Available online on 15.03.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

# Formulation Development and Evaluation of New Albendazole Tablets with Integrated Quality by Design (QbD) Approach

Dnyaneshwar G. Sitre*, Ravindra K. Kamble

*Bhupal Nobles University, Maharana Pratap Station Road, Udaipur 313001, Rajasthan, India*

Article Info:

Article History:

Received 07 Jan 2021;
Review Completed 23 Feb 2021
Accepted 06 March 2021;
Available online 15 March 2021

Cite this article as:

Sitre DG, Kamble RK, Formulation Development and Evaluation of New Albendazole Tablets with Integrated Quality by Design (QbD) Approach, Journal of Drug Delivery and Therapeutics. 2021; 11(2):123-134
DOI: http://dx.doi.org/10.22270/jddt.v11i2.4782

*Address for Correspondence:

Dnyaneshwar G. Sitre, Bhupal Nobles University, Maharana Pratap Station Road, Udaipur 313001, Rajasthan, India

## Abstract

Hydatid disease occurs in most areas of the world and currently affects about one million people. Albendazole is an orally administered broad spectrum anthelmintic drug approved by US FDA in 1996. Literature review suggests Albendazole is low solubility compound and most of the studies were performed to improve the solubility with traditional approach of product development. The present study was aimed to apply Design of Experiments (DoE) in the development and optimization of drug release from new Albendazole tablets using three factor two level ($2^3$) full factorial designs with integrated Quality be Design (QbD) approach. New Albendazole tablets were formulated using micronized grade of the Albendazole active and excipients were selected inline with market reference product. Quality target product profile (QTPP) and Critical quality attributes (CQAs) were designed. Risk assessment was used to identify the Formulation variables impacting CQA dissolution. The amount of Formulation variables were optimized on the basis of drug release profiles at 15 minutes and 30 minutes of different formulation batches manufactured based on $2^3$ full factorial design. Tablets were prepared by wet granulation technique and evaluated for various physicochemical parameters and *in vitro* drug release. Formulation trials dissolution results at 15 minutes and 30 minutes were evaluated to derive the concentration of Formulation variables which will achieve the release of more than 80%. Analysis of variance (ANOVA) analysis, Pareto chart and Contour plot were used to predict the values of formulation variables and their effect on dissolution. Updated risk assessment of the Formulation Variables was performed and justification was provided for reduction of risk from medium to low level. Optimized formulation from DOE had comparable dissolution profile with market reference tablet. Stability studies of new Albendazole tablets 200 mg were conducted at ICH accelerated conditions and found to be stable. Thus studies revealed that full factorial experimental design could efficiently be applied for optimization of formulation variables affecting drug release. New Albendazole tablets 200 mg successfully formulated with application of the integrated quality by design (QbD) and design of experiment (DOE) approach and thereby achieved comparable release profile with market reference product.

**Keywords:** Albendazole, Experimental design, Full Factorial Design, Design of experiment & Dissolution

## INTRODUCTION

Oral route is one of the most useful route for the systemic effect due to its ease of intake, convenient, non-invasive and most importantly, in terms of patient compliance. Sterile conditions are not required for the manufacturing of Solid oral delivery systems there by reducing the cost of production. Tablet dosage forms that are intended to be swallowed whole followed by disintegration and immediate release of medicaments in the gastrointestinal tract[1].

Albendazole is an orally administered broad-spectrum anthelmintic. Albendazole is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility[2]. Although the detailed mechanisms of action of albendazole are unclear, experimental evidence from exposure of intestinal helminths of several different species shows that the parasites suffer from metabolic disruption at a number of different sites, most of which are involved in energy production in the parasite[3].

Quality by Design is the modern approach for quality of pharmaceuticals. QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management[4]. DoE is a structured, organized method for determining the relationships among factors affecting a process and its output. It has been suggested that DoE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time that it would take to run one-factor-at-a-time experiments[5].

Literature review suggests that Albendazole is low solubility compound and most of the studies were performed to improve the solubility of the Albendazole with traditional approach of product development. This scientific work

comes with application design of experiments (DoE) in the development and optimization of drug release from new Albendazole tablets using three factor two level ($2^3$) full factorial designs with integrated Quality be Design (QbD) approach.

## MATERIALS AND METHODS

### MATERIALS

API Albendazole USP grade manufactured by Enaltec Labs pvt. Ltd. Mumbai India was used for the formulation development. Selections of excipients was based on excipients commonly found in medications available on the market and the inline with market reference product. Ingredients including Lactose monohydrate grade Pharmatose 200M (DFE Pharma), Microcrystalline cellulose grade Avicel PH 101 (FMC), Maize starch grade Maize starch B (Roquette), Polyvinyl pyrrolidone grade Povidone K-30 (ISP), Sodium lauryl sulfate grade Kolliphor SLS fine (BASF), Saccharin sodium (Spectrum), Sodium starch glycolate grade Primojel (DFE Pharma), Magnesium stearate grade Hyqual (Avantor) and Hypromellose E3 (Dow) were used for manufacturing of the product. Analytical grade and HPLC grade reagents were used for analytical part of this study during the pre-formulation and formulation stages.

