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Use of Quality by Design (QbD) Approach in Orodispersible Tablet Formulation of Fidaxomicin

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KEYWORDS

Fidaxomicin;
Orodispersible tablet;
Quality by design (QbD);
Palatability;
Stability

ABSTRACT:

The aim behind development of 200 mg Fidaxomicin formulation is to provide cost-effective and innocuous formulation for the pediatric population using Quality by design (QbD) approach to enhance stability and bioavailability. The formulation, comprising fidaxomicin and excipients like microcrystalline cellulose and croscarmellose sodium, was designed for rapid disintegration and high absorption in the gastrointestinal tract, improving efficacy in neonates. Multiple risk factors like physical stability of dispersion system and oral bioavailability are taken into consideration while developing this suspension using orodispersible tablet formulation. The QbD methodology defined critical quality attributes (CQAs) such as dissolution, microbial limits, and content uniformity, ensuring consistent performance while conducting the quantitative and qualitative studies on three batches. Taste optimization with artificial chocolate flavor enhanced pediatric acceptability. Dissolution studies showed over 92% release within 5 minutes, and compatibility studies verified excipient stability. The manufacturing process, utilizing dry granulation and compression, achieved robust tablet characteristics. Stability studies confirmed a 36-month shelf-life at 30°C, with no significant degradation in various vehicles. This orodispersible tablet offers dosing flexibility, preservative-free composition, and a favorable safety profile, addressing unmet needs in pediatric Clostridium difficile infection (CDI) treatment with improved bioavailability and patient compliance, supported by a comprehensive control strategy for quality assurance.

1. Introduction

Fidaxomicin is a neoteric, narrow-spectrum macrolide antibiotic drug which used to treat the Clostridium difficile infection (CDI) in adults and children [1]. Fidaxomicin formulation is available as film coated tablets, granules for suspension, and granules. Currently, In the market ready to use oral suspensions are available as Fidaxomicin as an active Pharmaceutical Ingredient but concerning the better shelf life and intended for pediatric use are very rare [2]. For the pediatric population, most suitable dosage form is orodispersible tablets as its bioavailability will be high and is suitable for conversion from orodispersible tablet to the palatable suspension form [3]. During this research work, formulation has been developed as an orodispersible tablet for oral suspension, in 200 mg/mL dosage form. While making direct suspension, stability and shelf-life issues arises [4].

QbD approach has been used for the pharmaceutical development which begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality Target Product Profile (QTTP) were assessed, and all relevant parameters associated with it were tested and verified. Critical Quality Attributes (CQA) and Critical Material Attributes (CMA) were identified, and their risk has been reduced from high to a low by conducting necessary tests. This data-driven approach had helped to serve the progressive manufacturing environment, as it gives drug developers a better understanding of manufacturing processes, precise quality and decreases the number of batch failures, gives more effective control of change and provides a robust formulation with a better stability profile [5].

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2. Objectives

While developing the fidaxomicin orodispersible tablets, a series of formulation and development studies were conducted to ensure that developed formulation is robust and effective in the pediatric population. These studies include but not limited to solubility, permeability, palatability, dissolution, excipient compatibility, disintegration, determination of microbial limits, % assay purity and shelf-life establishment study. The results obtained from these studies were in compliance with the standard limits mentioned in the USP and Ph.Eur. monograph of the general chapters. Concerning this tablet for oral suspension, shelf-life has been achieved up to 48 months and has a better absorption rate compared to direct tablet and direct suspension form [6].

3. Methods

3.1 Materials

Fidaxomicin API was procured from Montage Laboratories, India. and Excipients, Microcrystalline Cellulose [UF-711] (CAS: 9004-34-6) was procured from Asahi Kasei, Japan. Croscarmellose Sodium [Ac-Di-Sol, SD711 NF] (CAS:74811-65-7) was procured from Dupont, Canada. Colloidal Silicon Dioxide [Cab-O-Sil® MSP] (CAS:112945-52-5) was procured from Cabot, USA. Magnesium Stearate [Ligamed MF-2-EV] (CAS: 557-04-0) was procured from Peter Grevan, Netherlands. Sodium Lauryl Sulfate (CAS:151-21-3) was procured from Merck, Germany. Opadry II Yellow and artificial chocolate flavor were acquired by Kentreck Laboratories, India.

3.2 Implementation of Quality by Design (QbD) approach in drug development

3.2.1 Quality Target Product Profile (QTPP)

The quality target product profile (QTPP) has been used as the basis of Fidaxomicin tablet drug product development. As summarized in Table 1, the QTPP for the Fidaxomicin tablet, 200 mg, was defined based on the properties of the drug substance, characterization of the drug product, and consideration of the label and intended patient population. The formulation was designed to achieve all the attributes of the QTPP [7].

