MINISTRY OF HEALTH
HANOIUNIVERSITY OF PHARMACY

SOCIALISTREPUBLIC OF VIETNAM
Independence-Freedom-Happiness

ABSTRACT OF THE DISSERTATION

1. Introduction:

Dissertation:"Study to prepare pantoprazole lyophilized injectable powder"

Specialized in: Pharmaceutics

Code number: 62.72.04.02

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Names of academic advisors:

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Name of academic institution: Hanoi University of Pharmacy

2. Summary

2.1. Objectives

- Study and preparation of pantoprazole lyophilized injectable powderat laboratory level (maximum 200 vials/batch).

- Scale up from laboratory level to 4100 vials/batch and production implementation of pantoprazole lyophilized injectable powder at certified standard GMP – WHO factory of Central Pharmaceutical Joint Stock Company No.1 (PHARBACO).

2.2.Materials and methods

2.2.1. Materials:

Sodium pantoprazole sesquihydrate (Spain - EP 7), Mannitol (Roquette, French - EP/BP), Na_2EDTA (Xilong,China – BP), Hydroxypropyl beta cyclodextrin (Roquette,French –EP), Sodium hydroxide (Germany), phial 10 ml (Germany), lyophilized rubber stopper with diameter 18,8 mm (Germany), standard sodium pantoprazole sesquihydrate(MOEHS IBÉRICA S.L (Spain - USP), Pantoloc (produced in 10/2011, Nycomed Gmb (Germany), Pipanzin (produced in 11/2011, PYMEPHARCO Company).

2.2.2. Study methods

2.2.2.1. Quantitative method and limitation defining of impurities of pantoprazole lyophilized injection

Using HPLC method with condistions and proceduresas follows:

*Conditions:

- Column: RP 18 (250 x 4,6 mm, 5 μm) or equivalent column.
- Column temperature: 30^0C.
- Mobile phase: acetonitril: Buffer phosphat pH 7,6 (300:700). Buffer phosphat pH 7,6: dissolve 1,12 g dinatri hydrophosphat and 0,18 g natri dihydrophosphat in 1000 ml water, adjust to pH 7,6 by 1N sodium hydroxyd solutionorphosphoric acid.
- Detector UV: 290 nm.
- Flow rate: 1.5 ml/min.
- Injection volume: 20 μl.

* Procedures:

- Define specifity andselectivity of method;
- Base line establishment;
-Validation: Linear degree,accuracy and reproducibility level of method.

2.2.2.2. Preparation method

Lyophilization method used:

- At laboratory level (maximum200 vials/batch), use freezer dryer LABCONCO (USA) with parameters: Freeze (temperature -70^{0}C, time: 6 hours; primary drying: temperature 15^{0}C, heating rate 0.5^{0}C/min, time: 20 hours; second drying: temperature 22 à 35^{0}C, heating rate 0.25^{0}C/min, time: 18 à 24 hours.

- At level 4100 vials/batch, freezer dryer Telstar (Spain) with parameters: Freeze (temperature -50^{0}C, time: 2 hours; primary drying: temperature 15^{0}C, heating rate 0.5^{0}C/min, time: 20 hours; second drying: temperature 30^{0}C, heating rate 0.25^{0}C/min, time: 6 à 14 hours.

2.2.2.3.Method of quality evaluation

- Evaluation method of pantoprazole lyophilized injectable powder

According to standards of treatises of DĐVN IV and BP 2013 on: form; qualitative; water content; volume differential; pH; clear degree and colour of reconstitutedsolution; sterility; endotoxin; reconstitutiontime; small molecule of powder

Active principle content and impurity rate by HPLC method

- Evaluation method of stability of pantoprazole lyophilized injectable powder

Defining active principle content impurity rate according to conditions: harsh condition (temperature 100^{0}C with time 2 hours, 4 hours); accelerated condition (temperature 40^{0}C±2, humidity 75%±5).

Evaluation of pH, reconstitutiontime, active pharmaceutical ingredientcontent, impurity rate at actual conditions at laboratory of Pharmacy (Hanoi University of Pharmacy) with temperature 25 – 35^{0}C, humidity 55 – 85%.

Evaluation of pH, reconstitutiontime, active principle content, impurity rate at storage conditions not exceed 30^{0}C, keep away from light.

- Evaluation method of systematic property-Frozen and dried powder

+ Photograph by scanning electron microscope (SEM).
+ Differential Scanning Calorimetry (DSC).
+ Diffraction spectrum X (X – Ray).

2.2.2.4. Validation of production process of pantoprazole lyophilized injectable powder at scale 4100 vials/batch

By traditional method (experimental method) with following steps:

- Verification preparation;
- Parameters verfication;
- Statistical control.

2.3.Official results and conclusion

2.3.1. Studied and prepared pantoprazole lyophilized injectable powder at laboratory level

- Formation of quantitative method and defining related impurity rate of pantoprazole lyophilized injectable powder.Method was checked at facility where certified standard GLP by the Ministry of Health so it is reliable to evaluate quality of studied product.

- Investigatedeffect of formula factors and technical parameters on stability of pantoprazol and pantoprazole lyophilized injectable powder

- Developed formula and preparation process of pantoprazole lyophilized injectable powderat laboratory level.

- Established standards for pantoprazole lyophilized injectable powder. Drug was issued registration number by the Ministry of Health.

- Produced pantoprazole lyophilized injectable powder at laboratory level with formula and selected frozen and dried process, drug is stable within 24 months at storage conditions and 6 months at lightning aging conditions.

2.3.2. Scaled up and implemented production of pantoprazole lyophilized injectable powder at level 4100 vials/batch.

- Scaled up preparation of pantoprazole lyophilized injectable powder from laboratory up to 4100 vials/batch.

- Production process of pantoprazole lyophilized injectable powder (Cafocid) was tested at factory whichhas certified standard GMP – WHO of Central Pharmaceutical Joint Stock

Company No.1. The Drug is stable at storage conditions (below 30^0C, keep away from light), reconstitutedsolution in sodium chloride solution 0.9% is also stable in 12 hours in surveys.

-. There is no difference from Diffraction spectrum X-Ray between pantoprazole lyophilized injectable powder is produced at laboratory level and at level 4100 vials/batch (no found pictures of crystal of Pantoprazol).

- In comparison of a number of quality targets and stability of frozen and dried powder by HPLC, DSC, X-ray methods: Studied product has stability and quality equivalent to generic drug.

- This is the first time pantoprazole lyophilized injectable powder is fully studied from laboratory level to production level. Drug was issued registration number by the Ministry of Health and put into markets with prices equal 1/3 compared with genetic drug but has equivalent stability and quality.

The scientific advisors | Doctoral Candidate

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