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Research article

Process development, evaluation and controlling of parameters during formulation development of Loratadine as an ODT by QBD concept

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Abstract

Quality by design (QbD) refers to an advanced approach toward drug development. QbD is a vital part of the modern approach to pharmaceutical quality. There is much confusion among pharmaceutical scientists in generic drug industry about the appropriate element and terminology of QbD. The purpose of this paper was to discuss the pharmaceutical QbD for formulation development with a case study of oral disintegrated tablets (ODT) of Loratadine. The QbD means designing and developing formulations to ensure predefined product quality. The study describes elements of the QbD for Loratadine ODT, include: Defining quality target product profile, identifying critical quality attributes, establishing design space, control strategy. Loratadine ODT was prepared by wet granulation using microcrystalline cellulose USNF and level of other components were optimized, factorial design was used as part of risk analysis to optimize the level of other excipients with hardness of 2-5 KPa. The study concluded thethe adoption and implementation of QbD for formulation development using QbD and could increase efficiencies, provide regulatory support, flexibility and pharmaceutical quality is assured by understanding and controlling formulation variables.

Keywords: Quality by design (QbD), formulation development, Loratadine

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1. Introduction

Quality has been given an importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in terms of service, product, and process. Many of these quality related activities reflect need for companies to excel in global competition. Quality activities must try to detect quality problems early enough to permit actions without requiring compromise in cost, schedule or quality. The emphasis must be on precaution rather than on just correction of quality problems. Quality can be the driving force to empower results in other parameters. Hence the quality has to be built in the product as well as services through proper planning, so that the forth coming failure can be avoided.

The concept of quality by design (QBD) was summarized by a well-known quality expert Joseph Moses Juran; he believed that quality could be planned and that most quality associated problems have their origin in the way which quality was planned in the first place. The principles of QbD have been used to advance the product and process quality in every industry. The information and knowledge gained from pharmaceutical studies and manufacturing provide a base for scientific understanding to support establishment of design space, specification and manufacturing control. Information from pharmaceutical

development studies can be a root for quality risk management.

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. 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.[1-3]

The main concept of QbD is that all final product-critical quality attributes are affected by raw materials and process parameters. Hence, if we identify the cause and effect relationship between the various inputs and responses by carefully designed experiments, we can control the quality of the product by simply controlling the inputs like raw material specifications or process parameters etc. As a result, the final product will always conform to the quality specifications.

Advantages of QbD can be summarized as: Patient safety and product efficacy are focused; Scientific understanding of pharmaceutical process and methods is done; It involves product design and process development; Science based risk assessment is carried; Critical quality attributes are identified and their effect on final quality of product is analyzed; It offers robust method or process; Business benefits are also driving force to adopt QbD.

The focus of the current investigations was to apply quality by design (QbD) approach to the development of Loratadine 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.

The marketed product is an orally disintegrating tablet, disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. Claritin® RediTabs is used for the relief of sneezing, runny nose, itchy watery eyes and itchy nose or throat. Description of Claritin® RediTabs is white to off white round blister formed tablets impressed with letter ‘C10’ on one side.

The first step in implementing QbD system is, understanding 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). [4] After the designed experiments are executed, the results are analyzed and studied to identify the cause and effect relationships between input parameters and responses. 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 the implementation of design space. If certain inputs, such as excipient 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 QbD2. [5]

Loratadine is a BCS Class II compound. Claritin® RediTabs, the marketed product is an orally disintegrating tablet, disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be

subsequently swallowed with or without water. Claritin® RediTabs is used for the relief of sneezing, runny nose, itchy watery eyes and itchy nose or throat. Description of Claritin® RediTabs is white to off white round blister formed tablets impressed with letter 'C10' on one side. By applying Quality by Design (QbD) approach, IN -House Loratadine Orally Disintegrating Tablet 10 mg has been developed and it is pharmaceutically and therapeutically equivalent to the marketed product. [6-9]

2. Materials and methods

Loratadine, 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 Loratadine Orally Disintegrating Tablet USP 10 mg, the CQA's included are assay, uniformity of dosage units, organic impurities, disintegration time and dissolution.

Polymorphism study

Polymorphism was studied using X-Ray Powder Diffraction method obtained from the analysis of three commercial scale batches of Loratadine drug substance and the patterns were compared with pattern of the FDA patent. Stability of the product was also analyzed using X-ray power diffraction at 6 month interval.[10]

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 Loratadine and selected excipients was assessed by subjecting the binary mixture of Loratadine API with excipients in glass vials (perforated condition). The changes in physical and chemical attributes upon exposure to one Month at 40ºC/75%RH in perforated condition were compared against initial samples. [11]

Risk assessment for drug substance attributes

According to ICH Q9 Quality Risk Management, it is important to note that "it is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) canal to be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry' so bligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators." All formulation and process parameters are evaluated for risk by using failure mode and effects analysis (FMEA) method [12]. Based on the physicochemical and biological properties of the drug substance, the initial risk assessment of drug substance attributes on drug product CQAs classified into 3 classes low, medium, high.

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

Loratadine, mannitol, pregelatinized starch and microcrystalline cellulose was sifted through 600 µm mesh (ASTM, # 30 sieve).The material of step 1 was loaded in Rapid Mixer Granulator and mixed for 10 minutes. The material of step 2 was granulated using purified water (50% w/w of dry mix) over a period of 1 - 2 minutes

with impeller and chopper at slow speed. The wet mass was kneaded with impeller at slow speed for a period of 1 minute to get the desired granules. Extra quantity of purified water (10% w/w of dry mix) was added over a period of not more than 1 minute with impeller & chopper at slow speed. The wet mass was kneaded with impeller & chopper at slow speed for a period of 1 minute to get the desired granules. The material of step 6 was driedin rapid drier at an inlet temperature of 55°C ± 10°C to get LOD 2.0– 4.0% w/w at 105°C auto mode using IR moisture analyzer. The dried granules of step 7 were sifted through 600µm mesh (ASTM, # 30 mesh) and the retentions were milled through Quadro co-mill with 1016 micron screen (040G) at slow speed. Extra granular materials Crospovidone, aspartame and peppermint flavor were sifted through 600µm mesh (ASTM, # 30 sieve).Sodium stearyl fumarate was sifted through 250µm mesh (ASTM, # 60 sieve).The granules of step 8 and material of step 9 were loaded in low shear blender and blended for 10 minutes. The material of step 10 was loaded into step 11 and mix for 5 minutes. The tablets were compressed using suitable compression machine.

In- vitro dissolution study

The in vitro dissolution studies of Loratadine orally disintegrating tablet were performed and compared against marketed product.

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

Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated [11].

Defining design of space

It consists of the established range of process parameters that have been demonstrated which provide assurance of quality. The change emphasizes the multidimensional interaction of input variables and closely binds the establishment of a design space to a conduct of a DOE that includes interactions among the input variables. Adesignspace may be constructed for a single unit operation, multiple unit operations, or for the entire process [11].

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 [11].

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

3. Results and discussion

Quality target product profile (QTPP) characteristics

Clinical, 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 Loratadine ODT USP 10 mg. Both quality and critical quality attributes (CQA's) were identified. CQAs included product Assay, Content Uniformity, Disintegration Time, Dissolution & Organic impurities, 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.