The equipments including Analytical balance (Sartorius BT2245), Rapid mixer granulator (Sainath boilers & pneumatics), Dryer (Retsch dryer), Octagonal blender (Karnawati eng. Ltd.), Compression machine (Cadmach) & Tablet coating machine (Neocoata) were used to manufacture and coat tablets. In-process instruments used for the tablet evaluation includes Moisture analyzer (Sartorius MA150), Tablet hardness tester (Dr. Schleuniger), Disintegration test apparatus (Electrolab), Friability test apparatus (Electrolab), Density measurement apparatus (Electrolab). Analysis equipments including a Ultraviolet–visible spectrophotometer, Dissolution test apparatus (Electrolab) & High-performance liquid chromatography system (Agilent) with Column: Inertsil- ODS-3V, 250 x 4.6mm, 5µ & Rotatory shaker were used. The factorial design in the Minitab software was used to generate and evaluate the trial batches. A p-value less than 0.05 (typically ≤ 0.05) indicate result as statistically significant.

### METHODS

#### Preformulation studies

Preformulation studies were designed to identify physicochemical properties of Albendazole and excipients that may influence formulation design and method of manufacture. Studies performed include Bulk density (BD), Tapped density (TD), Hausner's ratio (HR) & Compressibility index (CI) of Albendazole. In addition Loss on drying, Melting point, Solubility study & Drug-Excipients interaction studies were performed. Analytical UV and HPLC methods were developed for the analysis of dissolution and assay[6,7].

#### Formulation development with integrated QbD approach

Following steps are involved in the Formulation development of new Albendazole tablets with integrated QbD approach.

- Design of Quality target product profile (QTPP)[8]
- Identification of Critical quality attributes (CQA)[9]
- Initial Risk assessment to identify Formulation variables[10]
- Design of experiment (DOE) method selection[11]
- Execution and evaluation of the Formulation trials based on the DOE output
- Analysis of the DOE dissolution results[12]
- Updated Risk assessment of Formulation variables

#### Preparation of Formulation batches of New Albendazole tablets 200 mg

Tablets were prepared by wet granulation technique[13,14]. Each batch of tablets (T1 – T9) has varied amount of Povidone K 30, Sodium Lauryl sulphate & Sodium starch glycolate. All ingredients were weighed accurately in required quantity. Albendazole, Lactose monohydrate, Microcrystalline cellulose and Maize starch were sifted through #40 mesh and blended for 10 minutes in rapid mixer granulator at impeller speed of 200 rpm and chopper off for 10 minutes. Granulation fluid was prepared by dissolving Povidone K30 in Purified water. Sodium lauryl sulfate was added under stirring to the binder solution. Binder Addition was performed at 200 rpm impeller speed and chopper off for 2 minutes and kneading for 1 minute at 200 rpm impeller speed and chopper speed of 200 rpm. Wet granules were dried at 60°C in dryer till LOD reaches below 2%. Dried granules were sifted through #24 mesh. Sodium starch glycolate, sodium saccharin and Colloidal silicon dioxide were sifted through #40 mesh and mixed into the octagonal blender for 10 minutes. Magnesium stearate was sifted through ASTM #60 mesh & mixed with blend for 5 minutes. Lubricated blend was compressed into tablets by using 11.50 mm Round standard concave tooling using compression machine. HPMC E3 (Methocel E3 Premium LV) was dispersed in purified water to get the 10% dispersion. Core tablets were loaded into the coating pan and warm it for few minutes. Start spraying of solution and continue till the weight gain achieves to the 2%. Formulation of tablets batches of new Albendazole tablets are represented in table 1.

**Table 1: Formulation of batches of new Albendazole tablets**

| Ingredients | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 |
|---|---|---|---|---|---|---|---|---|---|
| **Dry Mix** | | | | | | | | | |
| Albendazole | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 |
| Lactose monohydrate | 195.9 | 195.9 | 195.9 | 195.9 | 195.9 | 195.9 | 195.9 | 195.9 | 195.9 |
| Microcrystalline cellulose | 91.5 | 91.5 | 91.5 | 91.5 | 91.5 | 91.5 | 91.5 | 91.5 | 91.5 |
| Maize starch | 120.0 | 120.0 | 120.0 | 120.0 | 120.0 | 120.0 | 120.0 | 120.0 | 120.0 |
| **Binder** | | | | | | | | | |
| Povidone K30 | 20.0 | 20.0 | 10.0 | 10.0 | 20.0 | 10.0 | 15.0 | 10.0 | 20.0 |
| Sodium lauryl sulfate | 1.0 | 2.0 | 2.0 | 2.0 | 2.0 | 1.0 | 1.5 | 1.0 | 1.0 |
| Purified water | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| **Pre-lubricants** | | | | | | | | | |
| Sodium saccharin | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Sodium starch glycolate | 4.6 | 4.6 | 4.6 | 14.6 | 14.6 | 14.6 | 9.6 | 4.6 | 14.6 |
| Colloidal silicon dioxide | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 |
| **Lubricant** | | | | | | | | | |
| Magnesium stearate | 4.8 | 4.8 | 4.8 | 4.8 | 4.8 | 4.8 | 4.8 | 4.8 | 4.8 |
| **Total weight** | **640.0** | **640.0** | **640.0** | **640.0** | **640.0** | **640.0** | **640.0** | **640.0** | **640.0** |
| **Coating** | | | | | | | | | |
| Hypromellose 2910 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 |
| Purified water | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| **Total weight** | **652.8** | **652.8** | **652.8** | **652.8** | **652.8** | **652.8** | **652.8** | **652.8** | **652.8** |

**Evaluation of the Lubricated blend**[15,16,17]

Lubricated blend was evaluated for the following parameters

**Bulk Density**

Bulk density is used to determine the amount of drug that occupies the volume in g/mL. The bulk density of the ingredients was evaluated using a graduated cylinder. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed quantity of powder into a graduated measuring cylinder and the volume was noted. It is expressed in g/mL and is calculated by using following formula

$$\text{Bulk density} = \frac{\text{Mass of powder blend}}{\text{Volume of powder blend}}$$

