RESEARCH ARTICLE

Design and Optimization of Ibuprofen and Ranitidine Hydrochloride Tri-Layer Tablets in Immediate Release Formulation by Quality by Design

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Received: 12th May, 2024; Revised: 16th July; Accepted: 17th August, 2024; Available Online: 25th Septemper, 2024

ABSTRACT

The current trend in pharmaceutical process development and optimization is known as quality by design (QbD). This methodical approach is founded on the concept that quality should be integrated into the product from the start, rather than assessed after manufacture. In this study, we demonstrate methods to improve the process parameters for making tri-layer tablets by applying QbD principles in a methodical way. Dependent elements with high to medium impact on the process. According to the study's results, all systems showed signs of instant release. It appears that the structure of each formulation and the properties of the polymer utilized have a significant impact on the rate and mechanism of drug release. Substantial medication release is observed in the three-layer formulations. Both the pace and mechanism of drug release are significantly affected by the tablet's geometrical features and structure, as well as the weight and thickness of the barrier layers. While data suggested that Fickian diffusion was primarily responsible for drug release in two-layer tablets, three-layer tablets showed signs of either anomalous diffusion or erosion/relaxation. Therefore, the drug was stabilized as immediate-release directly compressible triple layered Average core weight of tri-layered tablets (mg) was 1000 for ibuprofen, 100 for placebo and 200 for ranitidine, thickness (mm) was 9.00 ± 0.3, hardness (N) was 110 ± 25, core tablet weight was 1300.000 ± 2% mg and coated tablet weight was 1325 mg. Using other moisture-sensitive medications. This study provides the foundation for future research into optimizing the properties of tablets made by direct compression.

Keywords: Ibuprofen, Ranitidine, Triple-layer tablets, Hygroscopicity, Optimization, Diffusion.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.23

How to cite this article: Karthikeyan V, Soni R. Design and Optimization of Ibuprofen and Ranitidine Hydrochloride Tri-Layer Tablets in Immediate Release Formulation by Quality by Design. International Journal of Drug Delivery Technology. 2024;14(3):1408-1414.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The primary concern in formulation manufacture should be maintaining the drug's and dosage form's integrity, even though there are multiple pathways for drug distribution into the body.[1] Processing variables, components, and the real-time performance of the dosage form during stability studies or shelf-life[2] should depict stable homing of contents and direction of molecular structure. The drug's instability could be caused by its physicochemical qualities, its susceptibility to temperature, or its inability to endure moisture. Drugs with a high degree of physicochemical instability are compelled to take the tablet form.[3] Predicting the instability of a therapeutic molecule, moisture and temperature sensitivities highlight the need for cautious formulation of such agents during large-scale pharmaceutical manufacturing.[4, 5] Still, tradition holds that a drug's stability increases in proportion to the dryness of its dose form. Because moisture-sensitive medications are more likely to break if added to the production process at any point.[6] The most reliable base for pharmaceuticals that are sensitive to moisture are those that are not made using the wet approach.[7, 8]

Many different methods have been proposed to address the problem of moisture-sensitive medication breakdown both during and after manufacture. But here, we see the direct compression method in action. The rationale behind this is that loading a medication into a tablet securely can be as simple as using a less hydrophilic material.[9] Some of the many benefits of the direct compression method include a less difficult and more cost-effective way to make tablets. It requires fewer steps in the processing, uses less labor, and consumes less time. Protecting medications that are sensitive to heat or moisture must, in principle, be the primary concern.[10] In contrast, an excipient's role is best described as the material's ability to enhance the drug product's function, appearance, flavor, quality, performance, and production.

