IMPLEMENTATION OF QUALITY BY DESIGN (QBD) APPROACH IN FORMULATION AND DEVELOPMENT OF RITONAVIR PELLETS USING EXTRUSION SPHERONIZATION METHOD

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ABSTRACT

Objective: Ritonavir is an antiretroviral drug used for HIV-AIDS treatment. The purpose of this research work was to implement the quality by design (QbD) approach in formulation of ritonavir sustained-release pellets by industrially applied extrusion spheronization technique.

Methods: Pellets were prepared by extrusion spheronization method and evaluated for their physicochemical properties. Initially, on the basis of prior knowledge Quality Target Product Profile (QTTP) element was identified and further Critical Quality Attributes (CQA) elements were defined. Risk assessment (RA) was done by two tools as failure mode and effect analysis (FMEA) and fishbone diagram (Ishikawa plot). Plackett Burman design was implemented as a screening design using seven high-risk factors (spheronization speed, spheronization time, extrusion speed, drying method, PVP K 30, cross povidone, and solvent). Optimization study was done by 2^7 full factorial design with three critical factors as (spheronization speed, extrusion speed and PVP K 30). The in vitro drug release was studied in both gastric and intestinal fluids for 12 h using USP 1 apparatus.

Results: Among all batches obtained in 2^7 full factorial design, batch R7 was found to be effective with carr’s index value of 5.281, percentage yield of 69.6%, time required to release 50% drug was 8 h and percent drug release after 12 h was found 83.132 %. R7 batch was selected as optimized batch. Statistical analysis showed model terms were significant.

Conclusion: We can conclude that sustained-release pellets of ritonavir were successfully designed using QbD approach.

Keywords: Extrusion, Spheronization, Pellets, Quality by Design (QbD), Plackett-Burman Design, Optimization

INTRODUCTION

Quality by design (QbD) is the combination of three International Conferences of Harmonization Guidelines i.e. (Q8) pharmaceutical development, (Q9) quality risk management and (Q10) pharmaceutical quality system [1]. QbD is defined as “A systematic approach to development that begins with predefined objectives and important product and process understanding and process control, based on robust supporting science and quality risk management” [2]. The aim of QbD is to build the product quality process than the simple test process which is based on four important elements: (i) Identification of Quality Target Product Profile (QTTP), (ii) Determination of Critical Quality Attributes (CQAs) by Critical Process Parameters (CPP), Critical Material Attributes (CMA), (iii) Assessment of risk by Failure Mode Effect Analysis (FMEA) and Ishikawa Plot (Fishbone Diagram), (iv) Establishment of Design Space (DS) and Control Space (CS) [3, 4]. Design Space (DS) is defined as “The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality” [5, 6].

Pellets are defined as spherical, free-flowing granules with a narrow size distribution typically varying between 500 to 1500 μm for pharmaceutical applications. Sustained release drug delivery system in form of pellets formulation comes up with plenty of advantages like less gastric irritation, maximized drug absorption, improve drug bioavailability, improve flow properties, reduce drug plasma fluctuation and reduce potential side effects, Wang et al. [7]. Extrusion spheronization technique was used to prepare pellets. The critical factor that impact extrusion spheronization are spheronization speed, spheronization time, extrusion speed, drying method, PVP k30, crosspovidone, solvent, mixing time, spheronization load and extruder time all these factors were evaluated as per QbD principles, Sirisha et al., Kandukuri et al. [8, 9].

Ritonavir is an antiretroviral drug used for HIV-AIDS treatment. Sustained-release oral delivery systems are designed to achieve fluctuation and reduce potential side effects, Wang et al. [7].

MATERIALS AND METHODS

Material

Ritonavir was obtained from Mylan lab (Sinner, Nashik), Polyethylene 10 lauryl ether as a solubilizer purchased from Venus Ethoxyether Pvt. Ltd (Gos, India) Polyvinyl pyrrolidone (PVP k-30), Crosspovidone, Lactose, Aerosil 200 were obtained from Sinhgad College of Pharmacy, (Pune, India)

Experimental method

Identification of quality target product profile (QTTP) and to define critical quality attributes (CQA) elements

QTTP elements for ritonavir pellets were identified based on a thorough literature survey and prior knowledge. From QTTP elements CQA elements were defined.

