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Research

Design of experiment of albendazole chewable tablets 400mg without overages of api and preservatives with quality by design (QBD) approach

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Abstract

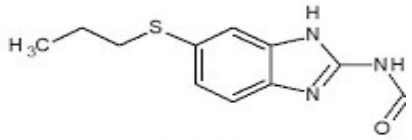
Objective of the research work is Design of experiment of Albendazole Chewable Tablets 400 mg without overages of API and preservatives with Quality by Design (QbD) Approach. Development trials of Albendazole Chewable Tablets 400 mg have been carried out with the remove of overages of API and preservatives (Parabens) from the established formula of Albendazole Chewable Tablets 400 mg to finalize the manufacturing process and specifications. Trial batch was evaluated for feasibility of manufacturing process and designed target product profile.

Keywords: Albendazole, Preservatives, Excipients, Factorial design, Optimization

INTRODUCTION

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 levels 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 in line with market reference product. 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. 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.

Drug Profile
Chemical formula: $C_{12}H_{15}N_3O_2S$



Albendazole
Mol. wt: 265.33
Mol. formula: $C_{12}H_{15}N_3O_2S$

Albendazole is a carbamate ester that is methyl 1H-benzimidazol-2-ylcarbamate substituted by a propylsulfanyl group at position 5. It is commonly used in the treatment of parasitic worm infestations. It has a role as a tubulin modulator, a microtubule-destabilising agent and an anthelminthic drug. It is a carbamate ester, a benzimidazolylcarbamate fungicide, an aryl sulfide and a member of benzimidazoles. Albendazole Chewable Tablets 400 mg, are available as, white to off-white coloured oblong. Shaped biconvex, uncoated tablet with break line on one side and plain on other Side. Pack Size -A HDPE bottle with CRC cap 1 X 100 Tablets. Excipients were selected based on literature review and as per Innovator product composition.
All open and closed samples were stored at 25°C ± 2°C/ 60 % ± 5% RH, 40°C ± 2°C/ 75 % ± 5% for one month and 60oC/80% RH for 15 days. Samples were kept as wet open and wet closed condition. Samples were analysed for description, assay and related substances. The results of Drug-Excipients compatibility study are found okay.

Selection of manufacturing process: Commonly used methods for manufacturing of tablet dosage forms are
Wet Granulation: This method commonly used if dose of drug is high along with poor flow property. This method also provides more uniform mixing so as to prevent blend uniformity related issues.

Dry Granulation: This method is used when the API used is heat and moisture sensitive. This method Improve tablet disintegration since it does not involve the use of water so it increases water-uptake ability of the disintegrates.

Direct Compression: This method involves fewest processing steps as compare to other processes. It is also useful for moisture and heat sensitive APIs. Albendazole API is having poor flow properties and its concentration in formulation is about 66.67 %. Hence wet granulation method was selected for further development.
Design of the Drug product is: Components of Drug Product, Manufacturing Process Development, Compatibility Identical excipient types to the reference product were selected for our product development. The selection of excipient grade was based on previous formulation experience, regulatory requirement and knowledge about the excipients that have been used successfully in approved product manufactured by wet` granulation method.

Sr#	Ingredient	Reference to Quality Standard	Reason for Inclusion
1	Sodium Starch Glycolate	BP	Disintegrant
2	Microcrystalline cellulose	BP	Diluent
3	Sodium Lauryl Sulphate	BP	Anionic Surfactant
4	Maize Starch	BP	Diluent
5	Maize Starch (P)	BP	Binder
6	Purified Water	BP	Solvent
7	Colloidal Anhydrous Silica (Aerosil)	BP	Glidant
8	Aspartame	BP	Sweetener
9	Mixed Fruit Flavour	In-House	Flavour
10	Purified Talc	BP	Glidant
11	Magnesium Stearate	BP	Lubricant

BP: British Pharmacopoeia

During process development, the manufacturing steps and critical process parameters that controlled each of the mechanistic factors were identified. This application seeks marketing authorisation for Albendazole Chewable Tablets 400 mg. Albendazole (Methyl 5- propylthio -1H-benzimidazol-2-ylcarbamate), is a broad spectrum anthelmintic drug, producing high cure rates in the treatment of hydatid cysts caused by Echinococcosis, Cystic Echinococcosis & Alveolar Echinococcosis. The wide spectrum of activity, high efficiency and ease in administration as exhibited by Albendazole mean that it is now widely used to treat hydatid cysts. Albendazole is included by WHO in the Model List of Essential Drugs as a reference for similar clinical performances within the intestinal anthelmintics pharmacological class. All the structural and physico-chemical characteristics of the drug substances have been studied and the information from this study is used to justify the initial design of the formulation. From the obtained data out of these studies, the formulation and the manufacturing technology has been designed, in order to achieve the suitable formulation and manufacturing technique. Thus, a product that complies with the established specifications is obtained, having also the experience of the actual marketed product (product of reference).Albendazole Chewable Tablets 400 mg is formulated as uncoated tablet for oral use in a 400 mg strength, with the packaging in HDPE bottle of 100 Tablets.