The product quality attributes listed in the QTPP are a subset of the total CQAs for the drug product. They are target elements of the drug product and are achieved through appropriate formulation, process design, development and, when appropriate, by applying globally accepted compendial standards [8].

3.2.2 Critical Quality Attributes (CQA)

For Fidaxomicin tablets, appearance, identification, content (assay), uniformity of dosage units, degradation products, dissolution, microbial limits, residual solvents, and elemental impurities were identified as the drug product critical quality attributes (CQAs) [9].

3.2.3 Critical Material Attributes (CMA)

Standard excipients for solid oral dosage forms were selected for formulating a Fidaxomicin tablet, 200 mg and their physical properties and functions in the formulations are well evaluated by the pharmaceutical industry. Thus, the critical material attributes (CMAs) from the formulation excipients do not impact the final formulation [10].

3.3 Orodispersible Tablet Formulation

Based on the regulatory guidelines and literature, the parameters like dosing flexibility (dose levels, administration vehicle and population), preservative free formulation, physical and chemical compatibility, dose acceptability (taste, texture and mouth feel), manufacturability and shelf-life were considered as the desirable features for an oral pediatric dosage formulation. Orodispersible Tablets are uncoated tablets intended to be dispersed in a vehicle (distilled water or clear liquid) before administration [11]. Orodispersible tablets are expected to disintegrate and disperse within 5 minutes in an appropriate volume of vehicle [12].

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Table 1 Quality Target Product Profile

QTPP Element		**Target**	**Justification**
Route of Administration		Oral, once a day	To ensure safety, efficacy and adequate bioavailability and to provide convenient administration of drug to pediatric patient.
Dosage Form		Immediate-release, film-coated tablet	To enhance compliance of pediatric patients. This ensures that dosage form is palatable and easy to swallow. To ensure robustness during transportation.
Dosage Strength		200 mg	To provide acceptable tablet size and pill burden for oral administration.
Drug Product Quality Attributes	Appearance	Oval shaped, film-coated tablet with color coat	An oval shaped, film-coated tablet of 349.27 mg is easy to swallow. The color coat enhances identification.
	Content	100% label claim	To ensure safety and efficacy.
	Uniformity of dosage units	Meet the pharmacopeial requirement	To ensure safety and efficacy.
	Degradation products	Meet ICH Q3B limits	To ensure safety.
	Dissolution	Meet the specification	To ensure consistent lot to lot in vitro performance.
	Microbial limit	Meet the pharmacopeial requirement for solid oral dosage form	To ensure safety.
Container Closure System	HDPE bottle (with desiccant and coil) and child-resistant cap	Qualified container closure system for Fidaxomicin tablets provides sufficient drug supply to patients	To ensure product quality is maintained through shelf-life. Provide container for compliance of patient administration. To ensure tablet integrity during shipping.
Shelf Life		At least 24 months at or below 30 °C	To ensure end-to-end stability of the drug product from its entry into the supply chain to patient. To provide convenient access for patients, eg, no cold storage required.

3.4 Physicochemical Properties of Fidaxomicin Drug Substance

An orodispersible tablet was formulated consistent with rapid disintegration for optimal absorption in the gastrointestinal tract. A compressibility study of Fidaxomicin using different grades of microcrystalline cellulose (MCC) was carried out. These compressibility studies use a hydraulic punch (manufacturer: Zhuzhou, Model No. ZP33) to form slugs. The results indicated Fidaxomicin slugs had low hardness. The study demonstrated that UF-711 MCC (microcrystalline cellulose) provided a higher compressibility for

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Fidaxomicin drug substance showed higher slug hardness than PH101 MCC.

3.5 Physicochemical Characteristics of the Drug Substance

3.5.1 Solubility

The solubility of the Fidaxomicin drug substance in aqueous media (at various pH values) and in simulated gastrointestinal fluids was conducted with the shake flask method. Since based on the Biopharmaceutics Classification System (BCS), Fidaxomicin drug substance is classified as a Class 4 compound, its aqueous solubility is not high in most ingested conditions, an immediate-release tablet was formulated consistent with rapid disintegration for maximal absorption in the gastrointestinal tract. Solubility study has been conducted in three different buffer media at pH 1.2, 4.5 and 6.8. At pH 1.2, 97 mM HCl and 50 mM KCl was used, and solubility was 1.06 mg/mL. At pH 4.5, 40 mM orthophosphate buffer was used, and solubility was 0.030 mg/mL. Lastly, at pH 6.8, 50 mM orthophosphate buffer was used, and solubility was 0.032 mg/mL.