Risk assessment

The fish-bone diagram was considered as to identify the potential risks factor of formulation and development, which affects % drug release, % yield, and flow properties to identified as the QAs. Based
on prior knowledge, the failure mode and effect analysis (FMEA) method were further applied in the initial risk analysis of the parameters of the pellets. Each variable was scored in terms of severity (S), detectability (D) and probability (P). All the more comprehensively, Severity is the wellbeing and viability of the last item. Detectability characterized that a disappointment mode can be recognized. The last parameter probability is considered as the event likelihood or the probability of a disappointment. For each hazard, S, D, P scores were increased together to deliver a “Risk Priority Number” (RPN). The RPN limit was set at 15; any procedure parameter with a RPN 15 was viewed as a potential basic factor which sways on CQAs and in item security and viability, while factors with a lower RPN can be disposed of from further investigation [7, 11].

Establishment of design space

Design space was established by using Plackett-Burman design as screening design and 2^3 factorial Design as an optimization design.

Preparation of ritonavir pellets by extrusion spheronization

Ritonavir pellets were prepared by the method of extrusion spheronization. Ritonavir and various excipients such as PVP K 30, lactose, crospovidone and aerosil 200 were mixed in mortar pestle. The granulating liquid was added slowly to the powder blend, which was then mixed until a homogeneous, cohesive wet mass was obtained. The resulting wet mass was extruded at a mesh of size 1.5 mm. Then spheronization was performed in a spheronizer with a rotating chequered plate with cross-hatch geometry (size-3.25 mm) for 3 min. Then prepared pellets were air-dried [15].

Plackett-Burman design as screening design

According to the risk assessment results, Plackett-Burman study was used to screen 7 critical parameters that may impacts on process and formulation development. The sustained release pellets which contained ritonavir 200 mg, lactose as diluent which was 55% and Aerosil 200 as glidant 1.44% of the amount was kept constant. 7 critical parameters which are, X_1: Spheronization speed; X_2: Spheronization time; X_3: Extrusion speed; X_4: drying method; X_5: PVP K30 conc.; X_6: Crosspovidone conc.; X_7: solvent were evaluated at low [-1] and high [+1] levels. The responses were carr’s index (Y_1), (Y_2) % yield, (Y_3) time required to release 50% drug and (Y_4) % of drug release in 12 h, Sona et al. [13].

2^3 full factorial design as optimization design

Depend on the results of the Plackett-Burman screening study. Three supercritical parameters were evaluated at 2 levels as high [1] and low [-1]. Three critical parameters selected were X_5: Spheronization speed; X_6: Extrusion speed; X_7: PVP K30 concentration. Total 8 batches were prepared. The responses were carr’s index (Y_1), (Y_2) % yield, (Y_3) time required to release 50% drug and (Y_4) % of drug release in 12 h.

Evaluation of prepared pellets

Flow properties of pellets

The flow properties of prepared pellets were evaluated by parameters like tapped density, carr’s index, Hausner’s ratio, angle of repose. The flow properties of prepared pellets were evaluated by parameters like tapped density, carr’s index, Hausner’s ratio, angle of repose.

Particle size and spherical shape

For determination of particle size of pellets by using Digital Vernier caliper was used. About 20 pellets particle from the representative sample were randomly taken, and pellets particle size was measured and the Average particle size was calculated.

Percentage yield

Percentage yield Determine whether the preparation procedure chosen for incorporating a drug into the polymers is efficient. The raw materials, amount of active compound was weighed and yield was determined by weighing the ritonavir pellets and then finding out the percentage yield with respect to the weight of the input materials, i.e., the weight of drug and polymers used. The formula for calculation of % yield is as follows:

\[
\% \text{ yield} = \frac{\text{wt of pellets}}{\text{wt of drug+wt of polymer}} \times 100
\]

Pellets hardness

About 20 pellets particle from the representative sample were randomly taken, and pellets hardness were measured using digital pellets hardness tester. Average hardness was calculated.

