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Review Article

A Review Article on: Drug Discovery and Development

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ABSTRACT

The drug discovery has now evolved into a much more scientific and rational process due to better understanding of biological processes and the underlying chemistry, owing to the progress made due to advances in high throughput experimental techniques and availability of high performance computation resources. The process has matured to the stage where drugs are designed rather than being discovered. The development and validation of analytical methods play important roles in the discovery, development, and manufacture of pharmaceuticals. Method development is the process of proving that an analytical technique is acceptable for use to measure the concentration of an active pharmaceutical ingredient (API) in a particular compound dosage form. This allows simplified procedures to verify that a proposed analytical method will accurately and consistently perform reliable measurements of APIs in a given drug preparation. The validation of analytical method is essential for its development, whereby it is extensively tested for specificity, linearity, accuracy, precision, range, limit of detection, limit of quantitation, and robustness. Thus, the development and validation of analytical methods allows one to confirm that accurate and reliable measurement of the potency a pharmaceutical preparation can be performed. The present review highlights the process of drug development, its phases, and analytical methods, including chromatographic, spectroscopic, and electrochemical techniques, which have been applied in the analysis of pharmaceuticals.

INTRODUCTION

The pharmacokinetic and pharmacodynamic standards administering the activity and mien of effective opioid analgesics, inward breath anesthetic specialists, sedative/hypnotics, and muscle relaxantshave been superior caught on as a result of various creature and human ponders. These comes about suggest that the skin, as well as the mucous layers of the mouth, nose, and throat, may be utilized as elective conveyance frameworks for analgesics and anesthetics. Comparable progressions with other substances

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have given rise to an wealth of novel instruments, thoughts, and strategies together alluded to as controlled-release innovation (CRT). Drugimpregnated tablets, typified cells, transdermal and transmucosal controlled-releasen conveyance frameworks, ml6 nasal and buccal vaporized showers, iontophoretic gadgets to regulate drugs through skin, and a assortment of programmable, embedded drug-delivery gadgets are a few cases of CRTs. The creation of these novel apparatuses, thoughts, and strategies is being fueled by a assortment of sources. In spite of being broadly utilized, routine pharmaceutical organization methods have a number of disadvantages that unused procedures may be able to address[1].

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Fig 1: Drug discovery and development[14].

Internationally, India became a member of world organization (WTO) in 1995 & agreed to adhere to the product patent regime by 2005.A well-designed and executed study has built-in provisions to ensure patient rights & safety. In fact, a patient may be far easier in a clinical trial than in routine medical care because careful observations are made in safety (toxicity) and efficacy. Historical events like sulfanilamide & thalidomide disasters are required to be avoided with appropriate clinical trials. Two conferences were held on 10-12 October 2007in Hyderabad on the titles discovery to innovation"& "clinical trials in India". It had shown that how international & Indian companies are actively incorporating India as apart of a global strategy to accelerate drug discovery[3].

Stages of Drug discovery and development.

1. Target identification.
2. Drug discovery.
3. Formulation and Development
4. Lead Optimization.
5. Target Validation.
6. Identification of Lead.
7. Preclinical Testing.
8. Clinical Research

1. Target identification.

The first step in the discovery of a drug is identification of the biological origin of a disease, and the potential targets for intervention. Target identification starts with isolating the function of a possible therapeutic target (gene/nucleic acid/protein) and its role in the disease[4]. Identification of the target is followed by characterization of the molecular mechanisms addressed by the target. An ideal target should be efficacious, safe, meet clinical and commercial requirements and be 'druggable'. The techniques used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines[5].

Approaches:

 Data mining using bioinformatics

— identifying, selecting and prioritizing potential disease targets

 Genetic association

— genetic polymorphism and connection with the disease

 Expression profile

— changes in mRNA/protein levels

 Pathway and phenotypic analysis

— *In vitro* cell-based mechanistic studies

 Functional screening

— knockdown, knockout or using target specific tools[6].