Dissolution method development and pilot bioequivalence studies

Loratadine is considered to be low soluble and classified as BCS class II. Dissolution time points 3 min, 6 min and 10 min were selected for ease of sampling for the development batches instead of 2 min, 4 min, 6 min and 10 min as mentioned in FDA dissolution database. Later, for Pilot Bio batch and Exhibit batches 2 min, 4 min, 6 min and 10 min were proposed as dissolution time points as per

Table 1. QTPP for generic Loratadine orally disintegrating tablets USP 10 mg

QTPP Element		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: Same dosage form
Dosage design		Orally disintegrating tablets	Orally disintegrating tablets needed to meet label claim
Route of administration		Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength		10 mg	Pharmaceutical equivalence requirement: Same strength
Pharmacokinetics		Fasting Study and Fed Study 90% CI of the PK parameters should fall within bioequivalence limits	Bioequivalence requirement
Stability		At least 24-month shelf-life at control room temperature	Equivalent to or better than MARKETED PRODUCT shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendia or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Disintegration time		
	Dissolution		
	Water by KF		
	Organic impurities		
	Residual solvents		
Container closure system		Blister pack	Needed to achieve the target shelf-life and ensure tablet integrity during shipping.
Alternative methods of administration		None	No other route of administration is recommended in the marketed product labeling.

FDA dissolution database. The comparative dissolution profile in USP recommended dissolution media for test and reference product is presented below:

Dissolution profile was compared for both marketed as well as test product. It was observed drug release was similar for both products (figure 1) and hence, USP recommended dissolution methodology

Table 2. Critical quality attributes of loratadine orally disintegrating tablets USP 10 mg

Drug product quality attributes		Target	Is this critical	Justification of criticality
Physical attributes	Appearance	Color, size and shape acceptable. No visual tablet defects observed.	No	Color, size, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but they can affect patient acceptability. As it is an orally disintegrating tablet, sweetener and flavor were added to ensure patient compliance.
	Score configuration	Un scored	No	The Reference product is un scored tablet; therefore, the generic tablet will be Un scored.
	Friability	NMT 1.0% w/w	No	Friability is a routine test as per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Drug substance identification should match with reference standard	Yes¥	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		95 - 105% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in drug content in formulation will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Disintegration time		NMT 1 min	Yes	Failure to meet the disintegration time specification may impact drug release. Both formulation and process variables affect the disintegration time. This CQA will be investigated throughout formulation and process development.
Dissolution		NLT 80% (Q) of labeled amount of Loratadine is dissolved in 6 min	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.
Residual Solvents		USP <467> option 1	Yes¥	Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Therefore, formulation and process variables are unlikely to impact this CQA.
Organic impurities		Loratadine related compound C - NMT 0.2 Individual unspecified impurity-NMT 0.1 Total Impurity-NMT 0.3	Yes	Degradation products can impact safety and must be controlled based on compendia/ICH requirements or MARKETED PRODUCT characterization to limit patient exposure. Formulation and process variables can impact Organic impurities. Therefore, Organic impurities will be assessed during product and process development.
Water Content (By KF %w/w)		NMT 7.0 % w/w	No	Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. However, in this case, Loratadine is not sensitive to hydrolysis and moisture will not impact stability.

was adopted for routine quality test.

¥Formulation and process variables are unlikely to impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and should be addressed accordingly.

Note: Non-compliance with microbial limits will impact patient safety. In this case, the risk of microbial growth is very low because the drying step ensures the removal of excess water and further it is justified with water activity i.e., 0.457 Aw of final drug product.

Table 3. Comparative dissolution profile of Claritin® reditabs v/s loratadine orally disintegrating tablets USP 10 mg

% Drug dissolved		
Product Name	Claritin®Redi Tabs	Loratadine Orally Disintegrating Tablets USP 10 mg
Batch No → Time (mins) ↓	K-EBT-46	BR(1484)016
03	96	97
06	100	102
10	103	103

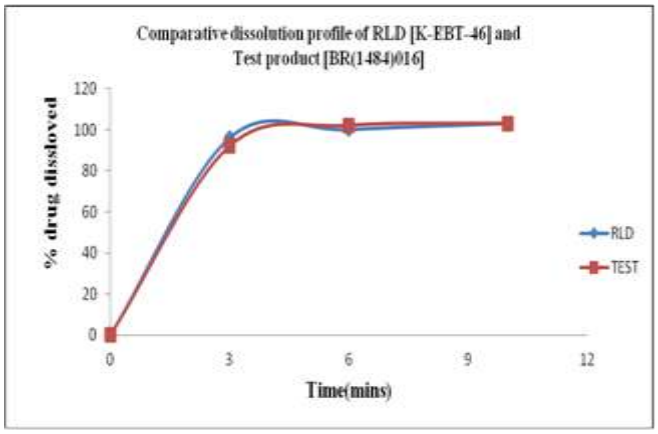


Figure 1. Comparative dissolution profile of marketed (RLD [K-EBT-46]) and test (BR[1484]016) products.

A pilot BE study (Fasting, Study No. 329-13 and Fed, Study No. 330-13) was performed in 12 healthy subjects (Two-way crossover, one prototype formulation with Batch No:BR (1484) 078 and the marketed product with Batch No: K-EBT- 46 at a dose of 10 mg) was conducted and it was observed that test and innovator products are predicted to be bioequivalent under Fasting and Fed conditions and hence, the same formula was considered for further development (unpublished data).

Drug component study

As reported in the literature, Loratadine USP drug substance is white to off-white off powder and non-hygroscopic in nature with melting point between 134°C-136°C. It was observed that Loratadine has pH dependent solubility profile with maximum solubility in acidic media.

Loratadine drug substance polymorphism

Loratadine is known to exhibit Polymorphism. Difference Crystalline Polymorphic Forms of Loratadine drug substance, namely, Form I and Form II have been reported in chemical literature (Ref: US Patent application 2008/0194823). The polymorphic identity of Loratadine drug substance is routinely confirmed by FT-IR absorption spectroscopy.

The samples of three commercial scale batches of Loratadine were analyzed by X-Ray Powder Diffraction System and observed that commercial scale batches of Loratadine drug substance are identical to each other, as well as those are concordant with the pattern reported for Loratadine Form I in US Patent application 2008/0194823.

The X-ray powder diffraction of Loratadine Orally Disintegrating Tablets, exhibited the diffraction peaks at 2-theta values, which are characteristic of Loratadine drug substance. This indicated that polymorphic form of Loratadine drug substance remains unchanged during the process of tablet formulation as well as after 6 months of stability storage at 40 ± 2^0C/75 ± 5% RH (figure 2a and 2b).

Chemical stability of Loratadine

Stress testing (forced degradation) was carried out on the drug product to evaluate the susceptibility of Loratadine in various stress conditions and observed that Loratadine is stable in various stress conditions as presented below in table 4.

Table 4. Stability of Loratadine in different stress condition

Degradation Mechanism	Degradation Condition	Loratadine area	Degradation	Loratadine Peak Purity	
				Purity Angle	Purity Threshold
Undegraded Sample	-	13030190	-	0.190	1.242
Acid Degradation	5M HCl / 85°C / 120 minutes	13123635	Nil	0.206	1.239
Base Degradation	5M NaOH / 85°C / 120minutes	12711900	2.4	0.186	1.242
Peroxide Degradation	30% H_2O_2 / 85°C / 120minutes	12981888	0.4	0.013	0.262
Thermal Degradation	105°C / 120 hours	12649613	2.9	0.016	0.262
Photolytic Degradation	White Fluorescent Light, 1.2 million Lux hours and UV light, 200 watt- hours / square meter	12991878	0.3	0.174	1.283
Humidity Degradation	90% RH / 25°C / 120 hours	13014638	0.1	0.181	1.292

