Innovations in Pharmaceuticals and Pharmacotherapy

www.innpharmacotherapy.com

eISSN: 2321–323X
pISSN: 2395-0781

Research article

Control strategy of generic loratadine orally disintegrating tablets 10 mg during scalable manufacturing

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Abstract

Loratadine is a second-generation peripheral histamine H1-receptor blocker used to treat allergies. The designing and formulation is key factor to commercial any product. Quality by Design (QbD) is increasingly becoming an important and widely used technique in pharmaceutical product development. The present work aims to propose control strategy for commercial manufacturing of Loratadine as an ODT. The control strategies including proposal of different parameters including strategies for raw materials, mixing time, speed of impeller and chopper, inlet temperature, screen size and mill speed, blending and lubrication time, and tablet compression.

Keywords: Loratadine, disintegrating tablets, histamine H1-receptor, Quality by Design (QbD

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1. Introduction

Orally disintegrating tablets contain a wide variety of pharmaceutical actives covering many therapeutic categories, and can be particularly good applications for pediatric and geriatric treatments. The time for disintegration of orally disintegrating tablets is generally considered to be less than one minute, although patients can experience actual oral disintegration times that typically range from 5-30 seconds [1]. Orally disintegrating tablets are characterized by high porosity, low density, and low hardness. When administered, an in-situ suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed [2].

Tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. Patients often experience difficulty in swallowing conventional tablets when water is not available nearby. Furthermore, pediatric and geriatric patients may also feel the inconvenience of swallowing because of under developed and degenerating nervous systems1 respectively. Researchers have formulated ODT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response [3]. These include neuroleptics, cardiovascular agents, antihistamines and analgesics. ODT is synonyms with fast dissolving tablet, mouth dispersible tablet, melt in mouth tablet, rapimelt, porous tablet or rapidly disintegrating tablet. ODTs are tailor made for these patients as they immediately release the active drug, when placed on the tongue, by rapid disintegration, followed by dissolution of the drug. European pharmacopoeia2 defines “Or dispersible tablets are uncoated tablets intended to be placed in the mouth where they

disperse rapidly before being swallowed". Or dispersible tablets disintegrate within 3 minutes. Orally disintegrating tablets combine the advantage of both liquid and conventional tablet formulations allowing the ease of swallowing the drug in the form of liquid dosage form [4]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach.

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick intake of water into the tablet matrix, which creates porous structures and result in rapid disintegration. Hence the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation [5]. To name a few technologies used by researchers to prepare the ODT can be mentioned here like Freeze drying (Lyophilization), tablet molding, spray drying, sublimation, direct compression, cotton candy process and mass extrusion.

Quality by Design (QbD) is increasingly becoming an important and widely used technique in the pharmaceutical industry. QbD can be considered to be systems-based approach to the design, development, and delivery of any product or service to a consumer. QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphases product and process understanding and process control [6]. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD 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. The main concept of QbD is that all final product-critical quality attributes are affected by raw materials and process parameters [7].

Quality by design implementation

The first step in implementing Quality by Design system understands the cause and effect relationship between the raw material attributes, process conditions and the critical quality attributes of the final product by employing design of experiments (DOE). There are several designs of experiments that are available in any commercial software that a formulator can use. Examples:- factorial designs, Taguchi designs, mixture designs, response surface designs, etc. And within each design there several options available for the formulator to suit the needs and goals of the experiments. Examples: Blocking, confounding, fractional factorial, 3 factorials, Placket-Burmann designs, Latin Squares design, etc1. After the designed experiments are executed, the results are analyzed and studied to identify the cause and effect relationships between input parameters and responses [8,9]. The next step in implementing QbD is scaling up the experiments either to the manufacturing level or intermediate level. In this processes, one can use prior knowledge to run fractional designs that will eliminate the need to run several large-scale experiments. The last step in implementation of QbD is defining the control strategies for raw materials and manufacturing process parameters. The implementation of control strategy inherently addresses implementation of design space. If certain inputs, such as recipient particle size or drug crystal surface area, are related to the performance of the final product, then it is logical, in QbD, to control the particle size or surface area to the ranges dictated by the experiments. Once the control strategies are identified, manufacturer should procure, install, commission and validate the control systems to implement QbD

Elements of quality by design

Various elements of quality by design as described in ICH Q8 (R2) include Target product profile, Identification of quality attributes, Risk assessment to identify process/product risk, Design space development and Control strategies.

Identifying a quality target product profile (qtpp)

The quality target product profile (QTPP) is a summary of the quality characteristics or attributes of a drug product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product. The QTPP forms the basis of design for the development of the product. It is both prospective, that is, it describes the goals for the development team, and dynamic, that is, the QTPP may be updated or revised at various stages of development as new information is obtained during the development process.

Identification of Critical Quality Attributes (CQA)

Pharmaceutical development consists of product and process design and development. The TPP provides the basis for the ideal dosage form. A critical quality attribute is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in-process materials), and drug product. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy.

