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Original Article

A QBD WITH THE FRACTIONAL FACTORIAL DESIGN WAS USED TO MATCH THE SIMILARITY BETWEEN RANOLAZINE EXTENDED-RELEASE TABLETS 500 MG AND 1000 MG

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ABSTRACT

Objective: Formulation and development of Ranolazine extended-release Tablets 500 mg and 1000 mg by using QBD with Fractional factorial design to match the similarity with Branded formulation (RANEXA®).

Methods: Ranolazine extended-release tablets were developed by using various polymers, Polyquid PA100 and ETHOCEL ™standard 7 premium and Hypromellose with a wet granulation process. QBD (Quality by Design) approach was used to identify the formulation and process variables that may affect the CQAs (critical quality attributes). Excipient compatibility studies were conducted to identify the interaction between API (active pharmaceutical ingredient) and selected excipients. Additionally, using a two-level, fractional factorial (2^2+3) design, the DOE (design of experiments) was employed to confirm the impacts of key process factors (fluid uptake and kneading time) on the formulation's ability to match the dissolution (f2) compared to RLD (reference listed drug) and establish a stable formulation.

Results: Initial risk assessment was carried out to identify the various attributes such as API flow properties, solubility, PSD, Hygroscopicity, formulation, and process variables to impact the quality of the drug product. Flow properties of API indicate poor flow. Drug and excipients compatible study results indicate that excipients used in the compatibility study are considered compatible with the active ingredient. As per the saturation solubility studies and sink conditions, dissolution media was selected. Significant differences were found among the drug release profile by examining the various levels of polymers and binders. Using a two-level, fractional factorial (2^2+3) design, optimum process parameters were identified with selected formulation to match the dissolution (f2) similarity with the reference listed drug (RLD); finally, XRD (X-ray diffraction) studies confirm that the crystalline polymorphic forms (Form 1) peaks in optimum formulation (F07) comparable to the reference listed drug.

Conclusion: Optimized formulation and process were established with QbD (quality by design) that provides the consistent drug release to match the f2 similarities with the extended-release tablets of RANEXA®(Ranolazine) 500 mg and 1000 mg.

Keywords: Ranolazine, Extended-release tablets, DOE, QbD, Fractional factorial design, Design expert

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INTRODUCTION

For therapeutic agents' systemic effects, oral medication delivery is the most desirable and preferable way of administration when compared to other routes of administration. Because of patient acceptance, ease of administration, and a cost-effective manufacturing process, oral medications are typically regarded as the first route studied in the discovery and development of new pharmaceutical active ingredients and pharmaceutical formulations. Extended-release formulations are those in which the dosage frequency can be reduced by at least two times compared to the drug's immediate release (conventional) dosing form. Ranolazine is a novel drug used in the treatment of chronic heart diseases such as angina. Previously, it was believed that ranolazine prevented the metabolism of free fatty acids, but it is now clear that this effect only happens at serum concentrations higher than those obtained during clinical use [1]. A more important mechanism of action is the prevention of both calcium overload and the subsequent increase in diastolic tension due to the inhibition of the late inward sodium channel [2]. The initial dosage of ranolazine is 500 mg twice daily; this can be increased to a maximum of 1 g twice daily. A ranolazine extended-release (ER) oral formulation has been created to enable twice-daily delivery and sustain therapeutically appropriate plasma concentrations. Ranolazine extended-release monotherapy was demonstrated to increase exercise duration through plasma drug concentration in individuals with chronic stable angina in a dose-dependent manner as compared to placebo [3-6]. Extended-release dosage forms are types of dosage forms that extend the absorption and release of the drug for a prolonged period. The goal of the current study was to create and formulate extended-release (ER) matrix tablets of ranolazine using various polymers, binders, and filler combinations, to optimize process parameters by fractional factorial design for various drug release variables, and to compare the *in vitro* dissolution of the optimized product with reference listed drug products [7-9].

MATERIALS AND METHODS

Materials: Ranolazine API (active pharmaceutical ingredient) is procured from MSN laboratories, microcrystalline cellulose (avicel pH 101) is procured from signet chemical corporation private limited, methacrylic acid, ethyl acrylate copolymer (Polyquid PA-100) procured from gangwal chemicals private limited, hypromellose (methocel E5PrLV) procured from colorcon asia private limited, sodium hydroxide procured from Merck limited, magnesium stearate (ligamed MF-2-V) procured from S. Zhaveri Pharmakem private limited, ethocel standard 7FP premium procured from dupont, INDIA, hypromellose, opadry II 85F530135 orange and opadry II 85F32553 yellow are procured from colorcon asia private limited.

