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Pharmaceutical product development and preformulation studies: early approaches, present scenario and future prospects

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ABSTRACT

The inherent instability nature of a new drug will alter its desired form into undesired form when presented in a suitable dosage form with the excipient/s upon storage. The series of processes related to overcome such unwanted changes in the properties of drug is referred to as formulation development. The pre-formulation stage is an integral part of the pharmaceutical product development process, which supports the dosage form design of a new drug and its quality control. Hence, pre formulation is the initial step in the rational dosage form design of a drug alone and in its combined form. In early days this process was confined only for assessing few characteristics, but today this process is being considered as a formulation strategy and the tremendous technological advancement has been achieved in this field which enables us to save the time and money through planned management system. Use of glorious statistical softwares even based on artificial neural networking are made the task of preformulation and optimization process easier. The present article is framed with the objective to provide an in-depth insight into the basics and advancements taking place in the pharmaceutical product development process.

Keywords: Pre-formulation, Optimization, Product development, Artificial neural networking, Factorial design softwares

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INTRODUCTION

For the five decades, determination of few scientific data is collectively known as pre-formulation studies and has been developed for supporting the dosage form design. Historically, the concept of pre-formulation studies gained momentum in the late 1950s as a result of major shift in industrial pharmaceutical product development process. Till the mid 1950s, the main focus of product development process was to develop only elegant dosage forms and considerations related to interference of added excipients on stability and bioavailability of a final product. During this period, in fact, biopharmaceutics and pharmacokinetics were in their infancy stage, and however stability was a major consideration, most of the analytical methodologies were unable to detect the gross decomposition of drug in the formulation. When the advancement in analytical methods was took place, the concept of pre- formulation was originated. But the methods available were to detect the incompatibility of drug with added excipients involves lobour hours and money. With the birth of term pre-formulation it became easy and logical to check, ahead of time. By this way, the disaster is being prevented in advance.

Before the advent of pre-formulation study, developing the dosage form depended on the formulator's experience, some knowledge of the excipients used, and the basic functional product testing. Such a study is build on a knowledge of physical pharmaceutics, the study of physico-chemical principles, biopharmaceutics and the study of influence of formulation on the therapeutic availability of a drug product. The pre-formulation concept thus originated was initially meant for the benefit of drug producers. Later on this process imposed scientific principles and rationale on formulation development process to minimize the trial and error effects. Now it is an integral part of official requirement for INDs (Introductory New Drugs) and NDAs (New Drug Applications). [1]

Intelligent preformulation design is an important stage in the product development process. Application of advance technologies in this field made the formulation scientist to achieve his goal easier and the final outcomes expected to be more accurate and precise. Formulation scientist apart from his experience and knowledge have to effectively and significantly utilize these advanced technologies in the preformulation research study to meet the cost and time efficiency and to assure the quality of a final product. The softwares based on factorial design and artificial neural network methods available for preformulation research are generous tools offer interesting atmosphere and encouragement to the preformulation scientist to carryout his work efficiently.

Objectives of the preformulation studies

The pre-formulation study works on the following few basic goals and objectives,

- The study establishes the required physicochemical parameters of a new drug substance.

- The study also determines the kinetic rate profile of a pharmaceutically active compound.
- The study establishes the physical characteristics of the drug and
- The study finds out the compatibility of drug with commonly used excipients.

The physico-chemical properties of the drug molecule can affect the structure and stability of drug in the final formulation and alter the bioavailability and its therapeutic efficacy. Hence, due consideration should be given before the dosage form design. This can be achieved by evaluating the preliminary parameters of a pharmaceutically active compound. The study comprises determination of identity of the drug molecule, structure of the compound, molecular formula and molecular weight, various therapeutic indications, potential hazards, initial bulk lots and different analytical measures.

VITAL ARIAS OF PREFORMULATION REASERCH

Study of organoleptic properties

A typical pre-formulation process should always start with the study of organoleptic descriptions such as colour, odour and taste of the new drug and same is kept as reference to compare with the subsequent batches. These properties must be thoroughly screened for their influence on stability and bioavailability of the drug.

Bulk characterization

Crystal habit and internal structure of a drug substance can affect bulk and physicochemical properties which range from flowability to chemical stability. To obtain an appropriate dosage form it is very much essential to optimize the factors such as degree of crystallinity, hygroscopy, fine particle characterization, and powder flow properties.

Physico-chemical characterization

Preformulation solubility analysis focuses on drug solvent system that occurs during delivery of the drug candidate. It is also essential to study the effect of some physicochemical factors on solubility of a drug, because, solubility is directly proportion to absorption and ultimate therapeutic effect. Analytical methods that are particularly useful for solubility measurement include high profile liquid chromatography and gas chromatography. Preformulation solubility studies include effect of ionization constant on solubility, pH solubility profile, partition co-efficient, common ion effect and thermal effects.

