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RESEARCH ARTICLE

Process Development, Evaluation and Controlling of Parameters during Formulation Development of Granisetron HCl as an ODT by QBD Concept

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ABSTRACT

The present investigation was focused on application of QbD approach to seethe effect of formulation va riables on oraldisintegratingtablets containing antiemetic drug, Granisetron HCl. Risk assessment of critical material and process parameters are linked to criticalquality attributes (CQAs) of the product with respect to obtain target quality product profile (TQPP). Preliminary screening was done to characterize the effects of microcrystalline cellulose, crospovidone, croscarmellose sodium and magnesium stearate on drug release. The effects of critical parameters (concentration of two superdisintegrants crospovidone and croscarmellose sodium) were investigated by executing design of experimentation (DoE) using 3 level full factorial designs. A. The aim of this research work was to prepare orally disintegrate tablets of a model drug, Granisetron HCl by direct compression method that releasing not less than 99% of drug than that of commercial reference sample with respect to time. The prepared tablets were evaluated for their physicochemical properties and in vitro release. The relationship between the independent and dependent variables was found with linear prediction equation. The response and equation data was used to draw the contour plot, 3- Dplot, ANOVA design space.

KEYWORDS

Orally disintegrating tablets, Granisetron HCl, Superdisintegrants, 3 level full factorial design, Design space, Quality by design

INTRODUCTION

Quality by Design – Principles & Elements

Quality by Design (QbD) is increasingly becoming an important and widely used technique in the pharmaceutical industry which can be considered to be systems-based approach to the design, development, and delivery of any product or service to a consumer. It is a systematic approach to pharmaceutical development that begins with predefined objectives and emphases product and process understanding and process control.

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It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. It identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess and establish how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics[1,2].

Quality by design (QbD) is an intelligent approach to built quality in products and process. This can be achieved by constructive planning and the previous data available. Although it is based on risks, but it has its fruits that it

minimises the end product testings and increases the chances of regulatory acceptance. QbD was first proposed by a well known researcher Joseph Moses Juran. Later it has been accepted by ICH, US-FDA and other regulatory bodies. The principles of QbD is best explained by ICH Q8, ICH Q9 & ICH Q10, which gives the guidelines on Science & Risk-based assessment, product's life cycle and its approach, and the various method designs. US-FDA also highlights the key role of QbD in Process Analytical Technology (PAT) which is nothing but a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance[3,4,5]. The various advantages of QbD include the patient's safety and satisfaction, core understanding of any pharmaceutical process and its design and development in a better way. Apart from this, other business benefits and reduced expenditure on PAC (Post Approval Changes).

The elements of QbD include:

- New objective design
- Critical quality attributes determination and their assessment
- Assessment of Risk
- Development of experimental design
- Implementation of designed-Control Strategy and
- Continuous improvement.

The focus of the current investigations was to apply quality by design (QbD) approach to the development of Granisetron HCl ODT tablets. Critical material and process parameters are linked to the critical quality attributes of the product. Variability is reduced by product and process understanding which translates into quality improvement, risk reduction and productivity enhancement. The risk management approach further leads to better understanding of the risks, ways to mitigate them and control strategy is proposed commensurate with the level of the risk.

Granisetron hydrochloride is the antagonist of serotonin 5-HT3 receptors, located peripherally on vagal nerve terminals, enteric neurons in the GI tract, and centrally in the chemoreceptor trigger zone. During chemotherapy, mucosal enterochromaffin cells from the small intestine release serotonin .which stimulates the 5-HT3 receptors. This evokes vagal afferent discharge, inducing vomiting. Granisetron hydrochloride is potent; freely water soluble, possesses longer half life ($t_{1/2}$) and acceptable taste. So, present work was undertaken to develop ODT of granisetron hydrochloride employing superdisintegrants using cost effective direct compression method. Superdisintegrants i.e. crosspovidone and croscarmelose sodium were used in formulation of ODT because of their high swelling indices and greater solubilization potential.

