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REVIEW ARTICLE

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A Study on Validation Method in Pharmaceutical Dosage Form

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INTRODUCTION

The pharmaceutical industry is fundamental element of health care systems. These Industries discover, develop, manufactures and commercialize the medicines for human and animal health. A pharmaceutical dosage form contains active pharmaceutical ingredient (API) and inactive substances (excipient). A biologically active material in pharmaceutical dosage forms are called as an active pharmaceutical ingredient. Some dosage form may contain more than one active ingredient. Pharmacologically inactive substance is called as an excipient. It is usually utilize as a carrier for the active pharmaceutical ingredients. Some time, an active pharmaceutical ingredient (API) cannot be administered simply because API will not absorb in the human body. In this cases an excipient are used, to dissolve or mixed with drug substance. For a potent API sometime excipients are used for bulk up formulations which is useful for accurate dosage. Different types of excipients can be utilized based on medication form and the route of administration.

Pharmaceutical dosage forms are exists based on the method of administration. Majorly these dosage forms are classified in three types like liquid, solid and semisolid dosage forms. Liquid forms of dose are called as a liquid dosage form where in administration liquid form of dose of chemical compound given as a medication. General dosage forms include tablet, capsule, syrup, suspension and parental dosage forms. Based on the dosage form the route of administration for drug delivery is selected.

As different medical treatment requires different route of administration, for a single particular drug, different dosage forms are available and can be used. In some case like nausea and vomiting oral administration is critical, in that case alternative dosage form like parental, nasal, inhalation etc. can be used.

Moreover, for a particular drug it can be used in specific dosage form only as because of molecule chemical stability and other pharmacokinetics concerns. Some of the drug cannot be given oral administration as they degrade or convert in to metabolism in gastrointestinal tract (GIT) before to reach to site of action.

Drug development process must ensure through several stages in order to produce a product that is safe, efficient, quality, and has complies with all regulatory requirements. The prime target for pharmaceutical development that product should be commercially present in required dosage form. This systematic product development process undergoes several logistics cycle. In this process if it lose center of concentration at any stage, the process results long and complex outcome. Over the time the pharmaceutical industry has significantly increased concentration during development on safety, efficacy and efficiency.

For all the scientists and laypersons the clinical study is best known and the most noticeable during product development. Pharmaceutical dosage form cannot be commercialized without successful clinical study.

OBJECTIVE

The present work objective is to develop a analytical method which is stability indicating for determination of active content, antioxidant content, rate of dissolution, and majorly impurity profile in pharmaceutical dosage form which covers all process related impurities and degradation impurities. The Present work also extended for identification, isolation and characterization by hyphenated techniques for potential degradation impurities which are found during stability testing, manufacturing process and stress study of formulation drug products.

Based on above objective and literature search we have selected following different pharmaceutical dosage form drug for performing research in analytical method development and method validation.

1. Fexofenadine RS method development and by Reverse phase-Ultra Performance LC

2. Identification and characterization of a novel potential degrading and; development and validation of stability indicating RP-LC method for Nicardipine impurities in injectable dosage form.

3. Development and validation of a reverse phase-liquid chromatographic method in paricalcitol hard gelatin capsule dosage form.

4. Development and validation of a stability indicating RP-LC method for the estimation of process related impurities and degradation products of Dipyridamole Retard capsules.

Discovery Research

Discovery research is the mechanism where a particular drug will be discover in a molecule level which will use for target defected cell. This drug identification process derived from the biochemistry of the disease. This research process generally starts with biochemical target identification which is triggered for disease. First of all model compound is projected and advanced different types of scientific toll are used to design new molecule.

Several similar molecules are manufactured to develop a model. At this phase, most of the pharmaceutical companies believe in hyphenated techniques to determine the chemistry. This advanced technologies and screening is foundation at this stage. In the drug discovery information on human genome via genomics will give direction for targets for discovery of drug.

Preclinical Phase

Preclinical phase is the stage where before dosing new developed drug to human body, verification performed for its safety and efficacy. The pharmaceutical company generally distinguishes this drug in laboratory only by cell culture of species. In preclinical phase first test are performed on animal to check safe usage and sufficient effectiveness to test on humans. Pharmaceutical company needs to take approval from regulatory bodies before dosing new developed compound to human.

Clinical Phases

Generally these clinical trials are carried out on humans who have specific disease.

The prime aim of this exercise is to confirm the assumption. For establishment of presumed outcome, these clinical trials are well planned by established systematic protocol. This protocol has structured mechanism which specifies about acceptance criteria of results and endpoint determination classification. Protocol designed acceptance criteria is generally not change during the study. During this clinical study responsible in charge called as Principal investigator is tracking the complete study.

Analytical method developments to monitor the synthesis process and drug product development are very important aspect in pharmaceutical product development. Generally, this process quality determination performed by assay, related substance and drug dissolution rate. It is also some time required to check moisture content (by Karl fisher method), uniformity of dosage form and specificity of test. These all developed analytical methods are validated as per regulatory guideline to support clinical phase trials.

API and Finished Product Common Studies

To understand the stability nature of API and finished dosage forms few initial study needs to performed. To gain information on physicochemical property of the drug substance and finished product, stability studies are carried out like open dish (i.e.; none protected) and photo stability study. Stability studies are also conducted in different packaging configuration.