3.5.2 Permeability

Permeability study for fidaxomicin was conducted with the focus on predicting how a drug will permeate the intestinal membrane, by using SwissADME tool. Input parameters were physicochemical properties like molecular weight, Log P (partition coefficient), pKa, solubility across pH range and certain drug-specific properties like permeability (Caco-2, PAMPA), BCS classification, disintegration time, particle size distribution, drug release profile (from dissolution studies). Impact was analyzed of formulation changes (e.g., surfactants, micronization) on permeability. Key predicted outputs were Fraction absorbed (Fa), efective permeability (Peff), Cmax and Tmax as full PBPK modeling is done.

3.5.3 Palatability

Orodispersible tablets (ODT) of fidaxomicin were prepared by using direct compress tablet process. The availability of various technologies and its advantages of ODT had improved patient compliance, minimum dosing for pediatric population, rapid onset of action, better disintegration, less side effect, and enhanced stability of drug substance. Taste masking agent and flavor (chocolate) had played a crucial role in palatability for compression method [13]. Compressed method process was highly cost effective, easy to dispense, better administration to neonates, easy to carry, and highly stable at normal storage conditions. Tablets manufactured using lyophilization had shown high hardness, difficulty in packing, required special storage and transportation condition, and difficult to take tablet from the pack [14]. Compressed tablet process was an effective, low cost and much better alternative approach compared with the lyophilization process. Therefore, based on the palatability evaluation study results, compression method was chosen. Palatability assessments using a hedonic scale were conducted in conjunction with the morning dose of fidaxomicin. The scale used for the palatability assessments was 1=’Super Bad’, 2=’Bad’, 3=’Maybe Good or Maybe Bad”, 4=’Good’ and 5=’Super Good’. The mean score per group was summarized.

The assessment was completed by a caregiver for subjects in Groups 1-4. Subjects that received Fidaxomicin dosage via NG tube. Total four formulations were selected for palatability evaluation study, in that one is commercially available reference formulation (Dificid®, Manufactured by Merck & Co., Inc), one is positive control (Placebo for fidaxomicin), one is negative control (Placebo for Taste masking agent-artificial chocolate flavor) and one in-house test product. Detailed assessment of palatability study is provided in results section.

Table 2 Data assessment of palatability study

Assessment parameters	**Formulation 1 (Placebo) Group 1 Positive control**	**Formulation 2 (Available Market formulation-Dificid®) Group 2 Reference**	**Formulation 3 (Final optimized formulation-with flavor) Group 3 In-house tablets**	**Formulation 4 (Pure drug without flavor) Group 4 Negative control**

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Calculated Points	89.1	86.9	97.6	20.4
Overall Ranking	5	4	5	2
Assessment Questionnaire completed	Yes	Yes	Yes	Yes
Palatability	Very good	Good	Very good	Bad

3.6 Compatibility of the Drug Substance with the Excipients

The chemical compatibility of the Fidaxomicin drug substance with the formulation excipients under accelerated storage conditions (40 °C/75% RH) was evaluated. The MCC intragranular and extragranular concentrations (unit weight %) of the final formulation are 27.30% and 7.44%, respectively. To optimize disintegration of the drug product tablets, croscarmellose sodium is added in both the intragranular and extragranular formulations at 0.99% and 0.25%, respectively. The total concentration of colloidal silicon dioxide in the tablet formulation is 0.75% w/w, which is within the commonly used concentration range (0.1% to 1.0% w/w) in solid oral dosage forms. SLS (CAS No: 151213) was selected as a surfactant in the fidaxomicin tablet, 200 mg, and added to the extragranular formulation at a concentration of 1.49% w/w. This concentration is in the range of most used concentrations (0.5% to 2.5% w/w). The total concentration of magnesium stearate formulated in fidaxomicin tablet, 200 mg, is 2.23%, which is within the typical usage level of 0.25% to 5.0% in solid oral dosage forms.

3.7 Manufacturing Process Development for Fidaxomicin Orodispersible Tablet, 200 mg

The common blend approach was used as part of the proposed manufacturing process, leveraging the knowledge and experience acquired in formulation development and production. The proposed manufacturing process for the Fidaxomicin orodispersible tablet, 200 mg, incorporates the intragranular and extra granular processes to enhance tablet compressibility and provide efficient product disintegration properties. Direct compression aspect was used in the manufacturing operations.