MATERIAL AND METHODS

Granisetron HCl, other chemicals and solvents were obtained commercially.

Study of QTPP for Formulation

The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product. The QTPP is a quantitative substitute for aspects of clinical safety and efficacy. The QTPP was defined based on the physicochemical properties of the drug substance, characterization of the marketed product and consideration of the marketed product label. Our investigation during pharmaceutical development focused on the critical quality attributes (CQAs) that could be impacted by a realistic change to the drug product formulation or manufacturing process. For Granisetron HCl Orally Disintegrating Tablet, the CQA‟s included are assay, appearance, disintegration time, dissolution and content uniformity.

Excipient Compatibility Study

A compatibility study of drug with excipients is an early risk reduction strategy which precludes the use of excipients, which may interact with the drug substance. The physical and chemical compatibility between Granisetron HCl and selected excipients was assessed by subjecting the binary mixture of Granisetron HCl API with

excipients the changes in physical and chemical attributes were done by using FTIR spectroscopy.

Risk Assessment for Drug Substance Attributes

According to ICH Q9 Quality Risk Management. The risk assessment of the drug substance attribute was performed to evaluate the impact each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying the justification is provided as a summary in the pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium and low, based on principals of quality by design. The high risk attribute warranted further investigation whereas the low risk attribute required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk.

Initial Risk Assessment of Formulation Variable

In this initial risk assessment for formulation development, the detailed manufacturing process has not been established. Thus, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established. For these studies, formulation CQAs as well as level of formulations components were considered as formulation variables.

Manufacturing Process

All the ingredients including drug, and excipients were weighed accurately according to the batch formula (table 3), the ingredients except lubricant were in the order of ascending eights and blended for 10min in a glass mortar. After uniform mixing of ingredients, lubricant was added and again mixed for 2min. the prepared blend (150 mg) of each formulation was precompressed, on a single tablet punching machine having faced tablet of 8 mm diameter.

Formula Optimization

Formulation optimization studies were focused on evaluation of the medium risk formulation variables as identified in the initial risk assessment. In the formulation optimization study impact of concentrations of disintegrant, diluent (mannitol) and lubricant on the drug product CQAs were evaluated. Most of the levels of excipients were selected based on lab scale study and prior experience of the similar kind of dosage form. Formulation optimization studies were conducted at laboratory scale.

Updated Risk Assessment of Formulation Variable

Acceptable ranges for the medium risk formulation variable have been established and are included in the control strategy. Based on the results of the formulation development studies, the risk assessment of the formulation variable was updated.

Defining Control Strategy

It consists of the planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The control scan include parameters and attributes related to: Drug substance, drug-product materials and components, facility and equipment operating conditions, in-process controls, finished-product specifications, the associated methods[6].

Statistical Analysis

Mean, standard deviation, coefficient of variance were calculated for different variables. Analysis of variance (ANOVA) was used to identify mean difference between different groups. P value less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Quality Target Product Profile (QTPP) Characteristics

Pharmacokinetic (PK) characteristics, in-vitro dissolution data and physicochemical characteristics of the marketed product were analyzed and used to define quality target product profile (QTPP) was defined for generic Granisetron HCl ODT. Both quality and critical quality attributes (CQA's) were identified. CQAs included product Assay, Content Uniformity, Disintegration Time, Dissolution, which have

potential impact on the formulation and/or manufacturing process variables. QTTP and CQAs for the product are detailed below in table 1 and 2.