In this packaging study, primary, secondary and tertiary packs are evaluated for API and finished product stability testing. This study can be performed in presence of light and thermal to evaluate stability of API and finished product.

Based on safety and efficacy results of new developed compound, conclusion can be taken to move forward for clinical phase-III. In this clinical phase-III, bigger populations of patients are administered with new developed drug. The outcome of the study can be new drug is similar to the marketed or reference product. Final outcome of the study is if successful than the new drug product can be commercialized followed by regulatory submission and approval.

New Drug Product-Impurities Level

Understanding of impurity profile (specified and unspecified degradation product) in new dug product is very important aspect of pharmaceutical finished dosage forms. At this stage impurity reporting and control in drug product are decided. Based on this study pharmaceutical drug product storage conditions are recommended. If any unknown impurity are increasing during this study than its route cause are identified like impurity are because of degradation or drug excipient interactions. Sometime impurity may rise from packaging material and conditions. If unknown impurity are crossing the identification threshold than it needs to isolate, identified and characterized by advanced technique. Degradation products which are toxic and potent identification of those degradant are necessary. Impurity profile of

new developed drug is always compared with marketed product.

This investigation stage related to impurity profile give preliminary direction to development scientist to understand the chemical behavior of the drug product. Based on impurity profile of drug product degradation pathways can be predicted, finished dosage form expiry date can be predicated and, packaging and storage condition can be finalized.

Impurities in Drug Substance

Understanding the impurity profile in drug substance is almost same like drug product. In new drug substance impurity profile process related and degradation related both impurities are monitored. Residual solvent used in synthesis of drug substance are also monitored. Analytical method are systematically developed and validated as per regulatory requirement. LOD and LOQ are established, LOQ should be less than the safety level. Based on this study specification and impurity edition/deletion are done at this stage.

Drug Substance Development

The processes to manufacture the drug substance are finalized. To understand the stability of drug substance stability studies are conducted with predefined protocol and validated analytical method.

Formulation Development

Based on information of clinical phase I/II the formulation strategy for new drug product are designed. Basically, inferences for selection of strategy are medical requirement and market requirement. Manufacturability of new formulation drug product is checked at large scale. Stability testing for new formulation is initiated as per protocol to check its chemical stability during stability. Before selecting an excipient for new formation Drug-Excipient compatibility study are performed for its physic-chemical property.

Regulatory Submission

The formulation drug product is being made ready if clinical phase-III study is positive. All data are submitted to regulatory agencies which include clinical phase data, chemical stability data and analytical related document. If regulatory bodies approve the new drug product application, pharmaceutical company prepares to commercialize the product.

Pharmaceutical company also should perform clinical phase-IV in large number of populations to further prove clinical phase-III data. The company at this stage also starts awareness programs with doctors, specialist and other related personals for prescribing their new drug product.

Regulatory bodies of pharmaceutical/medical related in the world:

- World Health Organization (WHO)
- International Conference on Harmonization (ICH)
- World Trade Organization (WTO)
- Heads of Medicines Agencies (HMA)

Analytical Development Lab Quality system

The pharmaceutical company generally develops a finished product dosage form globally. Simultaneously analytical scientist also should develop a method and validate the method in such way that it can be applied globally. Analytical method should fulfill all global requirements which are guided by regulatory agency. To achieve this harmonized method goal, need to make quality system which meets the entire regulatory requirement. Analytical method validation should be performed with predefined protocol which has acceptance criteria. This activity should be systematically performed, document and monitor by superior.

All personal involved in this activity should be qualified in this area. All instruments and facility also need to qualify before use for this purpose.

ANALYTICAL CHEMISTRY

The quality, safety and efficacy of a pharmaceutical product is monitored and maintained throughout the process of manufacture and stability of product by a series of tests from quality control. The quality control test involves methods which embrace chemical, instrumental, microbiological or simply biological procedures. The pharmaceutical medicines testing are based on the separation, identification and purification of a pharmaceutical.

Analytical chemistry includes two important steps in analysis, are identification and estimation of the component of a compound. These techniques are also describes as qualitative analysis and quantitative analysis. Qualitative analysis is technique which estimates the particular compound presence or absence and quantitative analysis is a technique which estimates, how much quantity present in mass or chemical mixture. The qualitative method is

relatively simple but quantitative analysis is more complicated.

Furthermore, Analytical methods can be classified into two analysis like classical analysis and instrumental analysis. Classical analysis is also called as wet analysis; separation is achieved from precipitation method, extraction method and distillation method.

Instrumental analysis is achieved from light absorption, fluorescence, conductivity of the analyte by chromatography and electrophoresis methods. Various types of separation techniques are exists which includes adsorption, centrifugation, chromatography, crystallization, decantation, distillation, electrophoresis, evaporation, extraction, precipitation and magnetic separation. Different type of quantitative methods are present such as chromatographic techniques are HPLC,UPLC,GC, TLC, Ion chromatography and column chromatography etc. and spectroscopy techniques are atomic absorption spectroscopy, UV/Visible, FT-IR, Mass and NMR.

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