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Analytical Chemistry, Preformulation Research and Regulatory Requirements

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Abstract: *Experimental data for preformulation study is significant to develop a stable and safe drug product and forms the basis of preliminary information required to develop and design the final formulation. The experience, knowledge of drug substance components and ingredients planned to use in formulation, plays an important role in designing the preformulation studies. Co-ordination between the departments such as mainly analytical research and formulation research in conducting these studies i.e., interdepartmental co-ordination, exchange of information and knowledge to perform research experimentation is necessary, to understand the knowledge of the complete lifecycle of the drug product. Analytical chemistry deals with methods of analysis developed and planned to use for content determination of related substances/impurities leads to get noteworthy information required to develop stable formulation and to determine the stability of the drug product. The usage of multiple instrumental techniques for identification, estimation and characterization techniques are essential to get the results of the research studies. The cGMP and GLP requirements should be fulfilled and followed as per the respective country specific regulatory guidelines.*

Keywords: Analytical Instrumental Techniques, Methods of Analysis, Pharmaceutical Regulatory Authorities, Preformulation Study

I. INTRODUCTION

Preformulation experiments for further research, is a very important step and is base in designing of final formulation. The search and collection of scientific data as essential to develop new formulation and its quality control are part of these studies. The rationale to implement and apply the scientific concepts to design the drug product formulation, is to avoid the multiple trials by saving time and the related efforts so as to achieve the optimized formula of the final formulation with few experimentations based on the scientific principles.

Many parameters as well as experimental factors need to be considered such as experience, knowledge of drug substance component and ingredients.

In this process of research study, multiple aspects should be considered such as the drug substance i.e., API, the drug product, the excipients/ingredients that are going to be used in the formulation, and such as physical properties, chemical properties of all ingredients, analytical method to analyze all the ingredients of interest along with pharmacokinetic as well as pharmacodynamic properties of active compound. The research goal should be set, in such a way that the final product is safe as well as stable and is effective for its use.

To ensure, the final optimized drug product formula by performing various carefully designed formulation trials, for the safe as well as effective use, the experimentation studies executed should not be limited only to the characteristics/characterization of the active pharmaceutical ingredient but also to the ingredients/excipients planned to use in the product and their possible interactions which may generate impurities/related substances which could be possibly controlled by avoiding the planned use of the particular excipient in the formulation which may further lead to degrade the active drug substance component and in turn, the stable formula can be achieved.

The development stage of research, the manufacturing stage and the post marketing studies/research should be conducted to gain the confidence as a part of assessment to ensure the safety and stability.

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The research experimentation carried out by proper coordination of analytical research department, formulation research department and quality control departments are necessary and are carried out for the related parameters throughout the development and lifecycle of the product.

Preformulation study, development of drug product, analytical methods of analysis, quality control, stability and post marketing studies are interrelated and the entire sequence is necessary to consider in the experimental studies, should be checked at each of the selected time point to understand well. The references [1-14]are studied as of the literature search, available to gain and understand the knowledge, information and related specific guidelines.

The regulatory considerations as specified/mentioned by regulatory agencies/bodies (e.g., ICH, Food and Drug Administration-FDA, EU guidelines) should be followed to meet the regulations and compliance, as specified.

This article discussed about scientific aspects and approaches considering regulatory documentation and compliance. The opinions or views, procedures and the related acceptance limits as described, are based on the literature/documents/guidelines and to describe in a systematic way however each nation/country related specific applicable guidelines from the regulatory agencies/bodies should be used.

II. Preformulation Research

At the start of project initiation, the study of the preformulation experiments should be performed because the information obtained at an early stage of project initiation/development stage is needed to assess and evaluate the parameters and to collect necessary information as obtained and required. Delay in executing the experimental studies will not be of so much useful as the time and resources will be already utilized to optimize the formulation. If any critical observations are not obtained at an early stage of research during development and at later stage of the research are observed which may be cause of re-work of research, this can be avoided as late stage received information at an advanced stage of formulation will not be useful to save time with resources, which could have been possibly avoided, if the experimental data obtained from preformulation study performed is available after initiation of research work.