Table 1: QTPP for generic Granisetron HCl orally disintegrating tablets

QTPP Elements	Target	Justification
Dosage form	Orally Disintegrating tablets	Pharmaceutical equivalence requirement**:** same dosage form.
Dosage design	Orally Disintegrating Tablets	Similar to RLD
Route of administration	Oral	Pharmaceutical equivalence requirement**:** same route of administration
Dosage strength	2 mg Granisetron HCl	Pharmaceutical equivalence requirement
Pharmacokinetics	Orally disintegrating tablets Bioequivalent to RLD	Bioequivalence requirement
Stability	At least 24 months shelf-life at room temperature.	Equivalent to or better than RLD
Physical attributes	The color and shape are acceptable to the patients. No visual tablet defects observed.	Pharmaceutical equivalence requirement. Must meet the same quality standards (i.e. disintegration, assay and quality)
Disintegration	Rapid disintegration	
Assay	Not less than 97% and not more than 102% of the labeled amount of Granisetron.	
Content uniformity	Conforms to USP <905> Uniformity of dosage Units	
Dissolution	NLT 85% within 15min	Pharmaceutical equivalence requirement. Must meet the same quality standards.
Description of Hardness	Robust tablet able to transport and handling.	
Container closure system	Ambered coloured container.	Needed to achieve the target shelf-life and to ensure the tablet integrity.

Compatibility Study by FTIR

The compatibility study was carried out using IR. All the major peaks of Granisetron Hydrochloride were found in the sample. The functional peaks include C-H stretch at 1474.54cm^{-1} , N-H stretch at 3234.76 cm^{-1}, amide stretch at 1555.68 cm^{-1}, C=C stretch at 1647.28 and 1611.59 cm^{-1} and C-N stretch at 1350.23 cm^{-1}, C=N stretch at 1437.03 $cm^{-1,}$ the complex region of 900-600cm^{-1} indicates skeletal vibration and an aromatic ring in the drug structure. On combining Granisetron hydrochloride with other ingredients, there was no disappearance of any peak. The final optimized formulations containing Granisetron hydrochloride along with all the excipients showed the major peaks. The IR study concluded that there was no incompatibility between Granisetron Hydrochloride and any of the excipients. The IR of all the samples is represented in Figure 1.

Table 2: Critical quality attributes of loratadine orally disintegrating tablets

Quality Attributes of Drug Product	**Target**	**Is this a CQA?**	**Justification**
Physical Attributes			
Appearance	Color and shape acceptable to patients. No visual tablet defects observed.	Yes	Changes in color, shape and appearance can be an indication of physical and chemical degradation linked to safety and efficacy. Therefore, they are not critical. Target is set to ensure acceptability.
Odor	No unpleasant Odor	No	Neither Granisetron HCl nor the excipients have an unpleasant odor. No organic solvents is used in Tablet manufacturing process; therefore, odor is not considered critical.
Size and Shape	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, tablet dimension set according to pharmaceutical equivalence requirement.
Friability	NMT 1.0 % w/w	No	Friability is a routine compendia requirement for tablet. A target of NMT 1.0 % w/w of mean weight loss assures a low impact on safety and efficacy.
Assay	100 % w/w of label claim	Yes	Assay variability will affect safety and efficacy. In tablet, API is approx. 2 %w/w of finished product weight so process variables may have high impact on assay. Thus, assay will be evaluated throughout product and process development.
Dissolution	NLT 85 %within 15minutes	Yes	Failure to meet the dissolution specification can impact the bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.
Disintegration	NMT 15mins	Yes	Faster the disintegration more faster the rate of dissolution.

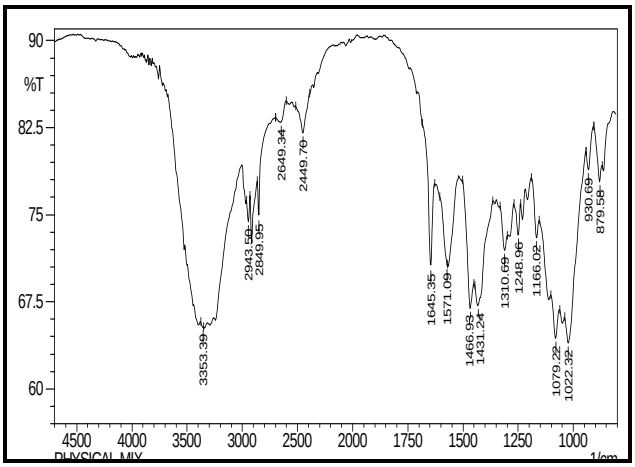

Figure 1: FTIR spectra of physical mixture

Risk Assessment of Drug Substance Attributes

A risk assessment of the drug substance attributes was performed to evaluate the impact of drug substance attributes on the drug product CQA"s. Based upon the physicochemical and biological properties of the drug substance, the initial risk assessment of drug substance attributes on drug product CQAs is shown in the below table 3.