The analgesic and antipyretic effects of ibuprofen are contained in the tablet form of the drug. Its exact mechanism

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of action is still unknown. However, it may have anything to do with inhibiting prostaglandin synthetase, like other nonsteroidal anti-inflammatory drugs.[11,12] One example of a reversible, competitive inhibitor of histamine action at histamine H2-receptors is ranitidine, which can be found on stomach cell receptors. In cases of hypercalcemia, ranitidine has no effect on serum Ca++ levels.[13]

During the creation of pharmaceuticals, we focused special attention to CQAs that can be affected by practical adjustments to the formulation or production method of the therapeutic product. This CQA set for generic ranitidine and ibuprofen Tablets USP covered assay, content consistency, dissolution and degradation products, and similar products. Quality by design (QBD) was thus employed to optimize the study's procedure, which aimed to manufacture tri-layer tablets containing ibuprofen and ranitidine hydrochloride for immediate release.

MATERIAL AND METHODS

FMC BioPolymer Europe of Brussels, Belgium, for donating Hypromellose E 15 LV and CCS (Ac-di-sol), and Discovery Fine Chemicals of Dorset, UK, for the ibuprofen and ranitidine.

Solubility

The solubility of ibuprofen and ranitidine was determined in 0.1N HCl, acetate buffer (pH 4.5), and phosphate buffer (pH 6.8 and pH 7.2).

Dissolution Method Development

The development process started with the USP dissolution method, which is recommended for both ibuprofen and ranitidine. This method involves using a pH 7.2 phosphate buffer, 900 mL of ibuprofen and water, and USP apparatus II (Paddle) at 50 rpm for ranitidine. In order to evaluate Ranitidine and Ibuprofen tablets made during drug product development, researchers intended to create a dissolve method that may serve as the best predictor of reference product-like pharmacokinetics.[14,15]

Elements of QbD

Results from the preliminary screening studies and the literature analysis led to the identification of CQAs. The development method then made use of risk assessment to determine the necessary variables to be examined by identifying potentially high-risk input and process parameters.[16] A risk assessment tool was used to compare the CPPs to the CQAs. Based on their potential effect on the quality of the end product, we assigned a risk ranking to each input and process parameter. In addition, the risk assessment that predicted the product's failure due to unfulfilled CQAs was used to identify the final product's CQAs. We categorized the risks as low, medium, or high. The DOE study utilized concerns that were evaluated as medium or high as independent factors, whereas risks that were ranked as low were not.[17]

Design of Experiment (DoE)

With the help of MODDE 8.2 (Umetrics Inc., NJ, USA), the DOE was statistically designed. A D-optimal design was selected because of the uneven distribution of controls for two critical process variables: process speed and airflow. Occasionally, the asymmetric nature of the chosen D-optimal design makes it feasible to assess repeatability (i.e., variation in response under the same conditions, pure error) at levels other than middle values.[18] Because of this, the software will automatically set the run accuracy to a high level. We were able to decrease the potential of error during the model design by maintaining a condition number of 10.55 and a G-efficiency of 85.15% (recommended > 60–70%)[19]. Using the partial least squares (PLS) method, a quadratic polynomial was used to fit the model. Response surface modeling (RSM) was employed to assess the non-linear multidimensional association between the independent components and CQAs. Out of the twenty-six runs that were created to fit the quadratic model with D-optimal design, four runs were used to estimate the study's pure error (Table 1). There was no predetermined sequence for the experiments.

Optimization

Studying the effects of varying concentrations of hypromellose, pregelatinized starch, and croscarmellose sodium on solubility, test results, and consistency in content was the main reason for this formulation development effort. The suggested formulation's robustness was another aim of this investigation. To investigate how the formulation factors/variables affected the response/drug product CQAs, researchers employed a fully factorial DoE design with three levels of factors and two center points. While optimizing the formulation variables at various ratios, tablet weight was kept constant at 230 mg by compensating with intragranular lactose monohydrate. Since croscarmellose sodium quantity in a unit composition is distributed both intra-granularly and extra-granularly, the ratio of croscarmellose sodium level kept constant at low level and high level (i.e., Intragranular to extragranular). Furthermore, the purified water required quantity to make dispersion was kept constant as 1.58% w/w to hypromellose quantity in all designed experiments.[20]

Method of preparation of Tri-layer tablets

Similarly, three-layer tablets were made utilizing a direct compression process and flat-faced punches with a diameter