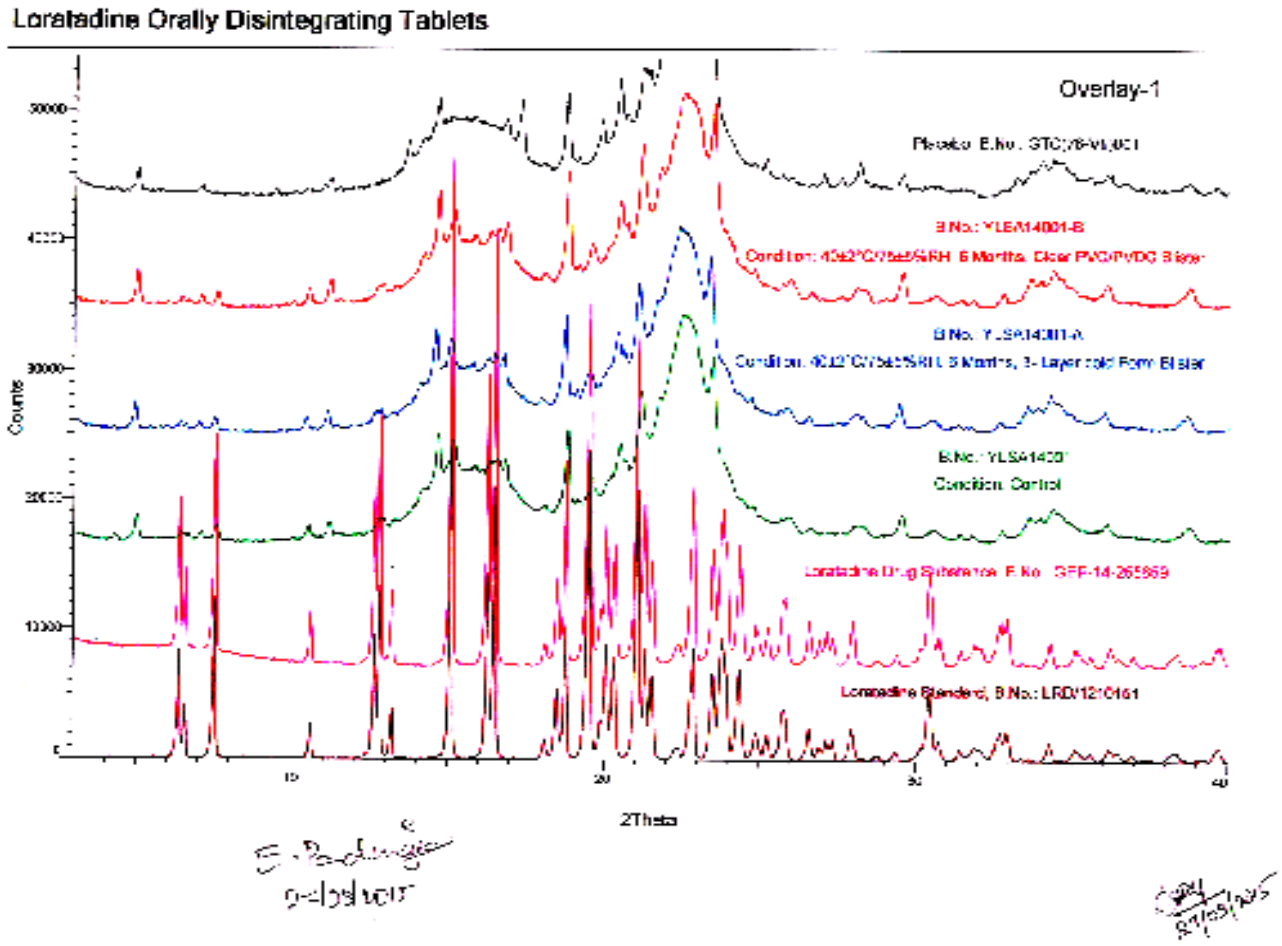


Figure 2a. 1) Loratadine standard.B.No:LRD-1210151; 2) Loratadine drug substance , B.No:GEP-14-255659; 3) Loratadine Orally Disintegrating Tablets,10 mg(control),B.No:YLSA14001; 4) Loratadine Orally Disintegrating Tablets, 10 mg (After storage at 40±2^{0}C/75±5% RH for a period of 6 months), B.No: YLSA14001-A (3 layer cold form blister) and YLSA14001-B (clear PVC/PVDC blister); 5)Placebo B.No: GTC (76-VII) 001.

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 5.

Table 5.Initial risk assessment of the drug substance attributes

Drug Product CQA's	Drug substance attributes							
	Solid state form	Particle size	Solubility	Moisture content	Residual solvents	Process impurities	Chemical stability	Flow properties
Assay	Low	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low	Low	Low	Low
Disintegration time	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	Low	Low	Low
Organic impurities	Low	Low	Low	Low	Low	Low	Low	Low

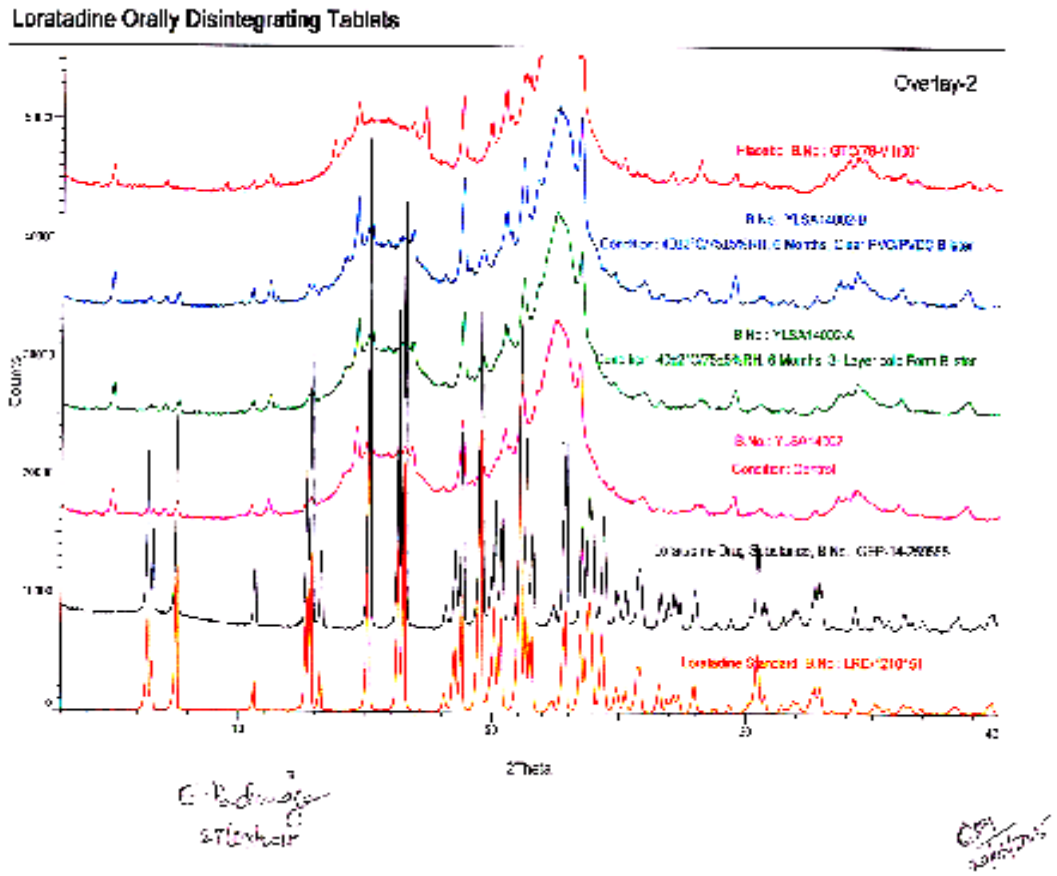


Figure 2b. 1) Loratadine standard.B.No:LRD-1210151; 2) Loratadine drug substance , B.No:GEP-14-259585; 3) Loratadine Orally Disintegrating Tablets,10 mg(control),B.No:YLSA14002; 4) Loratadine Orally Disintegrating Tablets, 10 mg (After storage at 40±2^{0}C/75±5% RH for a period of 6 months), B.No: YLSA14002-A (3 layer cold form blister) and YLSA14002-B (clear PVC/PVDC blister); 5) Placebo B.No: GTC (76-VII) 001.