3.8 Dissolution Study

The dissolution method was developed for the purpose of quality control to assess the consistency of Fidaxomicin orodispersible tablets, and to ensure continuous product quality following changes including process parameters, and scale of the manufacturing process. Fidaxomicin orodispersible tablets were designed as an immediate-release (IR) oral solid dosage form.

3.9 Disintegration Study

Disintegration study is very important test for tablets for oral suspension. 1 tablet was placed in each of 6 beakers containing 200 mL of water. The suitable beaker had a nominal volume of 300 mL. Tablets were kept for 5 minutes as per USP general chapter 701.

Numerous bubbles of gas had evolved. After 5 minutes the evolution of gas around each tablet fragments has ceased. Each tablet was disintegrated and has been dispersed in the water so that no appreciable agglomerates remain. Hence, it can be concluded that tablets disintegration profile is up to the mark.

3.10 Formulation Stability studies

A shelf life of 36 months is proposed for Fidaxomicin orodispersible tablets, 200 mg, at the proposed storage condition of “Store at or below 30°C” [15]. The stability of Fidaxomicin orodispersible tablets has been evaluated at long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability storage conditions by ICH Q1A. Additionally, an alternate long-term storage condition of 30°C/75% RH was implemented in the registration stability program to support the proposed storage condition; it also serves as the intermediate storage condition for 25°C/60% RH storage [16].

4. Results

4.1 Excipient Compatibility results

At the designated time points, the powder mixture samples in bottles were pulled and the chemical stability of Fidaxomicin was assessed by a reverse phase high performance liquid chromatography (HPLC) analytical

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method (Model 1260 Infinity III LC, Agilent technologies). The results are summarized in Table 3.

Table 3 Fidaxomicin and Excipient Compatibility Study at 40 °C/75% RH

Time Points	Time Zero			1 Month					3 Month				
Excipients	**Fdn (% area)**	**Impurity (% area)**	**Total Impurities (% area)**	**Fdn (% area)**	**Impurity (% area)**			**Total Impurities (% area)**	**Fdn (% area)**	**Impurity (% area)**			**Total Impurities (%area)**
		(RRT 1.04)			**RRT 0.17**	**RRT 0.49**	**(RRT 1.04)**			**RRT 0.17**	**RRT 0.49**	**(RRT 1.04)**	
Microcrystalline Cellulose (UF-711)	99.8	0.19	0.19	99.8	–	–	0.23	0.23	99.8	–	–	0.22	0.22
Croscarmellose Sodium	99.8	0.22	0.22	99.8	–	–	0.22	0.22	99.8	–	–	0.22	0.22
Sodium Lauryl Sulfate	99.8	0.21	0.21	99.7	0.04	0.02	0.21	0.27	99.7	0.02	0.02	0.21	0.25
Magnesium Stearate	99.8	0.22	0.22	99.8	–	–	0.21	0.21	99.8	–	–	0.23	0.23
Colloidal Silicon Dioxide	99.8	0.22	0.22	99.8	–	0.02	0.19	0.21	99.8	–	0.02	0.18	0.20
Opadry II Yellow Coating System	99.8	0.20	0.20	99.8	–	–	0.22	0.22	99.8	–	–	0.22	0.22

Fdn: Fidaxomicin drug substance; ≤0.02% (peak area)

The purity of the Fidaxomicin drug substance (99.7% to 99.8%) in all powder mixtures did not change over time. The levels of other impurities (RRTs 0.17 and 0.49) were in the range of 0.02% to 0.04%, which is below the reporting threshold of 0.05%.

4.2 Manufacturing Process Development Stage results

4.2.1 Dry Granulation Process Development

The development batch data from Fidaxomicin orodispersible tablets did not show the impact of roller gap on tablet characteristics for friability, disintegration, and dissolution. But due to the necessity to consistently manufacture tablets at the target hardness requires the definition of the roller gap as a CPP. The granules generated from both types of roller compactors (Minipactor and Macropactor) exhibited no impact on tablet characteristics and dissolution. Therefore, the acceptable roller gap for final production was defined in the range of 2.0 to 4.5 mm based on the orodispersible tablet development data.

Investigated Process Parameters and Process Responses are as follows:

Roller Gap (0.8, 1.0, and 1.5 mm): Granule particle size (% fine granules at < 250 µm)

Roll Force (low, medium, and high): Granule bulk density

Screen Size (0.85, 1.0, and 1.2 mm): Granule flow, Ribbon thickness

Roller Compaction Force: To assure that CQAs are consistently met, the roller compaction force is included as a CPP. Therefore, the acceptable compaction force for final production was defined in the range of 4.0 to 8.0 kN/cm based on the orodispersible tablet development process.

