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ASSAY TEST PROCEDURE AS A CPP AT BULK-SOLUTION STAGE - ESOMEPRAZOLE SODIUM INJECTION 40MG

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ABSTRACT

To develop & validate the analytical Assay Test procedure as a Critical Processing Parameters at the Bulk-Solution stage during manufacturing of Esomeprazole Sodium Injection 40mg. As per current available literature and the references, Esomeprazole active substance is available in market in five forms, i.e. Esomeprazole as Plan active [Tablet]; Esomeprazole Magnesium Trihydrate [Tablet, Capsule Delayed Release]; Esomeprazole Potassium [Tablet & Capsule]; Esomeprazole Strontium [Capsule Delayed Release] and Esomeprazole Sodium [Injectable]. Assay test for Active & other dosage forms [Tablet, Capsule] were available. Available Test procedure are based on either Potentiometory Titration or HPLC basis. Esomeprazole Sodium Injection 40mg Dosage form is not in any pharmacopeia. As per available reference & literature assay test method for intermediate testing & finished product is based on HPLC. Intermediate testing [In-Process Testing] require as Critical Process Parameters [CPP] to ensure the quality i.e. appropriate bulk-solution purity, before to proceed for filling of Bulk-solution in unit dosage form [Vials]. To test the bulk solution purity approx. 5-6 hours required. Which leads to hold the Bulk solution, further it impact & may risk bio-burdon of bulk solution. Also it impact & reduce the productivity of line by 5-6 hours. HPLC testing required special skilled manpower & cost. Considering all above concerns of current available test methods; this article project is selected to develop & validate the analytical Assay Test procedure as a Critical Processing Parameters at the Bulk-Solution stage during manufacturing of Esomeprazole Sodium Injection 40mg.

KEYWORDS: Validation, Intermediate Test, In-process Test, CPP - Critical Process

Parameters, Injectable Dosage Form.

1. INTRODUCTION

Product Formulation: Lyophilized Injectable Esomeprazole Sodium Injection 40mg

Category: Non-steroidal - Anti-inflammatory drug

Therapeutic Use: Proton Inhibitor in Gasteroesophageal Reflux Disease, Peptic Ulcer

Active: Esomeprazole Sodium

IUPAC-Name: Sodium5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H- benzimidazol-1-ide

Molar Formula: $C_{17}H_{18}N_3NaO_3S$ Molar Mass: 367.4 g/mol

Structure

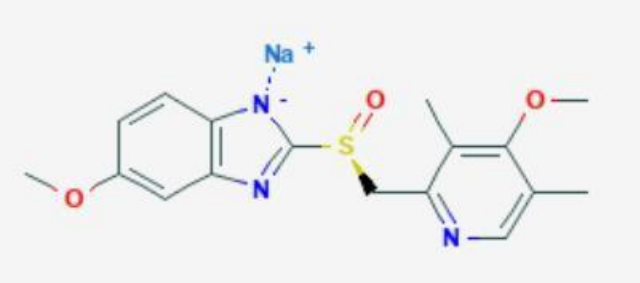


Figure No. I.

HISTORY

It was patented in 1993 and approved for medical use in 2000.

It is available as a generic medication and sold over the counter in a number of countries.

In 2016 it was the 69th most prescribed medication in the United States with more than 11 million prescriptions.

Five molecule of Esomeprazole drug used in market

1. Esomeprazole [Plan] : Tablet
2. Esomeprazole Magnesium Trihydrate : Tablet & Capsule
3. Esomeprazole Potassium : Tablet & Capsule
4. Esomeprazole Strontium : Capsule
5. Esomeprazole Sodium : Injectable

The Injectable Dosage form approved by US in 2005

In India *Esomeprazole Sodium Injection 40 mg* are available under different brand as lyophilized Powder e.g. Nexium IV; Esoz Injection; Geltop Injection, Esofic Injection;

Recifer Injection; Esozi Injection, Yes Injection etc.