In vitro drug release studies

The in vitro release of the drug from pellets of all formulation batches were performed using USP apparatus type I (basket) Lab India DS 8000, at 50 rpm. The dissolution media was maintained at 37±2 °C. “0” size capsules filled with pellets were tested for drug release for 12 h in 0.1N HCl (900 ml) by adding polyoxyethylene 10 lauryl ether for 1° two hrs. Then the dissolution medium was changed to phosphate buffer (pH 7.4) by adding 10M of potassium di-phosphate 8 ml in 0.1N HCL, and drug release was studied further for 12 h. The amount of drug released at each time interval was determined by UV spectrometer at 245 nm [21].

RESULTS AND DISCUSSION

QTPP of ritonavir and CQAs identification

Study of QTPP for the formulation

The QTPP contains a prospective summary of the quality characteristics of a drug product that will be ensure the desired quality, safety and efficacy of the drug product[12]. QTPP was performed on ritonavir drug pellets. QTPP for ritonavir pellets were listed in table 3.

Risk assessment

Risk assessment aims to obtain all the potential high impact factors which will be subjected to study to establish a product or process design space. A fishbone diagram was preformed according to ICH Q8 R2, to identify critical process parameters and critical material attributes of CQAs that affects the quality of pellets shown in fig. 1. The first step in the risk assessment was to systematically gather up all the possible factors that could influence product quality. Based on the literature data, previous study experiences. After gathering all possible factors secondary risk assessment was done by failure mode and effect analysis (FMEA) as shown in fig. 2.

| QTPP elements            | Target                                      | Justification                              |
|--------------------------|---------------------------------------------|--------------------------------------------|
| Dosage form              | Sustained released pellets in capsule        | Pharmaceutical equivalence requirement     |
| Route of administration  | Oral                                        | Pharmaceutical equivalence requirement     |
| Dosage strength          | 200 mg                                      | Same route of administration               |
| Stability                | At least 24 mo shelf life at room temp      | Pharmaceutical equivalence requirement     |
| Drug product quality     | Physical attributes                         | Equivalent to or better than RLD shelf-life|
| attributes               | Identification                              | Pharmaceutical equivalence requirement     |
|                          | Assay                                       | Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality) |
|                          | Content uniformity                          |                                            |
|                          | Drug release                                |                                            |
|                          | Melting point                               |                                            |
|                          | Flow properties                             |                                            |
|                          | Water content                               |                                            |

Based on scientific prior knowledge and preliminary studies from the initial risk assessment of formulation variables, the flow properties as carr’s index, % yield, the time required to release 50% drug and % of drug release in 12 h were selected as critical quality attributes [12].
After risk assessment, further design space was established by using Plackett-Burman design as a screening design and 2^4 Factorial Design as an optimization design.

**Plackett-Burman design as a screening design**

Eight batches were formulated (PB1–PB8) containing various ratios of lactose and PVP K30 and crospovidone as shown in Table 2. Out of all these batches, five batches were excluded from the study as no satisfactory results were obtained from them. Then the remaining three batches as PB3, PB6 and PB8 were selected for studies. The PB3, PB6 and PB8 batches were studied for the particle size analysis, bulk density, tapped density, Carr’s index and % drug release. The results showed that the percent drug release of Ritonavir from PB3, PB6 and PB8 formulations under acidic medium after 2 h was 20.19 ± 2.0%, 16.20 ± 1.2%, and 17.48 ± 2.3% respectively and pH 7.4 after 12 h, 77.47 ± 4.2%, 80.47 ± 5.1% and 80.74 ± 5.3% respectively as shown in Table 3.

As PB8 formulation had shown better results of dissolution than that of all batches; therefore, PB8 batch was selected for further studies. Percent drug release after 12 h for batch PB1 to PB8 is shown in Fig. 3 and Fig. 4.