Excipients Grade Selection

Based on the results of the drug-excipient compatibility studies and in order to meet the target product profile, tablet excipients with appropriate functionality were assessed based on scientific and prior knowledge. The chosen excipients had been used successfully for a direct compression formulation of an analogous agent.

Formulation Development

Based on the clinical, pharmacokinetic and physicochemical characterization of the marketed product, the initial formulation strategy for generic product was defined and justified as follows: Design a bioequivalent formulation that disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. Such a system is similar to marketed product.

Initial Risk Assessment of the Formulation Components

Based on scientific and prior knowledge of the excipients used in ODT formulation, a risk assessment was conducted to determine the potential impact of the excipients on final product quality. The excipients identified as high risk were investigated in more detail throughout the formulation and manufacturing process development presented in table 4 and 5.

Table 3: Risk Assessment of drug Substance Attributes

Drug Product CQAs	Drug Substance Attributes						
	Solid state form	Particle size distribution (PSD)	Solubility	Moisture Content	Chemical stability	Flow Properties	Hygroscopicity
Assay	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	Low	Low
Degradation products	Low	Low	Low	Medium	High	Low	Low

Table 4: Initial Risk Assessment of the Formulation Variables

Drug CQA	Formulation variables				
	API PSD	Microcrystalline cellulose	Crospovidone	Croscarmellose sodium	Magnesium stearate
Assay	Medium	Medium	Low	Low	Low
Content uniformity	High	High	Low	Low	Low
Disintegration	Low	Low	High	High	Low
Dissolution	Low	Medium	High	High	High
Degradation	Low	Low	Low	Low	Medium

Table 5: Justification for Initial Risk Assessment of the Formulation Variables

Formulation variables	Drug CQA	Justification
Drug 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, the risk is high.
	Dissolution and disintegration	The drug substance is a BCS class III compound; therefore, PSD can affect dissolution. The risk is low
Microcrystalline cellulose	Assay and Content uniformity	MCC/Lactose ratio can impact the flow properties of the blend. This, in turn, can impact tablet CU. The risk is high. Occasionally, poor CU can also adversely impact assay. The risk is medium.
	Dissolution and disintegration	MCC ratio can impact dissolution via tablet hardness. However, hardness can be controlled during compression. The risk is medium. But the risk is low for disintegration
	Degradation	Since both MCC and lactose are compatible with the drug substance and will not impact drug product degradation, the risk is low.

Crospovidone and Croscarmellose sodium	**Assay and Content uniformity**	Since the level of both superdisintegrants used is low and its impact on flow is minimal, it is unlikely to impact assay and CU. The risk is low.
	Dissolution and disintegration	Both super disintegrants level can impact the disintegration time and, ultimately, dissolution. Since achieving rapid disintegration is important for a drug ODT product, the risk is high.
	Degradation	Superdisintegrants is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
Magnesium Stearate Level	**Assay and Content uniformity**	Since the level of magnesium stearate used is low and its impact on flow is minimal, it is unlikely to impact assay and CU. The risk is low.
	Dissolution and disintegration	Over-lubrication due to excessive lubricant may retard dissolution. The risk is high. Low for disintegration
	Degradation	Though it formed adduct with the drug substance in the binary mixture compatibility study (magnesium stearate/DS ratio 1:1), the interaction compatibility study showed that the adduct formation is negligible when magnesium stearate is used at a level representative of the finished drug product composition (magnesium stearate/DS ratio 1:10). Thus, the risk is medium.