Excipients selection

The excipients used in Loratadine Orally Disintegrating Tablets USP 10 mg were selected based on the excipients used in the marketed product and some of its generics, excipient compatibility studies and the literature related to wet granulation process.

Drug excipient compatibility study

The physical and chemical compatibility between Loratadine and selected excipients was assessed by subjecting the binary mixture of Loratadine API with excipients in glass vials (perforated condition). The changes in physical and chemical attributes upon exposure to one Month at 40ºC/75%RH in perforated condition were compared against initial samples and observations are presented in below table. The results indicated that there was no considerable change in physical and chemical attributes of binary mixture of Loratadine and selected excipients. Hence, it concludes that Loratadine is compatible with all the selected excipients.

Table 6. Changes in physical and chemical attributes upon exposure to one Month at 40ºC/75%RH in perforated condition were compared against initial samples

Sample	Assay		Organic impurities			
	Initial	40° C/75% (1M) (perforated)	Loratadine related compound C		Total Impurities	
			Initial	40° C/75% (1M) (perforated)	Initial	40° C/75% (1M) (perforated)
LRD	99.90	99.87	ND	ND	NIL	NIL
Loratadine +Microcrystalline cellulose (1:19)	99.88	99.88	ND	ND	NIL	NIL
Loratadine + Citric acid anhydrous (1:0.6)	99.80	99.79	ND	ND	NIL	0.01
Loratadine +Pregelatinized starch (1:2.4)	99.89	99.87	ND	ND	NIL	NIL
Loratadine + Mannitol (1:3.9)	99.88	99.87	ND	ND	NIL	NIL
Loratadine + Crospovidone (1:0.9)	99.88	99.87	ND	ND	NIL	NIL
Loratadine + Aspartame (1:0.8)	99.88	99.88	ND	ND	NIL	NIL
Loratadine + Peppermint 501500 TPO504 (1:0.2)	99.88	99.85	ND	ND	NIL	NIL
Loratadine +Sodium Stearyl Fumarate (1:0.2)	99.89	99.87	ND	ND	NIL	NIL
Loratadine + Blend^ (1:28)	99.85	99.84	ND	ND	NIL	0.02

NCC– No Characteristic Change with respect to the Initial samples; ND– Not Detected' ^ Blend consist of all the excipients proposed for formulation; Study was conducted by taking 10% w/w water to the contents of vial.

Excipients grade selection

Based on the results of the drug-excipient compatibility studies and excipients used in marketed product, excipients were selected for generic drug product development. The selection of excipient grade was based on our prior knowledge with similar dosage forms.

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. [15]

Initial risk assessment of the formulation components

The initial risk assessment of the formulation variables were evaluated (table 7 and justification of the same has been presented in table 8).

Table 7. Initial risk assessment of the formulation components

Initial Formulation Risk Assessment				
Formulation components				
Drug Product CQA	Level of Disintegrant (Pregelatinized starch)	Level of Diluent (Mannitol)	Level of Disintegrant (Crospovidone)	Level of Lubricant (Sodium Stearyl Fumarate)
Assay	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low
Organic impurities	Low	Low	Low	Low
Disintegration time	Medium	Medium	Medium	Medium
Dissolution	Medium	Medium	Medium	Medium

Sweetener/Flavor (Aspartame/Peppermint) is added in the formulation for patient compliance and it doesn't have any impact on the Drug product CQA's, hence it is not discussed in the risk assessment. However the concentration of the sweetener in the formulation has been optimized.

Table 8: Justification for the Initial risk assessment of the formulation components

Formulation Attribute	CQA's	Justification
Level of Disintegrant (Pregelatinized starch)	Assay	Pregelatinized starch as a disintegrant doesn't have any impact on the Assay of the drug product, hence the risk is low.
	Content uniformity	Content uniformity depends on the flow of the blend, however as wet granulation process is being adopted, concentration of Pregelatinized starch doesn't have impact on the flow of blend, hence the risk is low.
	Organic impurities	Pregelatinized starch is compatible with the drug substance and will not impact the organic impurities. Thus, the risk is low
	Disintegration time	Pregelatinized starch can impact the disintegration time and hence drug release, the risk is medium.
Level of Diluent (Pearlitol SD 200)	Assay	Mannitol as a diluent doesn't have any impact on the Assay of the drug product, hence the risk is low
	Content uniformity	Content uniformity depends on the flow of the blend, however as wet granulation process is being adopted, concentration of Mannitol doesn't have impact on the flow of blend, hence the risk is low.
	Organic impurities	Mannitol is compatible with the drug substance and will not impact the organic impurities. Thus, the risk is low.
	Disintegration time	Being a soluble diluent, concentration of Mannitol can impact the disintegration time and hence dissolution of the drug product. Hence risk is medium.
	Dissolution	
Level of Disintegrant (Crospovidone)	Assay	As proper blending process has been followed, the low level usage of crospovidone used in extra-granular part is unlikely to impact assay and uniformity of dosage units. The risk is low.
	Content uniformity	
	Organic impurities	Crospovidoneis compatible with the drug substance and will not impact the organic impurities. Thus, the risk is low.
	Disintegration time	Crospovidone can impact the disintegration time and rate of drug release from formulation. Hence the risk is medium.
	Dissolution	
Level of Lubricant (Sodium Stearyl Fumarate)	Assay	As proper blending process has been followed, the low level usage of sodium stearyl fumarate is unlikely to impact assay and uniformity of dosage units. The risk is low.
	Content uniformity	
	Organic impurities	Sodium stearyl fumarate is compatible with the drug substance and will not impact the organic impurities. Thus, the risk is low.
	Disintegration time	Sodium stearyl fumarate can impact the disintegration time and drug release to a certain extent hence the risk is medium.
	Dissolution	

Drug substance particle size selection for product development

Physical characterization of API

The physical properties of the drug substance indicate very poor flow characteristics of the API.

From the literature[1], it was found that innovator has used micronized API in the formulation; hence a particle size limit of D_{90} NMT 10 µm was proposed to obtain similar dissolution profile to innovator and to be bioequivalent with innovator product. Physical characterization of API was performed and results were tabulated in below table 9.

Table 9.Physical parameters of the API

Parameters	B. No. LRD/1303033	B. No. LRD/1311131	B. No. LRD/1210151
Bulk density (g/ml)	0.17	0.21	0.17
Tapped density(g/ml)	0.28	0.31	0.28
Compressibility index (%)	39.29	32.25	39.29
Hausner's ratio	1.65	1.47	1.65

Process selection

Development batches were initiated with an intention to develop orally disintegrating tablets containing 10 mg of Loratadine, which is in-line to the reference drug product. As the concentration of API was low in the formulation (6.667%w.w), wet granulation process was adopted to get uniform distribution of API. The excipients were selected based on their functionality and the recommended level of use.
A lab scale batch was fabricated and qualitative and quantitative composition is given below in table 10.