The response Carr’s index (Y1), (Y2) % yield, (Y3) time required to release 50% drug and (Y4) % of drug release in 12 h. Data are presented as mean±SD (n=3)

| Runs | X1rpm | X2 min | X3rpm | X1 | X2% | X3% | X4 | Y1% | Y2% | Y3 h | Y4% |
|------|-------|--------|-------|----|-----|-----|----|-----|-----|------|-----|
| PB1  | 900   | 10     | 45    | Room | 1.5 | 4.5 | Ethanol | 10.45±1.2 | 45.56±3.1 | 8.30±1.4 | 57.87±3.1 |
| PB2  | 1200  | 10     | 45    | Oven | 3.0 | 2.5 | Ethanol | 13.34±0.8 | 43.78±2.4 | 9.30±0.8 | 54.36±2.8 |
| PB3  | 1200  | 20     | 45    | Oven | 1.5 | 4.5 | Ag     | 0.98±0.6  | 55.78±3.8 | 7.0±0.7  | 71.66±4.1 |
| PB4  | 900   | 20     | 55    | Oven | 1.5 | 2.5 | Ag     | 15.87±0.9 | 56.79±2.9 | 8.30±1.1 | 56.78±2.9 |
| PB5  | 1200  | 10     | 45    | Oven | 1.5 | 2.5 | Ag     | 10.87±0.2 | 54.83±2.9 | 8.30±1.7 | 66.95±3.5 |
| PB6  | 900   | 20     | 45    | Room | 3.0 | 2.5 | Ag     | 1.04±0.1  | 50.37±2.1 | 6.30±2.0 | 75.79±3.7 |
| PB7  | 900   | 10     | 55    | Oven | 3.0 | 4.5 | Ethanol | 11.45±1.3 | 42.73±2.5 | 8.30±1.1 | 56.39±2.4 |
| PB8  | 1200  | 20     | 55    | Room | 3.0 | 4.5 | Ag     | 3.71±0.5  | 61.68±2.6 | 6.0±0.7  | 76.83±3.9 |

X1: Spheronization speed; X2: Spheronization time; X3: Extrusion speed; X4: Drying method; X5: PVP K30 conc.; X6: Crospovidone conc.; X7: Solvent. The responses are Carr’s index (Y1), (Y2) % yield, (Y3) time required to release 50% drug and (Y4) % of drug release in 12 h. Data are presented as mean±SD (n=3).
Table 3: Evaluation of three screening batches as PB3, PB6 and PB8

| Trial batches | Particle size (mm) | Bulk density (gm/cm³) | Tapped density (gm/cm³) | Carr’s index (%) | % D. R 0.1N HCL (2h) | % D. R pH7.4 (12h) |
|---------------|--------------------|-----------------------|------------------------|------------------|----------------------|-------------------|
| PB3           | 1.02               | 0.706                 | 0.713                  | 0.981±0.1        | 20.191±2.0          | 77.467±4.2       |
| PB6           | 0.98               | 0.854                 | 0.863                  | 1.042±0.2        | 16.203±1.2          | 80.467±5.1       |
| PB8           | 0.97               | 0.777                 | 0.807                  | 3.714±0.2        | 17.484±2.3          | 80.743±5.3       |

Data are presented as mean±SD (n=3)

Fig. 3: % drug release in 12h (PB1-PB4), data are presented as mean±SD (n=3)

Fig. 4: % drug release in 12h (PB5-PB8), data are presented as mean±SD (n=3)

2³full factorial design as optimization design

2³ factorial design studies the response surface methodology (RSM) of various variables with help of design expert 8 applied on the optimal ritonavir sustained-release pellets using extrusion spherization. Results of the factorial design are shown in table 4. Carr’s index (Y1) was found in range of 0.368±0.0 to 5.281±0.2, percent yield (Y2) from 48±2.4% to 69.6±3.4%, the time required to release 50% drug (Y3) ranges from 6.30 to 8 h and percent drug release after 12 h from (Y4) 73.44±4.1% to 83.14±4.19%. The statistical analysis results were studied by using Design Expert 8 software. 3FI model was found to be best fit model and polynomial equation shows which variables had the most potential effect on the response. Percent drug release for batches R1 to R8 is shown in fig. 5 and fig. 6. It was differentiated that from all the above batches R7 batch had shown maximum percentage yield of 69.6±3.4% and highest drug release of 83.14±4.19% after 12h. So that R7 batch was considered as optimized batch.