The need to conduct the preformulation research studies, is that the specifications, for the drug product are essential to be established to check and as a part to get data for impurity estimation/content determination, so that the control of impurity/related substances at the initial stage of research/development can be possible, by getting the required data/results by performing the preformulation research study. By this study, information, results, data and from the observations obtained, specifications at an early stage of study can be established.

To ensure the quality of proposed drug product, specifications prepared are tentatively set at an initial development stage and can be changed based on the results obtained during development stage of the research study and as within the allowed limits as specified in the guidelines. Specification includes tests such as identification, description, assay test, content uniformity, dissolution test, water content or loss on drying, chirality, related substances or organic impurity content, residual solvents determination etc.

Chemistry, materials, chemical properties and physical aspects of the all the constituents of formulation should be studied before initiation of development. The drug excipient study helps to understand the compatibility of the drug with each excipient, gives results for degradant impurities generated by interaction of excipients with the drug and from these observations, particularly selected excipient/ingredient leading to generation of potential degradant impurities can be avoided and such a particular excipient/ingredient compatible with the drug substance can be chosen for, in the next step of optimization of the formulation. This can help to save time required along with resources to optimize the final formulation by avoiding multiple efforts for the trials required by use of different excipients during formulation, as information is available for each excipient and choice to select specific excipients compatible in the formulation studies. The drug and the excipient interaction studies should be planned to execute at initial condition as well as at different time of intervals as depending the data to be obtained for stability information requirements which is helpful in assessment for prediction of stability of the drug substance with excipients and also from these studies, possible degradation impurities or related substances can be predicted which aids to develop a stable as well as safe drug product.

The evaluation of physical properties of the components, chemical properties of materials and information required as necessary to develop analytical methods should be studied. This forms the basis for analytical method development.

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Excipient/ingredient information, drug product formulation design, and main component characteristics should be studied before proceeding to preformulation research. The experiments should be planned to perform preformulation research studies. Methods required for estimation of contents are finalized to determine targeted contents, research experiments should be planned and executed. After at each stage, data obtained should be carefully examined to get maximum information and formulation batches should be planned based on the information obtained. During these research studies, other developmental studies consisting as a part of these research studies such as friability test, dissolution testing, hardness test, and disintegrating testing should be planned and performed.

The packing studies should be performed and should be selected based on stability as well as suitability for different types of dosages forms, as required.

Stress study experimentation to assess the potential degradants (to predict the possible pathways) should be conducted and to control the degradants in the drug product. The stress conditions, time intervals and analytical testing should be carried at the conditions as mentioned in the stability guidance documents and at time intervals specified. The studies should be conducted on exposed conditions as well as marketed packing containers.

After completion of entire research studies, a comprehensive report including all the experimental design and results should be prepared. The conclusion should be drawn from the obtained results, helpful for further studies.

III. Analytical Chemistry For Preformulation Research

Analytical methods are very important in estimation of targeted contents in the drug products. Analytical methods of analysis can be used to analyze the samples qualitatively as well as quantitatively and appropriate analytical technique or instrument with proper method is vey essential to get the results of the research studies. The use of various analytical techniques or instruments such as IR, UV spectrophotometer, XRD, NMR, Mass spectroscopy, HPLC, GC, Ion Chromatography, SFC, DSC etc. are required to get the data essential and necessary for the research studies.

The solubility studies should be performed for drug substance as the information from solubility studies is helpful in method development as well as from the studies at different pH and in organic solvents, the absorption of drug at specific pH can be established and from solvent solubility, solvents planned to be used in the diluent can be optimized. Intrinsic solubility of the drug substance and in mixture with different excipients should be conducted at room temperature and 37.0°±0.5°C in different buffers across pH range selected for the study.

The solubility study by the way of equilibrium method i.e., saturation solubility study performed by dissolving excess substance in the medium for longer time till the equilibrium is reached, as this solubility study is required to perform because the percentage drug release of the drug substance from the drug product havean effect due to solubility, if in case of poorly soluble drugs.

The data obtained from solubility studies and the knowledge of permeability together can estimate the BCS classification from class I to class IV and can be assessed to categorize amongst these classes from class I to class IV. This information will be useful and is the basis in bioavailability as well as bioequivalence studies.