Table 10. Unit composition of Loratadine orally disintegrating tablets 10 mg[B.No: BR (1484)078]

Formula Ingredients	Qty per unit (mg)
Intra-granular ingredients	
Loratadine USP *	10.000
Microcrystalline Cellulose USNF (PH-101)**	98.000
Mannitol USP (Pearlitol SD 200)	19.500
Pregelatinized Starch USNF (Starch 1500)	12.000
Binder solution	
Purified Water USP@	q.s
Extra granular ingredients	
Crospovidone USNF (Polyplasdone XL)	4.500
Aspartame USNF (Nutrasweet® Custom Granular 60)	4.000
Peppermint 501500 TP0504 IH	1.000
Sodium Stearyl Fumarate USNF	1.000
Total Tablet Weight	150.000

--: Not Applicable; IH: In-house;q.s: Quantity Sufficient; *The quantityis based on100% w/w assay (on dried basis) and nil LOD of Loratadine USP; **Quantity to be adjusted with Microcrystalline Cellulose USNF (PH-101) to the final weight based on actual Assay (on dried basis) and Loss on drying of Loratadine USP; @Processing solvent, not present in the final product, except in traces

Physical attributes of blend and tablet are tabulated in the below table 11.

Table 11.Physical parameters of Blend and Tablet

Blend parameters	
Bulk density (gm/ml)	0.45
Tapped density (gm/ml)	0.61
Compressibility index (%)	25.00
Hausner ratio	1.33
Tooling details	
Tooling Dimensions (mm) & Shape	7.5 mm round shape
Embossing of Tooling	Lower Punch - '9' & Upper Punch - 'K'
Core tablet Parameters	
Tablet weights (mg)	148-153 mg
Thickness (mm)	3.76-3.88 mm
Hardness (kp)	3.2-4.0 kp
Friability (%w/w)	0.03%
Disintegration time	7-9 secs

The tablets were compressed using compression machine and evaluated for *in vitro* drug release profiles.

***In- vitro* dissolution study**

The *in vitro* dissolution studies of Loratadine orally disintegrating tablet were performed and compared against marketed product. The comparative results were tabulated below and shown in the figure.All the physical parameters of blend and tablets were found to be satisfactory. The *In-vitro* drug release profile was found to be similar to marketed product. Hence, this composition was used for optimization studies.

Table 12.Comparative *in-vitro* dissolution data of marketed product and Generic drug product

Loratadine orally disintegrating tablets 10mg		
Time (mins)	Marketed product[K-EBT-46]	Test product [BR(1484)078]
	% Drug release	
2	91	94
4	101	98
6	101	101
10	102	101

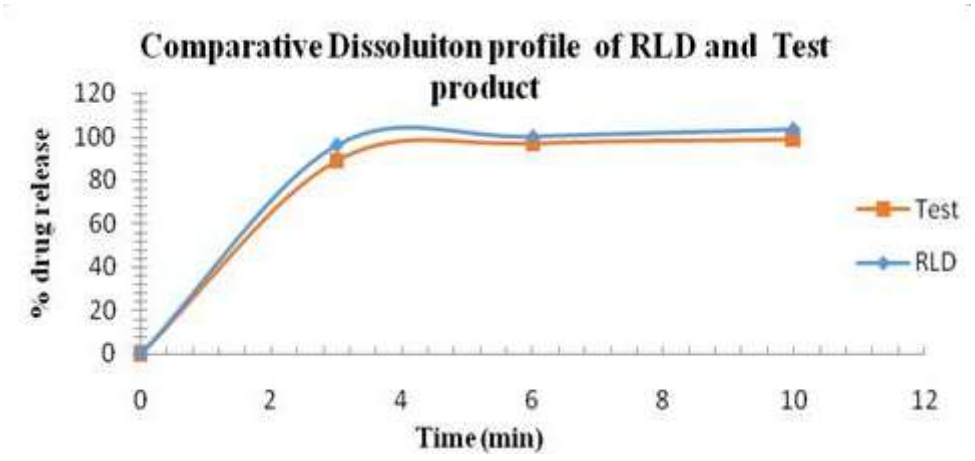


Figure. 3 Comparative dissolution profile of marketed and test products.

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.

Optimization of diluent, disintegrant and lubricant levels

As per the risk assessment and justifications given for the risk assessment, the levels of pregelatinized starch USNF, mannitol USP, crospovidone USNF and sodium stearyl fumarate USNF plays an important role in affecting disintegration time and the drug release kinetics of the drug product. Hence, 2- level factorial design was used with 11 trial runs to study the impact of formulation factors on the key response variables. In this study design as per fractional factorial (2^{n-1}) DOE, quantities of pregelatinized starch, mannitol,crospovidone and sodium stearyl fumarate were considered as factors while the disintegration time and drug release at 6 min were considered as responses. Study design and summary of the design is tabulated below.

Table 13. Design of the 2^{4-1} fractional factorial DOE

Factors: Formulation Variables			Levels		
			-1	0	+1
A	Pregelatinized Starch (mg)		8	12	16
B	Mannitol (mg)		9.8	19.5	29.2
C	Crospovidone (mg)		2.0	4.5	7.0
D	Sodium stearyl fumarate (mg)		0.5	1.0	1.5
Response		Goal	Acceptable Range		
Y1	Disintegration Time (min)	Minimize	NMT 1min.		
Y2	Dissolution at 6 min. (%)	Maximize	≥ 85%		

The experimental results for responses of the DOE batch tablets are presented in the following table 14.

Table 14. Experimental results for responses of the DOE batch tablets

Batch No	Factor 1 (Pregelatinized starch in mg)	Factor 2 (Mannitol in mg)	Factor 3 (Crospovidone in mg)	Factor 4 (Sodium stearyl fumarate in mg)	Response 1 Disintegration time (secs)	Response 2 Dissolution @ 6 mins
BR(1484)092	16.0	29.2	7.0	1.5	7	102
BR(1484)094	8.0	9.8	7.0	1.5	10	99
BR(1484)096	16.0	29.2	2.0	0.5	9	104
BR(1484)110	12.0	19.5	4.5	1.0	8	100
BR(1484)112	8.0	9.8	2.0	0.5	9	96
BR(1484)118	8.0	29.2	2.0	1.5	10	102
BR(1484)120	8.0	29.2	7.0	0.5	9	99
BR(1484)122	12.0	19.5	4.5	1.0	9	96
BR(1484)130	12.0	19.5	4.5	1.0	8	96
BR(1484)132	16.0	9.8	7.0	0.5	7	94
BR(1484)134	16.0	9.8	2.0	1.5	8	99

Analysis of response-disintegration and dissolution time

Pareto chart was prepared for different factors (pregelatinised starch, mannitol, crosspovidone and sodium stearyl funarate) affecting disintegration time. It was observed that pregelatinized starch affected the response (disintegration time) significantly when compared to other factors. Analysis of variance (ANOVA) showed significant value (P=0.0104) forpregelatinised starch while no role of curvature effect (P=0.578). Noise to signal ratio of 5.739 observed indicating an adequate signal; It ws also observed that mannitol affected the dissolution time at 6 min when compared to others (P=0.0184) with no effect of curvature (P=0.2216) and signal ratio of 4.702. Following the observation, it was considered that this model can be used to navigate the design space.