Compatibility studies

Based on a literature search and prior knowledge of formulation development, the above list of excipients used for the study and vials containing drug-excipient blends were exposed at 40 °C/75 % relative humidity (RH) for a period of 30 d (open condition), 60 °C for a period of 15 d (closed condition), and initial (closed condition) at room temperature and observed for change in physical and chemical attributes. Room temperature was used to store the controlled samples [10-12].

The setting of QTPP and CQAs

The characteristics of the RLD (reference listed drug product) product, the RLD label, and the intended patient population were taken into account when defining the quality target product profile (QTPP). Critical quality characteristics (CQAs) for drug products were established when the QTPP was established. Our research during the pharmaceutical development process concentrated on the CQAs that might be impacted by a practical modification to the manufacture or formulation of the drug product. Assay, homogeneity of dosage units (CU), dissolution, and related substances (organic impurities) were all considered CQAs [13, 14].

Risk assessment for the drug substance attributes and formulation and process variables

To find formulation factors that might have an impact on the CQAs of the drug product, a preliminary risk assessment was carried out. Each attribute's relative risk was graded as high, medium, or low. Due to the active substance's low solubility and insoluble nature, PSD may have an impact on how well it dissolves. The homogeneity may be impacted by the API's poor flow characteristics. The polymorphic form could alter due to hygroscopicity. The drug release may be impacted by process variables like fluid uptake and kneading time. Therefore, these aspects are taken into account for development. Similarly, the aforementioned excipients may affect how well the drug product dissolution and releases the drug. As a result, these highly essential excipients are assessed at different levels and during dissolution.

Formulation development

There are several methods for extending the release of the drug. The initial formulation option was created using direct compression, and weight fluctuation was seen in conjunction with API's (active pharmaceutical ingredients) poor flow characteristics. To further enhance the final blend's flow characteristics and weight uniformity, the design was modified to use a wet granulation technique [15-19]. Excipients were chosen as part of the development approach using the RLD (reference-listed drug) RX list and literature search. The target of the drug product was extended to release the drug for 24 h by using various polymers to treat chronic angina [20-22]. A therapeutic action similar to Ranexa® (Ranolazine) extended-release Tablets 500 mg and 1000 mg was produced by QTPP (quality target product profile) through *in vitro* testing in order to achieve the drug's availability in plasma levels. The QbD (quality by design) approach was used to create a formulation that would result in the consistent release of the medicine for 24 h throughout the development phase, and risk assessment through DOE (design of experiments) was employed to discover formulation variables that could pose a high risk. These formulation variables helped to identify the critical material attributes (CMAs) and critical process parameters (CPPs). Which research was required to produce a steady, reliable product [23–33].

Dissolution method development

In comparison to pH 4.5 acetate buffer and pH 6.8 phosphate buffer, the dissolving medium with 0.1N HCl has a higher drug release based on saturation solubility data and has a higher sink factor. And 0.1N HCl was chosen as the dissolution media in accordance with dissolution methods for approved ranolazine extended-release tablets [34, 35].

Punch tooling

During the formulation and process development study for ranolazine extended-release tablets of 1000 mg and 500 mg, respectively, core tablets of the test formulation were targeted to 1330.00 mg and 665.00 mg with hardness ranges of 16-32 kP and 14-24 kP at compression stage by using punch tooling of 21.50 X 10.40 mm and 16.50 X 8.00 mm.

Table 1: Initial risk assessment of the formulation and manufacturing process variables

Drug product CQAS	API PSD	Diluent (MCC)	Binder (Polyquid PA-100/ethocel standard 7FP premium)		Alkalizer (NAOH)	Binder (HPMC/ klucel EXF)	Lubricant (mgst)
Assay (%)	Low	Low	Low		Low	Low	Low
Uniformity of dosage units (UOD)	Low	Low	Low		Low	Low	Low
Dissolution (%)	Medium	Medium	High		Medium	Medium	Medium
Organic impurities (%)	Low	Low	Low		Low	Low	Low
Drug Product CQAs	**Process Steps**						
	Dry mixing	Granu lation	Drying	Milling	Blending and lubrication	Com pression	Film coating
Assay	Low	Low	Low	Low	Low	Low	Low
Uniformity of dosage units	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	High	Medium	Medium	Medium	Medium	Medium
Organic impurities	Low	Low	Low	Low	Low	Low	Low

Table 2: Composition details of ranolazine extended-release tablets 500 mg and1000 mg