All of the test methods customarily required to support the control of active and inactive ingredients in a finished pharmaceutical and for stability monitoring of the product are thoroughly validated.

The stability study of Albendazole Chewable Tablets 400 mg were performed with the selected excipients and found there was no significant change in appearance, potency and other physical parameters, hence it was concluded that the proposed excipients were

Procedure and validation approach

Verification of the Analytical Method for Assay by HPLC: The HPLC assay method has been verified in compliance to the USP monograph for Specificity, System suitability, Linearity, System precision, method precision, intermediate precision and Accuracy,

Validation of the Analytical Method for Dissolution by UV: The HPLC assay method has been validated for Specificity, System suitability, Linearity, System precision, method precision, intermediate precision, Accuracy, Stability of Analytical solution and Robustness,

Validation of the Analytical Method for Related Substance by HPLC: The HPLC assay method has been validated for Specificity, System suitability, Linearity, System precision, method precision, intermediate precision, Accuracy, Stability of Analytical solution ,Robustness, Limit of detection and Limit of quantitation.

Validation of the Analytical Method for Microbiological Purity: The microbial limit test has been validated for the quantitative validation of total viable counting and qualitative validation for the specified organisms.

MATERIALS AND METHODS

Vibrator sifter, Rapid Mixer, Granulator, Multimill, FBP, Blender, Compression Machine, Metal Detector, DE duster, Stirrer, coating machine, Balance, Hardness tester, Friability Tester, DT apparatus, Moisture Analyser. Sodium starch Glycolate, Microcrystalline Cellulose, Sodium Lauril Sulphate, Maize starch, Pregelatinized starch, Purified water, Aerosil, Aspartner, Mixed fruit flour, Purified talc, Magnesium stearate.

Approach of Finished product Development

The formulation development of Albendazole Chewable Tablets 400 mg was designed by evaluating the following critical attributes.

1. Reference product characterization
2. Small Scale Development Trial and Finalization of Formula
3. Stability Study of exhibit Batches
4. Pharmaceutical Equivalency Studies
5. Product Quality Review of the year 2016
6. Pharmaceutical Equivalency Studies

Approach of Finished product formula and process development

Development trials of Albendazole Chewable Tablets 400 mg have been carried out with the remove of overages of API and preservatives (Parabens) from the established formula of Albendazole

Chewable Tablets 400 mg to finalize the manufacturing process and specifications. Trial batch was evaluated for feasibility of manufacturing process and designed target product profile.

Batch Size: 1000 Tablets

Sr #	Ingredient	Reference to Quality Standard	Label Claim	Qt/Tab (mg)	Standard Quantity/Batch (in gm.)
1	Albendazole (Micronized)	Ph.Int.	400 mg	400.00	400.00
2	Sodium Starch Glycolate	BP	---	48.50	48.50
3	Microcrystalline cellulose	BP	---	100.00	100.00
4	Sodium Lauryl Sulphate	BP		8.00	8.00
5	Maize Starch	BP		179.30	197.23
6	Maize Starch (P)	BP	---	30.00	30.00
7	*Purified Water	BP	---	0.494 ml	0.494 ml
8	Colloidal Anhydrous Silica (Aerosil)	BP	---	8.00	8.00
9	Sodium Starch Glycolate	BP	---	24.00	24.00
10	Microcrystalline cellulose	BP	---	9.20	9.20
11	Aspartame	BP		8.00	8.00
12	Mixed Fruit Flavour	IH		12.00	12.00
13	Purified Talc	BP		13.00	13.00
14	Magnesium Stearate	BP		10.00	10.00
Total Weight of Core Tablet				850.0 mg	850.0 g

Test Parameters and Results:

TEST	SPECIFICATION	Trial batches
		AB 230
Description	White to off-white coloured, oblong shaped, biconvex uncoated tablets with break line on one side and plain on other side.	White coloured, oblong shaped, biconvex uncoated tablets with break line on one side and plain on other side.
Identification By HPLC By UV	In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution. The absorption spectrum of the test solution, when observed between 220 and 340 nm, exhibits maxima at about 231 nm and at 308 nm; the absorbance at 308 nm is about 0.59.	Confirms
Uniformity of Weight (Individual Weight of 20 tablets)	850.0 mg ± 5.0 % (Min 807.50 mg, Max 892.50 mg)	- 1.58 % + 1.44 %
Average Weight	850.0 mg ± 5.0 % (Min 807.50 mg, Max 892.50 mg)	853.2 mg
Hardness	Not less than 3.0 kg/cm^2	12 to 15 kg/cm^2
Friability	NMT 1.0 % w/w	0.19 %
Thickness	5.80 mm ± 0.20 mm (Min 5.60 mm, Max 6.00 mm)	5.88 mm to 5.96 mm
Water Content	Not More Than 7.0 %	3.20 %
Related Substances	Impurity A : NMT 0.75 % Impurity B&C: NMT 0.75 % Impurity D : NMT 0.75 % Impurity E : NMT 0.75 % Impurity F : NMT 0.75 % Unknown Impurities : NMT 0.2 % Total impurities: NMT 3.0 %	0.057 % 0.041 % 0.264 % Not Detected 0.312 % 0.125 % 0.758 %
Dissolution	Not less than 75.0% (Q) of L.C. is dissolved in 30 minutes.	95.67 %
Assay of Albendazole	90.0 % to 110.0 % on Label claim 400 mg	99.04 %

On critical observation of the results of Trail it is concluded that the composition of the product and method for manufacturing is OK. From the results it has been observed that the physical and chemical parametrs are found to be complies with all the pre-determined specification. Hence it is decided to take the exhibit batch with this modified formulation.

Results as depicted in trial and pilot scale-up batches clearly indicate that

1. Trial batches of Albendazole Chewable Tablets 400 mg (AB 230) qualify the specifications in all respects.
2. Assay and dissolution is found within the acceptance limit.
3. On the basis of stability results of established batches we concluded that the active ingredient is compatible with the excipient and also with the container and closure because all parameters are with limit as per specification under stress conditions.
4. Based on the results of the trial batches and prior experience with Albendazole Chewable Tablets 400 mg, used formulation and manufacturing procedure in exhibit batches was finalized for the finished drug product. Hence, we can say that the quantity proposed for all ingredients are compatible or physio-chemically stable and further validate the procedure of above mentioned formula and process in exhibit batches

Pharmaceutical Equivalency Studies

In-vitro dissolution study has been performed to evaluate the similarity of the Albendazole Chewable Tablets 400 mg with the reference product ESKAZOLE.

Overage in the product

There are no overages of Active Pharmaceutical Substance in the taken drug product. Following the master formula of the finished product, the exact amount of active ingredients to be added in the finished product by considering the assay and loss on drying of the active ingredients between batches. Excipient(s): 10 % overages of Maize Starch BP is taken in the batch formula to compensate process loss during manufacturing

Physicochemical and biological properties

The performance, safety of the formulation is based on the following
Description: A white to off-white coloured oblong shaped biconvex, uncoated tablet with break line on one side and plain on other Side.

Average weight: 850 mg ± 5 %,
Water Content: Not More than 7.0 %,

Assay: The performance of the dosage form is based on the content of the drug in the formulation.

Assay method has been developed with reference to USP monograph and the assay limit for Albendazole is 95% –105% ensures the release of the product and 90% –110% ensures the performance of the formulation throughout shelf-life.

Related Substance

The performance of the dosage form is based on the control of impurities throughout the product shelf life. Related substance method has been developed with reference to BP monograph of Albendazole API and the acceptance limit unknown impurities are set incompliance to ICH guideline.

Dissolution

The target is an immediate release product, so dissolution in the stomach and absorption in the upper small intestine is expected suggesting the use of dissolution medium with low pH. Development began with the quality control dissolution method recommended for this product by the International pharmacopoeia with 900 ml 0.1 N HCl, using apparatus 2 at 75 rpm.
The following dissolution method was finalized for Albendazole chewable Tablets 400 mg.

USP Apparatus	II (Paddle)
Dissolution media	0.1 N Hydrochloric Acid
Volume	900 ml
RPM	75
Time	30 minutes
Temperature	37.0°C ± 0.5°C
Detector	UV 308 nm
Acceptance Limit	Not less than 75 % (Q) dissolved in 30 mins.

Manufacturing process development

Initial evaluation of physicochemical properties of the Albendazole and in-house formulation experience provided the basis for the selection of wet granulation manufacturing process. The target product profile states that the manufacturing process should be robust and reproducible. The drug product produced meet the specification for the drug product and all critical quality attributes. In below each process steps are briefly described and each process steps in the manufacturing process is listed in the sequence of occurrence. Manufacturing process of Albendazole Chewable Tablets 400 mg evaluated for final manufacturing involves the following steps: Dispensing, sifting, dry mixing, paste preparation, granulation. Granulation is a process of producing granules generally. In pharmaceutical manufacturing, granulation process implies the techniques that are, used to combine powdered particles to form relatively bigger ones called granules. Granulation Semi Drying & Milling Drying Sifting & Milling, lubrication, compression. Packing: Primary Packaging Tertiary Packaging.