2. Drug discovery.

Medicate revelation is troublesome, perilous, costly and time-consuming. It more often than not takes 10 to 15 a long time for a medicate to come to advertise. Luckily, we can speed up this prepare with the offer assistance of computational chemistry and computational sedate disclosure. Since computational strategies are an vital portion of intrigue pharmaceutical investigate, it is critical to get it the instruments utilized and their openings and impediments. The best medicate revelation unit combines the logical information of a few areas, such as science, chemistry, and clinical science[7].

3. **Formulation and Development[8].**

Pharmaceutical formulation is a stage of drug development during which the physicochemical properties of Active Pharmaceutical Ingredients (APIs) are characterized to produce a bioavailable, stable and optimal dosage form for a specific administration route.

During preformulation studies the following parameters are evaluated:

- Solubility in different media and solvents.
- Dissolution of the active pharmaceutical ingredient (API)
- Accelerated Stability Services under various conditions
- Solid state properties (polymorphs, particle size, particle shape etc.)
- Formulation Services and Capabilities:
- Formulation development of new chemical entities (NCE)
- Optimization of existing formulations
- Process development for selected dosage forms
- Novel formulations for improved delivery of existing dosage forms
- Controlled release and sustained release formulations
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Sub-micron and nano-emulsions

4. Lead Optimization[9].

It follows the lead finding process. The aim of lead optimization to synthesize lead compounds, new analogs with improved potency, reduce off-target activities, as well as to optimize this with respect to other properties viz. selectivity, metabolic stability, etc. This

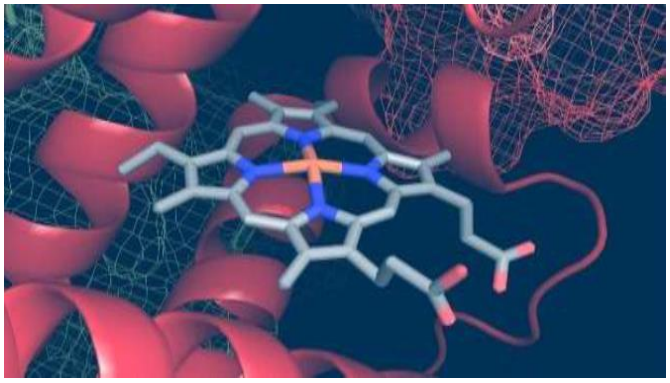

Fig 2: Lead Optimization[15].

optimization is accomplished through chemical modification of the hit structure, with modifications chosen by employing structure-activity analysis (SAR) as well as structure-based design if structural information about the target is available.

The lead compound should have a good druglikeness & would not interfere with the cytochrome P450 enzymes or with the P-glycoproteins.

5. **Target Validation[10].**

   After the selection of target, the researchers must confirm that the targets are the potential cause of disease. This stage is considered essential as it saves the times and avoids unproductive results. Target validation can be done by following steps:

- Reproducibility: The targets can be identified by literature review or by specific technique. However, it is considered almost essential to repeat the experiments again to confirm the targets are the cause of disease.
- Creating Variation to Ligand Target Environment:

  (I) It should be feasible to alter the affinity of the drug to the target by modulating the activity of drug molecule.

  (II) The effect of the drug should or should not be modified by altering the change cell or tissue type.

  (III) Introducing mutations in to the binding domain of the protein target should result in either modulation or loss of activity of the ligand.