Formulation Development Study

Formulation development focused on evaluation of the high risk formulation variables as identified in the initial risk assessment shown in Table 11. The development was conducted, the formulation study evaluated the impact of the two superdisintegrants Crospovidone, and croscarmellose sodium ratio on the drug product CQAs. This study also sought to establish the robustness of the proposed formulation. A D-optimal Design of Experiments (DOE) was used to study the impact of these formulation factors on the response variable.

A randomized 3 level full factorial design using two factors was adopted to systematically study the formulation of ODT of Granisetron HCl. A total of 18 experimental run with 3 centre points were performed at all possible combination.

The amount of Crospovidone l (X1) and concentration of croscarmellose sodium (X2) were selected as independent variable. The dissolution at 5minutes was selected as dependent variable. The responses were analyzed for analysis of variance (ANOVA) using Design Expert version 8.0 software. Statistical models were generated for each response parameter. The models were tested for significance listed in table 6 and 7.

Updated Risk Assessment of the Formulation Variables

Acceptable ranges for the medium risk formulation variable have been established and are included in the control strategy. Based on the results of the formulation development studies, the risk assessment of the formulation variable was updated as given in table below with justification.

Table 6: Design of the 3 level full factorial DOE

Level of factor	Coded values	Independent variables		Response
		Amount of Crosspovidone(mg)	Amount of Croscarmellose sodium (mg)	
High	+1	5	5	Drug release at 5 min
Medium	0	3.5	3.5	
Low	-1	1	1	

Table 7: Experimental results for responses of the DOE batch tablets

Batch No	Factor 1 Crosspovidone (mg)	Factor 2 Croscarmellose sodium (mg)	Response Drug release at 5 min
F1	5	3.5	98.33 ± 0.25
F2	1	5	99.08 ± 0.35
F3	1	1	99.61 ±0.56
F4	5	1	98.79±1.54
F5	3.5	1	99.75±1.53
F6	1	3.5	100.53±0.43
F7	3.5	3.5	102.01±1.11
F8	3.5	5	99.25 ± 0.32
F9	5	5	99.88 ± 0.45

Table 8: Updated Risk Assessment of the Formulation Variables

Drug CQA	Formulation variables				
	API PSD	Microcrystalline cellulose	Crospovidone	Croscarmellose sodium	Magnesium stearate
Assay	**Low***	**Low***	**Low**	**Low**	**Low**
Content uniformity	**Low***	**Low***	**Low**	**Low**	**Low**
Disintegration	**Low**	**Low**	**Low***	**Low***	**Low**
Dissolution	**Low**	**Low***	**Low***	**Low***	**Low***
Degradation	**Low**	**Low**	**Low**	**Low**	**Medium**

Table 9: Justification for Initial Risk Assessment of the Formulation Variables

Formulation variables	Drug CQA	Justification
Drug PSD	**Assay and content uniformity**	The particle size of drug has much less effect on the formulation hence its size is taken into consideration while formulation and the risk is low
Microcrystalline cellulose	**Assay Content uniformity and dissolution**	MCC/Lactose ratio The concentration of MCC was optimized during formulation development and hence risk associated with its impact on the assay, dissolution, content uniformity on finished product is lowered.
Crospovidone and Croscarmellose sodium	**Dissolution and disintegration**	Both superdisintegrants level can impact the disintegration time and, ultimately was optimized during formulation development and hence risk associated with its impact on the dissolution and disintegration on finished product is lowered.
Magnesium Stearate Level	**Dissolution and disintegration**	The concentration of Magnesium stearate was optimized during formulation development and hence risk associated with its impact on the dissolution and disintegration on finished product is lowered.

ANOVA analysis was done to determine the factors affecting the formulation. With the results obtained ANOVA was done with the help of software to determine the factor affecting the formulation with respect to dissolution.