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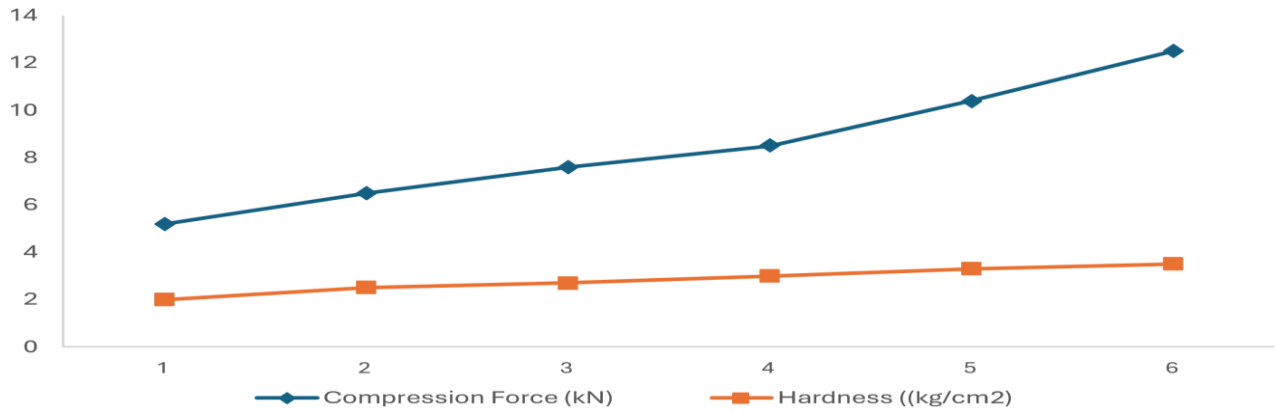

Fig. 1. Tablet Hardness vs Tablet Compression Force Profiles (1.5 mm Roller Gap)

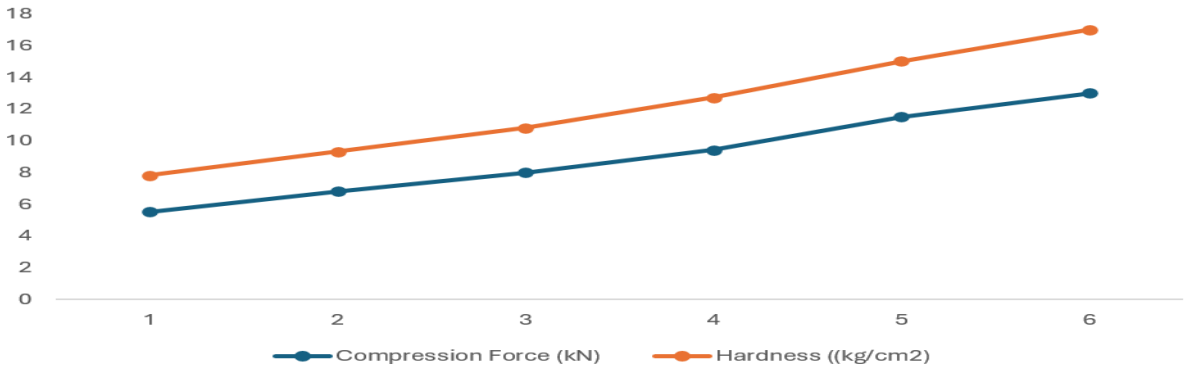

Fig. 2. Tablet Hardness vs Tablet Compression Force Profiles (3.5 mm Roller Gap)

4.2.2 Final Blending Process Development

The bulk content uniformity was demonstrated by consistent assay values tested at ten different locations in the blender with a low RSD ranging from 0.4% to 1.2 %. With the high drug load formulation, in-process controls were not required with effective mixing, i.e., the fixed proven number of revolutions. The final blend material was not defined as CMA.

4.2.3 Tablet Compression Process Development

Based on the tablet hardness data presented in Table 4 and graphically presented in Figure 3, two trends of tablet hardness vs compression force were observed: tablet hardness increased from 2.0 to 3.5 kg/cm^2 with an increase of compression force from 5.2 to 12.5 kN, and tablet hardness increased from 2.2 to 4.6 kg/cm^2 with an increase of compression force from 5.5 to 13 kN.