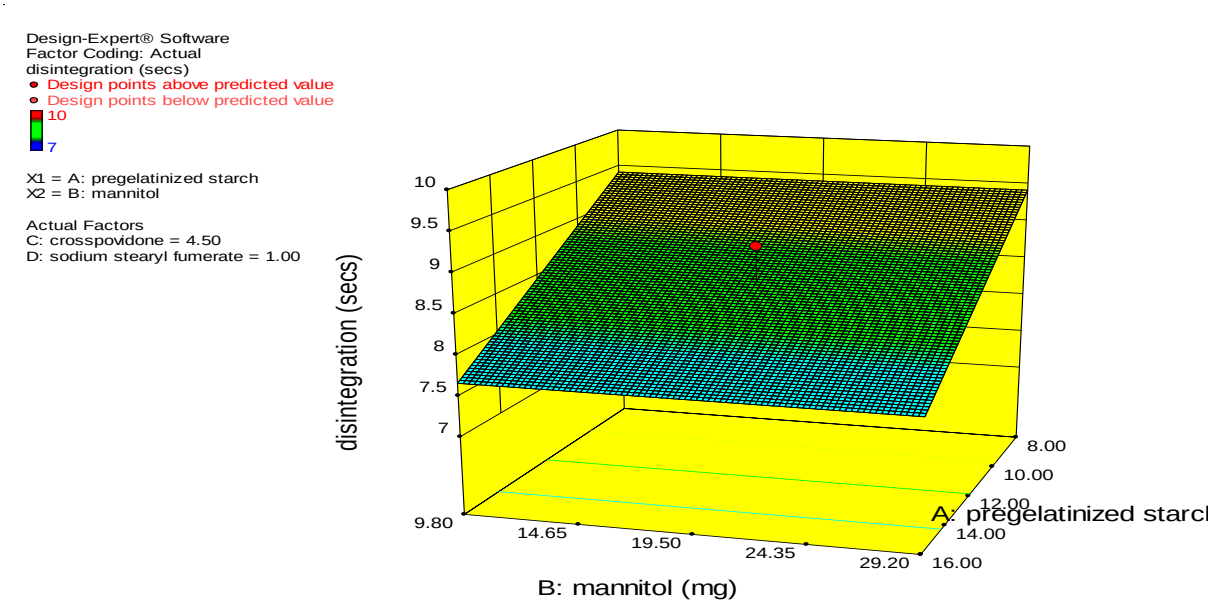


Figure 4. 3D representation of disintegtation time response of pregelatinised and mannitol.

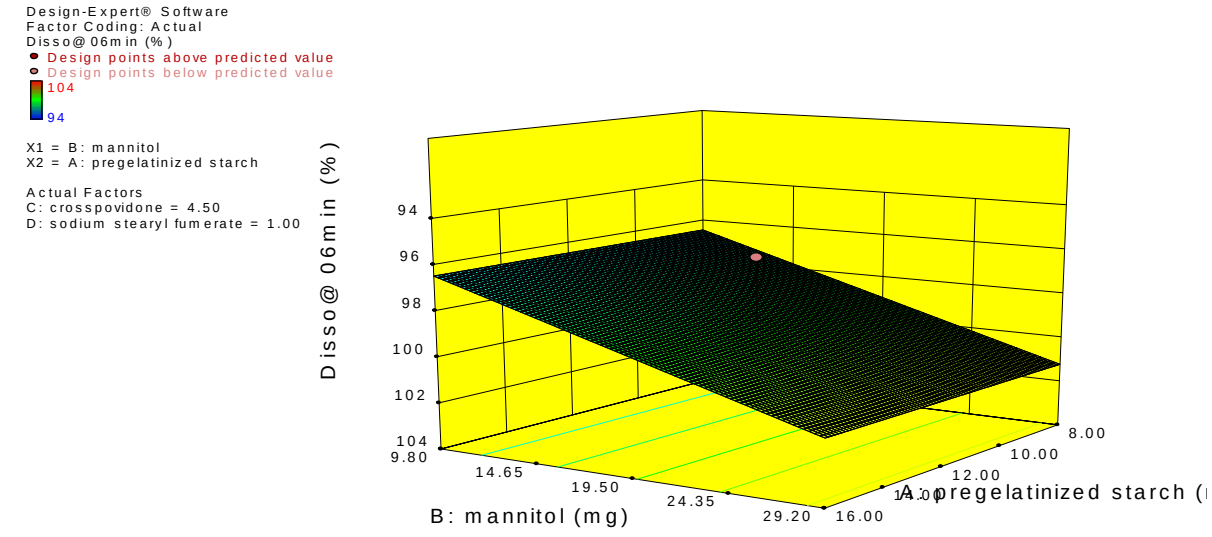
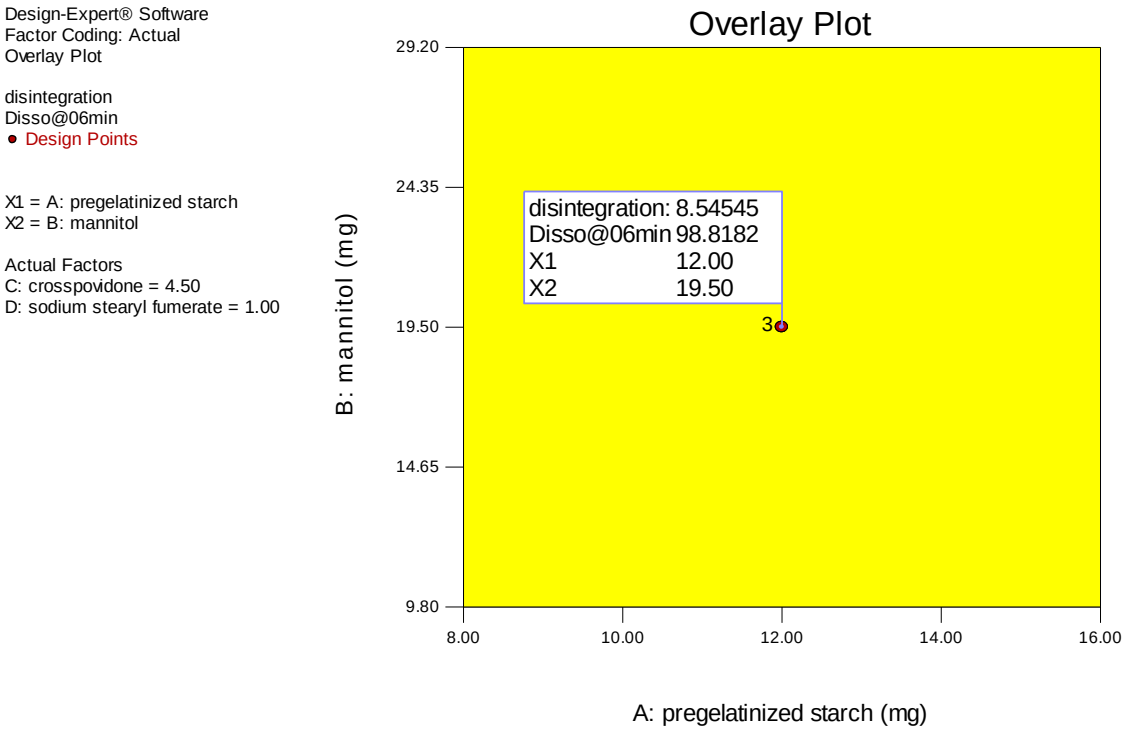


Figure **5.** 3D graphical representation of Dissolution time response curve of pregelatinised starch and mannitol

An over lay plot is given below which shows the design space with in which we can operate to obtain the responses within the selected acceptance limits.



It was inferred that the disintegrant (pregelatinized starch) quantity of 12.0 mg, disintegrant (crospovidone) quantity of 4.5 mg, diluent (mannitol) quantity of 19.5 mg and lubricant (sodium stearyl fumarate) quantity of 1.0 mg was suitable to get required disintegration time and drug release of NLT 85% at 6 min. Hence these concentrations of respective excipients were considered as optimum concentration.

Effect on drug release using different grade of microcrystalline Cellulose USNF

The effect of alternate source/vendor of excipients used in the formulation on the product quality was evaluated. It was observed that similar drug release profiles of batches fabricated using excipient from different source/vendor. Hence it was concluded that there was no effect of selection of alternate source/ vendor of excipient (Microcrystalline cellulose US NF) on the product quality. The batches were evaluated for dissolution studies and the data is summarized below.

