	Medium	Medium
Content Uniformity	High	High
Dissolution	Medium	High

PROPRANOLOL HYDROCHLORIDE TABLETS

Table 15: Justification regarding impact of process parameters on product CQAS

Process Attributes	Drug Products CQAs	Justification
Blending	Assay	Blending and lubrication may cause variable flowability of the blend. The risk is medium
	Content Uniformity	The PSD and cohesiveness of the drug substance adversely impact its flowability which affects CU. The risk is high
	Dissolution	Blending may impact the distribution of starch in the blend which could impact disintegration of the granules and dissolution of the tablets. The risk is medium.

Compression force	Assay	In extreme cases, tablet weight variability can lead out of specification assay results. The risk is medium.
	Content Uniformity	Compression variables such as feed frame paddle speed and press speed can cause tablet weight variability which could cause tablets to fall out-of-specification for CU. The risk is high.
	Dissolution	Tablet hardness may be impacted if compression force. Over-lubrication of the blend by the feed frame paddle may also slow dissolution. The risk is high.

11.2 DOE (Design of Experiments) Blending Process

A (22) factorial design was implemented to evaluate the effect of blending process on the formulation and it yielded the following set of experiments.

Table 16: Factorial design to optimize the blending operation

		Factor 1	Factor 2	Response 1	Response 2
Std	Run	A:Blend RPM	B:Blend Time	Assay	CU
			Min	%	%rsd
2	1	60	5	95.16	1.34
3	2	30	10	99.36	0.961
4	3	60	10	100.73	0.663
1	4	30	5	93.23	1.74

12 Evaluation of Tablet Blend :

12.1 Assay

Assay of all the batches was performed and it was found out that batch F2 gave the highest percent of assay. Assay was carried as per the method mentioned in the experimental part.

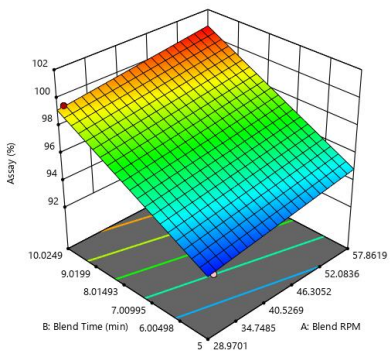


Fig 7 (a) : Response surface curve depicting the effect of blending time and RPM on % assay

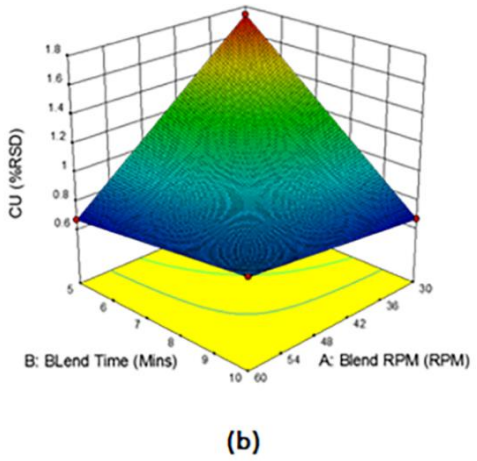
Figure 7 (a) . Shows the response surface curve for the effect of blending on the assay and is represented by the equation 7.

%Assay = +97.12+2.92*B. ……..... [Equation 4]

According to the equation 4 we can directly co-relate the effect of blend time is significantly higher and positive. As the blend time is increased there is increase in % assay of the tablets. For this formulation, the blend RPM has not significant impact on the % assay.

12.2 Content Uniformity

Blend samples (10 no) equivalent to 10 mg of drug were weighed and diluted appropriately to get Concentration of 20µg/ml. It was seen that assay and content uniformity for 60 rpm 10 min, 60 rpm 5 min, 30 rpm 10 min, 30 rpm 5 min was 100.73% with % RSD 0.663, 95.16% with 1.34 %RSD, 99.36 % with 0.961 %RSD,93.23% with 1.74% RSD respectively.



(b)

Fig 8 (b) : Response surface curve depicting the effect of blending time and RPM on content uniformity

Figure 8 (b) . Shows the response surface curve for the effect of blending on the Content Uniformity (CU) of the blend and the equation is represented as

CU= 0.98-0.23*A-0.23*B+0.31*AB. ……..... [Equation 5]

According to the equation 8 the as the blend RPM and blend time is decreased there is increase in the % RSD of the blend. Blend time and RPM have combined effect on the content uniformity.

12.3 Updated Risk Assessment

After addressing the risks and optimizing the manufacturing process an updated risk assessment is given in the table 17.

Table 17: Updated risk assessment for manufacturing process variables

Drug Product CQA's	Manufacturing Process Attributes	
	Blending	Compression force
Assay	Low*	Low*
Content Uniformity	Low*	Low*
Dissolution	Low*	Low*

* indicates the risk factors reduced to low from the initial risk assessment

14. CONTROL STRATEGY

Control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. Manufacturers are also not permitted to make changes to the operating parameters specified in the batch record or other process changes without filling supplements with the FDA. [13] The end product testing only confirms the quality of the product. The control strategy for the commercial manufacture of Propranolol Hydrochloride Tablets, 10 mg, is proposed and presented in Table 18. The control strategy includes Propranolol Hydrochloride and excipient material attributes to be controlled, in-process controls, high risk process parameter ranges studied during development and the proposed operating ranges for commercial manufacture. The purpose of the controls is also briefly discussed. The release specification for the final product is provided in Table 18.

Table 18: Control strategy for propranolol hydrochloride tablets

Factor	Attributes or Parameters	Range studied (lab scale)	Purpose of control
Starch	Ratio	10-15%	To ensure proper disintegration
MCC:Lactose	Ratio	34-51%	To ensure good compressibility.
Octagonal-blender	Number of revolutions*	60 rpm 5 min	Assay is used for endpoint determination to ensure CU is met consistently.
Operating condition	Temperature	25 -30 ˚ C	To ensure proper operating conditions and avoid contamination or degradation of drug and drug product.
	Humidity	45% RH	

15. CONCLUSION :

Qbd approach adopted for development of IR tablet formulation of Propranolol Hydrochloride with required QTPP was implemented successfully through risk management was done prior to the any development which gave an idea about where the product could possibly fail and these risks which were addressed in the later development stages.

During manufacturing process development, manufacturing process was defined based on The knowledge gained during development was useful to device a strategy for process control. DOE was used to establish design space for the development of the formulation.

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