DRUG PROFILE

Absorption

The pharmacokinetic profile of *Esomeprazole Sodium I.V. for Injection 40 mg and 20 mg* was determined in 24 healthy volunteers for the 20 mg dose and 38 healthy volunteers for the 40 mg dose following once daily administration of 20 mg and 40 mg of *Esomeprazole Sodium I.V. for Injection 40 mg and 20 mg* by constant rate over 30 minutes for five days. The results are shown in the follows,

Pharmacokinetic Parameters of Esomeprazole Sodium I.V. for Injection 40 mg and 20 mg IUM Following I.V. Dosing for 5 days

Parameter	20 mg	40 mg
AUC(µmol*h/L)	5.11	16.21
Cmax (µmol/L)	3.86	7.51
t½ (h)	1.05	1.41

Values represent the geometric mean (95% CI)

During administration of Esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours (for a total of 24 hours) in healthy volunteers (n = 24), Esomeprazole PK parameters [Geometric mean value (95 % CI)] were as follows: AUCt 111.1 µmol*h/L (100.5-122.7 µmol*h/L), Cmax 15.0 µmol/L (13.5-16.6 µmol/L), and steady state plasma concentration (Css) 3.9 µmol/L (3.5-4.5 µmol/L).

In a Caucasian healthy volunteer study evaluating Esomeprazole 80 mg over 30 minutes, followed by 8 mg/h over 23.5 h, systemic Esomeprazole exposures were modestly higher (~17%) in the CYP2C19 intermediate metabolizers (IM; n = 6) compared to extensive metabolizers (EM; n = 17) of CYP2C19. Similar PK differences were noted across these genotypes in a Chinese healthy volunteer study that included 7 EMs and 11 IMs. There is very limited PK information for poor metabolizers (PM) from these studies.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of Esomeprazole lack anti-secretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Esomeprazole Metabolism Pathway

Esomeprazole, is a proton pump inhibitor (PPI) class drug that suppresses the final step in gastric acid production. In this pathway, esomeprazole is taken orally and is oxidized in the stomach to form the active metabolite of esomeprazole. This active metabolite then binds covalently to the potassium- transporting ATPase protein subunits, found at the secretory surface of the gastric parietal cell, preventing any stimulus. Because the drug binds covalently, its effects are dose-dependent and last much longer than similar drugs that bind to the protein non-covalently.

This is because additional ATPase enzymes must be created to replace the ones covalently bound by pantoprazole. Esomeprazole is used to manage gastroesophageal reflux disease, to prevent stomach ulcers, and can be used to help treat the effects of a H. pylori infection.

Excretion

Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. Esomeprazole is completely eliminated from plasma, and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous Esomeprazole is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous Esomeprazole.

During administration of Esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours plasma clearance (CL) is approximately 5.9 to 7.2 L/h.

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S-and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide.