Table 15.*In-vitro* dissolution profiles of the formulations with excipients from different vendors

B.No	% Drug dissolved	
	B. No: BR(1484)078(Grade: PH 101)	B. No: BR(1484)186 (Grade: Avicel PH -101)
Dissolution at 2 min	94	84
Dissolution at 4 min	98	96
Dissolution at 6 min	101	101
Dissolution at 10 min	101	103

Optimization of sweetener and flavor

Further, a study was conducted for evaluation of taste and mouth feel of Loratadine Orally Disintegrating Tablets 10 mg developed by APL and were compared with the reference listed product Claritin RediTabs 10 mg. The study was conducted using three member technical panel of American Society of Testing and Materials (ASTM) trained sensory judges. It was concluded that BR (1484)050 was comparable to marketed product w.r.t Sensory Characteristics. Hence 4.00 mg of Aspartame and 1.00 mg of Peppermint was finalized in the formulation

Table 16. Comparison of characteristics of marketed and test products.

Ingredients↓	Marketed Product	BR(1484)050
Aspartame USNF (mg)	-	4.00
Peppermint 501500 TP0504 (mg)	-	1.00
Observations↓		
Odor	Odorless	Comparable to marketed product Similarity Rating:8**
Flavor	Sweet, sour, peppermint, bitter	Comparable to marketed product Similarity Rating:6**
Mouth feel	Easily dissolves, cooling, slight numbing	Comparable to marketed product Similarity Rating:6**

**Similarity Rating: 0-8; Very different to Identical
A Similarity Rating of 6.0 or greater is considered comparable to the national brand

Based on the lab scale batch and formulation optimization studies, a scale up batch with batch size of 37000 units was fabricated. The composition and the procedure was same as the batch (Batch no: BR (1484)078).

In- vitro dissolution study

The *in vitro* dissolution studies of Loratadine 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 similar to marketed product.
The comparative results were tabulated below and shown in the figure

Table 17. Comparative *in-vitro* dissolution data of marketed product and test product

Loratadine orally disintegrating tablets 10mg		
Time (min)	Marketed Product[K-EBT-46]	Test product [GTC (76-VII) 013]
	% Drug release	
3	96.0	81.5
6	100.0	93.9
10	103.0	98.1

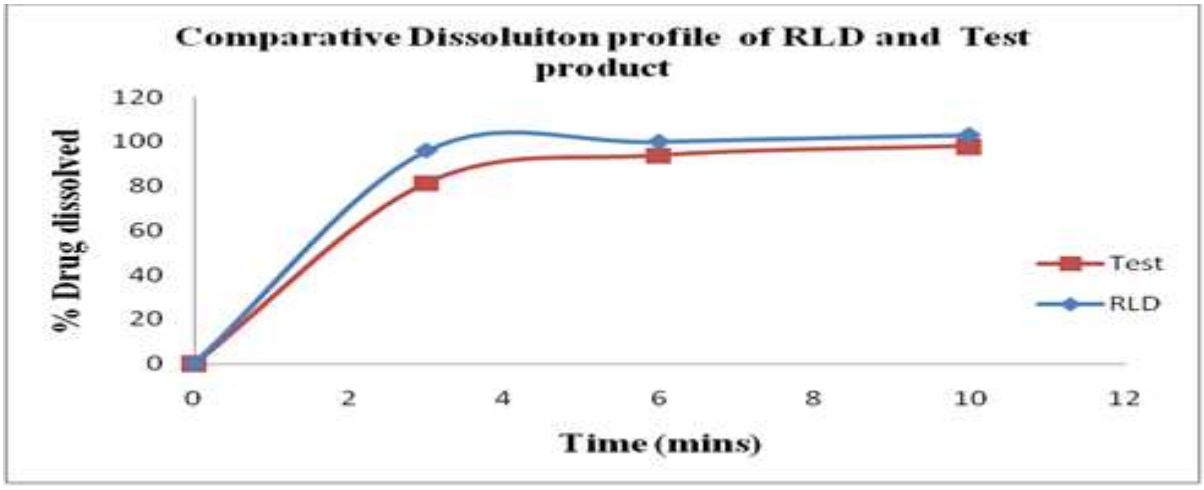


Figure 6. Comparative dissolution profile of marketed and test product

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.

Table 17. Final composition of formula

Formula Ingredients	Qty per unit (mg)	Qty in % (w/w)
Intra-granular ingredients		
Loratadine USP	10.000	6.667
Microcrystalline Cellulose USNF (PH-101)	98.000	65.333
Mannitol USP (Pearlitol SD 200)	19.500	13.000
Pregelatinized Starch USNF (Starch 1500)	12.000	8.000
Binder solution		
Purified Water USP	Q.S	--
Extra granular ingredients		
Crospovidone USNF (Polyplasdone XL)	4.500	3.000
Aspartame USNF (Nutrasweet® Custom Granular 60)	4.000	2.667
Peppermint 501500 TP0504 IH	1.000	0.667
Sodium Stearyl Fumarate USNF	1.000	0.667
Total Tablet Weight	150.000	100.00

Updated risk assessment of the formulation variables

Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated and presented in table 18 and 19.

Table 18. Updated formulation risk assessment

Updated Formulation Risk Assessment				
Formulation components				
Drug Product CQA	Level of Disintegrant (Pregelatinized starch)	Level of Diluent (Mannitol)	Level of Disintegrant (Crospovidone)	Level of Lubricant (Sodium Stearyl Fumarate)
Assay	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low
Organic impurities	Low	Low	Low	Low
Disintegration	Low*	Low*	Low*	Low*
Dissolution	Low*	Low*	Low*	Low*

* The level of risk is reduced from the initial risk assessment

Table 19 Justification for the Updated risk assessment of the formulation attributes

Formulation attribute	CQA's	Justification
Level of Disintegrant (Pregelatinized starch)	Disintegration time Dissolution	The optimization studies indicate that desired disintegration time and drug release can be achieved within the studied range. Hence the risk is reduced from medium to low.
Level of Diluent (Mannitol)		
Level of Disintegrant (Crospovidone)		
Level of Lubricant (Sodium Stearyl Fumarate)		

Scale-Up from lab to pilot, exhibit and proposed commercial scale

Process parameters at the exhibit and commercial scale were proposed based on criticality of parameters, optimization study results at the lab scale, scale dependency or independency of the parameters and our prior knowledge with similar kind of process and dosage form.

Manufacturing of exhibit batch

Based on the scale up and feasibility batches, a cGMP exhibit batch of 1, 50,000 units were manufactured. The in-process and the final release results are summarized below:

Table 20. In-process testing results for the exhibit batch

Tests	In-process controls	Results		
		YLSA14001	YLSA14002	YLSA14003
LOD of granules (%w/w)	2.0% - 4.0w/w	3.29	2.75	2.87
Tablet Compression				
Average weight (mg)	150.0 mg ± 3.0%	150.13	150.96	150.20
Weight of 10 tablets	1.500 g ± 3.0%	1.4925-1.5090	1.5049-1.5139	1.4957-1.5075
Hardness (kp)	2.0 - 5.0 kp	3.7-4.7	3.7-4.8	3.3-4.6 kp
Thickness (mm)	3.70 ± 0.30mm	3.50-3.70	3.64-3.73	3.65-3.78
Friability (%)	NMT 1.0 % w/w	0.1	0.1-0.2	0.1-0.2
Disintegration time (min)	NMT 1 min	8 – 9 sec	8 – 9 sec	7 – 9 sec
Uniformity of weight	150.0 mg ± 5.0%	149.1-151.8	149.4-152.5	148.4-151.2

