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Research

Design of experiment (doe) of a new formulation of Praziquantel by using Microcrystalline depolymerized cellulose

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Abstract

The scope of the work is carried out for the development a new design of experiments of a new formulation of Praziquantel by using Microcrystalline depolymerized Cellulose. The Development trials of Praziquantel tablets USP 600 mg have been carried out with the remove of overages of API and preservatives (Parabeens) from the established formula of Praziquantel tablets USP 600 mg to finalize the manufacturing process and specifications. Trial batch was evaluated for feasibility of manufacturing process and designed target product profile. The compatibility studies were based on the composition of drug and Excipients, the collected 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 and were analyzed for description, assay and related substances.

Keywords: Praziquantel, Microcrystalline depolymerized crystalline, Preservatives, Excipients

INTRODUCTION[1,2]

Praziquantel is an anthelminthic used in most schistosome and many cestode infestations. Praziquantel affects the permeability of the cell membrane resulting in the contraction of schistosomes. The drug further causes vacuolization and disintegration of the schistosome tegument. The effect is more marked on adult worms compared to young worms. An increased calcium influx may play an important role. Secondary effects are inhibition of glucose uptake, lowering of glycogen levels and stimulation of lactate release. The action of Praziquantel is limited very specifically to trematodes and custodies; nematodes (including filarial) are not affected.

Absorption: Praziquantel is well absorbed (about 80%) from the tract. Praziquantel has a serum half-life of 0.8 to 1.5 hours in adults with normal renal and liver function. Maximal serum concentration is achieved in 1-3 hours after dosing

Distribution: Praziquantel was found to distribute throughout the body and concentrate especially in the liver and kidneys. Praziquantel is highly protein-bound (~80%, nearly exclusive to albumin)

Metabolism: Praziquantel undergoes an extensive first-pass metabolism in the liver by the CYP system (CYP1A2, CYP3A4, CYP2B1, CYP3A5 and CYP2C19).

Elimination: Elimination of more than 80% is completed after 24 h.. Excretion is predominantly as metabolites and parent drug. In humans about 80% of a dose is excreted in urine. Praziquantel and its principal metabolites are found in human milk at levels about 25-30% of those in maternal plasma.

Test	Target	Justification
Description	White to off white , biconvex ,film coated with triple break line on both side	Similar to reference product
Dosage designed	Immediate release	To meet the reference product
Route of administration	oral	Same route to reference product as per reference molecule
Dosage strength	600 mg	Pharmaceutical equivalence requirement: same route with dose form
Pharmacokinetics	Immediate release tablets enabling t max in 1 to 3 hours .Bioequivalent to RLD	Bioequivalent requirement

Drug quality attributes, Physical attributes Identification Assay Content of Uniformity Dissolution Disintegration of the product Disintegration of the product Residual solvent Water content Microbial limit are meet the reference product and meet pharmacopeia limits

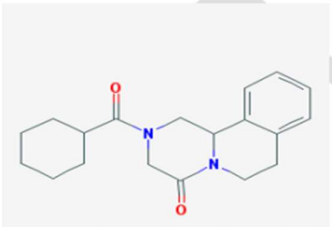
Drug profile and product information

2.1 Component of drug product

2.1.1 Drug substance

A) Name of Drug : Praziquantel Ph. Eur

- **Chemical Name** : 2-cyclohexanecarbonyl-1H,2H,3H,4H,6H,7H,11bH-piperazino [2,1-a]isoquinolin-4-one
- **Chemical Structure** :



- **CAS No.** : 55268-74-1
- **Molecular formula** : $C_{19}H_{24}N2O_2$
- **Molecular weight** : 312.41
- **General properties**
  - **Description** : White to almost white, crystalline powder.
  - **Chirality** : Does not exhibit Chirality
  - **Solubility** : Freely soluble in chloroform and Dimethyl sulfoxide, soluble in ethanol and very slightly soluble in water.
  - **Polymorphic form** : Crystalline

Development, manufacturing process

The method of manufacture is a wet granulation followed by drying, milling, lubrication, compression. For tablet Excipients are Microcrystalline Cellulose (Flocel 102), Pregelatinized starch, Maize starch, Sodium lauril sulfate, Povidone (PVP K30), Magnesium Stearate. Adequate in-process controls are provided to ensure tablet quality.