The main objective of tertiary packaging is safeguarding primary and secondary packaging from the external environment during storage and transportation. The most popular Pharma product tertiary packaging are plane boxes, cardboards, and shrink wraps.

Manufacturing flow

Sifter Mesh: Sift Albendazole (Micronized) Ph.Int through 40 #, Sodium starch glycolate BP, Sift Albendazole (Micronized) Ph. Int through 10 #, Sodium starch glycolate BP, Microcrystalline Cellulose BP, Sodium Lauryl Sulphate BP and Maize Starch BP through 1150# sieve by using Mechanical Vibrator Sifter and collect in double lined poly bags. Pass Maize Starch BP through 150# sieve by using Mechanical Vibrator Sifter and collect in double lined poly bags.

Dry Mixing

Load the sifted material of step in Rapid Mixer Granulator with fast speed of impeller & chopper off.

Granulation

Add step 3.3 to step 2 in Rapid Mixer Granulator with Impeller at Slow Speed and Chopper "OFF" for 90 seconds. 2. Mix material of step 4.1 in Rapid Mixer Granulator with Impeller at Fast Speed and Chopper at fast speed for 30 seconds. Then mix it for 180 seconds in Rapid Mixer Granulator at Fast speed of Impeller and Chopper 'OFF' then collect to the fluid bed dryer bowl. 3. Then unload the wet mass in FBD bowls.

Fluid bed drier (FBD)

Semi dry the wet granules of Step – 4.3 in Fluid Bed Dryer for 15 minutes with inlet temperature not more than 65°C. 2. Pass the semi dried mass of Step- 5.1 through 6.0 mm screen of multimill at slow speed and knife forward direction & collect in FBD bowls. Dry the milled granules of step-5.2 in fluid bed dryer at inlet temperature of NMT 65°C to get outlet temperature at the end of drying between 44°C -48°C till the loss on drying achieve NMT 3.0 %. 4. Sift dried granules through 20 # sieve of sifter. 5. Those granules have not passed through 20 # sieve, crush through 1.5 mm screen of multimill at slow speed and knife forward direction and collect in double lined polybags.

Pre-Lubrication

Sift Mixed Fruit Flavour IH through 100 # sieve by using Mechanical Vibrator sifter and collect in Double Lined a polybags. 2. Sift Micro Crystalline cellulose BP & Sodium Starch Glycolate BP through80# sieve and collect in polybag. Then mix it with Colloidal Anhydrous Silica BP and pass through 20 # sieve and collect in Double Lined a polybags.3Sift Aspartame BP through 30 # sieve by using Mechanical Vibrator Sifter and

collect separately in Double Lined a polybags. 4. Sift Magnesium Stearate BP & Purified talc BP through 61000 # sieve by using mechanical Vibrator Sifter and collect in Double Lined a polybags.5. Load step-6.1, step-6.2, step -6.3 & step-5.5 in a blender & mix for 30 minutes.

Lubrication: Add step –6.5 in a blender of step 6.4 and mix for 8 minutes in a Blender
Compression: Compress the lubricated granules in compression area using 51 station double rotary compression machine equipped 19.6 x 9.2 mm oblong shape biconcave punch having break line on one side and plain on other side.

Controls on in-process critical parameter

Factor	Control Parameter
API	Drug substance particle size was found as below D_{90} less than 10 µm
Excipient	Excipient grades were finalized based on development trail batch.
Manufacturing process	
Dry mix	Based on development trial (Dry mix time 10 minutes at slow impeller speed and chopper off for 10 minutes)
Granulation	Based on process optimization kneading time and mixing was achieved
Drying	Based on optimization trial the loss on drying was 1 % - 3 % w/w finalized.
Lubrication	Lubrication should be 3 minute based on process optimization data
Compression	Speed of compression machine was finalized based on physical parameter.
Hardness	Based on physical parameter of tablet Hardness limit was finalized as 120 N to 200 N

Drug product without Primary Pack: No significant change observed for description, assay and related substances with reference to initial results. Drug product without primary pack under dark control: No significant change observed for description, assay and related substances with reference to initial results.Drug product with Primary pack: No significant change observed for description, assay and related substances with reference to initial results.

CONCLUSION

Photostability results for product (Praziquantel tablets USP 600 mg) with and without primary pack and dark control complies with shelf life specifications and no significant change is observed. Hence, no special storage condition is required for product. Also no significant changes were observed for P API (Drug substance without primary pack and drug substance without primary pack under dark control.

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