Moisture content or hygroscopic nature should be studied as it will have impact on formulation of manufactured batches and is useful in controlling the conditions required to avoid the increase in moisture content or hygroscopic nature. The materials that are hygroscopic in nature are not given preference to use in the formulation trials and are less likely considered if it shows stability even if upon the material shows tendency towards to moisture, provided that the material is stable and does not have effect on the formulation of drug product. Special storage conditions are required for high hygroscopic materials and if used in manufactured batches, there may be possibility of batch-to-batch variation in the moisture content, if it is not stored in proper recommended conditions. Due to the nature of hygroscopicity, there are possibilities of chances of increase of impurities, if the drug substance is likely susceptible to the degradation for the condition of hydrolysis and also may have possibility of an effect on dissolution rate/release during dissolution testing of the product at initial and stability conditions of different time intervals.

Along with solubility, polymorphic form should be studied, as different polymorphic forms may have different physical and chemical propertiesand have effect during manufacture of a drug product processes such as granulation process, milling process and compression stage. The most stable polymorphic form which does not change its ratio during stability and does not have effect on safety and efficacy is selected.

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In the preformulation study, determination of the dissolution rate is essential, as this plays a significant role in the bioavailability of the drug. Dissolution rate is affected by particle size of the drug substance, crystalline nature of the drug substance such as polymorphs, hydrates and pH of buffer and its concentration.

Forced degradation studies such as acid, base, oxidation, hydrolysis, photostability, heat and humidity should be conducted so as to evaluate the potential degradants along with the pathways can be assessed and to control the degradants in the drug product.

The tests during formulation studies such as assay, content uniformity, dissolution, water content or loss on drying, related substances or organic impurity content are very important and limits for the specifications can be established based on the data obtained within allowed limits as per the guidelines.

The recommendations from U.S.FDA to use of PAT i.e., process analytical technique for drug substance as well as drug product as it a system for design, analyze and control of manufacture by timely measurements for critical attributes for a drug product quality.

Analytical methods should be validated as per the respective guidance documents for the targeted market and regulatory bodies, for the application intended. Validation of the analysis of method is the procedure by way of performing scientific studies to generate evidence along with data, with predefined limits. Validation of method of analysis approves that the method planned to use further for analysis is specific as per established criteria.

IV. Regulatory Requirements

The preformulation studies are significant. Good manufacturing practice i.e., GMP are recommended to follow by regulatory authorities as it is mandatory requirement for the manufacture of drug products to safeguard the quality and as a control for the quality standards for the intended use.

Good laboratory practice i.e., GLP are required to following the laboratory as per SOP i.e., standard operating procedures available in an organization and prepared as recommended by regulatory authorities as it is mandatory requirement as a procedural step to control and ensure the quality of manufactured drugs products. These are quality systems for non-clinical health studies by plan, monitor, record, archive and report for intended purpose.

The compliance documents are required to present during audit or the inspection of the facility of the site by the health authorities. These documents include SOPs (standard operating procedures) , development reports, validation protocols and reports, STP (standard test procedure) or MoA (method of analysis), technology transfer reports, preformulation development reports, stability protocols and reports, CoA (certificate of analysis), standard characterization reports, specifications, investigation reports, OOS (out of specification) reports, incidents and deviations, batch profile results, change controls, software validation protocols and reports, laboratory notebooks, cleaning validation protocols and reports, analytical data, batch manufacturing records etc.

Regulatory documents for application of NDA or ANDA and the related compliance are necessary to get approval from authorities. If any observations are noted by the respective authorities, upon fulfillment of the compliance of such observations, approvals are granted for the product. Post marketing studies should be conducted as a part of constant assessment and evaluation of a drug product.

V. Conclusion

The data from preformulation research studies helps in planning, design of formulation of a drug product at an early stage of initiation of development of formulation of drug product and is helpful in saving of time with resources. This scientific data obtained is useful in lifecycle of a drug product development. The use of multiple analytical technique is essential to obtain the data required during the research studies. All the applicable respective current good manufacturing practices and good laboratory practices (cGMP & GLP) should be followed as a part of mandatory requirement for regulatory filing and approvals with respect to the respective country specific regulatory guidelines, such as ICH, US-FDA, EU guidelines etc. The drug product developed and manufactured as per proper scientific studies and meeting the acceptance criterions as laid by the regulatory bodies during the entire life as mentioned for the drug product is safe and effective for human consumption.

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