Manufacturing Process: All the raw material was dispensed as per the composition and sifted through Praziquantel (20 mesh), Microcrystalline Cellulose (40 mesh), Pregelatinized Starch (40 mesh), Maize Starch (40 mesh), and Magnesium Stearate (60 mesh)

- Praziquantel, Microcrystalline Cellulose, Pregelatinized Starch and Maize Starch was loaded into RMG and dry mixed for 10mins at slow impeller speed.
- Binder preparation was done by, A. Sodium laurel sulfate Solution: Sodium laurel sulfate was added into purified water and stirred continuously till it forms clear solution B. Povidone K 30 + Pregelatinized Starch Dispersion: Purified water + Povidone K 30 + Pregelatinized starch under continuous stirring.
- Wet Granulation of dry mix in RMG was done by using binder solution A completely and then added dispersion B to get granules/wet mass of desired consistency. If required add additional quantity of purified water
- Drying was done in Fluidized bed dryer at 600C to obtain a LOD 1 – 3%
- Dried granules were sized through 20#, Retention over 20# milled by using mutimill fitted with 1.50 mm screen. Milled granules again passed through 20#, Retention over 20# again milled by mutimill fitted with 1.00 mm screen. Milled material again sized through 20#
- Sized granules then loaded into suitable blender and mixed for 05mins and then lubrication was done by using magnesium stearate for 03mins
- Compression was done at optimized parameters

Equipments: Vibrator sifter, Rapid Mixer Granulator, Mutimill, Blender, Compression Machine Metal Detector DE duster Stirrer Coating Machine Balance Hardness tester Friability Tester. DT apparatus Moisture Analyser. Materials: Praziquantel Microcrystalline Cellulose Maize Starch BP Croscarmellose Sodium Croscarmellose Sodium Lauryl Sulphate Magnesium stearate Polyvinyl PyrrolidonePregelatinized starch, Povidone Microcrystalline Cellulose.

Manufacturing process development: 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: the right materials to the right batches prior to the manufacturing process are a key activity in life sciences and other process industries.
Sieving & filtering: is the process to eliminate impurities or grade the material. Pharmaceutical industries are the most hygienic among others. All the machines used in pharma industries are made with high-quality stainless steel, food grade rubber items and requires clean environment.

Mixing: is an important part of pharmaceutical production. Operations can include dissolving solids and powders, preparing emulsions, combining raw materials, enabling chemical reactions, and milling active pharmaceutical ingredients (APIs)

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: Pharmaceutical lubricant concentration used in different solid oral preparations for lubrication during manufacturing. Lubricants are agents added in small quantities to tablet and capsule formulations to reduce the friction and improve certain processing characteristics

Compression: A tablet compressing machine converts granulated powder into pressed tablets of uniform size and weight. A tablet press machine is widely used in the pharmaceutical industry as it converts various powdered materials into tablets by using the basic principle of compression. Manufacturers use dye and punches to transform powdered materials into pills.

Packing: Product packaging maintains drug quality. It protects the product from physical damage as well as biological degradation. Some sensitive drugs require protection from light and water as they have sensitive substances. The packaging for pharmaceuticals also needs to disseminate important information. There must be proper and clear labelling—correct information needs to be disseminated.
Product packaging is a crucial part of any product. But in the pharmaceutical industry, it is critical given the nature of the products. Life-savings drugs and medicines require the utmost care in the form of cover. Besides, stringent packaging standards also apply to pharmaceutical products.

Primary Packaging: There are three types of packing in the Pharma industry - primary, secondary, and tertiary Also known as sales packaging, primary packaging is significant for Pharma companies. This packaging is in direct contact with drugs and medicines. Therefore, the packaging needs to be inert and should not cause any alteration to the salt in the dosage. If the primary packaging is not done correctly, it may affect the drug, and you won't be sure about the medicine quality and its purity.
The material used for primary packaging must be neutral to ensure it doesn't interact with the pharmaceutical product during its entire life. However, if the packaging fails, the drug may become life-threatening for the patients who may consume it. The most common material used for primary packaging includes non-reactive substances, like aluminium and PVC. Likewise, high-quality plastic is used for liquid doses instead of glass. This ensures that the products don't spill or get damaged during transportation from the factory to the pharmacy. The most common plastics used for tablets and pills include polyethylene, polyvinyl chloride, nylon, polycarbonate, and polyethylene tetra phthalate.