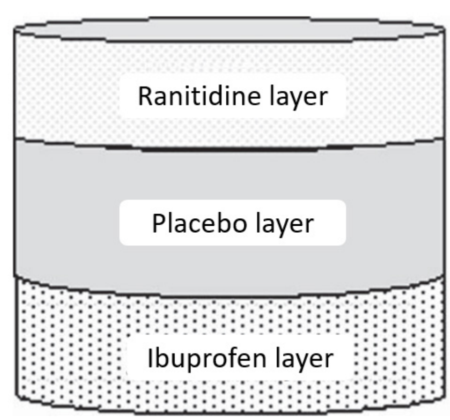

Figure 1: Schematic representation of triple-layered tablet

Table 1: Design of 2^3 full factorial DoE for formulation study #1 (For Ibuprofen Layer)

Std. order	*Run order*	*Center point*	*Blocks*	*Formulation variables (mg/tab)*		
				PG Starch 1500	*CCS (Ac-di-sol)*	*Hypromellose E 15 LV*
1	6	1	1	50	40	30
2	3	1	1	30	60	10
3	7	1	1	30	60	30
4	1	1	1	30	40	10
5	10	0	1	40	50	20
6	9	0	1	40	50	20
7	4	1	1	50	60	10
8	8	1	1	50	60	30
9	5	1	1	30	40	30
10	2	1	1	50	40	10

of 10 mm.[21] Layers of ibuprofen, placebo, and ranitidine were carefully and sequentially added to the die using calculated quantities of each mixture. Beginning with the ibuprofen layer at the base of the die and compressed to around 100 kg, the next layer was the placebo, also compressed to about 100 kg, and lastly, the ranitidine, also compressed to about 100 kg. It was then coated onto the tablet. The average core weight of tri-layered Tablets (mg) 1000 for ibuprofen, 100 for placebo and 200 for ranitidine. Thickness (mm) was 9.00 ± 0.3, hardness (N) was 110 ± 25, core tablet weight was 1300.000 ± 2% mg and coated tablet weight was 1325 mg. The three-layer tablet formulations prepared is shown in Figure 1.

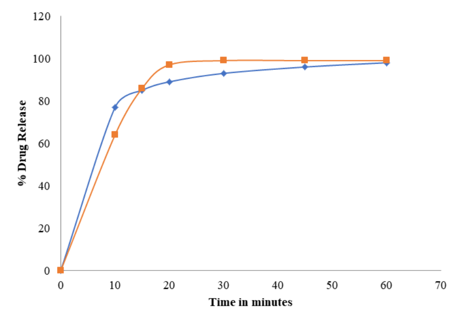

Figure 2: Comparative dissolution profile of ibuprofen vs ranitidine in test tablets

Table 2: Solubility assessment of ibuprofen and ranitidine in different media for 24 hours

S. No.	*Media*	*Approx. pH*	*Volume (mL)*	*Solubility(mg/mL) for ibuprofen*	*Solubility (mg/mL) for ranitidine*
1	0.1N HCl	1.2	250	0.07	667
3	Acetate buffer (pH 4.5)	4.5	250	0.20	680
4	Phosphate buffer (pH 6.8)	6.8	250	0.25	726
5	Phosphate buffer (pH 7.2)	7.5	250	0.30	714
6	Milli Q water	7.00	250	0.02	786

Table 3: Test and reference product dissolution profiles compared

Time (min)	*Tablets*				*Test product*			
	Ibuprofen part		*Ranitidine part*		*Ibuprofen Part*		*Ranitidine part*	
	%DR	*%RSD*	*%DR*	*%RSD*	*%DR*	*%RSD*	*%DR*	*%RSD*
10	77	4.80	84	2.55	64	4.36	96	0.65
15	85	2.73	96	1.08	86	3.86	97	0.98
30	93	1.26	97	0.75	99	0.48	98	0.89
45	96	1.34	97	1.17	99	0.48	97	0.88
60	98	1.35	98	1.4	99	0.77	98	0.87