By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

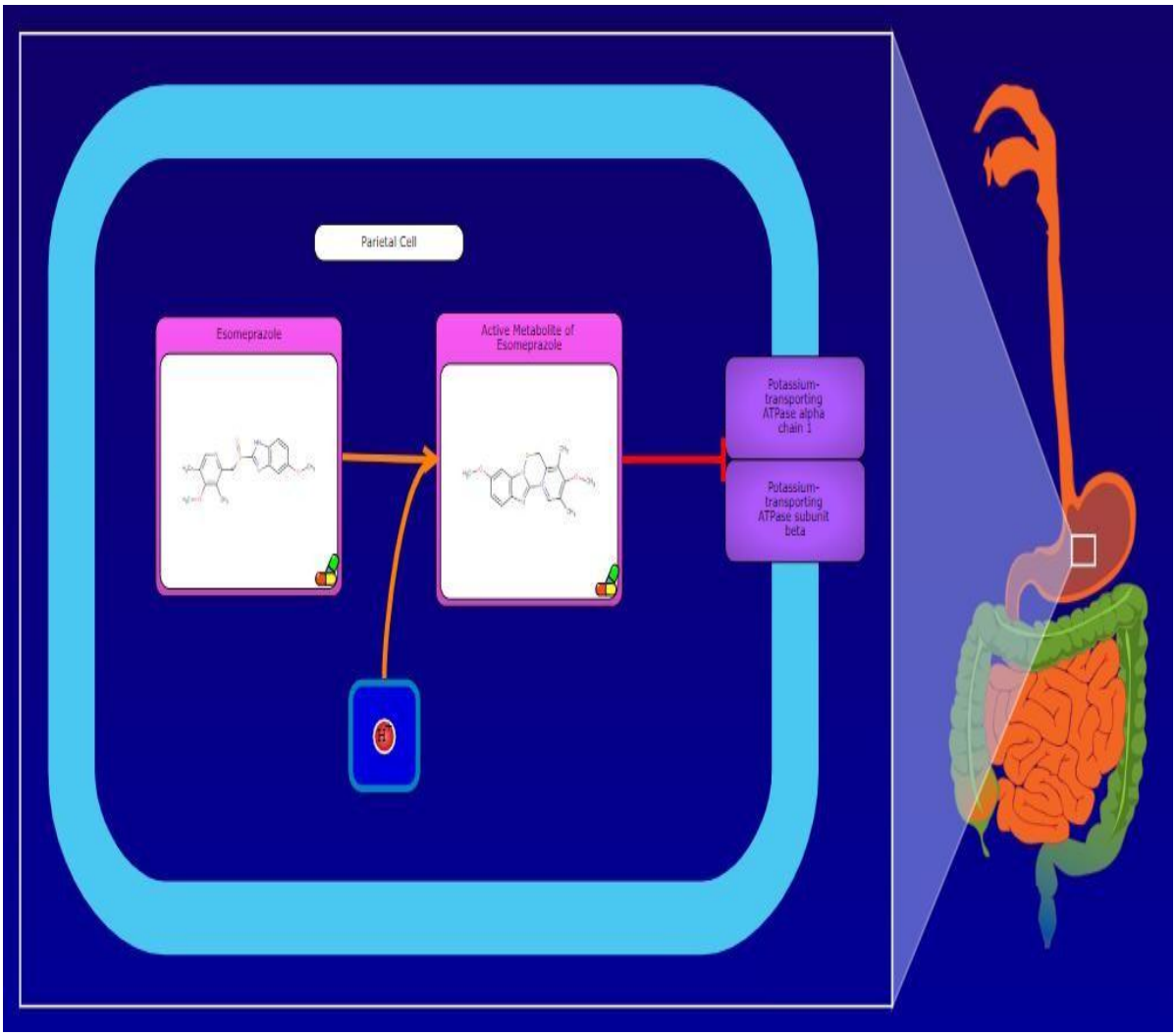
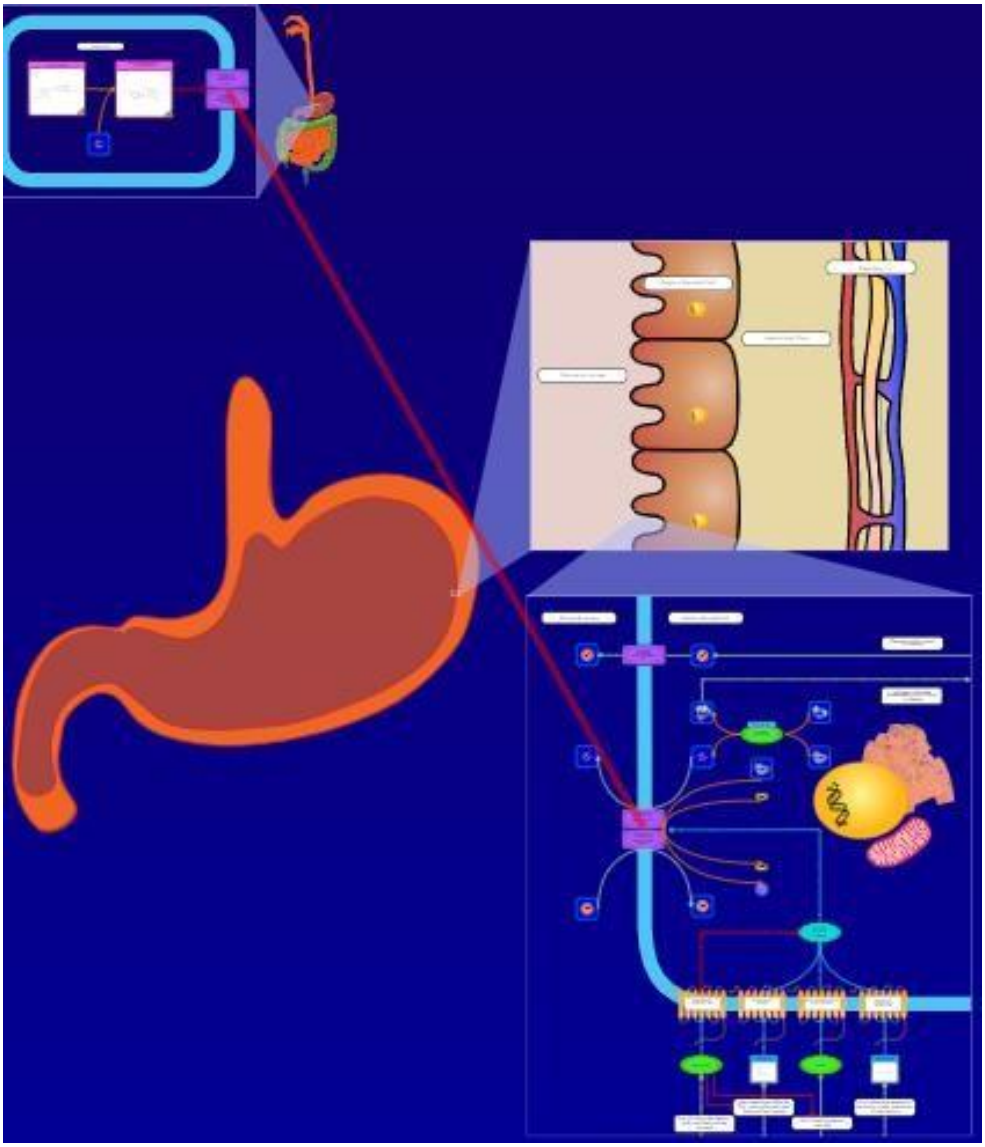