6. **Identification of Lead.**

   A chemical lead is defined as a synthetically stable, feasible, and drug like molecule active in primary and secondary assays with acceptable specificity, affinity and selectivity for the target receptor. This requires definition of the structure activity relationship as well as determination of synthetic feasibility and preliminary evidence of in vivo efficacy and target engagement. Characteristics of a chemical lead are:

   SAR defined

   Drug ability (preliminary toxicity, hERG)

   Synthetic feasibility

   Select mechanistic assays

   In vitro assessment of drug resistance and efflux potential

   Evidence of in vivo efficacy of chemical class

   PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

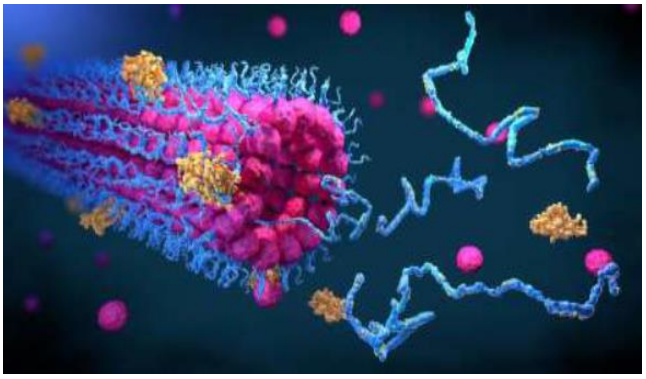

Fig 3: Identification of Lead[12].

In order to decrease the number of compounds that fail in the drug development process, a drug ability assessment is often conducted. This assessment is important in transforming a compound from a lead molecule into a drug. For a compound to be considered druggable it should have the potential to bind to a specific target; however, also important is the compound‘s pharmacokinetic profile regarding absorption, distribution, metabolism, and excretion. Other assays will evaluate the potential toxicity of the compound in screens such as the Ames test and cytotoxicity assay[11].

7. **Preclinical Testing.**

Pre-clinical research in drug development process involves evaluation of drug‘s safety and efficacy in animal species that conclude to prospective human outcome. The pre-clinical trials also have to acquire approval by corresponding regulatory authorities. The regulatory authorities must ensure that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective. ICH has established a basic guideline for technical necessities of acceptable preclinical drug development[13].

Preclinical ponders are planned to give data approximately the security and adequacy of a sedate candidate some time recently it is tried in people. Organ Dissemination, Lead or Candidate Pharmacokinetics and Harmfulness For occasion, PET measures the retention and dissemination of unused neuropharmacological specialists in test creatures and interfaces the official of these specialists to the comparing target structure[16].

8. **Clinical Research**

Clinical trials are conducted in people (volunteer)and intended to answer specific questions about the safety and efficacy of drugs, vaccines, other therapies, or new methods of using current treatments. Clinical trials follow a specific study protocol that is designed by the researcher or investigator or manufacturer. As the developers design the clinical study, they will consider what they want to complete for each of the different Clinical Research Phases and starts the Investigational New Drug Process (IND), a process they must go through before clinical research begins. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives[17].

a. **Phase 0 clinical trial**

Phase 0 implicates investigative, first-in-human (FIH) trials that are conducted according to FDA guidelines. Phase 0 trials besides termed as human micro dose studies, they have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging

specific targets without exerting pharmacological actions. Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans[18].

b. Phase I clinical trials

The first question in drug research is to find out the safety of drug in humans. Phase I studies, sometimes called "first in man", starts to answer this question by testing the investigational product in healthy volunteers. If the drug has a potential for toxic adverse events, it may be given only to subjects with the targeted condition to reduce risks to healthy subjects (i.e. anticancer drugs are never tested I healthy volunteers). The main purpose of the initial phase I studies is to establish a safe dosage ranges. These studies are designed to determine the metabolic and pharmacologic actions to the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During phase I, sufficient information about the drug`s pharmacokinetics (ADME) and pharmacological effects should be obtained to permit the design of well controlled, scientifically valid phase II studies. The union minister may allow phase I clinical trials for the drugs discovered abroad soon. Currently, phase I trial cannot be initiated in India for new drug substance discovered in other countries unless phase I data from other countries is mad available to Indian authorities. The DTAB (Drug Technical Advisory Board) has recommended to the health ministry to give approval to the phase I trial in the country for the drug discovered in other countries[19].