**Tapped density**

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder 10, 500, 1250 taps in tap density apparatus. The blend was subjected for 500 taps; % Volume variation was calculated and subjected for additional 1250 taps, % variation is calculated.

$$\text{Tapped Density} = \frac{\text{Mass of powder blend}}{\text{tapped volume of powder blend}}$$

**Compressibility index (Carr's index)**

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. A material having values of less than 20% is defined as the free flowing material.

$$\text{Carr's index} = \frac{\text{Tapped Density- Bulk Density}}{\text{Tapped Density}} \times 100$$

**Hausner's ratio**

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

**Loss on drying**

Loss on drying was carried out by using halogen moisture analyser at 105˚C for 5 minutes with 1.0 – 2.0 g powder samples[18].

**Evaluation of Core tablet Compression parameter[19]**

Tablets are evaluated as per Pharmacopoeial specification

**Weight of tablet**

Ten tablets were randomly selected from each batch and individually weighed. The average weight of ten tablets was calculated.

**Tablet Dimensions**

Thickness of the tablets was measured using a Vernier calliper. It was determined by checking ten tablets from each formulation batch. It is expressed in mm.

**Hardness:**

Hardness indicates the ability of a tablet to withstand mechanical shock while handling. For each formulation, ten

hardness of tablet was determined by using hardness tester. It is expressed in N.

**Friability**

Sample of whole tablets corresponding to about 6.5 g was withdrawn. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablet in the Roche friabilator. The friability was operated at 25 rpm at 100 revoluation then remove any loose dust from tablets and weigh them accurately. A maximum loss of weight not greater than 1.0 % is acceptable for tablet. The percent friability was calculated by using following equation.

$$\% F = 1 - \frac{W}{W_0} \times 100$$

Where, % F = friability in percentage
W = weight of table after revolution
W0 = Initial weight of tablet

**Disintegration Time**

In vitro disintegration time of tablets from each formulation was determined by using disintegration apparatus. In vitro disintegration test was carried out at 37± 2˚C in 900 ml by using disintegration media water. Six tablets of each formulation were taken and placed in tubes of disintegration apparatus. The time taken for complete disintegration was noted.

**In vitro drug release study**[20]

In vitro dissolution study was carried out for all formulations of new Albendazole tablets and market reference product in 900 mL of 0.1N HCl, Apparatus II at 50 rpm and analyzed at 308 nm by UV spectrophotometer. Dissolution of the DOE batches was compared with market reference product using F2 (Similarity factor) criteria. Batch with F2 more than 50 is considered as comparable with market reference product.

**Stability Study**

The final formulation from DOE studies was subjected to accelerated stability study (40ºC/75% RH) for the period of three months as per ICH guidelines. Physical stability was analyzed by recording the change in appearance and chemical stability was analyzed by the change in the assay, impurities, water by KF and in vitro drug dissolution at the end of three months[21].

## RESULTS

**Preformulation studies**

Albendazole was found to have very poor compressibility and flow properties ( BD: 0.196 g/mL, TD: 0.300 g/mL, Carr's index of 34.66% and Hausner's ratio of 1.53) hence wet granulation method was opted to achieve better compression and good flow property for the preparation of the new Albendazole tablets 200 mg. Albendazole is low solubility drug. The drug has pH dependent solubility nature. It has good solubility in strong acidic condition with 0.385 mg / ml. Melting point of Albendazole was found to be in range as given in literature (205-210˚C).

**Design of Quality target product profile (QTPP) for new Albendazole Tablets, 200 mg** Based on the clinical and pharmacokinetic characteristics as well as the in vitro dissolution and physicochemical characteristics of the market reference product, a Quality target product profile (QTPP) was defined for new Albendazole Tablets, 200 mg and represented in below table 2.

**Table 2: Quality target product profile (QTPP) for new Albendazole tablets 200 mg**

| QTPP Elements | Target | Justification |
|---|---|---|
| Dosage form | Tablet | Pharmaceutical equivalence requirement: same dosage form. |
| Dosage design | Immediate release tablet without a score | Immediate release design needed to meet label claims. |
| Route of administration | Oral | Pharmaceutical equivalence requirement: same route of administration |
| Dosage strength | 200 mg | Pharmaceutical equivalence requirement: same strength |
| Pharmacokinetics | Bioequivalent to Reference product | Bioequivalence requirement Needed to ensure rapid onset and efficacy |
| Stability | At least 24-month shelf-life at room temperature | Equivalent to or better than reference product shelf-life |
| Drug product quality attributes | Physical Attributes | Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality). |
| | Identification | |
| | Assay | |
| | Content Uniformity | |
| | Dissolution | |
| | Degradation Products | |
| | Residual Solvents | |
| | Water Content | |
| | Microbial Limits | |
| Container closure system | Container closure system qualified as suitable for this drug product | Needed to achieve the target shelf-life and to ensure tablet integrity during shipping |
| Administration / Concurrence with labeling | Similar food effect as reference product | The product can be taken without regard to food. |

**Identification of Critical Quality Attributes (CQAs) of New Albendazole Tablets, 200 mg**

Critical Quality Attributes (CQAs) of New Albendazole Tablets, 200 mg are represented in the following table 3.