RESULT AND DISCUSSION

Solubility

Ranitidine was determined to be highly soluble in all tested media, in contrast to ibuprofen, which exhibited poor solubility across the entire surface. Acetate buffer (pH 4.5), phosphate buffer (pH 6.8), and 0.1N HCl were used to dissolve ibuprofen at concentrations of 0.07, 0.20, 0.25, and 0.30 mg/L respectively. For ranitidine, the solubility curves in different pH buffers are as follows: 0.1N HCl, acetate (pH4.5), phosphate (pH6.8), and phosphate (pH7.2) (Table 2). Results from the study found a way to increase the solubility of ibuprofen.[22]

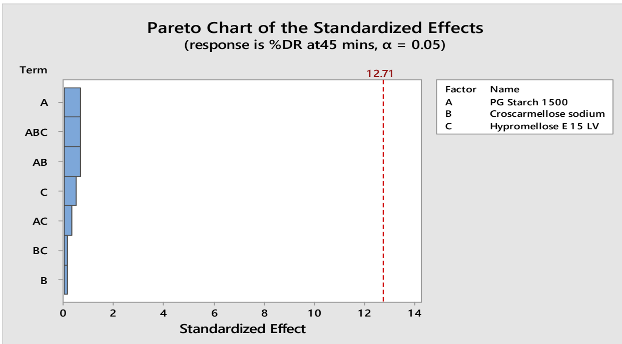

Figure 3: Pareto chart effect of PG starch, CCS and hypromellose E15 LV on dissolution at 45 minutes

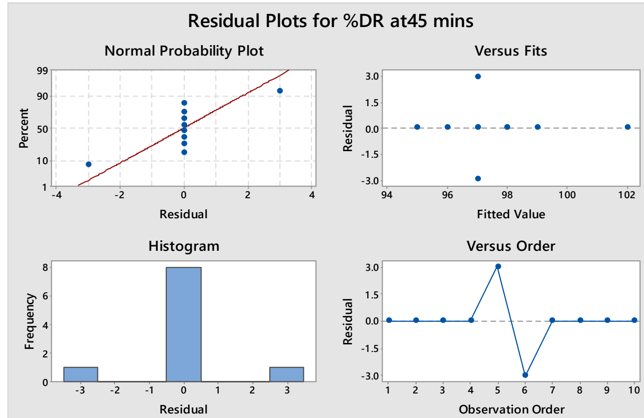

Figure 4: Residual plot effect of PG starch, CCS and hypromellose E15 LV on dissolution at 45 minutes

Table 4: CQAs of ibuprofen and ranitidine

Quality Attributes of Drug product		*Target*	*Is this a CQA?*	*Justification*
Physical Attributes	Appearance (Colour & shape, Size)	White to off white, oblong, 19.00 mm;	No	Tablet size should be similar or smaller to the reference product for ease of swallowing, patient acceptance, and treatment compliance. However, this parameter will not affect medicine quality or efficacy. Thus, it is not CQA.
	Odour	No unpleasant odour	No	Neither the medicine nor the excipients smell bad in this product. No organic solvent will be used in development.
	Friability	NMT 1.0% w/w	No	According to tablet standards, friability is tested regularly. Patient safety, efficacy, and customer complaints are minimized using an NMT 1.0% w/w mean weight reduction target.
Identification		Positive for ibuprofen and ranitidine	Yes*	The quality management system can control and monitor this CQA at medication product release.
Assay		100% w/w of Label Claim	Yes	Varying assays affect safety and efficacy.
Content Uniformity (By weight variation)		Conforms to USP <905> Uniformity of dosage units	Yes	Formulation and process factors affect content uniformity.
Dissolution		Media as per USP	Yes	Bioavailability might be affected by dissolution specification failure.
Degradation Products		Conforms as per ICH	Yes	ICH detection threshold determines impurity targets. Formulations and processes affect degradation products. During product and process development, degradation products will be examined.
Residual solvents		Conforms as per USP <467> option 2	Yes*	Process and formulation variables are unlikely to affect this CQA.
Water Content		NMT 5.0% w/w	No	Water content can be a CQA and effect therapeutic product degradation and microbiological proliferation. In this instance, ibuprofen is not hydrolyzable and moisture will not affect stability.
Microbial Limits		TYMC- NMT 10^2 TAMC-NMT 10^3 E.Coli- Should be absent	Yes*	Missing microbial limits affects patient safety. However, drying to the required LOD% following granulation reduces the possibility of microbial development. This CQA is unlikely to be affected by formulation or process factors.