c. Phase II clinical trials

This stage includes clinical trials in huge bunches of patients with the target illness to decide its viability and advance assess its safety. The volunteers in this stage are to be taken are 100 to 300 The reason of this stage is to assemble more data almost the drug's adequacy and side impacts and too indentifying the precise measurements renge, greatest and least amount of the medicate is indentified in this phase. The sedate my rejected at this stage since of not accomplishing restorative impact. Stage I clinical trials are conducted to assess the security, toxicology, and pharmacology of novel drugs at shifting measurements. They take after pre clinical labouratory investigation[21].

d. Phase III clinical trials.

Phase 3 studies are expanded, controlled, and uncontrolled trials. They are performed after preliminary evidence of effectiveness has been obtained in Phase 2. These are formal therapeutic trials carried out Multicentre (1000 - 3000 patients) in a double blind, randomized, placebo controlled manner. The Newly formed drug compared to alternatives.

Good Clinical Practice guidelines followed which controls all aspects of conduct jof clinical trials (selection, ethics, data collection, methods, and record of info, statistics, and documentation). After phase 3 studies both the sponsor and drug control authority are satisfied and it is approved for marketed for general use[20].

e. **Phase IV clinical trials.**

Phase 4 trials are conductedwhen the drug or devicehas been approved by FDA.These trials are also recognized as post-marketing surveillance involving pharmacovigilance and continuing technical support after approval. There are numerous observational strategies and assessmentpatterns used in Phase 4trials to evaluate the efficacy, cost-effectiveness, and safety of an involvement in real-world settings. Phase IV studies may be required by regulatory authorities (e.g. change in labelling, risk management/minimization action plan) or may be undertaken by the sponsoring company for competitive purposes or other reasons. Therefore, the true illustration of a drug‘s safety essentiallyrequires over the months and even years that mark up a drug‘slifespan in the market. FDA

reviews reports of complications with prescription and OTC drugs, and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions[22].

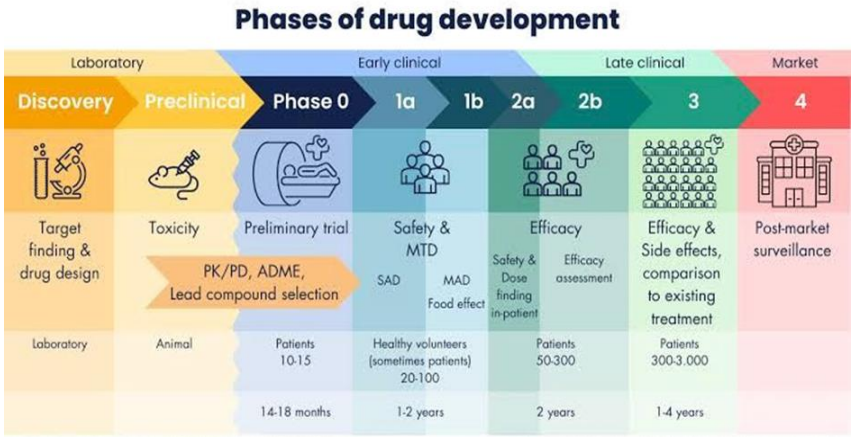

Fig 4: Phases of drug development[23].

CONCLUSION

Although it typically takes 10-12 yrs. & millions of dollars to bring one new drug to market the success rate is small. Clinical development is complex & is highly sensitive to globally accepted quality, ICH, GCP & ethics standards. Clinical trials registry (CTRI), global clinical trial programme & foundation of knowledge based industry, very less service tax, are attracting developed countries. But in developing countries (like India) no company or institute wants to or can, invest such time & resources for marginal improvement in responses over existing therapies. Even for new molecules due to inappropriate checking at regulatory level itself, though obtain patent but due to no industrial applicability cannot be applied appropriately through IND to DCGI .Thus, there is no appropriate reason, why clinical research cannot follow in those footsteps

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