Figure No. II.



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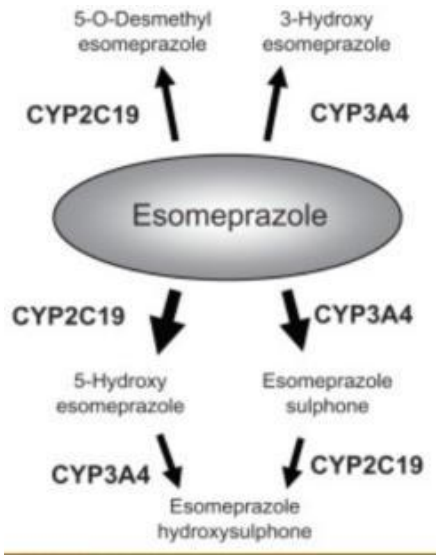

Figure No. IV.

Manufacturing Flow

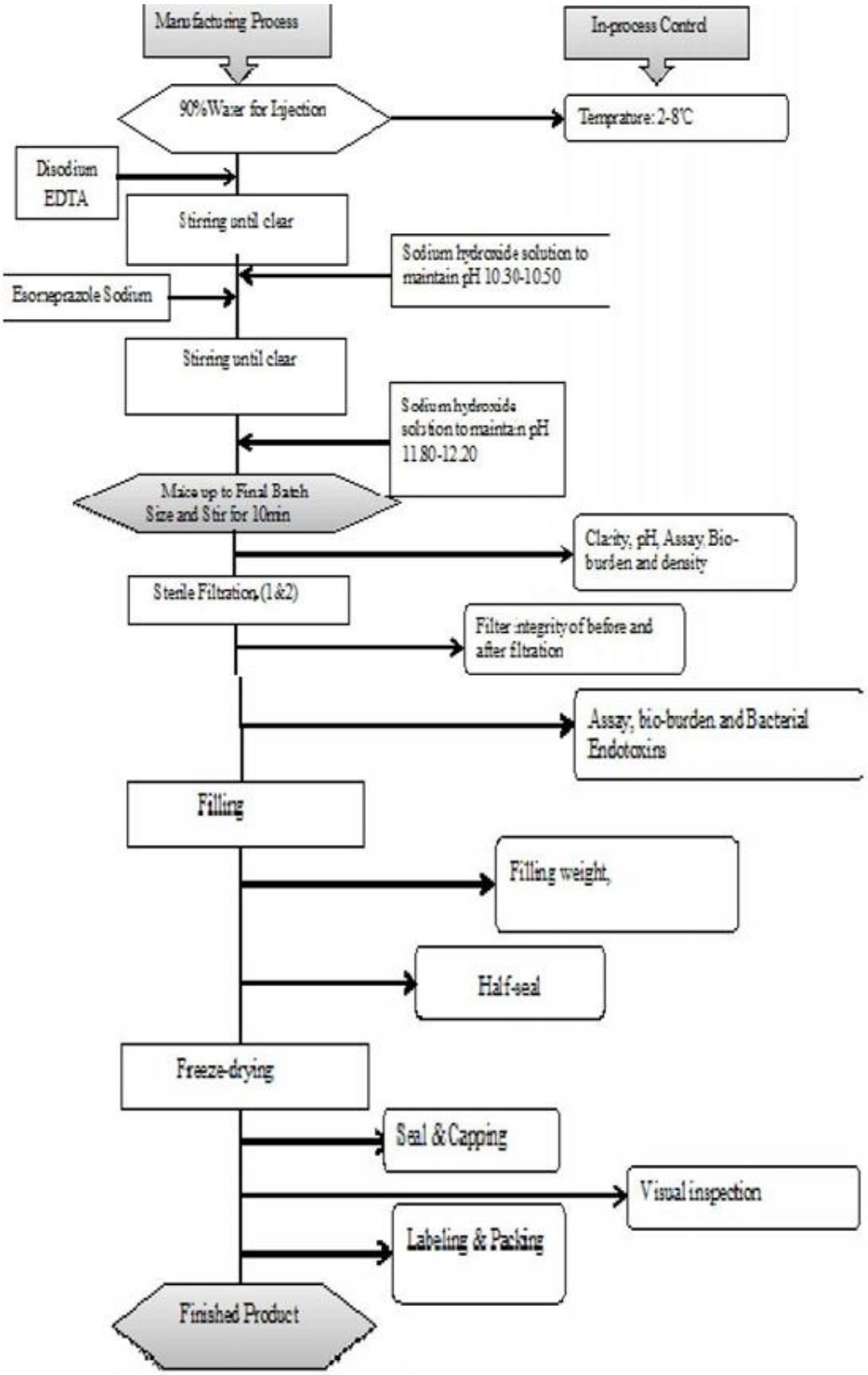

Figure No. V.