Table 5: Initial risk evaluation of Ibuprofen medication characteristics

Drug Product CQAs	*Drug substance PSD*	*Solubility*	*Residual solvents*	*Hygroscopicity*	*Process impurities*	*Flow properties*	*Solid state form*	*Moisture content*	*Chemical stability*
Content uniformity	Low	Low	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
Degradation products	Low	Low	Low	Low	Medium	Low	Low	Low	Low
Dissolution	Low	medium	Low	Low	Low	Low	Low	Low	Low

Table 6: Initial risk assessment of ranitidine medication components

Drug Product CQAs	*Drug substance PSD*	*Solubility*	*Residual Solvents*	*Solid state form*	*Hygroscopicity*	*Moisture content*	*Process impurities*	*Flow properties*	*Chemical stability*
Content uniformity	Low	Low	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
Degradation products	Low	Low	Low	Low	Low	Low	Medium	Low	Low
Dissolution	Low	Low	Low	low	Low	Low	Low	Low	Low

Dissolution Method

The product is intended for immediate release; hence, it is recommended to use a USP dissolving medium. The dissolution method that was chosen for the product development involved using a pH 7.2 phosphate buffer, 900 ml of ibuprofen and water in a dissolution apparatus with a paddle at 50 rpm, and 900 ml of ranitidine in the same apparatus, both kept at 37°C (Table 3). The dissolution media recommended by USP and the same dissolution media further used for the test product (Figure 2). The drug release pattern of the ibuprofen part and the ranitidine part of test product is the same as compared to a reference sample. However, both the reference product and test product show 80% (Q) at the end of 15 minutes in FDA-recommended dissolution media for the ibuprofen part and ranitidine part, respectively. Phosphate buffer with a pH of 7.2, USP II apparatus (paddle), 900 mL volume, and 50 rpm speed for the ibuprofen and ranitidine components, respectively. A comparable investigation on the solubility of ibuprofen was carried out by Ruiz.[23]

Critical quality attributes (CQA's) of generic Ibuprofen and Ranitidine Tablets USP

The intended product quality depends on a CQA being within an appropriate range, distribution, or limit. Physical, chemical, biological, or microbiological. To identify a CQA from the QTPP, consider the possible patient injury if the product deviates from the allowed range for that feature.[24] Table 4 lists content uniformity (CU), dissolution, and degradation products as CQAs that this product assay formulation and process variables may effect. Table 5 lists ibuprofen dangers, while Table 6 has ranitidine concerns.

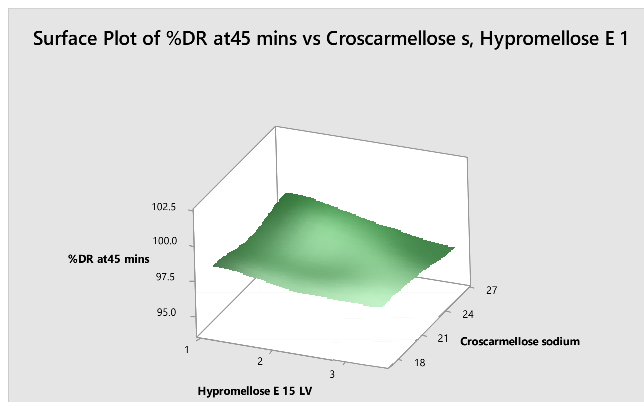

Figure 5: Surface plot of CCS and hypromellose sodium E 15 LV on Dissolution at 45 minutes