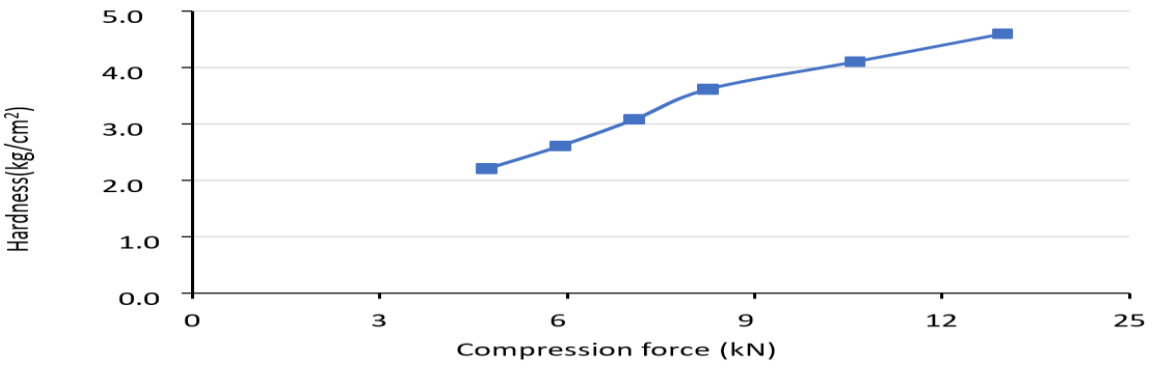

Fig. 3. Determination of Tablet Hardness – Tablet Hardness vs Compression

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Based on the data of development lots, and the compression profile data, a conservative range for tablet compression was set between 5 to 13 kN. Although the orodispersible tablets with a hardness range of 2.5 to 4.6 kg/cm^2 displayed acceptable characteristics including friability, disintegration and dissolution in the development studies, the PAR range was set between 5 to 13 kN to ensure that a margin for acceptable tablet characteristics is maintained to support potential raw material variation and packaging stress. Since tablet hardness has an impact on the dissolution profiles, tablet hardness, a proxy for compression force, was defined as a CPP. Note that the compression force is a result of multiple interactions between the press and blend parameters and is not directly set.

4.3 Dissolution study results

The studies conducted for the evaluation of dissolution of orodisperaudisible fidaxomicin tablets by using USP Apparatus 2. Vessel Size taken as 100 mL and Paddle Speed was kept at 100 rpm for 15 minutes. Temperature was 37°C ± 0.5°C. pH 1.2 (acidic medium) 0.1N HCl with 0.5% SLS (pH 1.2) was taken. The dissolution method validation included linearity and range, accuracy, precision, solution stability, filter recovery and robustness of the quantitation by HPLC (Model 1260 Infinity III LC, Agilent technologies). The robustness of the dissolution conditions was also evaluated. Release tablet acceptance criteria were set as not less than 80% (Q) in 5 minutes. In three trials, 12 tablets (n) taken and found that tablets were completely soluble at pH 1.2. Based on the results, Mean (Q) was 92.5% and Relative Standard deviation (RSD) was 1.03%. Hence, by adding the SLS, disintegration time has been reduced drastically, and desired dissolution time has been achieved.

4.4 Stability study results

The shelf life for the Fidaxomicin drug product is determined by primary stability data on the registration stability lots using a bracketing strategy of Stability Studies. Initially both open and tightly closed condition was evaluated. The primary purpose of stability testing under open conditions was to assess how the drug substance is affected after exposure to the environment, such as air and light, after the package was opened. Later, the long term closed container study was conducted, and supportive stability data have also been acquired for 3 lots of Fidaxomicin orodispersible tablets, 200 mg. Results of the optimized batch no. FDN002 are presented below:

Table 4 Stability Study Result (Long term-25°C/ 60% RH) for Fidaxomicin Tablet, 200 mg [Closed condition]

Tests	Specifications	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Description	**White to light yellow colour**	Complies	Complies	Complies	Complies	Complies	Complies
Identification	**IR spectrum**	Positive	Positive	Positive	Positive	Positive	Positive
pH	**Between 2.5 and 4.5**	3.2	3.0	3.0	2.9	2.8	2.9
Related substances (HPLC)	**MAX individual impurity NMT: 0.4%** **Total impurities NMT: 0.8%**	0.099% 0.18%	0.089% 0.18%	0.111% 0.22%	0.12% 0.24%	0.125% 0.29%	0.135% 0.37%
Assay of API (HPLC)	**90.0-110.0%**	99.1%	100.3%	100.3%	101.5%	99.7%	99.4%
Microbial Limits	**1. TAMC:Max 100 CFU/mL** **2. TYMC: Max 10 CFU/mL**	<10 CFU/mL	ND	<10 CFU/mL	<10 CFU/mL	<10 CFU/mL	<10 CFU/mL