Critical Steps of Product Manufacturing & Related Role

1. **Dispensing:** Dispensing of Raw material & Primary packaging materials as bill of material required for batch quantity. Quality of all in-put materials should be ensure before use & supply from valid vendor.
2. **Preparation**: Preparation of in-put components and accessories including Cleaning, Sterilization & de-pyrogenation of Stoppers, Vials, Seals & Product contact machine parts & accessories including services like gas line.
3. **Manufacturing:** Product solution manufacturing carried out as master manufacturing formula. including monitoring of critical process parameters like Assay, pH, Temperature, Volume make-up etc.
4. **Filtration:** After getting results of Bulk Solution, next step is 0.22 micron Filtration using sterile membrane, vessels & accessories.
5. **Filling:** Aseptic Filling carried out under Grade- A environment with monitoring of critical parameters and Half Stoppering
6. **Lyophilization:** Lyophilization is carried out using a simple principle of physics sublimation. Sublimation is the transition of a substance from the solid to the vapour state, without passing through an intermediate liquid state. Lyophilization is performed at temperature and pressure condition below the triple point [Utetic Point], to enable sublimation of ice. Liquid filled- half stoppered vials loaded in lyophilizer. After formation of lyophilized powder-cake, full stoppering carried out under vacuum with sterile nitrogen blanketing and stoppered vials un-loaded & taken for final sealing with aluminum seals.
7. **Leak Testing & Inspection**: 100% units were inspected for required quality with random leak testing of vials.
8. **Labeling & Packing**: Labeling and packing with carried out with proper label details like Label claim, manufacturer License number, Manufacturer/ marketer name & address, Batch Numbers, Manufacturing date & expiry, Storage conditions, MRP, Precautions & administration & usage instruction with leaflet.
9. **Finish Product Testing:** Testing of FG performed as per specification to ensure product quality with respect to Identification, Purity, Impurity, Quality / Quantity, Sterility, Endotoxin & Particulate load etc.
10. **Batch document Review & Release**

Batch document of production /packaging, Testing, In-process checks & monitoring reviewed by QA. After satisfaction of all records & results, batch can be release for market distribution.

OBJECTIVE OF RESEARCH

To develop & validate the analytical Assay Test procedure as a Critical Processing Parameters at the Bulk-Solution stage during manufacturing of Esomeprazole Sodium Injection 40mg for the following reasons:

- To reduce the Assay testing cost.
- To reduce the Testing period
- To have assay results in minimum time More Particle approach to increase line productivity.

Need of Assay Test Development

Esomeprazole Sodium Injection 40 mg is sterile dosage form. Being Sterile dosage form it is necessary to handle the product process within minimum possible time. However as per current manufacturing process flow, 5-6 hours required to sample & test the bulk solution for Assay by HPLC method. Which leads to holding of bulk solution during manufacturing. It may risk to bio-burden.

Hence different approach needs to introduce & develop which help to reduce testing time period.

Category of Analytical Method

Qualitative Analysis: It deals with the identity of materials. It's far challenge with what factors or compound found in Sample.

Quantitative analysis: It presents numerical records concerning the quantity of analyte in measured quantity of sample.

Modern-day bodily strategies of evaluation are extremely touchy, providing precise and particular facts from small samples of materials, those are part of maximum element, swiftly implemented and in trendy. The observation of analytical chemistry presents ideal of education for almost all scientists. The course in quantitative evaluation is a totally crucial hyperlink inside the chain of research that develops the clinical potential inside the chemist with its a couple of emphases on concept, laboratory work and high accuracy. Quantitative evaluation is one of the maximum precious courses. There are various strategies used in Quantitative evaluation that are widely labeled as Chemical/Classical strategies.

Sampling Methods

Sample of bulk solution shall collected from the bottom of manufacturing vessels, after completion of manufacturing process & final volume make-up.

Sample should collect in clean dry USP-I glass bottle for chemical / instrument testing and use clean/sterile bottle for microbial tests.

Analytical Techniques

For Pharmaceutical evaluations is the fundamental part of the pharmaceutical sciences. In pharmaceutical analysis section, the studies analyst is chargeable for 3 critical capabilities viz:

a) Improvement of analytical method for raw substances, lively components and chemical intermediates of the product.
b) Improvement of analytical strategies for selective analysis of drug, excipients, degradation products and impurities together with identity of deterioration product, degradation and volume of deterioration while saved at ambient and accelerated conditions.
c) Development of test method for micro and semi- micro quantities of drugs and its metabolites in organic system.
d) Sampling testing of intermediate & in-process checks.