S. No.	Ingredients	F01	F02	F03	F04	F05	F06	F07	F07A
1	Ranolazine	1000.00	1000.00	1000.00	1000.00	1000.00	1000.00	1000.00	500.00
2	Microcrystalline cellulose	132.50	163.50	140.00	125.00	141.00	151.00	146.00	73.00
3	Methacrylic acid and ethyl Acrylate copolymer	130.00	N/A	122.50	145.00	N/A	115.00	125.00	62.50
4	Ethocel standard 7FP premium	N/A	140.00	N/A	N/A	125.00	N/A	N/A	N/A
5	Hypromellose	N|A	N/A	40.00	26.00	N/A	30.00	30.00	15.00
6	Hydroxypropyl cellulose	40.00	N/A	N/A	N/A	30.00	N/A	N/A	N/A
7	Sodium hydroxide pellets	3.50	4.50	5.50	6.0	6.0	6.0	7.00	3.50
8	Purified water	447.30	447.30	447.30	447.30	447.30	447.30	447.30	447.30
9	Magnesium stearate	24.00	22.00	22.00	28.00	28.00	28.00	22.00	11.00
Core tablet weight (mg)		1330.00	1330.00	1330.00	1330.00	1330.00	1330.00	1330.00	665.00
10	Opadry Yellow	40.00	40.00	40.00	40.00	40.00	40.00	40.00	N/A
11	Opadry Orange	N/A	N/A	N/A	N/A	N/A	N/A	N/A	20.00
Coated tablet weight (mg)		1370.00	1370.00	1370.00	1370.00	1370.00	1370.00	1370.00	685.00

The risk evaluation indicates that the dissolution risk for formulation variables is medium to high. These factors were justified. The intrinsic disintegration is influenced by API PSD and solubility. To increase compatibility and compressibility, microcrystalline cellulose is utilized. It barely affects dissolution. Tablet hardness may be a factor in how well a diluent dissolves. In order to break up

granules created during the granulation process, Polyquid PA100/ethocel standard 7FP premium is used as a releasing polymer. In the formulation, sodium hydroxide is utilized as an alkalizing agent. Any variation in sodium hydroxide content may affect how well the dissolution of the drug substance. In formulation, hydroxypropyl methylcellulose/hydroxyl ethyl cellulose is utilized as a binder, and any variation in hypromellose concentration may have an effect on the disintegration time of the tablet. An increase in magnesium stearate concentration might cause over-lubrication as a result of too much lubricant, which delays dissolution. The dissolution of the tablets is significantly influenced by granulation parameters like % Fluid uptake and kneading time. The risk is therefore regarded as high.

RESULTS AND DISCUSSION

Drug and excipients compatible study

Chemical compatibility data results at the initial (closed condition) were deemed satisfactory, and at 40 °C/75% RH-30 d, no appreciable rise in impurities was noted (open condition).

Table 3: Drug and excipients compatible study of ranolazine formulation

S. No.	Composition	Impurity-A		Impurity-B		Impurity-C		Impurity-D		Dimer		Maximum unknown		Total impurities	
		I	II	I	II	I	II	I	II	I	II	I	II	I	II
1	API (Ranolazine)	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.02	0.03	0.06
2	API+Microcrystalline cellulose (Avicel pH 101)	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.02	0.03	0.06
3	API+Methacrylic acid and Ethyl Acrylate copolymer (Polyquid PA-100)	0.01	0.01	ND	0.00	ND	0.00	ND	0.00	ND	ND	0.02	0.02	0.03	0.05
4	API+Ethocel standard 7FP premium	0.01	0.01	ND	0.01	ND	0.02	ND	0.02	ND	ND	0.03	0.02	0.04	0.09
5	API+Hypromellose (Methocel E5PrLV)	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.02	0.03	0.07
6	API+HPC	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.02	0.03	0.06
7	API+Sodium hydroxide	0.01	0.00	ND	0.00	ND	0.00	ND	0.00	ND	ND	0.02	0.01	0.03	0.01
8	API+Purified water	0.00	0.00	ND	0.00	ND	0.00	ND	0.00	ND	ND	0.01	0.01	0.01	0.01
9	API+Magnesium stearate	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.02	0.04	0.08
10	API+Opadry Orange 85F530135	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.02	0.02	0.09
11	API+Opadry Yellow 85F32553	0.01	0.01	ND	0.01	ND	0.00	ND	0.01	ND	ND	0.02	0.04	0.02	0.05

Note: ND: Not detected. Impurities presented in percentages (%)

Solubility studies

Studies on the solubility of drug substances were conducted in the pH range of 1.2 to 6.8 at 37 °C. Ranolazine was shown to be insoluble over the reported pH range according to the data from the solubility studies (1.2 to 6.8). A pharmacological substance is deemed extremely soluble by the biopharmaceutical classification system (BCS) when the highest dose strength is soluble in less than 250 ml of water over a pH range of 1.2 to 7.5. Ranolazine extended-release tablets, 500 mg and 1000 mg have a maximum dose strength of 1000 mg, which does not meet the requirements for a drug substance that is readily soluble in water and has a pH 6.8 phosphate buffer. Ranolazine can be thought of as an insoluble substance in nature based on the solubility statistics and stated data.0.1 N HCl was chosen as the dissolution medium for the development research based on the solubility studies.