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	3.*E.Coli*: Absence/mL	<10 CFU/mL Absence		<10 CFU/mL Absence	<10 CFU/mL Absence	<10 CFU/mL Absence	<10 CFU/mL Absence

Stability of Fidaxomicin after Dispersion in Dosing Vehicles

The Fidaxomicin orodispersible tablet, 200 mg is a single unit dosage form that does not require the addition of any preservatives in the formulation. The caregiver is expected to add the orodispersible tablet to a predetermined amount of distilled water or clear liquid and disperse it before administration. Fidaxomicin was found to be stable in all the vehicles evaluated after dispersion from Fidaxomicin orodispersible tablet, 200 mg. No major changes were observed for the impurity profile of Fidaxomicin for all the vehicles evaluated including distilled water, 0.1N HCl, 0.1M Sodium Phosphate Buffer, Sprite, and Whole Milk for up to 4 hours at both ambient temperature and at 40 ± 3°C.

4.5 Palatability study

There were no Adverse events or issues with study drug compliance that appeared to be related to the fidaxomicin palatability. Numerical gradings were assigned to each assessment, which were then summarized by group and for all subjects in Table 5. The mean palatability score for all subjects ranged from 2.6 to 3.2 on a scale of 1 to 5, with 5 representing the most palatable. Graphical representation of results based on statistical outcome has been provided in figure 4.

Data were analyzed using absolute and relative frequencies for qualitative variables or means (standard deviation [SD]), median, minima and maxima [min, max]) for quantitative variables. Descriptive analyses of outcome variables were stratified by formulation/preparation group and time of assessment.

Table 5 Palatability Evaluation Data Compilation

Formulation Code	**Average Points with calculated points**							**Calculated points**
	After 30 seconds				**After 5 minutes**			
	Initial taste		**Mouth feel**	**Flavor**	**After taste**		**Overall Acceptability**	
	Bitterness	**Sweetness**			**Bitterness**	**Sweetness**		
Group 1	14.1	15	10	15	14.1	14.4	15	89.1
Group 2 Reference	13.2	13.5	8.4	14.1	13.2	13.2	13.5	86.9
Group 3 In-house	12.9	12.9	9.2	12.9	12.9	12.9	13.2	97.6
Group 4	3	3	2.4	3	3	3	3	20.4

Table 6 Summary Statistics of Palatability Assessment

Treatment Group	Palatability Assessment					
	N	Mean	SD	Median	Min	Max
Group 1	10	2.6	1.07	2.5	1	5
Group 2 Reference	9	2.7	3.0	3.00	3	3
Group 3 In-house	10	3.1	1.81	3.0	1	5
Group 4	10	3.2	1.2	3.0	1	5

For group 1-4, Palatability assessment is completed by a caregiver.

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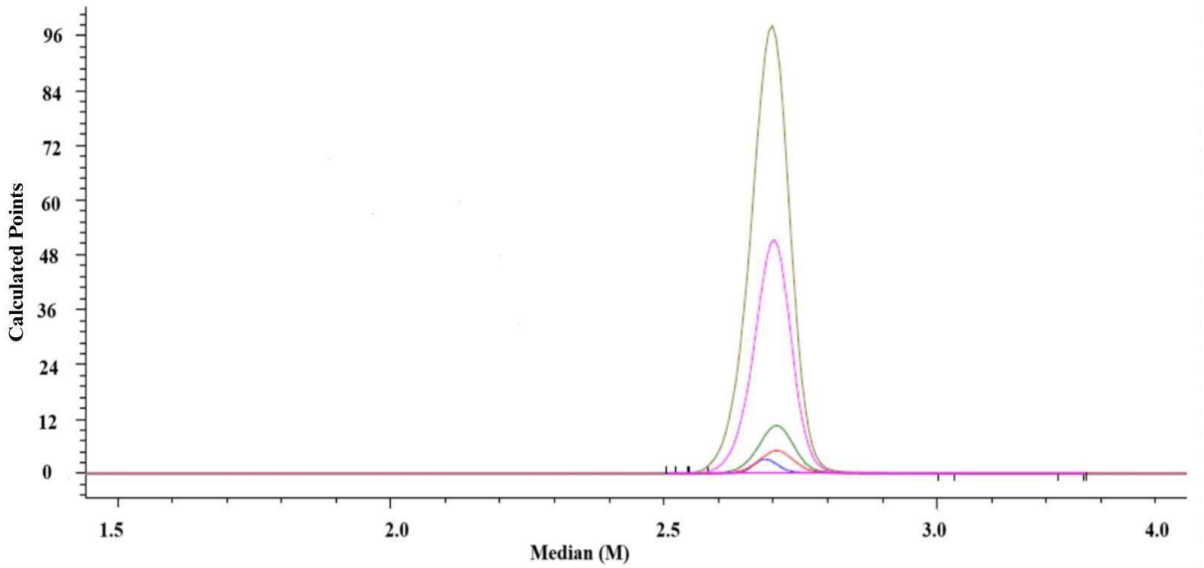