**Table 3: Critical quality attributes (CQA) for new Albendazole tablets 200 mg**

| Quality Attributes | Target | Is this CQA? | Justification |
|---|---|---|---|
| Appearance | Color and shape acceptable to the patient. | No | Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability. |
| Size | Similar to reference product | No | For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the reference product. |
| Score configuration | Unscored | No | The reference product is an unscored tablet; therefore, the new tablet will be unscored. |
| Friability | NMT 1.0% w/w | No | 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 | Positive for Albendazole | Yes* | Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development. |
| Assay | 100% 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 (CU) | Conforms to USP <905> Uniformity of Dosage Units | Yes | Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development. |
| Dissolution | Not less than 80% (Q) | 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. |
| Degradation Products | As per ICH guidance | Yes | Formulation and process variables can impact degradation products. Therefore, degradation products will be assessed during product and process development. |
| Water Content | NMT 4.0% w/w | No | Albendazole is not sensitive to hydrolysis and moisture will not impact stability. |

**The physicochemical characterization of the Market reference product tablet**

The physicochemical characterization of the Market reference product tablet was performed and results are summarized in Table 4.

**Table 4: Market reference product evaluation**

| | |
|---|---|
| Brand Name | Albenza® Albendazole tablets USP 200 mg |
| Lot No. | F4003 |
| Manufacturer | GlaxoSmithKine |
| Appearance | White to off-white, circular, biconvex, bevel-edged, film coated TILTAB tablet debossed "ap" and "550" |
| Average Weight of 10 tablets (mg) | 671.40 |
| Diameter (mm) | 11.59, 11.60, 11.58, 11.60, 11.62 |
| Thickness (mm) | 6.79, 6.89, 6.88, 6.87, 6.83 |
| Disintegration test | 6 minutes 1 second |
| Hardness (N) | 196 |

**Initial Risk Assessment of the Formulation Variables**

Initial Risk Assessment of the Formulation Variables was performed to determine the critical Formulation Variables which may impact the CQA dissolution of the new Albendazole Tablets. The initial risk assessment of the formulation variables is compiled in Table 5.

**Table 5: Initial risk assessment of the new Albendazole Tablets**

| Drug Product CQA's | Albendazole PSD | Microcrystalline cellulose | Lactose monohydrate | Maize starch | Povidone K30 | Sodium Saccharin | Sodium lauryl sulfate | Sodium starch glycolate | Magnesium Stearate | Methocel E3 LV |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dissolution** | Low | Low | Low | Low | Medium | Low | Medium | Medium | Low | Low |

Justification for initial risk assessment of formulation variables of the new Albendazole Tablets is represented in below table 6.

**Table 6: Justification for initial risk assessment of the new Albendazole Tablets**

| Formulation Variables | Drug Products CQAs | Justification |
|---|---|---|
| Drug Substance PSD | Dissolution | The drug substance micronized grade material is used for formulation development thus particle size distribution has low impact on dissolution. The risk is low. |
| Microcrystalline cellulose (Avicel PH 101) | | Microcrystalline cellulose can impact dissolution via tablet hardness. However, hardness can be controlled during compression. The risk is low. |
| Lactose monohydrate (Pharmatose 200M) | | Lactose monohydrate is a water soluble diluent and will not impact the dissolution of the drug product. The risk is low. |
| Sodium saccharin dihydrate | | Sodium saccharin doesn't have any impact on dissolution of the drug product. The risk is low. |
| Maize starch (Maize starch B) | | The concentration of maize starch used will not impact dissolution of the drug product. The risk is low. |
| Povidone K30 | | Povidone K-30 is used as binder and levels of binder may impact the disintegration and in turn, the dissolution of drug product. Thus the risk is considered as medium. |
| Sodium lauryl sulfate (Kolliphor SLS Fine) | | As it is a BCS class II drug substance, the surfactant concentration will have impact on dissolution profile of the drug product. Hence the risk is considered as medium. |
| Sodium Starch glycolate Type A (Primojel) | | As it is a class II drug substance, the disintegrant concentration will have significant impact on dissolution of the drug product. The risk is considered as medium. |
| Magnesium Stearate (Hyqual, vegetable source) | | Magnesium stearate is used at very low concentration in formulation and thus it will not impact the dissolution of the drug product. The risk is low. |
| Hypromellose 2910 (Methocel E3 Premium LV) | | Hypromellose 2910 is used as coating polymer in film coating system; the concentration used for coating does not affect dissolution of the drug product. The risk is low. |

Initial formulation variable risk assessment indentified PVP, SLS and SSG level as medium risk for the CQA dissolution of the new Albendazole tablets 200 mg.

**DOE Design:**

Three factor two level ($2^3$) full factorial design was employed for development of new Albendazole tablets. A translation of coded values of formulation variables and experimental design is executed is represented in table 7.

**Table 7: Execution of experimental design of the new Albendazole Tablets**

| **Factors: Formulation Variables** | **Levels (mg/tablet)** | | |
|---|---|---|---|
| | **-1** | **0** | **+1** |
| Povidone K 30 | 10 | 15 | 20 |
| Sodium Lauryl sulfate | 1 | 1.5 | 2 |
| Sodium starch glycolate | 4.6 | 9.6 | 14.6 |
| **Response (Goal)** | **Acceptable Ranges** | | |
| Dissolution at 15 min (%) (Maximize) | ≥ 70% | | |
| Dissolution at 30 min (%) (Maximize) | ≥ 80% | | |

Formulation DOE batches were manufactured and evaluated for the following parameters.