Technique Development

Approach validation is the manner used to verify that the analytical system employed for a particular take a look at is appropriate for its supposed use. Effects from technique validation may be used to decide the nice, reliability and consistency of analytical outcomes; it's miles a quintessential a part of any precise analytical practice. It’s miles the procedure of defining an analytical requirement, and confirms that the approach underneath consideration has overall performance capabilities consistent with what the application requires. Use of system this is within specification, working effectively and accurately calibrated is fundamental to the method validation process.

Pretty regularly method validation evolves from technique development and so the two sports are regularly carefully tied, with the validation observe employing the strategies and steps within the analysis as described with the aid of the method development. Analytical methods want to be proven or revalidated

- Earlier than their advent into ordinary use;
- Whenever the technique is changed and the trade is out of doors the unique scope of the technique
- Whenever the conditions exchange for which the method has been tested (e.g., an instrument with special traits or samples with a exclusive matrix); and

Instrumental strategies

Those strategies are primarily based upon the dimension of bodily residences of a substance inclusive of electric or optical and to correlate them for dedication of awareness of analyte. Those homes are being exploited for traits of analytical strategies together with spectrophotometry, HPLC, GLC, Polarography, etc.

Now a day's instrumental techniques of evaluation are widely accepted over the classical strategies. These methods are extremely sensitive, supplying specific and specific statistics from small pattern materials. Relying upon the character and form of fabric, either single or in mixture, an appropriate technique of analysis is followed.

Instrumental methods are typically a good deal faster than chemical methods and are applicable at attention a long way too small to be amenable to determination by way of chemical methods and find wide software in industry.

Benefits of Instrumental Techniques

- Small sample may be used
- Excessive sensitivity is acquired
- Measurements received are reliable
- The dedication may be very speedy
- Even complex pattern may be dealt with easily

Different Type of Testing Methods

1. Potentiometory Titration
2. HPLC Basis Analysis
3. UV Spectroscopy Testing

Advantages of Method Development on UV Spectroscopy basis with respect to other Test method for Bulk Solution stage

1. Less sample quantity required.
2. More accurate in compression with respect to Potentiometory Titration
3. Cost effective, HPLC test accuracy is satisfactory, but test method is costly & more time consuming.
4. Time period required less for sample preparation & testing.
5. Test method based on UV Spectroscopy is as accurate equally to HPLC test method results.

Mechanism & Working principle of Test Method: UV spectroscopy obeys the Beer-Lambert law, which states that: when a beam of monochromatic light is passed through a solution of an absorbing substance, the rate of decrease of intensity of radiation with thickness of the absorbing solution is proportional to the incident radiation as well as the concentration of the solution.

The expression of Beer-Lambert law is- $A = \log (I0/I) = Ecl$

Where, A = absorbance

I0 = intensity of light incident upon sample cell I = intensity of light leaving sample cell

C = molar concentration of solute L = length of sample cell (cm.)

E = molar absorptivity

From the Beer-Lambert law it is clear that greater the number of molecules capable of absorbing light of a given wavelength, the greater the extent of light absorption Molecules containing π-electrons or non- bonding electrons (n-electrons) can absorb energy in the form of ultraviolet or visible light to excite these electrons to higher anti-bonding molecular orbital's.[2] The more easily excited the electrons (i.e. lower energy gap between the HOMO and the LUMO), the longer the wavelength of light it can absorb. There are four possible types of transitions (π–π*, n–π*, σ– σ*, and n–σ*), and they can be ordered as follows: σ– σ* > n–σ* > π–π* > n– π*