Quality attributes important to the performance of the drug product

From a clinical perspective, safety and efficacy (product performance) is of prime importance. For example for an oral CR product, it is important to consider attributes that are potentially critical for performance. These may be drug dissolution/release, potency, polymer concentration, polymer viscosity, glass transition temperature (TG) of composite, etc., or any other attribute that can either be substituted for drug release or clinical performance.

Quality risk assessment

A key objective of risk assessment in pharmaceutical development is to identify which material attributes and process parameters affect the drug product CQAs, that is, to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQAs are within the desired requirements.

Critical process parameters

A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. For example the following are the process parameters and material attributes related to wet granulation process: Attributes related drug substance: Amount, Form, Particle size, Moisture content and Bulk density. Attributes related to excipients: Excipient amount, Excipient particle size and Excipient density. ¬ Granulation operating parameters: Chopper configuration, Impellor speed, Granulation time, Temperature, Spray nozzle type and Binder addition rate. Granulation state conditions: Power consumption and Temperature. Attributes after granulation: Blend uniformity, Granule size distribution, Agglomerate size, Moisture, Bulk density and Flow properties. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest for each process parameter. Criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR), which is the range of experimental observations that lead to acceptable quality.

Design space

Design Space is defined as the multidimensional combination of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally

initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Control strategy

A control strategy normally include input material controls, process controls and monitoring, design space around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness.

In our previous study, we have proposed formulation development of Loratadine as an ODT by QBD concept [10]. The study has been aimed to propose Control strategy for the commercial manufacture of Generic Loratadine Orally Disintegrating Tablets USP 10 mg.

Materials and methods

Loratadine and other reagents were purchased commercially.

Control strategy for raw materials

Control strategy for raw materials was studied to ensure batch to batch consistency. The different factors included API Particle Size Distribution, Microcrystalline cellulose; Pre gelatinized starch, Mannitol SD 200, Crospovidone, Aspartame, Peppermint 501500 TP0504, Sodium stearyl fumarate.

Control strategy for wet granulation

Control Strategy for Wet Granulation was proposed using granulation process parameters. Parameters included Dry mixing time, Impeller Speed, Chopper Speed, Fluid addition time, Fluid uptake.

Control strategy for drying

Drying Process Parameters was done using Inlet Temperature and LOD as parameter.

Control strategy for Milling

Parameters studied- Screen size and mill speed

Control strategy for blending and lubrication

Parameters studied- Blending time (min), Lubrication time (min)

Control strategy for tablet compression

Parameters studied- Machine Speed (RPM)

3. Results and discussion

Control strategy for raw materials

During formulation development, impact of different attributes of respective input material on product CQAs was studied. Excipient control strategy was based on the attributes of the selected grades.

Table 1. Control strategy for raw materials

Factor	Attributes or parameters		Range studied / finalized	Actual data for lab batch	Proposed range for future scalable batch	Purpose of control
Api particle size distribution	Psd	D (ύ,0.9)	Nmt 10 µm	6.372 µm and 6.045 µm	Nmt 10 µm	To ensure batch to batch consistency
Microcrystalline cellulose (ph 101)	Psd	Retained on 75 µm sieve	Nmt 30.0%	22.98%	Nmt30.0%	
		Retained on 250 µm sieve	Nmt1.0%	0.10%	Nmt1.0%	
Pre gelatinized starch	Psd	Passed through 150 µm sieve	Nlt 90%	99.8%	Nlt 90%	
		Passed through 425 µm sieve	Nmt 0.5%	0.0%	Nmt 0.5%	
		Retained on 2360 µm sieve	Nil	Nil	Should be nil	
Factor	Attributes or parameters		Range	Actual data for	Proposed	

			studied / finalized	lab batch	range for future scalable batch	
Mannitol sd 200	Specific rotation(alpha)25d(c=1)		Between +137° and 145°	142.9°	Between +137° and 145	
Crospovidone	Psd	Passed through on 38 µm sieve	Nmt 50%	25.9%	Nmt 50%	
Aspartame	Psd	Retained on 250 µm sieve	Nmt 10%	0.5	Nmt 10%	
		Retained on 150 µm sieve	Nmt 90%	73.51	Nmt 90%	
		Passed through 125 µm sieve	Nmt 10%	9.26	Nmt 10%	
Peppermint 501500 tp0504	Psd	Passed through on 850µm sieve	Nlt 99.0%	100.0%	Nlt 99.0%	
Sodium stearyl fumarate	Limit of sodium stearyl male ate		Nmt 0.25%	Less than 0.25%	Nmt 0.25%	
	Stearyl alcohol		Nmt 0.5%	Less than 0.5%	Nmt 0.5%	

Control Strategy for Wet Granulation

Based on the Lab batches data, 50-55 % w/w of dry mix fluid uptake was finalized as control strategy for wet granulation process. The granulation end point was determined based on physical feel of wet mass and visual observation. The Impeller and chopper amperage was recorded during the granulation not determine the end point. However, the granulation is a subjective process which varies by the batch size and load. Therefore, the Impeller torque and chopper amperage will be finalized based on retrospective batch data for further quantitative estimation.