Stability study of a drug

The stability is desired property for a drug delivery system, and stability study is one that ensures the quality of the product throughout its shelf life. In designing a drug delivery

system it is most important task to know the inherent stability of the pharmaceutically active compound. This gives an idea about selection of suitable excipient which is not responsible to form a toxic substance. The preformulation studies are usually the initial quantitative evaluation of chemical stability of a new pharmaceutically active compound. The aim of this evaluation is to predict, help, avoid and control the situations where the stability of drug is not compromised. This study includes preliminary compatibility tests, kinetic pH Profiles, solid state stability and liquid compatibility tests.

Dissolution study of drug and dosage form

The absorption of drug from dosage form depends on its dissolution profile. Dissolution of a drug particle is controlled by several physicochemical properties like crystal habit, particle size, solubility, surface area and wetting properties. Hence, this study can be used to identify potential problem areas. The study includes determination of biopharmaceutical aspects, semi in-vitro testing and in- vivo testing.

PREFORMULATION: A preliminary research process

Pre-formulation testing encompasses all studies enacted on a new drug compound in order to produce useful information for subsequent formulation of a stable and biopharmaceutically suitable drug dosage form.[2] This process is usually defined as the science of the physicochemical characterization of candidate drug. However, any study which defines the suitable conditions under which the drug should be formulated can also be called as pre-formulation [3].The scope of these studies to be carried out will depend not only on the expertise, equipments and substances available, but also on any organizational preference or restrictions. However, for smooth conduct of these studies, a close interaction between inter departments is essential.

Preformulation provides necessary understanding of the physicochemical properties of active pharmaceutical ingredient underpinning the total formulation development. This process is the foundation upon which success can be built. There are many different tests and investigations that can be included in a preformulation screen. The key to efficient preformulation screening is to carryout the tests only when necessary, rather than to undertake a blanket comprehensive screen, which can consume both time and material and thus become expensive. The service of a well experienced formulation scientist is very much essential to save the time and money and achieve success in the preformulation studies. With experience there is much that can be understood about the active pharmaceutical ingredient from knowledge of its chemical structure. An experienced formulation scientist can, even before any laboratory experiments have been undertaken, obtain information on solubility, absorbability, stability and taste. This helps with the practical investigation, and saves time and resources. Properly executed preformulation programmes can improve the chances of successful project, and more importantly, avoid costly mistakes in phase I, phase II, phase III clinical trials or post launch procedures.

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Characterization of the active pharmaceutical compound

The preliminary preformulation study describes the molecular, physicochemical, and crystallographic characteristics of drugs and offers comprehensive development services to characterize active pharmaceutical compound alone and interaction with added excipient, and understand the impact of processing variables on properties of the finished product. The characterization of active pharmaceutical compound includes; Solubility screening, phase transition and microscopic changes, investigation into polymorphic forms, forced degradation studies and identification of the degraded product, confirmation of chemical structure, study of impurities and related substances, material contact studies and photostability studies.

ADVANCE IN PREFORMULATION REASERCH TECHNIQUES

Over the fast few years, new analytical technologies have emerged to support preformulation research in pharmaceutical research and development. These technologies assist in the various areas such as preformulation potency and stability assays, chiral purity assays of active moieties, chiral interconversion possibilities, evaluation of in-situ selection of research compounds, preformulation vehicle selection, and equilibrium and intrinsic solubility assays of target compounds in intended vehicles. The primary goal of these analytical technologies are to provide accurate results in a rapid turnaround time for transfer to the formulator and assessment or other relevant drug research areas. New developments in the area of supercritical fluid chromatography, direct assay of pharmaceutical dosage forms and various hyphenated analytical techniques are being recently promoted by various pharmaceutical companies as highly efficient routine tools for preformulation assays. In addition, advances in techniques for characterization of solid dosage forms is leading to prediction of physical and chemical stability as a function of preparation and processing.

Computerization and aid of software in the preformulation studies

Every pharmaceutical research outcomes always originates from the results of processing analytical data. Proper analysis of results frequently requires knowledge of background chemical information.To develop an appropriate dosage form it necessitates involving in the simultaneous optimization of various physicochemical parameters such as solubility, degree of crycstallinity, hygroscopy, and solid state stability. This optimization technique is mainly based on the planned management and use of large quantities of analytical data, which can be greatly facilitated by the use of proper software. Utilization of such software for preformulation research is to automate the import of data from diverse sources and manage it in a way that accelerate single to high-throughput screening and selection of drug formulations. These softwares are capable of fast processing just with the click of a button one can predict various physicochemical parameters. Physicochemical parameters such as solubility, dissociation constants, etc., can be predicted with in seconds for various organic structures, which can save several hours of work and even unnecessary expenses.

Preformulation is increasingly moving towards front-loading as many number and types of studies are in order to reduce the risks of late stage attrition and to minimize costly problems. This means that extensive characterization of greater numbers of drug candidates and evaluation based on a myriad criterion create logistical problems in organizing, sharing, communicating, and evaluating data in a coordinated manner. Use of proper software helps in data interpretation across disparate sources, as well as processing, visualization, knowledge management, and archiving. This facilitates the management and interpretation of this information by automatically uniting raw data from different sources by using automatic importation and archiving capabilities. Application of these softwares in the preformulation research work, greatly reduces the time spent collecting and processing analytical data versus interpreting, speeds up decision making and reporting a single point of access, and facilitates interdepartmental and word wide collaboration via web-based access.