Analysis of Response-Drug Release at 5min

Pareto chart was prepared for factors (crosspovidone and Croscarmellose sodium) affect on dissolution. It was observed that Analysis of variance (ANOVA) showed significant value (P=0.0104) for both combination of superdisintegratns .Following the observation, it was considered that this model can be used to navigate the design space as shown in fig 2 and 3.

Formulation Development

The levels of the excipients were optimized in development of prototype formulations and the formulation optimization studies. The final composition is tabulated below 8.

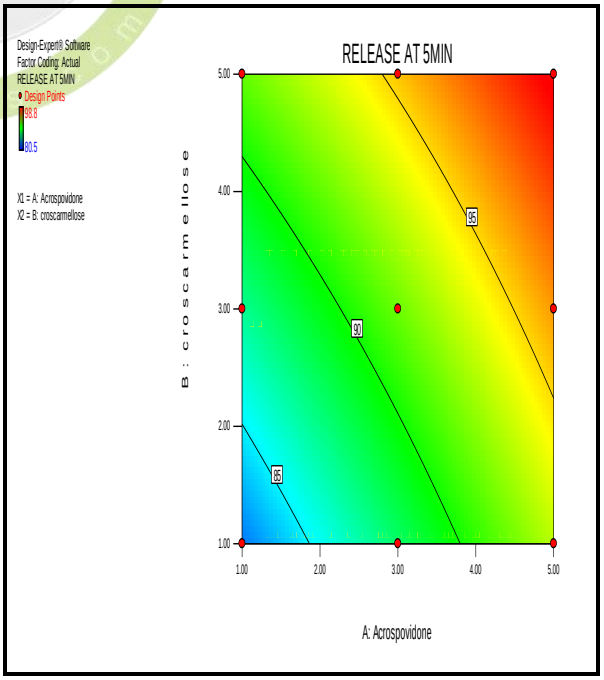

Figure 2: Anova-countor plot of percent drug release at 5 min

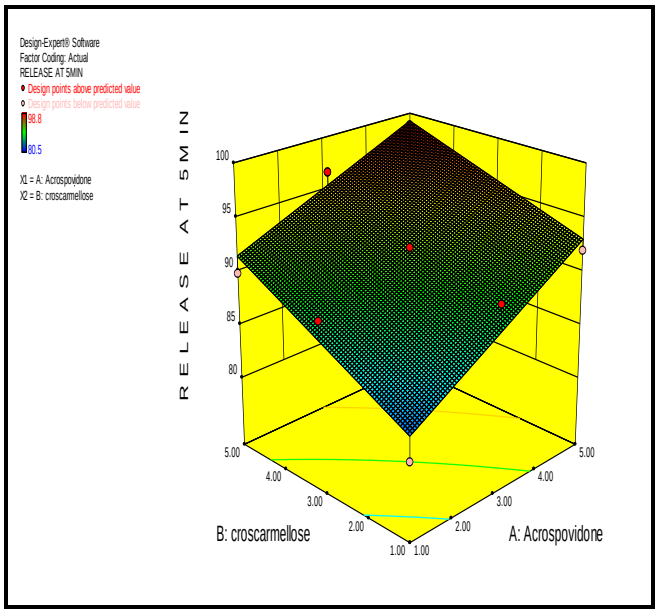

Figure 3: Anova -3-D plot of percent drug release at 5 min

Table 10: Final composition of formula

Ingredients	Quantity/Tablet (mg)
Granisetron HCl	2
Mannitol	94.5
Crospovidone	5
Croscarmellose sodium	5
Microcrystalline cellulose	36
Magnesium stearate	1.5
Strawberry	6
Total	150

In- vitro Dissolution Study

The in vitro dissolution studies of Granisetron HCl orally disintegrating tablet were performed and compared against marketed product. All the physical parameters of blend and tablets were found to be satisfactory. The In-vitro drug release profile was found to be greater than marketed product. The comparative results were tabulated below 9 and shown in the figure 4.