Table 2. Control strategy for wet granulation

Granulation process parameters						
Factor	Attributes or parameters		Range studied / finalized	Actual data for lab batches	Proposed range for scalable batches	Purpose of control
Rapid mixer granulator	Dry mixing time		10 min	10 min	10 min	To get similar homogeneity of the dry mix
	Impeller speed	During dry mixing	Slow	Slow	Slow	Although qualitatively speed is same across the scale however quantitatively it is different as inbuilt for the machine and hence kept same
		During purified water addition				
		During kneading stage				
	Chopper speed	During dry mixing	Off	Off	Off	Same across all the scale. To achieve uniform distribution of binder solution and to get uniform granule size.
		During purified water addition	Slow	Slow	Slow	
		During kneading stage	Off	Off	Off	
	Fluid addition time		2 -3 min	2-3 min	2-3 min	Similar across the scale to get similar wet mass and hence similar granules.
	Fluid uptake		50%-55%	50%-55%	50%-55%	

Control strategy for drying

An inlet temperature i.e., 55° ± 10°C was finalized as control strategy for drying to achieve the LOD of 2.0-4.0% w/w (at 150°C / Auto mode using IR moisture analyzer).

Table 3. Control strategy for drying

Drying Process Parameters					
Fluidized Bed dryer	Inlet Temperature	$55^0C \pm 10^0C$	$55^0C \pm 10^0C$	$55^0C \pm 10^0C$	Inlet temperature is scale independent and is considered to be kept constant
Drying In-Process Controls					
LOD	LOD of dried granules is maintained in the range of 2.0-4.0 % w/w using IR moisture analyzer in Auto mode.				

Control strategy for milling

Control strategy of milling is to mill the #30 (600μm sieve) retained granules using 1016 μm screen at slow speed to get the similar PSD at commercial scale.

The control strategy for blending the granules with extra granular materials is to maintain the targeted blending time of 10 min. For the granule lubrication with Sodium Stearyl Fumarate, the control strategy is to maintain the target lubrication time of 5 min.

Table 4. Control strategy for milling

Co-mill	Screen size	1016μm	1016μm	1016μm	Kept similar across the scale to get similar psd of the granules
	Mill speed	Slow	Slow	Slow	
Control strategy for blending and lubrication					
Blender [blending with extra granular materials]	Blending time (min)	5,10, 15	10	10	Blending time optimized and considered to be kept same across the scales.
Blender [blending with sodium stearyl fumarate]	Lubrication time (min)	3, 5 &7	5	5	Lubrication time optimized and considered to be kept same across the scales.
Blending and lubrication in-process controls					
Blend assay	95.0 – 105.0 %				

Control strategy for tablet compression

The control strategy for compression is to maintain the in-process attributes of weight, hardness, thickness and friability within the required ranges.

Table 5 a. Control strategy for tablet compression

Control strategy for tablet compression					
Factor	Attributes or parameters	Range studied / finalized	Actual data for lab batches	Proposed range for scalable batches	Purpose of control
Compression machine	Machine speed (rpm)	15-35	30	15-35	To ensure all tablets cqas (assay, content uniformity and drug release are met consistently)
Tablet compression in-process controls					
Description		White to off –white, round shaped biconvex tablet debossed with 'b' on one side and '6' on other side.			
Average weight (mg)		150.00 ± 3.0% (145.5-154.5 mg)			
Uniformity of weight (mg)		150.00 ± 5.0% (142.5-157.5 mg)			
Tablet thickness (mm)		3.7 ± 0.3 (3.40– 4.00 mm)			
Tablet hardness (kp)		2.0-5.0 kp			
Friability (%)		Nmt 1%w/w			
Disintegration time (minutes)		Nmt 1 min			

Table 5 b. Control strategy for tablet compression

In process test	Acceptance criteria
Appearance	White to off –white, round shaped biconvex tablet deposed with 'b' on one side and '6' on other side.
Average weight (mg)	150.00 ± 3.0% (145.5-154.5 mg)
Tablet thickness (mm)	3.7 ± 0.3 (3.40 – 4.00 mm)
Tablet hardness (kp)	2.0-5.0 kp
Friability (%)	Nmt 1% w/w
Uniformity of weight (mg)	150.00 ± 5.0% (142.5-157.5 mg)
Disintegration time (minutes)	Nmt 1 min

Conclusion

Control strategy for Raw material may be helpful for a formulator as guidance to finalize the excipients quantitatively during their development study as well as for keeping consistency in quality of the products.'

Quality by Design (QbD) is increasingly becoming an important and widely used technique in pharmaceutical product development. QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphases product and process understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. Implementing QbD concept in product development provide quality medicines to patients, production improvements to Manufacturers with significantly reduced batch failures and drug regulatory bodies will have greater confidence in the robust quality of products they are being asked to approve. As such QbD is becoming a promising scientific tool in quality assurance in pharma industry. In our previous study we have proposed formulation and development of Loratadine as an ODT by QBD concept. Once it is approved, it can be used to scalable manufacturing process according to proposed parameters.
Also, manufacturers may use this process parameters as a guideline before and during manufacturing the same product for billions of common needy people.

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