Optimization and Formulation of Tri-layer tablets 800/150 mg

Table 7 displays the optimized tri-layer tablets 800/150 mg. Film coating gives products a distinctive appearance and has several uses, including making them more appealing to patients, making them easier to swallow, and hiding unpleasant smells and tastes.[25] To make an immediate release tablet that is both effective and easily recognized, film coatings can add mechanical integrity, color, gloss, pearlescence, or moisture protection. Figures 3, 4 and 5 show the pareto chart, residual chart and surface chat effect of PG Starch, CCS and hypromellose E15 LV, respectively on dissolution at 45 minutes.

Table 7: Pharmaceutical composition of ibuprofen and ranitidine tri-layer tablets 800/150 mg

S. No.	*Ingredient*	*Spec.*	*Category*	*Qty./Tablets (mg)*
Ibuprofen part: (By wet granulation)				
Intra-granular stage				
1	Ibuprofen*	USP	Active	800.000
2	Microcrystalline cellulose (Avicel pH 101)	USP NF	Diluent	80.000
3	Colloidal silicon dioxide (Aerosil pharma 200)	USP NF	Anti adherant	5.000
4	Croscarmellose sodium	USP NF	Disintegrant	50.000
5	Lake blend red	USP/NF	Colorant	0.5
binder solution stage				
6	Hypromellose (Methocel E 15 LV)	USP NF	Binder	20.000
7	Purified water $^{\$\wedge}$	USP/NF	Granulating Aid	Q.S.
Extra granular material				
8	Pregelatinised starch	USP NF	Binder	40.000
Lubrication Stage				
9	Magnesium stearate	USP/NF	Lubricant	4.500
Theoretical weight of ibuprofen layer				1000.000
Placebo part: (By direct Mixing)				
Intra-granular stage				
10	Microcrystalline cellulose (Avicel PH 101)	USP NF	Diluent	60.000
11	Hypromellose (Methocel E5 LV)	USP/NF	binder	20.000
12	Croscarmellose sodium	USP NF	Disintegrant	19.500
Lubrication Stage				
15	Magnesium stearate	USP/NF	Lubricant	0.500
Theoretical weight of placebo layer				100.000
Ranitidine part: (By Dry Granulation)				
Intra-granular stage				
16	Ranitidine hydrochloride*	USP	Active	150.000
17	Microcrystalline cellulose (Avicel PH 101)	USP NF	Diluent	40.000
18	Croscarmellose sodium	USP NF	Disintegrant	9.000
19	Lake blend yellow	USP/NF	Colorant	0.500
Lubrication stage				
20	Magnesium stearate	USP/NF	Lubricant	0.500
Theoretical weight of ranitidine layer				200.000
Total tablet weight				1300.00
Film coating				
21	Opadry white Y-1-7000	IH	Film coating agent	25.000
22	Purified water	IH	Vehicle	Qs
Total Tablet weight				1325.00

*Quantity of *ibuprofen and ranitidine* shall be vary with % w/w Assay & %w/w LoD.
#Adjustment of Ibuprofen API after potency calculation to be done with pre-lubrication MCC.
#Adjustment of ranitidine API after potency calculation to be done with Intragranular MCC.
$Does not contribute to the final mass of the tablets.

CONCLUSION

The correct understanding of process factors, especially those having a direct impact on CQAs or desired results, was made possible by applying QbD principles in conjunction with a multifactorial design of experiments. For the optimization study, these were used. Ultimately, two general objectives were achieved by the methodical implementation of QbD concepts in this study. The first step is to find out which distinct combinations of factors affect the quality qualities you're attempting to improve, and the second is to figure out ways to optimize the system to ensure you can get the product you desire. Results showed that the formulations had both optimal drug release and drug release based on the Hixson-Crowell model. This led to the drug's stabilization as triple-layered tablets with an immediate-release formulation that could be directly compressed. Using other moisture-sensitive medications, this study lays foundations for future research into optimizing the properties of tablets made by direct compression.

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