Table 4: Drug substance solubility

S. No.	Medium	Solubility (mg/ml)*	Dose (1000 mg)/Solubility (ml)
1	0.1N hydrochloric acid (pH 1.07)	40.12±0.03	27.2
2	pH 4.5 acetate buffer (pH 4.52)	10.69±0.21	87.2
3	pH 6.8 phosphate buffer (pH 6.80)	1.06±0.13	1000.04
4	Water (pH 6.00)	0.62±0.16	1732.1

*n=4, mean±SD

Table 5: The dissolution profile of formulation variables (F01 to F07A)

Dissolution Media: 0.1 N HCl with deaeration, 900 ml, 50 rpm, Paddle with sinkers.								
Time	**F01**	**F02**	**F03**	**F04**	**F05**	**F06**	**F07**	**F07A**
***Drug release (%) at 0.5h (NMT 30%), at 4h (35% to 55%), at 12h (60% to 80%) and at 24h (NLT 80%)**								
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
0.5	12±8.9	14±8.9	16±8.6	12±9.5	20±6.9	13±5.9	15±6.5	17±4.8
2	38±4.9	44±4.4	35±3.9	30±2.9	50±3.9	43±3.9	32±4.2	35±3.6
4	48±2.9	56±2.6	49±2.6	38±4.9	65±2.1	56±3.2	44±2.9	49±2.2
8	61±1.9	63±1.6	58±2.0	54±2.1	78±1.8	70±1.4	62±1.8	66±1.4
12	68±1.4	73±1.2	65±1.1	59±1.5	80±1.4	76±1.8	71±1.6	74±2.1
24	85±1.0	91±0.05	96±0.2	79±1.1	96±0.9	96±0.5	94±0.1	95±0.3

*n=8, mean±SD

In vitro dissolution study for formulation and process variables

Ranolazine underwent QTPP (Quality target product profile) in order to create an extended-release formulation. Studies on solubility and physical-chemical characteristics were carried out to help choose the API. The wet granulation procedure was suggested to enhance the final blend's flow characteristics and maintain uniform weight during compression [10-15]. The quality of the drug

product and consistency of the outcomes were produced using the QBD approach. It was accomplished by carefully examining the formulation and process factors using a risk-based methodology, and risk was managed by employing DOE (design of experiments) to compare the outcomes to the predetermined limitations. The optimum concentration of the polymer (methacrylic acid and ethyl acrylate copolymer) and binder (hypromellose) were used to create the 500 mg and 100 mg ranolazine extended-release tablets, which release the drug to match the f2 values of more than 50 in comparison to the reference listed drug [16-18], [34, 35]. The desired extended drug release will be produced by mixing a pH-dependent polymer that has been partially neutralized with a pH-independent polymer in the proper ratio. Process factors such as fluid uptake are regarded to have a substantial impact on the medication release through a P value of less than 0.05 based on the fraction factorial design (2^2+3) by using design experts. The investigated range, on the other hand, offers a longer drug release of up to 24 h, which lowers the frequency of doses and improves patient compliance [19-29].

The specification for the dissolution criteria was set for the drug product's in-process and release in accordance with the dissolution profile of RLD (Reference listed drug). Formulations of F02, F05, and F06 fail to meet the specification limit of 35-55 % at 4 h, while F01 does not release the drug completely after 24 h. Formulation F04, on the other hand, offers a slower release than other formulations due to its higher polymer concentration (a copolymer of methacrylic acid and ethyl acrylate). In order to consistently achieve the specification parameters, the final formulation (F07) was optimized with a suitable polymer (methacrylic acid and ethyl acrylate copolymer) and binder (hypromellose) ratio. F07A is designed for the lower strength of 500 mg as a result.