**Evaluation of the Formulation DOE batches of the new Albendazole Tablets**

Lubricated blend was evaluated for the BD, TD, CI and H.R. Compressed core tablets were tested for weight variation, thickness, hardness, friability and Disintegration Time. Coated tablets were evaluated for the weight variation and Disintegration Time. Parameter results are represented in below table 8.

**Table 8: Core tablet physical parameters of the new Albendazole Tablets**

| **Batch** | **T1** | **T2** | **T3** | **T4** | **T5** | **T6** | **T7** | **T8** | **T9** |
|---|---|---|---|---|---|---|---|---|---|
| B.D. (g/ml) | 0.54 | 0.51 | 0.57 | 0.60 | 0.57 | 0.46 | 0.59 | 0.52 | 0.53 |
| T.D. (g/ml) | 0.67 | 0.70 | 0.72 | 0.74 | 0.68 | 0.67 | 0.80 | 0.76 | 0.79 |
| C.I. (%) | 19.50 | 27.02 | 21.70 | 18.49 | 15.38 | 31.03 | 26.35 | 31.43 | 32.91 |
| H.R. | 1.24 | 1.37 | 1.27 | 1.22 | 1.18 | 1.45 | 1.35 | 1.45 | 1.49 |
| **Core tablets** | | | | | | | | | |
| Weight (mg) | 640.1 - 646.0 | 638.9 - 643.4 | 642.0 - 647.0 | 637.0 - 643.0 | 638.0 - 644.0 | 637.0 - 642.0 | 637.0 - 646.0 | 636.7 - 646.7 | 640.0 - 645.0 |
| Thickness (mm) | 5.90 - 5.92 | 5.79 - 5.94 | 5.98 - 6.00 | 5.83 - 5.86 | 5.90 - 5.92 | 6.93 - 6.01 | 5.98 - 6.05 | 5.89 - 5.94 | 6.00 - 6.04 |
| Hardness (N) | 153 - 166 | 143 - 164 | 141 - 160 | 143- 155 | 146 - 164 | 143 - 159 | 147 - 160 | 143 - 168 | 144 - 145 |
| Friability (%w/w) | 0.25 | 0.22 | 0.32 | 0.21 | 0.10 | 0.15 | 0.37 | 0.27 | 0.12 |
| Disintegration Time | 6:25 - 7:00 | 7:05 - 7:59 | 4:08 - 4:49 | 7:10 to8:10 | 7:20 - 8:30 | 5:37 - 6:35 | 4:25 - 4:40 | 4:20 - 5:20 | 6:30 - 7:05 |
| **Coated tablets** | | | | | | | | | |
| Weight (mg) | 646.0 - 657.0 | 646.0 - 656.0 | 646.0 - 659.0 | 643.0 - 658.0 | 646.0 - 659.0 | 646.0 - 659.0 | 646.0 - 658.0 | 648.0 - 654.7 | 642.0 - 650.0 |
| Disintegration Time (min) | 8:18 - 9:13 | 9:12 - 9:37 | 5:59 - 8:46 | 6:50 - 8:35 | 5:45 - 7:46 | 8:09 - 8:58 | 5:26 - 6:39 | 5:25 - 6:51 | 9:15 - 9:37 |

Flow of the batches was acceptable and powder was flowing through hopper properly. Tablets were compressed with weight range of 640±10 mg, Thickness of 6.00±0.4 mm, Hardness of 150±20N, Friability of 0.10 to 0.37 and Disintegration time of less than 8 minutes 30 seconds. Coated tablets showed Weight of 653±10 mg and DT was 9 min 37 seconds.

**Dissolution study**

Final coated tablets were studies for the dissolution and results are represented in below table 9.

**Tablet 9: In vitro drug release studies of new Albendazole tablets 200 mg**

| Dissolution | RLD | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Time (minutes)** | **% Drug release** | | | | | | | | | |
| 5 | 29.0 | 16.0 | 25.0 | 23.0 | 48.0 | 41.0 | 50.0 | 21.0 | 20.0 | 26.0 |
| 10 | 62.0 | 24.0 | 30.0 | 51.0 | 68.0 | 45.0 | 64.0 | 58.0 | 39.0 | 31.0 |
| 15 | 77.0 | 35.0 | 38.0 | 60.0 | 79.0 | 48.0 | 78.0 | 74.0 | 55.0 | 37.0 |
| 20 | 84.0 | 65.0 | 68.0 | 82.0 | 90.0 | 75.0 | 88.0 | 83.0 | 78.0 | 79.0 |
| 30 | 89.0 | 80.0 | 82.0 | 90.0 | 100.0 | 85.0 | 100.0 | 95.0 | 94.0 | 85.0 |
| 45 | 95.0 | 96.0 | 95.0 | 97.0 | 104.0 | 101.0 | 100.0 | 98.0 | 100.0 | 101.0 |
| **F2** | | **30** | **33** | **53** | **49** | **41** | **50** | **66** | **43** | **34** |

DOE trials dissolution profiles were represented in below figure 1.