Tertiary Packaging: The last type of packaging, i.e. tertiary packaging, is important for the shipping process. The end consumers don't see this packaging. The retailers often remove them before they showcase the medicines in their shops or clinics.
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.
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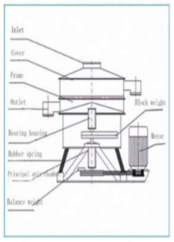
Manufacturing Process
Batches Taken: Step 1: Sifting of Material: All the raw material was dispensed as per the composition and sifted through Praziquantel (20 mesh), Microcrystalline Cellulose (40 mesh), Pregelatinized Starch (40 mesh), Maize Starch (40 mesh), and Magnesium Stearate (60 mesh).



Step 2: Dry Mixing: Load the sifted material of step in Rapid Mixer Granulator with fast speed of impeller & chopper off.Praziquantel, Microcrystalline Cellulose, Pregelatinized Starch and Maize Starch was loaded into RMG and dry mixed for 10mins at slow impeller speed Wet Granulation of dry mix in RMG was done by using binder solution A completely and then added dispersion B to get granules/wet mass of desired consistency. If required add additional quantity of purified water.

Paste preparation: Binder preparation was done by, A. Sodium laurel sulfate Solution: Sodium laurel sulfate was added into purified water and stirred continuously till it forms clear solution B. Povidone K 30 + Pregelatinized Starch Dispersion: Purified water + Povidone K 30 + Pregelatinized starch under continuous stirring.

Granulation: Drying was done in Fluidized bed dryer at 600C to obtain a LOD 1 – 3% Dried granules were sized through 20#, Retention over 20# milled by using mutimill fitted with 1.50 mm screen. Milled granules again passed through 20#, Retention over 20# again milled by mutimill fitted with 1.00 mm screen. Milled material again sized through 20#Sized granules then loaded into suitable blender and mixed for 05mins and then lubrication was done by using magnesium stearate for 03mins Compression was done at optimized parameters

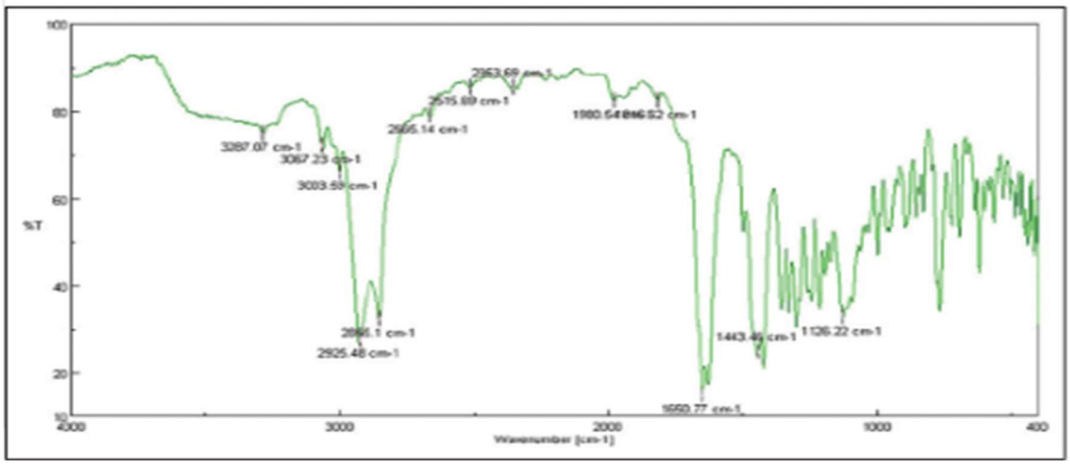
Compression: Compress the lubricated granules in compression area using 51 station double rotary compression machine equipped parameter was tested :a. Description b. Average weight c. Thickness d. Hardness e. Disintegration time f. Assay g. Related substances h. Dissolution

Product development

Melting point of drug: The melting point of Praziquantelwas found to be in the range of 134–138°C, which was similar to the standard melting point (137°C) Om, et al.: Formulation and evaluation of Praziquantel tablets by using solid dispersion approach.

RESULTS AND DISCUSSION

Solubility study: Infrared spectra's were recorded for pure Praziquantel drug and physical mixture K br(1:3). Characteristic peaks of drug appear in the spectra of physical mixture at the same wave number, indicating no modification or interaction between the drug and the polymer.