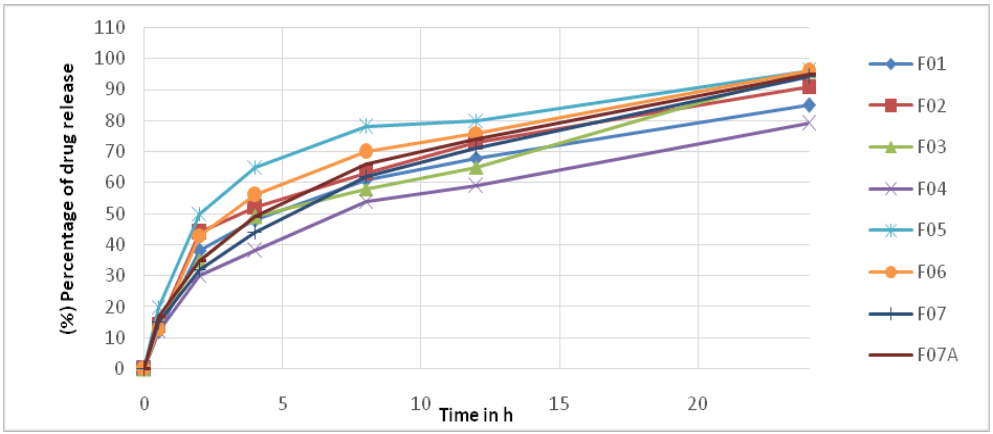


Fig. 1: Dissolution profile of formulation variables for ranolazine extended-release tablets. Error bars were omitted

Table 6: DOE (design of experiments) for the ranolazine extended-release tablets 1000 mg

Std.	Batch No	Process variables		Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
		Fluid uptake (%)	Kneading time (sec)	Drug release (%) at 0.5h (NMT 30%)	Drug release (%) at 4h (35% to 55%)	Drug release (%) at 12h (60% to 80%)	Drug release (%) at 24h (NLT 80%)	Similarity factor F2	Core tablet assay (%)
3	F08	32	240	16±12	43±06	68±04	89±01	61	99.1±1.0
6	F09	35	180	15±09	42±08	67±01	88±02	64	99.6±1.5
7	F10	35	180	16±11	43±09	68±02	91±02	58	99.5±1.2
4	F11	38	240	16±18	41±04	67±03	89±02	63	99.5±1.1
1	F12	32	120	16±10	43±06	66±05	87±01	66	99.6±1.8
5	F13	35	180	15±09	42±04	68±01	90±02	60	100.0±1.5
2	F14	38	120	15±08	42±06	66±02	87±02	67	100.1±2.0

*n=7, mean±SD

Lab scale batches (F01 to F014) with a batch size of 500 tablets were produced in accordance with the risk assessment and evaluation. The results of an ANOVA study show whether the chosen model is important for the particular response or not. If the p-value was less than the cutoff (p = 0.05), it was declared significant. The DOE (design of experiments) studies' statistical analysis was performed using design-expert ® software (11.0), Fractional factorial design (2^2+3) with 3 center points [36, 37]. Additionally, the half-normal plot is used to evaluate and choose significant components based on desired linearity and any remaining experimental data, if it is available. The three center points in our design allow us to examine whether the curvature impact is substantial or not. An uncorrected model for the curvature effect was used to model data most effectively if the curvature effect was not significant.

As the ANOVA data indicates, model and Factor-A fluid uptake are significant for drug release at 4 h, and the studied range may impact on the drug release at 4 h. Half normal plot (2 a) also reflects the same and away from the straight line. However, the studied range of fluid uptake will be used with kneading time range was observed to be no impact on the drug release from 0 to 24 h. The entire examined range (fluid uptake from 32-38% and kneading time 120-240 sec) is desirable as design space for the granulation process for the ranolazine extended-release tablet, according to the evaluation of DOE (design of experiments) study. This design range was utilized to determine a suitable range for each process parameter that would ensure the aims for all responses [Dissolution (Drug release (%), Similarity (F2 values), and Tablets assay)] are fulfilled concurrently.

The overlay plot (fig. 2b) demonstrates the proper design space (fluid uptake from 32-38% and kneading time 120-240 sec) for the DoE study. All batches (F08 to F014) of the granulation process optimization display satisfactory results in the investigated range when taking into account the design space.