Table 11: Comparison of dissolution study of optimized batch with marketed formulation

Sr. No	Time (min)	% Cumulative release	
		F9	Marketed Product
1	0	0	0
2	1	70.3	75.1
3	2	75.8	79.3
4	3	85.08	81.1
5	4	90.7	81.7
6	5	98.8	85.89
7	10	-----	89.9

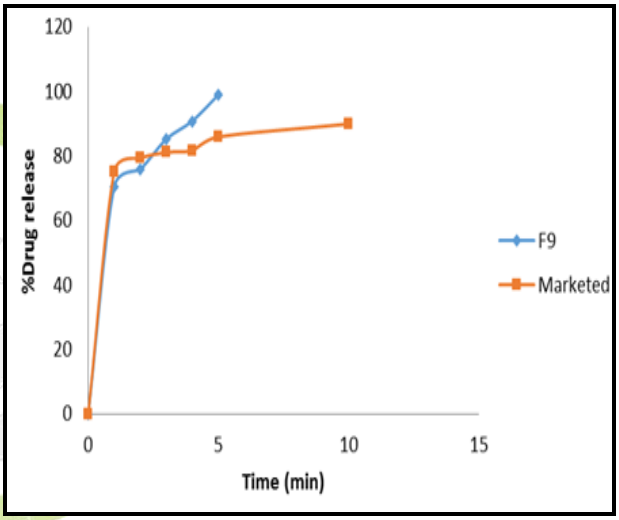

Figure 4: Dissolution profile of F9 and marketed formulation

Control Strategy

The control strategy is to detect and mitigate the risk. Thus, success of the overall product and process performance would depend on the execution of an operating plan, including an appropriate control strategy and appropriate process monitoring, model for control strategy which links QTPP to the manufacturing controls needed to deliver the objectives .The control strategy includes material attributes of Granisetron HCl and excipients to be controlled, in-process controls, process parameter ranges studied during development and proposed operating ranges for commercial batch.

Product Lifecycle Management and Continual Improvement

Upon approval, the manufacturing process for Generic Granisetron HCl Orally disintegrating tablets 2mg, will be validated using the lifecycle approach that employs risk-based decision making throughout the drug product lifecycle as defined in the FDA process validation guidance.

The QbD approach taken during pharmaceutical development of Generic Granisetron HCl Orally disintegrating Tablets 2mg facilitated product and process understanding relevant to Stages of process validation. The manufacturing facility for the exhibit and commercial batches would be designed according to cGMP regulations on Building and Facilities. Activities will be taken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. The protocol for process performance qualification will be written, reviewed, approved, and then executed to demonstrate that the commercial manufacturing process performs as expected. The goal of Stage 3 (Continued Process Verification) is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

Throughout the product lifecycle, the manufacturing process performance will be monitored to ensure desired quality attributes are achieved. If any unexpected process variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control.

CONCLUSION

The development report summarizes about the development of Granisetron HCl Orally disintegrating tablet, a generic version of the Innovator Product. The quality, efficacy and safety were ensured during development of the product.

The objective of the formulation development was to develop a stable Granisetron HCl Orally disintegrating Tablets which is pharmaceutically equivalent and bioequivalent to that of innovator.

During the Formulation development risk assessment study done by Design of Experiment has been carried out and the identified risk are reduced to certain to improve quality safety and efficacy.

Literature survey was carried out for Drug profile, Excipient profile & Innovator product.

After the procurement of API & Excipients, the drug substance was studied for physic-chemical properties and BCS solubility.

Various formulas were used for the development and in order to have comparable product with that of Innovator. The prepared tablets were evaluated for Physical and Chemical characterization.

During development, quality target product profile, critical process parameters and risk assessment which may affect the quality, safety and efficacy of the products were identified.

In Design of Experiment risk Factors affecting the formulation are identified and Optimize formulation has been calculated. After proposed action plan risk has been reduced to low level or medium level.

Final developed formulation was studied for accelerated stability study as per ICH guideline to see the effect of temperature and humidity on finished formulation

The developed formulation was evaluated for In-process parameter, disintegration, and dissolution study to match and compare with innovator product.

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