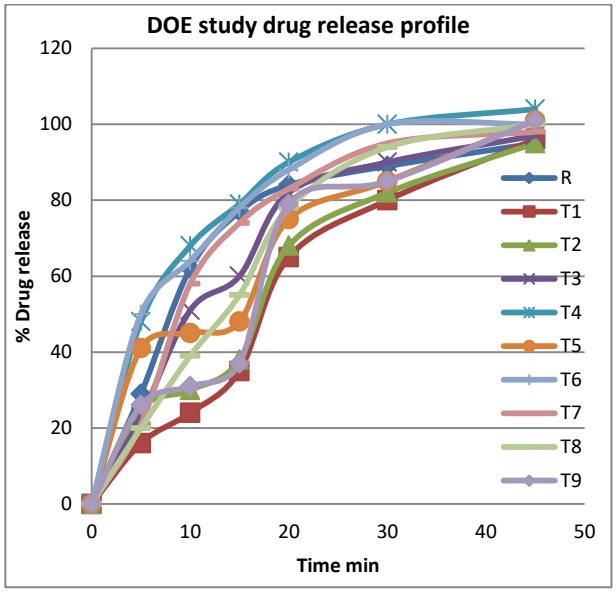


**Figure 1: Comparative % drug release profile of formulations**

Dissolution of Formula composition of T7 new albendazole tablets was comparable with innovator with F2 more than 60. Hence this batch was studies for stability evaluation. Dissolution data of the batches was analyzed with DOE to derive the optimized composition with DOE and to study the impact of formulation variables on the CQA drug dissolution.

**Statistical Analysis of DOE trials**

15 minutes and 30 minutes dissolution data obtained from the DOE studies were evaluated using DOE analysis to identify the perfect concentration ranges of formulation variables to achieve target dissolution and to study the impact of formulation variables on the CQA drug dissolution.

**Significant factors for tablet dissolution (at 15 minutes)**

15 minutes dissolution was studied and statistics of the model used was represented in below table 10.

**Table 10: Model data for 15 minutes dissolution**

| Source | DF | Adj SS | Adj MS | F-Value | P-Value |
|---|---|---|---|---|---|
| Model | 7 | 2526.00 | 360.86 | 20.05 | 0.170 |
| Linear | 3 | 2039.00 | 679.67 | 37.76 | 0.119 |
| PVP | 1 | 1624.50 | 1624.50 | 90.25 | 0.067 |
| SLS | 1 | 50.00 | 50.00 | 2.78 | 0.344 |
| SSG | 1 | 364.50 | 364.50 | 20.25 | 0.139 |
| 2-Way Interactions | 3 | 122.50 | 40.83 | 2.27 | 0.446 |
| PVP*SLS | 1 | 8.00 | 8.00 | 0.44 | 0.626 |
| PVP*SSG | 1 | 112.50 | 112.50 | 6.25 | 0.242 |
| SLS*SSG | 1 | 2.00 | 2.00 | 0.11 | 0.795 |
| Curvature | 1 | 364.50 | 364.50 | 20.25 | 0.139 |
| Error | 1 | 18.00 | 18.00 | | |
| Total | 8 | 2544.00 | | | |

P-Value observed for the model was 0.170 and for the formulation variables values were PVP: 0.067, SLS: 0.344 and SSG: 0.139.

**Pareto chart of dissolution at 15 min**

Pareto chart of the formulation variable effects on dissolution at 15 min is represented in below Figure 2.

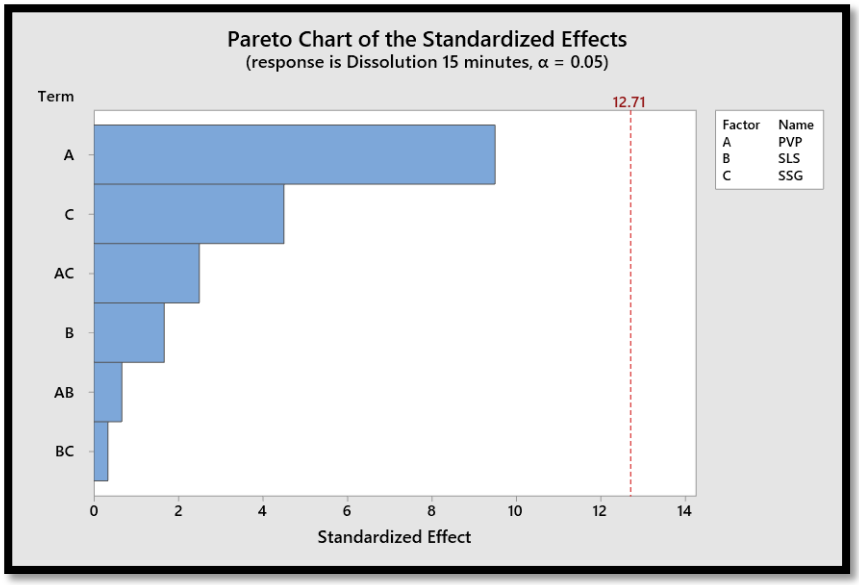


**Figure 2: Pareto chart of the formulation variable effects on dissolution at 15 min**

Pareto chart Results showed that significant factors impacting the dissolution of the new Albendazole Tablets, USP 200 mg tablet formulation at 15 min were identified as concentration of the PVP & SSG.

**Contour Plot of Dissolution 15 minutes**

Contour Plot of the formulation variable effects on dissolution at 15 min is represented in below Figure 3.