Table 7: ANOVA results of the model unadjusted for curvature effect

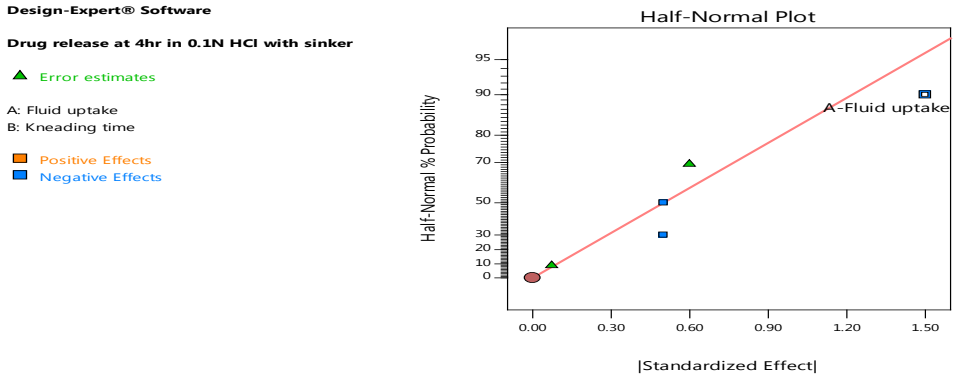
Response	Source	Sum of squares	df	Mean square	F Value	p-value Prob>F	Remark
Drug release (%) at 0.5h in 0.1N HCl with a sinker	Model	0.7500	3	0.2500	0.7778	0.5794	not significant
	A-Fluid uptake	0.2500	1	0.2500	0.7778	0.4428	not significant
	B-Kneading time	0.2500	1	0.2500	0.7778	0.4428	not significant
	AB	0.2500	1	0.2500	0.7778	0.4428	not significant
	Residual	0.9643	3	0.3214	-	-	-
	Lack of Fit	0.2976	1	0.2976	0.8929	0.4444	not significant
	Pure Error	0.6667	2	0.3333	-	-	-
	Cor Total	1.71	6	-	-	-	-
Drug release (%) at 4h in 0.1N HCl with a sinker	Model	2.25	1	2.25	9.55	0.0272	significant
	A-Fluid uptake	2.25	1	2.25	9.55	0.0272	significant
	Residual	1.18	5	0.2357	-	-	-
	Lack of Fit	0.5119	3	0.1706	0.5119	0.7137	not significant
	Pure Error	0.6667	2	0.3333	-	-	-
	Cor Total	3.43	6	-	-	-	-
Drug release (%) at 12h in 0.1N HCl with a sinker	Model	2.75	3	0.9167	1.31	0.4160	not significant
	A-Fluid uptake	0.2500	1	0.2500	0.3559	0.5928	not significant
	B-Kneading time	2.25	1	2.25	3.20	0.1714	not significant
	AB	0.2500	1	0.2500	0.3559	0.5928	not significant
	Residual	2.11	3	0.7024	-	-	-
	Lack of Fit	1.44	1	1.44	4.32	0.1732	not significant
	Pure Error	0.6667	2	0.3333	-	-	-
	Cor Total	4.86	6	-	-	-	-
Drug release (%) at 24h in 0.1N HCl with a sinker	Model	4.00	3	1.33	0.4242	0.7502	not significant
	A-Fluid uptake	0.0000	1	0.0000	0.0000	1.0000	not significant
	B-Kneading time	4.00	1	4.00	1.27	0.3413	not significant
	AB	0.0000	1	0.0000	0.0000	1.0000	not significant
	Residual	9.43	3	3.14	-	-	-
	Lack of Fit	4.76	1	4.76	2.04	0.2893	not significant
	Pure Error	4.67	2	2.33	-	-	-
	Cor Total	13.43	6	-	-	-	-
Similarity factor (F2) with RLD	Model	22.75	3	7.58	0.5593	0.6775	not significant
	A-Fluid uptake	2.25	1	2.25	0.1659	0.7111	not significant
	B-Kneading time	20.25	1	20.25	1.49	0.3089	not significant
	AB	0.2500	1	0.2500	0.0184	0.9006	not significant
	Residual	40.68	3	13.56	-	-	-
	Lack of Fit	22.01	1	22.01	2.36	0.2644	not significant
	Pure Error	18.67	2	9.33	-	-	-
	Cor Total	63.43	6	-	-	-	-
Core tablet assay	Model	0.5075	3	0.1692	3.04	0.1926	not significant
	A-Fluid uptake	0.2025	1	0.2025	3.64	0.1523	not significant
	B-Kneading time	0.3025	1	0.3025	5.44	0.1019	not significant
	AB	0.0025	1	0.0025	0.0450	0.8457	not significant
	Residual	0.1668	3	0.0556	-	-	-
	Lack of Fit	0.0268	1	0.0268	0.3827	0.5993	not significant
	Pure Error	0.1400	2	0.0700	-	-	-
	Cor Total	0.6743	6	-	-	-	-