Table 4: 2³full factorial design as an optimization design

| Batches | Factors | X₁ | X₂ | X₃ | Sph. speed | Extr. speed | PVP K30conc | Carr’s index | %yield | T₅₀% | 12h drug release |
|---------|---------|----|----|----|------------|-------------|--------------|--------------|--------|------|------------------|
| R1      | -1-1-1  | 900| 45 |   | 150%       | 3.195±0.1   | 54.5±2.1     | 6.30        | 79.843±4.2 |
| R2      | 1-1-1   | 1400| 45 |   | 150%       | 0.481±0.0   | 59.8±3.2     | 8.0        | 79.109±3.4 |
| R3      | 1-1-1   | 1400| 55 |   | 150%       | 0.368±0.0   | 48±2.4       | 8.0        | 82.060±4.8 |
| R4      | 1-1-1   | 1400| 55 |   | 150%       | 0.651±0.1   | 65.8±3.1     | 7.30       | 76.117±1.4 |
| R5      | -1-1-1  | 900 | 45 |   | 300%       | 2.098±0.2   | 49.8±3.0     | 7.0        | 81.897±5.3 |
| R6      | 1-1-1   | 900 | 45 |   | 300%       | 4.361±0.4   | 67.85±2.9    | 8.0        | 80.781±5.1 |
| R7      | 1-1-1   | 900 | 55 |   | 300%       | 5.281±0.2   | 69.6±3.4     | 8.0        | 83.142±4.9 |
| R8      | 1-1-1   | 1400| 55 |   | 300%       | 3.541±0.3   | 59.5±2.4     | 8.30       | 73.44±4.1  |

X₁: Spheronization speed; X₂: Extrusion speed; X₃: PVP K30 conc. The response carr’s index (Y₁), (Y₂) % yield, (Y₃) time required to release 50% drug and (Y₄) % of drug release in 12 h. Data are presented as mean±SD (n=3)
Statistical analysis for Y1, Y2, Y3 and Y4

Statistical analysis of the design was carried out by using registered Design Expert 8 (Stat Ease Inc. Minneapolis USA). The obtained data were fitted in the Design Expert Software to analyze different statistical parameters. The statistical analysis model explaining the effect of various factors on response surface methodology RSM of output variables like carr’s index, % yield, T_{50} (time required to release 50% of the drug) and % drug release in 12 h. The optimum preparations were selected. Optimum preparation was picked by the critical evaluation. The criteria for selection of optimum preparations is primarily based on maximum drug release at 12 hr. 3FI model is studied for Y1, Y2, Y3 and Y4 in detail to established the DS.

For Y1 (carr’s index) the 3 factor interaction (3FI) was found to be best fit model and polynomial equation is given below.

\[
Y1 \text{ (Carr’s index)} = +2.50-0.24X1-0.037X2+1.32X3-0.13X1X2+0.37X1X3+0.63X2X3-0.88X1X2X3 \text{ are in 3D plot in fig. 7.}
\]

\[
Y2 \text{ (percentage yield)} = +59.36+3.88\times X1+1.37\times X2+2.33\times X3-1.96\times X1\times X2-1.89\times X1\times X3+\times X2\times X3-5.08\times X1\times X2\times X3 \text{ is given in 3D graph fig. 8.}
\]

It shows that X3 (PVP K30) has shown a positive effect on and X1 (Spheronization speed) shown negative effect flow properties of pellets that is carr’s index. Increases with interaction with X3X1 spherization speed and PVP K30 give a good carr’s index and have a positive impact on the flow properties of pellets shown in fig. 7.