These softwares are equipped with centralized data analysis and visualization facilities which enable us to find results from all of the instruments stored in one accessible database, capture spectral data, including the experimental conditions and images, process all of the data in one software interface, and easily compare and overlay data across multiple sets for easy comparison, to quickly select forms that are worth considering for further evaluation. The analytical data management software can help us in reduce the risk and solve workflow bottlenecks. Automated data management helps in aggregates, and collates analytical data from different sources in real time, live data that is searchable and analyzable provides a unified and centralized work system and multi-user and multi-site sharing and visualization of knowledge presents data in a single interface with customizable data layouts. These analytical software tools helps in standardize and automate processing, chemically intelligent data interpretation, reporting and storage of spectral and chromatographic results from multiple analytical techniques. These also assist in high-throughput qualitative analysis and evaluation of the results that encompass the relationship between the molecular structure and corresponding spectral or chromatographic behavior. And, hence, automate the processes effectively and extract the results efficiently.

Optimization of formulations

In today's pharmaceuticals product development process, optimization is emerged as a technique for the best compromising answer to a particular question. The term optimization means to optimize something, or use something at its best. Many a times finding the correct answer is not a simple and straight forward, in such cases using an optimization procedure for best compromise is the smarter way to solve the problem. But optimization is not easy as stated. The word optimize is defined as to make as perfect, effective, or functional as possible. During a development of a new project one generally experiments by a series of logical steps carefully controlling the variable & changing one at a time until a satisfactory result is produced. But under the circumstances the best one is often simply the last one prepared. It is satisfactory but how close is it to the optimum [4]. The pharmaceutical formulators often face the challenges of finding the right combination of formulation variables that will produce a

product with optimum properties. One of the difficulties in the quantitative approach for formulation design is due to difficulty in understanding the real relationship between casual factors and individual pharmaceutical responses [5]. Factorial designs were used in the 19th century by John Bennet Lawes and Joseph Henry Gilbert. A factorial design allows the effect of several factors and even interactions between them to be determined with the same number of trials as are necessary to determine any one of the effects by itself with the same degree. Instead of conducting a series of independent studies it is possible for us to combine these studies into one. Finally, factorial designs are the only effective way to examine interaction effects [6].

Artificial neural network tool used in the factorial design

The optimization technique based on response surface methodology includes statistical experimental designs and multiple linear regression analysis under a set of constrained equations. In general, since theoretical relationship between response variables and casual factors are not clear, multiple regression analysis can be applied to the prediction of response variables on the basis of a second order polynomial equations. But this prediction is often limited to low levels, resulting in poor estimation optimal formulations [7,8]. To overcome the limitations associated with multiple linear regression approach, a multi-objective simultaneous optimization technique based on an artificial neural network (ANN) has been developed [9,10]. ANN is a learning system based on a computational technique which tries to simulate the neurological processing ability of the brain [11]. ANN could be applied to quantifying a non-linear relationship between the casual factors and pharmaceutical responses by means of iterative training of data obtained from a designed experiment. In recent years, pharmaceutical scientists have started to use ANN technology in the fields such as intelligent preformulation design and predictions, pharmacokinetic-pharmacodynamic studies, process development, invitro-invivo correlations, and product development [12-15]. In the optimization study model formulations are usually prepared according to 3×3 factorial design in order to reduce the number of experiments. The use of systematic experimental design along with mathematical optimization based on statistical and ANN is time and cost efficient and importantly assures the formulation quality [16]. Any pharmaceutical optimization process will begin with objectives to find out and quantify the formulations response and independent variables and to determine the settings of these formulation variables that produce the best response values. The process aims with designing a set of experimental conditions which are capable to measure the response variables. On this basis, mathematical model fitting and determining the optimum values of the independent variables that produce the best response can be done. The application of ANN in multiple regression analysis of formulation optimization process already successfully applied [17,18].

CONCLUSION

Due to the globalization and rapid advancement in the field of technology the pressure is exerted on each and every industry/institute. The traditional role of pre-formulation

scientists that involving manual approaches are no longer adequate to compete with the global market. Use of advanced technologies based on statistical softwares in the area of preformulation and product development research are the excellent tools which not only yield the accurate results but also reduces the precious time and resources. In the future days, the academic and research institutes across the world in collaboration with research and development divisions of the pharmaceutical industries together need to work hard in developing and utilizing the advanced technologies to achieve realistic economic constraints in the field of product development and preformulation studies. In the future days a rapid advancement in the said field is also highly expected to make our budding preformulation scientists more competent and achieve the cost/time efficient processes. Always, it can assure that the effective automation of process will yield the efficient final results.

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