Table 8: Comparative *in vitro* release dissolution

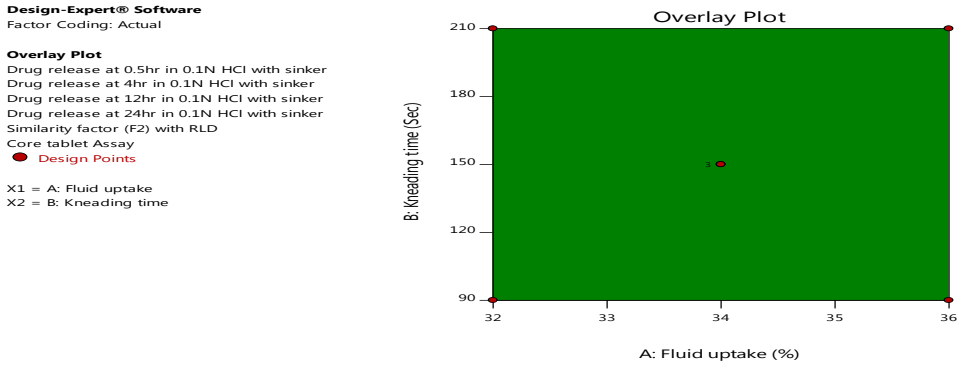
Dissolution media: 0.1 N HCl with deaeration, 900 ml, 50rpm, Paddle with sinkers						
Time	**F14_1000 mg**	**Ranexa® (RLD)_1000 mg**	**F14_500 mg**	**Ranexa® (RLD)_500 mg**	**F14_1000 mg**	**F14 _500 mg**
***Drug release (%) at 0.5h (NMT 30%), at 4h (35% to 55%), at 12h (60% to 80%) and at 24h (NLT 80%)**						
0	**0**	**0**	**0**	**0**	**0**	**0**
0.5	16±10.4	16±12.2	19±8.84	22±11.6	16±8.2	22±7.8
2	32±4.6	30±5.2	37±4.4	40±5.6	32±3.8	37±3.6
4	39±3.4	45±4.1	46±2.8	54±3.5	39±2.6	46±3.1
8	56±1.8	64±2.6	64±3.4	67±2.8	56±1.8	64±1.6
12	67±1.4	68±1.8	74±1.2	78±1.8	67±1.5	74±1.0
24	91±0.6	92±0.8	94±0.5	99±0.8	91±0.8	94±0.02
F2 Value	F14_1000 mg vs Ranexa® : 66		F14_500 mg vs Ranexa® : 66		F14_1000 mg vs 500 mg : 66	

*n=3, mean±SD

The final formulation of the batch was compared with RLD (reference listed drug) and the F2 values, along with the lower strength of 500 mg and dissolving profile, were comparable with RLD and lower strength after the formulation and important process parameters were addressed.

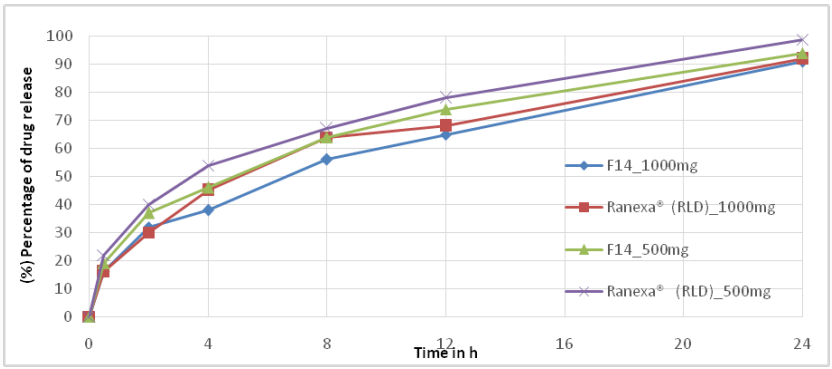


(2a)

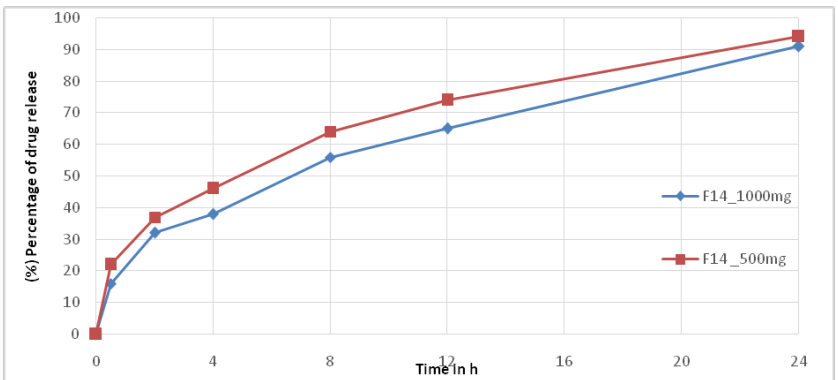


(2b)