The response surface for % yield was studied by polynomial equation by 3FI interaction it was seen that increasing the X1 and X2 i.e. spherization speed and extrusion speed gives good and positive impact on % yield up to 69 %. The DS was achieved within the value. As shown in fig. 8. 3D plot.
Based on the response surface model. For the third response, all three factors had shown positive effect on response. As the binder concentration increases the time required for release the 50% drug is improved plot as shown in fig. 9. For the response percent drug release. Binder concentration PVP K30 has positive effect on drug release. As the PVP K30 increases, the dissolution also improved. Extrusion speed and spheronization speed had shown same positive impact on the dissolution profile. The DS was achieved within the value as shown in fig. 10. The drug release was achieved at the range of 83.142±4.19 in 3D plot. The Y1 was found to be 5.281±0.2 as a good Carr's index for batch R7, percentage yield found 69.6±3.4%, time required to release 50% drug found to be 8 h, percent drug release was found 83.142±4.9% so from all the four responses batch R7 was found to be best batch and selected as optimized batch.

Development of control strategy for ritonavir sustained-release pellets

The process control was determined on the carr’s index (Y1<10), %yield (Y2>70%), T<sub>50%</sub> (Y3>8 h) and % drug release (>80%). According to the result of Plackett-Burman design and 2<sup>3</sup> factorial design, the final control space was defined in detail in table 5. Spheronization speed (12 00rpm), Spheronization time (20 min), extrusion speed (55rpm) and PVP K 30 (3.0%). In order to define the final control space, one formulation parameter was range to the final control space that is R7. Design space includes the control strategy. in which three factors were performed in 2<sup>3</sup> factorial design as final process for pellets by extrusion spheronization which are CPPs and CMAs from CQAs [12, 22].
the Plackett-Burman and 2^3 factorial design were used for screening that affect ritonavir sustained-release pellets product quality. Next, the significant factors and optimizing the variables range, respectively. The final aim of this approach to achieve Design space. Lastly control strategy was defined. It could be concluded that sustained-release pellets were successfully designed using QbD approach.

**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally.

**CONFLICTS OF INTERESTS**

The authors declare no conflicts of interest.

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**CONCLUSION**

QbD is an essential part of the modern approach to pharmaceutical quality. This current study demonstrated how QbD approach can be applied toward the development of a formulation of ritonavir SR pellets. This study teaches the use of QbD including an emphasis on the importance of the target product quality profile in a quantitative approach. QbD has been successfully applied toward the development of a formulation of ritonavir SR pellets. This current study demonstrated how QbD approach can be applied toward the development of a formulation of ritonavir SR pellets. This study teaches the use of QbD including an emphasis on the importance of the target product quality profile in a quantitative approach.

**Table 5: Control strategy for ritonavir sustained released pellets**

| Factor | Attributes or parameters | Range studied (lab scale) | Justification for range | Purpose of control |
|--------|--------------------------|---------------------------|------------------------|--------------------|
| Critical Material Attributes | Povidone K-30 Binder % | 3.0%-7.0% | Optimization range studied | To ensure batch to batch consistency |
| Critical Process Parameters | Extrusion speed | Time: 10 min Speed: 55rpm | Optimization range studied | To ensure all pellets CQAs (Yield, flow properties, Dissolution) are met consistently |
| Pellets Process Parameter | Spheronization speed | Time: 1400 rpm | Optimization range studied | To ensure batch to batch reproducibility for PSD of pellets, flowability, Dissolution |
| | Mixing | Time: 15 min | Optimization range studied | To ensure batch to batch reproducibility pellets properties like PSD |
| Drying Process Parameters | Hot oven | 110 °C | Optimization range studied | To ensure batch to batch reproducibility for PSD of pellets, flowability, Dissolution |
| | Drying time | 10 min-20 min | Optimization range studied | To ensure batch to batch reproducibility pellets properties like PSD |
| Extrusion-spheronization pellets | Individual weight | 500.0 mg±5.0 % | Parameter fixed based on lab scale development experience | To ensure all pellets CQAs (Drug content, Dissolution) are met consistently. |
| | Hardness | Limits: 0.365 kg/cm^2±5 kg/cm^2 | | |
| | Particle size | Limits: 1 ±0.5 mm | | |
| | Friability | NMT 1.0 % | | |
| | Spheronization speed | 1400 rpm | | |
| | Extrusion speed | 55rpm | | |
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