Fig. 4. Graphical representation of Palatability evaluation study based on Paired two sample t-test
Treatment group: Group 1[Red]= Neonates (6-9 months), Group 2[Pink]= Young children (2 years-3 years), Group 3[Gold]= Infants (28 days-12 months), Group 4[Green]= Toddlers (12 months-2 years), Green is for the baseline purposes

5. Discussion

Based on the solubility, permeability, and compatibility studies and the known characteristics of the drug substance and excipients, process unit operations were selected. Palatability analysis evaluates similarity using a paired t-test to determine if there is evidence that there is a difference between measurements taken with the two different formulation packages. In the paired t-test, each sample is tested with both reference and In-house packages, and the difference between the measurements has been found significant. In-house formulations taste masking ability is higher compared to the available marketed formulation. The overall safety profile of Fidaxomicin tablet, 200 mg is found to be acceptable, and available data support a favorable benefit-risk assessment for Fidaxomicin for patients aged six months to 3 years with Clostridium difficile infection. Based on the serious unmet need in this highly vulnerable pediatric patient population, limited treatment options, a novel mechanism of action of fidaxomicin that acts on the underlying pathophysiology of Clostridium difficile infection, and the demonstrated efficacy and safety profile of fidaxomicin, this approach will help in the betterment of healthcare domain.

6. Conclusion

So, by observing the impact of the QbD approach, it is analysed that the control strategy is based on a product quality risk assessment and established to ensure the unit operations for the Fidaxomicin tablet, 200 mg, manufactured meeting the defined quality. The initial product quality risk assessment led development activities to generate an enhanced level of formulation and process understanding for critical unit operations. This increased process understanding was used to define critical and noncritical process parameters for each unit operation. The critical quality attributes will be assessed throughout the product lifecycle using a suitable risk tool. Based on quality risk management, and knowledge obtained from development studies process controls were established based on direct and timely measurements of relevant material attributes and relevant process parameters. The proposed control strategy is based on the risks known at the time of submission. The updated risk assessment for the pre-blending process step demonstrates that the identified risk of blend uniformity has been reduced by increasing the number of revolutions. The control strategy of the pre-blending is to maintain the defined revolution numbers for production. The control strategy for roller compaction intends to maintain the process at a steady state to generate the granules with consistent

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characteristics of density and PSD. Under the studied range, the generated granules consistently produced tablets meeting the established acceptance criteria in the specification. The control strategy of dry granulation ensures that the operating parameters of the roller compactor equipment are set correctly for the roller gap, compaction force, and roller speed before operation. The screen size of 1.0 mm has been used throughout the development stage. Within the investigated parameter ranges for roller compaction, critical material attribute (CMA) control for granule properties is not needed. The updated risk assessment for the final blending process demonstrates that the identified risk of blend uniformity has been reduced by increasing the number of revolutions. The control strategy of the final blending is to maintain the defined revolution numbers. With the established revolution numbers and the defined blender, the final blend material is not defined as a CMA. The control strategy for compression is to maintain the in-process tablet attributes of weight, hardness, thickness, friability and disintegration within the required ranges. The target compression force required to produce tablets with the desired hardness, friability, and disintegration, is established at the beginning of each production run. At the end of each production run, friability and disintegration are checked again to bracket production. Before the start of compression, force reject limits are set based on the hardness CPP and weight IPC limits. Measured tablet properties provide the feedback for setting the measured force reject limits on the press. The compression force is continuously measured throughout compression for each tablet and compared to the desired compression force range set to meet the tablet hardness CPP. Any tablet that registers a compression force outside of the set-up range is automatically rejected by the tablet press. The control strategy for packaging maintains stable conditions for the storage and transportation of the coated tablets. Packaging for transport of the bulk coated tablets and the primary packaging in bottles for finished products provide adequate assurance of quality. Up to 24 months of primary stability data are available for Fidaxomicin orodispersible tablets with different strengths packaged in different packaging configurations stored under long-term storage conditions (25°C/60% RH and 30°C/75% RH). All acceptance criteria have been met, and no significant change or trend has been observed, which is consistent with the supportive stability studies for Fidaxomicin orodispersible tablets, 200 mg.

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