Fig. 2: Effect of factors (fluid uptake and kneading time) on dissolution (2 a) Half normal plot of the process variables effect on drug release at 4h in 0.1N HCl with a sinker and (2 b) overlay plot–effect of granulation process variables on responses



(3a)



(3b)

Fig. 3: *In vitro* drug release studies (3 a) The dissolution profile of ranolazine extended-release tablets 1000 mg and 500 mg with RLD (Ranexa®) (3 b) The dissolution profile of ranolazine extended-release tablets 1000 mg and 500 mg (Optimum formulation). The data are expressed as mean, n=6

The suggested amounts of sodium hydroxide, magnesium stearate, and methacrylic acid-ethyl acrylate copolymer are not greater than those found in (Food drug administration) FDA-approved products for the same method of administration and same context of use, according to the agency. Ranolazine Extended-Release Tablets 1000 mg are stronger and take into account the IID (Inactive Ingredient Database) limit for each excipient.

Polymorphic study

Ranolazine extended-release tablets 1000 mg (F07) and Ranexa® 1000 mg have characteristic peaks around 4.96, 9.92, 10.27, 12.15, 14.90, 15.92, 16.39, 19.25, 19.91, 21.31, 22.29, 23.34, 25.33, and 26.38. These peaks are consistent throughout the process and stable. The test product also displays a crystalline polymorphic Form (Form I). Peaks in test product characteristics that are comparable to RLD (Reference listed drug).

XRD data for the test formulation was compared to that of the reference listed drug, confirming that no polymorphic alterations had occurred in the drug product and ensuring that the developed formulation was more stable and resilient [33, 34].

Table 9: Summary of characteristic 2θ values in ranolazine extended-release tablets (F14) and Ranexa® 1000 mg

Form I	4.96	9.92	10.27	12.15	14.90	15.92	16.39	19.25	19.91	21.31	22.29	23.34	25.33
Optimum formulation (F14)	4.956	9.910	10.262	12.149	14.889	15.956	16.387	19.253	19.724	21.121	22.592	23.242	25.332
Ranexa ® 100 mg	4.904	9.860	10.228	12.110	14.838	15.897	16.362	19.252	19.800	21.212	22.250	23.315	25.282

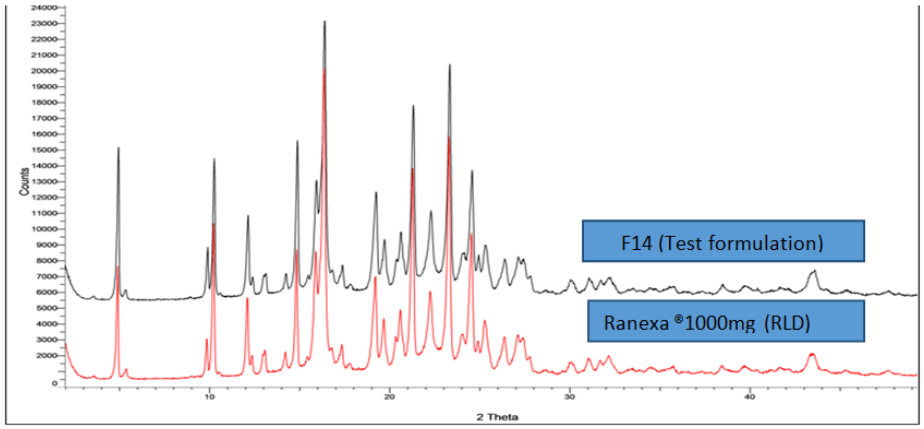


Fig. 4 XRD studies of ranolazine extended-release tablets (F14 vs Ranexa®)

CONCLUSION

Ranolazine extended-release tablets 500 mg and 1000 mg were successfully completed in various percentages of polymer, binder, and lubricants along with the process parameters by using the QbD approach, and design space was created by using fractional factorial design [design-expert ® software (11.0)] for the consistence release of the drug within the specification for 24 h. Based on the solubility studies of ranolazine, dissolution media (0.1 N hydrochloride) was selected. The compatibility studies concluded that the selected excipients have no impact on the final CQAs of the drug product and are compatible with the active ingredient. Optimum formulation yielded the dissolution results with f2 values of more than 50 and comparable with the extended-release tablets of RANEXA® (Ranolazine) 500 mg and 1000 mg. Finally, X-ray diffraction (XRD) data also revealed that there was no change in polymorphism (Form 1) for the optimum formulation compared to the reference-listed formulation. It can be concluded that the optimum formulation is designed with the QbD approach and it shows *in vitro* drug release (Similarity, f2) compared with the innovator formulation.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of the paper.

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