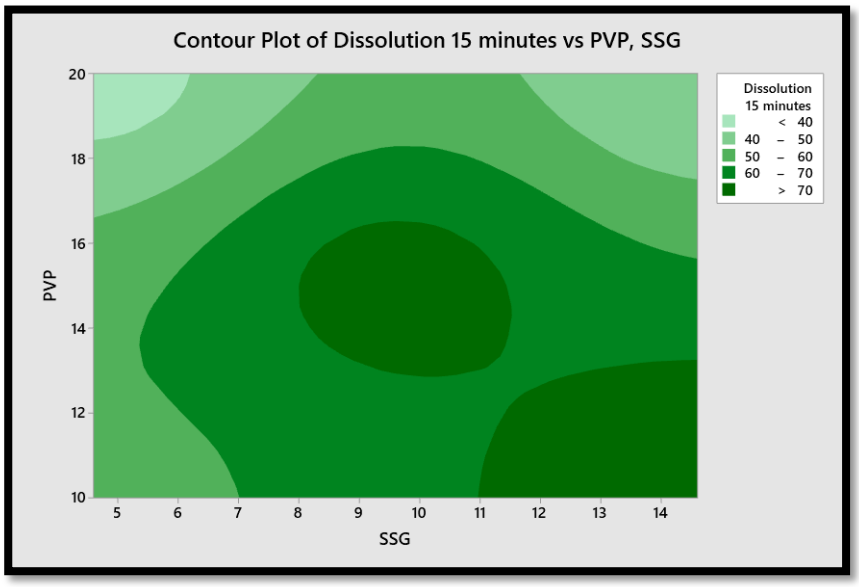


**Figure 3: Contour Plot of Dissolution 15 minutes vs PVP vs SSG**

Contour Plot Results showed that concentration of the PVP 10-13 mg per tablet & SSG 11-14 mg / tab will give dissolution more than 70% of the new Albendazole Tablets, USP 200 mg.

**Significant factors for tablet dissolution (at 30 minutes)**

30 minutes dissolution was studied and statistics of the model used was represented in below table 11.

**Table 11: Model data for 30 minutes dissolution**

| Source | DF | Adj SS | Adj MS | F-Value | P-Value |
|---|---|---|---|---|---|
| Model | 7 | 450.389 | 64.341 | 14.30 | 0.201 |
| Linear | 3 | 410.500 | 136.833 | 30.41 | 0.132 |
| PVP | 1 | 338.000 | 338.000 | 75.11 | 0.073 |
| SLS | 1 | 0.500 | 0.500 | 0.11 | 0.795 |
| SSG | 1 | 72.000 | 72.000 | 16.00 | 0.156 |
| 2-Way Interactions | 3 | 13.000 | 4.333 | 0.96 | 0.617 |
| PVP*SLS | 1 | 4.500 | 4.500 | 1.00 | 0.500 |
| PVP*SSG | 1 | 8.000 | 8.000 | 1.78 | 0.410 |
| SLS*SSG | 1 | 0.500 | 0.500 | 0.11 | 0.795 |
| Curvature | 1 | 26.889 | 26.889 | 5.98 | 0.247 |
| Error | 1 | 4.500 | 4.500 | | |
| Total | 8 | 454.889 | | | |

P-value for the model was 0.201 and values obtained for the formulation variable were PVP:0.073 SLS:0.795 and SSG:0.156.

**Pareto chart of dissolution at 30 min**

Pareto chart of the formulation variable effects on dissolution at 30 min is represented in below Figure 04.

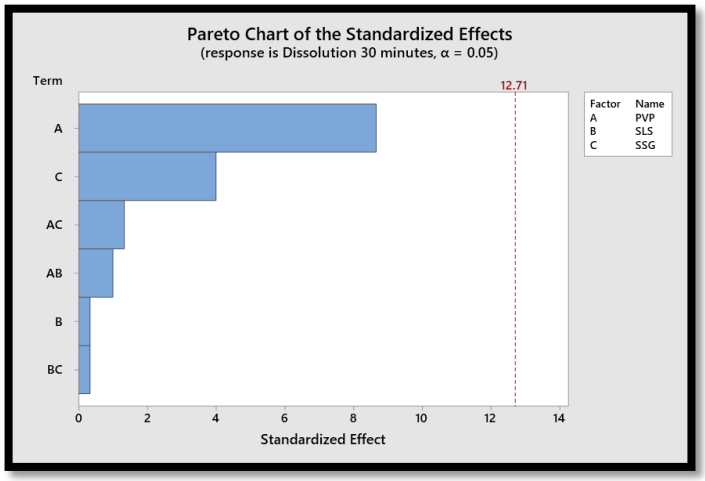


**Figure 4: Pareto chart of the formulation variable effects on dissolution at 30 min**

Pareto chart Results showed that significant factors impacting the dissolution of the new Albendazole Tablets, USP 200 mg tablet formulation at 30 min were identified as concentration of the PVP & SSG.

**Contour Plot of Dissolution 30 minutes**

Contour Plot of the formulation variable effects on dissolution at 30 min is represented in below Figure 5.

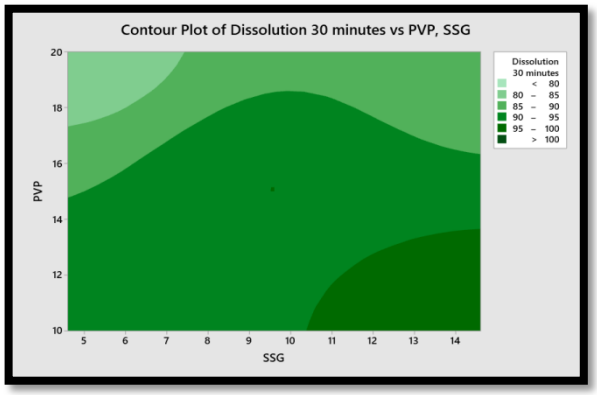


**Figure 5: Contour Plot of Dissolution 30 minutes vs PVP vs SSG**

Contour Plot Results showed that concentration of the PVP below 14 mg per tablet & SSG 5 mg / tab will give dissolution more than 80% of the new Albendazole Tablets, USP 200 mg.

**Updated Risk Assessment of the Formulation Variables**

The updated risk assessment of the formulation variables was performed based on the DOE experiment outcome and compiled in Table 12.