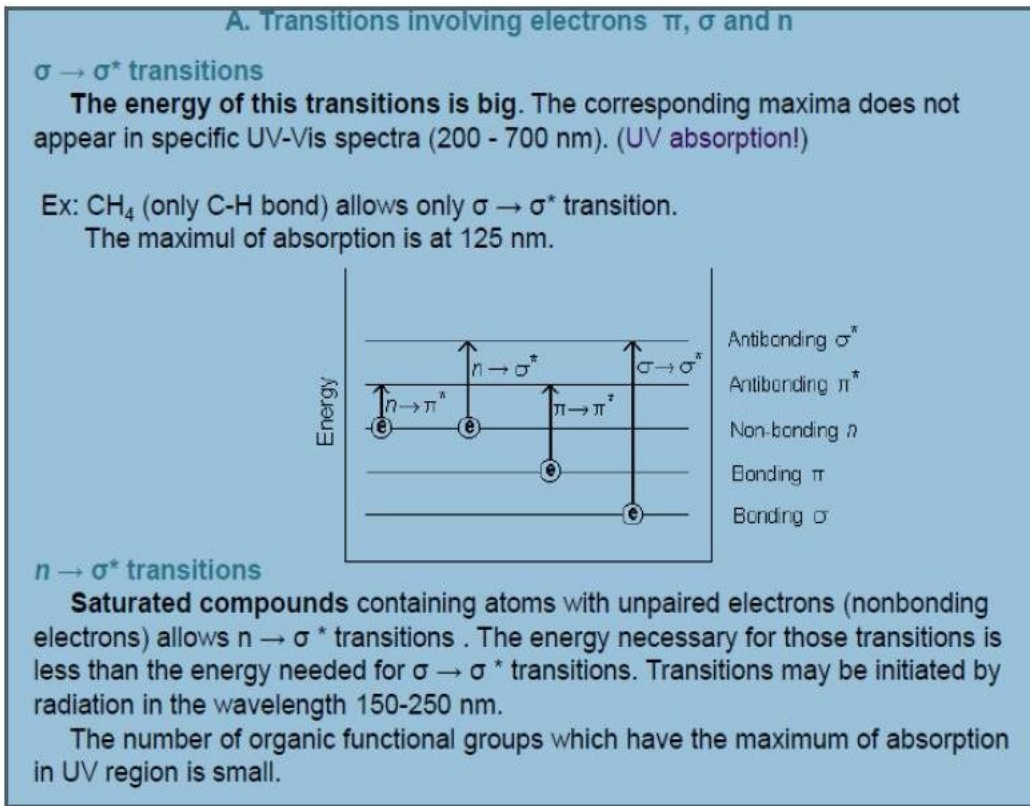

Figure No. VI.

METHOD VALIDATION

Once the technique for analysis has been chosen, it is very important to validate the method used. The validation of a method is very different from validation of recovery.

It is very important to scientifically establish the limits and acceptance criteria to validate the analytical method of analysis.

A validated method is one that is rugged and robust enough to measure the quantity, Purity.

It can Specificity, Accuracy, Linearity, Range, Precision, Intermediate-Precision, Repeatability, Reproducibility, Robustness, Ruggedness, Detection Limit, Quantitation Limit Validation Protocols.

VALIDATION PROTOCOL

A Validation Protocol is necessary to define the specific items, equipments / instruments required, Testing procedure required to validate the testing method. Documentation required to provide the at least following information:

- Background

- Purpose of the validation study
- Scope of the validation study
- Responsibilities for performing the validation
- Study
- Sampling procedure to be used
- Testing method to be used
- Acceptance criteria
- Change control
- Approval of protocol before the study
- Deviations

VALIDATION REPORTS

A validation report is necessary to present the results and conclusions and secure approval of the study. The report should include the following:

- Summary of or reference to the procedures used to sample and test.
- Physical and analytical test results or references for same, as well as any pertinent observations
- Conclusions regarding the acceptability of the results, and the status of the procedure(s) being validated
- Any recommendations based on the results or relevant information obtained during the study including re-validation practices if applicable.
- Approval of conclusions
- Review any deviations for the protocol that occurred.

CONCLUSION

To develop & validate the analytical Assay Test procedure as a *Critical Processing Parameters* at the Bulk-Solution stage during manufacturing of Esomeprazole Sodium Injection 40mg for the following reasons:

- To reduce the Assay testing cost.
- To reduce the Testing period
- To have assay results in minimum time
- More Particle approach to increase & enhance line productivity
- To reduce the risk related bio-burden of bulk- solution of product.

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