Table 21. Release testing results for the exhibit batch

Tests	Acceptance criteria	Results		
		YLSA14001	YLSA14002	YLSA14003
Description	White to off-white, round shaped biconvex tablet debossed with ‘K’ on one side and '9' on other side.	White, round shaped biconvex tablet debossed with ‘K’ on one side and '9' on other side.		
Identification (By HPLC)	The retention time of the major peak in the chromatogram of the sample solution should correspond to that in the chromatogram of the standard solution, as obtained in the Assay.	The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the Assay.		
Average Tablet weight (mg)	150.0 ±3.0 % (145.5 – 154.5 mg)	149.56 mg	149.91 mg	150.72 mg
Uniformity of Dosage Units (By Content uniformity) Acceptance value (%)	Not more than 15.0	1.6	1.8	4.1
Assay (By HPLC) Each Orally disintegrating tablet contains Loratadine ($C_{22}H_{23}ClN_2O_2$), in mg.	9.50-10.50 mg	10.079	10.191 mg	10.098
% Labeled amount	95.0 - 105.0	100.8%	101.9%	101.0%
Organic impurities(By HPLC)				
Loratadine related compound C	Not more than 0.2% w/w	Below LOD	Below LOD	Below LOD
Individual unspecified impurity	Not more than 0.1% w/w	0.05%	0.06%	0.05%
Total impurities	Not more than 0.3% w/w	0.05%	0.10%	0.09%
Water (by KF)	Not more than 7.0% w/w	3.89%	3.41%	3.55%
Dissolution (By UV)	Not less than 80% (Q) of the labeled amount of Loratadine ($C_{22}H_{23}ClN_2O_2$) dissolved in 6 min	Min:94.2% Max:98.9% Avg:96.8%	Min:94.6% Max:98.9% Avg:96.7%	Min:95.6% Max:97.4% Avg:96.5%
Disintegration time	NMT 1 min	19 sec	17 sec	17 sec
Residual solvents	Should comply USP<467> requirement (option 1)	Complies	Complies	Complies

Updated risk assessment of the drug product manufacturing process

During process development, the identified medium risks for critical process parameters were addressed. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented and to reduce the risk to an acceptable level. After experimentation, the initial manufacturing process risk assessment was updated in line with the current process understanding. The below table presents updated risk assessment of the manufacturing process.

Table 22. Updated risk assessment of drug product manufacturing process

Unit Operation	Drug product CQAs					
	Assay	BU	CU	Disintegration	Dissolution	Organic impurities
Granulation	Low*	Low*	Low	Low*	Low*	Low
Drying	Low	Low	Low	Low	Low	Low
Milling	Low	Low	Low	Low	Low	Low
Blending	Low	Low*	Low	Low	Low	Low
Lubrication	Low	Low*	Low	Low	Low*	Low
Compression	Low*	-	Low*	Low*	Low*	Low

*The level of risk reduced from initial risk assessment

Table 23. Justification for the updated risk assessment of the manufacturing process

Drug product CQAs	Justification
Granulation	
Assay	Impact of premixing time on the blend uniformity was evaluated at lab scale. There is no considerable impact at the studied range (5 to 15 min). With the finalized premixing time (10 min) all the development batches and scale-up batches achieved desired Blend uniformity. Therefore, the risk of premixing time on blend uniformity, content uniformity & Assay was reduced from medium to low.
Blend uniformity	
Content Uniformity	
Disintegration	Impact of granulation (% fluid uptake) on dissolution was studied and found that within the proposed range disintegration time and dissolution profile were found to be similar; hence the risk is reduced from medium to low for dissolution and disintegration.
Dissolution	
Blending:Blend uniformity	Impact of Blending on Blend uniformity was evaluated. There is no considerable impact at the studied range (5- 15min). With the finalized blending time (10min) all the developmental batches and Scale-up batches achieved blend uniformity. Therefore risk reduced to low for blend uniformity.
Lubrication	
Blend uniformity	Impact of Lubrication time on Blend uniformity was evaluated. There is no considerable impact at the studied range (3- 7min). With the finalized blending time (5min) all the developmental batches and Scale-up batches achieved blend uniformity. Therefore risk reduced to low for blend uniformity
Dissolution	Impact of lubrication time on dissolution was evaluated. There is no considerable impact at the studied range (5 to 7 min). With the finalized lubrication time (5 min) all the development batches and Scale-up batches achieved target dissolution. Therefore, the risk reduced from medium to low for dissolution
Tablet compression	
Assay	Impact of compression machine speed on content uniformity of the tablets has been evaluated at lab scale. There is no considerable impact of compression machine speed within the studied range of machine speed. Therefore, the risk is reduced from medium to low for content uniformity and Assay.
Content Uniformity	
Disintegration	Impact of hardness on the dissolution of tablets was investigated during scale up studies, indicating that there is no considerable impact within the range studied. Moreover, the impact of hardness on the physical characteristics of tablets was evaluated at the lower side and higher side of the target range at pilot scale indicating no considerable impact. With the finalized hardness range all the development and Scale-up batches achieved target disintegration time & dissolution. Therefore risk is reduced from medium to low for dissolution and disintegration.

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 (Davisetal., 2008). The control strategy includes material attributes of Loratadine and excipients to be controlled, in-process controls, process parameter ranges studied during development and proposed operating ranges for commercial batch. For Loratadine ODT, the control strategy was developed after the estimation of residual risk and an assessment for its acceptability and presented in table 24.

Table 24. Control strategy for Loratadine ODT

Attributes	Control Strategy
Raw material	
API Particle Size Distribution	NMT 10 µM
Microcrystalline cellulose (retained on 75 and 250 µm sieve	NMT 30% and 1%
Mannitol SD 200	Between +137° and 145°
Crospovidone (Passed through on 38 µm sieve)	NMT 50%
Aspartame (Passed through 125 µm sieve)	NMT 10%
Peppermint 501500 TP0504 (Passed through on 850µm sieve)	NLT 99.0%
Sodium stearyl fumarate (Limit of sodium stearyl maleate/Stearyl alcohol)	NMT 0.25%/NMT 0.5%
Rapid Mixer Granulator	
Dry mixing time	10 min
Impeller speed	Slow
Chopper Speed (During dry mixing & Kneading stage/purified water addition)	Off/Slow
Fluid addition time	2-3 min
Fluid uptake	50-55%
Drying	
Inlet temperature	$55^0C \pm 10^0C$
LOD	2-4% w/w
Co-mill (Screen size/mill speed)	1016µm/slow
Blending and Lubrication	
Blending/Lubrication time (min)	10/5
Blend assay	95-105%
Tablet compression	
Compression machine speed	15-35 RPM
Description	White to off –white, round shaped biconvex tablet debossed with ‘K’ on one side and ‘9’ 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

Product lifecycle management and continual improvement

Upon approval of the product, the manufacturing process will be validated at commercial scale 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 the product helped in in-depth understanding of product and process which ultimately facilitated in stage 1 (i.e. process design) of process validation.

Commercial manufacturing process was defined based on knowledge gained through development and scale up activities and based on that controlled strategy for the process was developed. The prime aim of stage 2 (i.e., process qualification) is to evaluate whether the process is capable for manufacturing of reproducible batches at commercial scale. The manufacturing facility will 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 performance. The process validation 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 (i.e., 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 that whether it is consistently delivering the product with desired quality attributes. Process stability and process capability will be measured and evaluated. 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 the additional knowledge gained during routine manufacturing will be utilized for adjustment of process parameters as part of the continual improvement of the drug product. As a commitment, the regulatory agency will be notified regarding each change in each condition beyond the limit already provided in this application.

Conclusion

QbD is an essential part of the modern approach to pharmaceutical quality. This study clarifies the use of QbD including emphasison the importance of the target product quality profile in articulating a quantitative performance target for QbD. Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process. Clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation input sand out puts. A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes. The role of the control strategy as the mechanism for in crement a implementation of QbD elements into practice. An efficient pathtoadesign space through the identification of non-interacting process variables and their exclusion from formal experimental designs. Thus, this study showed the application of QbD in formulation development of model drugs Loratadine ODT similar to marketed product Claritin® RediTabs.

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