**Table 12: Updated Risk assessment of formulation variables**

| Drug Product CQA's | Drug PSD | Avicel PH 101 | Pharmatose 200 M | Maize starch | Kollidon K-30 | Sodium Saccharin | Kolliphor SLS Fine | Primojel | Magnesium Stearate | Methocel E3 LV |
|---|---|---|---|---|---|---|---|---|---|---|
| Dissolution | Low | Low | Low | Low | *Low | Low | *Low | *Low | Low | Low |

*Updated

Justification for updated Risk Assessment of formulation variables is represented in below table 13.

**Table 13: Justification for updated Risk Assessment of formulation variables**

| Formulation Variables | Drug Products CQAs | Justification |
|---|---|---|
| PVP | Dissolution | Formulation variables PVP, SLS and SSG concentrations were identified, optimized and analyzed with DOE studies to achieve comparable release profile with market reference product and final composition was derived.<br>Thus risk of these factors is reduced from medium to low. |
| SLS | | |
| SSG | | |

**ICH Stability studies results of Albendazole Tablets, USP 200 mg**

Stability data of new Albendazole Tablets, USP 200 mg (T7) results are represented in below table 14.

**Table 14: Stability results of new Albendazole Tablets, USP 200 mg**

| **Packaging configuration** | 150 CC HDPE bottle with PP closure | | | | |
|---|---|---|---|---|---|
| **Stability Conditions** | | | **40ºC/ 75% RH** | | |
| **Tests** | **Specification** | **Initial** | **1 month** | **2 months** | **3 months** |
| **Assay (% w/w)** | NLT 90.0% and NMT 105.0% | 91.9 | 100.8 | 99.6 | 99.9 |
| **Related Substances (% w/w)** | | | | | |
| Impurity B | NMT 0.2% | 0.05 | 0.06 | 0.04 | 0.04 |
| Impurity C | NMT 0.2% | ND | ND | ND | ND |
| Any other individual impurity | NMT 0.2% | ND | 0.02 | 0.03 | 0.04 |
| Total Impurities | NMT 1.0% | 0.05 | 0.08 | 0.09 | 0.11 |
| **Water by KF (%w/w)** | NMT 7.0% | 3.7 | 3.4 | 3.7 | 3.9 |
| **Dissolution:** USP II, 900 mL, 0.1 N HCl and 50 rpm | | | | | |
| **Time** | NLT 80% (Q) in 30 minutes | **% Drug Release** | | | |
| 30 minutes | | 95 | 97 | 95 | 95 |

ND: Not detected

Results showed that the initial analytical results of new Albendazole tablets 200 mg were found to be satisfactory and meeting designed specification. During accelerated stability studies assay, related substances, dissolution and water content meets product specification with no significant changes.

## SUMMARY

Albendazole was found to have very poor compressibility and flow properties ( BD: 0.196 g/mL, TD: 0.300 g/mL, Carr's index of 34.66%, Hausner's ratio of 1.53) hence wet granulation method was opted for better compression and

good flow property for the preparation of the new Albendazole tablets 200 mg. Albendazole is low solubility drug. The drug has pH dependent solubility nature. It has good solubility in strong acidic condition with 0.385 mg / ml in acidic media. Melting point of Albendazole was found to be in range as given in literature (205-210˚C).

Quality target product profile (QTPP) and Critical quality attributes (CQAs) were designed for the new Albendazole tablets 200 mg which showed that dissolution is critical CQA. Market Reference product characterization was performed. Risk assessment showed that formulation variable PVP, SLS and SSG has medium impact on CQA dissolution. Experiments were designed with DOE software for this formulation variable with $2^3$ full factorial design and batches (T1-T9) were executed in the lab. Dissolution data was analyzed with DOE software to achieve drug release comparable with market reference product and studies impact of these formulation variables on CQA dissolution. Flow of the batches was acceptable and power was flowing through hopper properly. Tablets were compressed with weight range of 640±10 mg, Thickness of 6.00±0.4 mm, Hardness of 150±20N, Friability of 0.10 to 0.37 and Disintegration time of less than 8 minutes 30 seconds. Coated tablets showed Weight of 653±10 mg and DT was 9 min 37 seconds.Dissolution of Formula composition of T7 new albendazole tablets was comparable with innovator with F2 more than 60. Pareto chart Results showed that significant factors impacting the dissolution of the new Albendazole Tablets, USP 200 mg tablet formulation at 30 min were identified as concentration of the PVP & SSG.Contour Plot Results showed that concentration of the PVP below 14 mg per tablet & SSG 5 mg / tab will give dissolution more than 80% of the new Albendazole Tablets, USP 200 mg. Updated risk assessment was performed to justify the risk level of low from DOE studies for these variables. Results showed that the initial analytical results of new Albendazole tablets 200 mg were found to be satisfactory and meeting designed specification. During accelerated stability studies assay, related substances, dissolution and water content meets product specification with no significant changes.

## CONCLUSION

Tablets were manufactured by wet granulation technique with application of the QbD and DoE approach. The tablets exhibited drug release comparable to the market reference product. The amount of Povidone K 30, Sodium Lauryl sulfate & Sodium starch glycolate was optimized by $2^3$ full factorial design based on the drug release. The accelerated stability studies suggested no significant change in the drug content, physical properties and drug release. The developed generic albendazole tablet was found to be similar to the reference product on the market in terms of quality parameters, therefore can be produced as a generic formulation by an interested local pharmaceutical industry in the country.

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