Description of Product: Description of the Dosage Form: White to off white, biconvex, filmcoated caplets with triple break line on both sides

Photo stability: According to literature and Monograph Praziquantelis light sensitive. Hence Photostability study was performed for product as well as active pharmaceutical ingredients as per ICH guideline with Samples exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. Exposed samples were analysed for below mentioned test.

a. Description, b. Assay, c. Related substances.

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.

Photostability results for product Praziquantelle (Micronized) 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 Albendazole (Micronized) l API (Drug substance without primary pack and drug substance without primary pack under dark control.

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.

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 Praziquantel API (Drug substance without primary pack and drug substance without primary pack under dark control.

Selection Of Manufacturing Process**:** Selection of manufacturing process: Commonly used methods for manufacturing of tablet dosage forms are:

Wet granulation method 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 increaseswater-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. Praziquantel API is having poor flow properties Hence wet granulation method was selected for further development.

Design of the study: Components of Drug Product, Manufacturing Process, Development Compatibility

- Trial batches were taken with composition similar to reference product composition, initially slower Dissolution drug release profile was observed as compare to reference product (Biltricide 600 mg Filmblatten) and poor flow properties also observed.
- In sub sequent trials Surfactant concentration was increased so as to improve dissolution profile, results was observed satisfactory but at initial time points slow drug release was observed.
- So in further trials maize starch concentration was reduced and Pregelatinized starch was incorporated into binder to improve Dissolution profile as well as flow properties and results were found satisfactory and comparable to reference product.
- There was no significant impact of granules size was observed on dissolution profile. However increase in weight variation was observed with 24 mesh granules. During process optimization different physicochemical parameters were observed Optimization of Kneading time: With increase in kneading time from 140 sec to 200 sec, increase in tablet disintegration time was observed from 3 minutes 30 seconds to 4 minute 35 seconds. But no significant difference was observed in the dissolution profile the active. Hence kneading time of 140 seconds was finalized

Optimization of Lubrication time: With increase in lubrication time from 3 minutes to 5 minutes, no significant difference was observed in the disintegration time and dissolution profile. Hence lubrication time of 3 minutes was finalized.

Optimization of Loss on drying: No significant impact was observed on physicochemical parameters of tablet for loss on drying between 1.0 %w/w to 3.0%w/w. Hence loss on drying between 1.0 – 3.0% was proposed.

Optimization of Water concentration for binder: With lower water quantity for granulation – 396mg/tablet, flow of granule was satisfactory but less granules proportion was noted as compared to stability batch. With higher water quantity for granulation- 570mg/tablet, flow of granule was satisfactory and similar granules proportion as that of stability batch was noted. Dissolution profile was slightly slower to that of stability batch. Hence water quantity of 483 mg/tablet was finalised for granulation

Compatibility with closure system with product: Reference product Biltricide® 600 mg film tablleten. Manufactured by Bayer Pharma AG, Betrieb: 51368 Leverkusen is available in amber colored glass bottle with HDPE screw pack containing six tablets. However test product will be packed in HDPE containers with cap containing 100/500 and 1000 tablets, based on pack details of Competitor product, Praziquantel 600 mg tablets (Mfg. By: Cipla Ltd. India) and Market requirement of this product. Details of Container are provided below.

- 250cc HDPE container with 71 mm cap containing 100 tablets and silica gel bag
- 1200cc HDPE container with 119mm cap containing 500 tablets and silica gel bag.
- 1600cc HDPE container with 119 mm cap containing 1000 tablets and silica gel bag.

Analytical 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.

Microbial Attributes: The presence of certain microorganism in dosage form may have the potential to reduce or even inactivate the therapeutic activity of product

Finished product development

Praziquantelis an established product, Formulation of Praziquantelwas finalized, as per WHO recommendation for prequalification,With reference to ERP recommendation, one trial batch and three exhibit batches were taken withthe remove of overages of API and preservatives (Parabeens) from the existing formulation and have charged for the stability study.

In-vitro dissolution data of developed in-house product was compiled for understanding the behaviour of dosage form in different physiological pH.

The development activity has been performed The formulation development of Praziquantel 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 EquivalencyStudies

CONCLUSION

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 fordescription, 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.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 API (Drug substance without primary pack and drug substance without primary pack under dark control.

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