

PREFORMULATION– A FOUNDATION FOR FORMULATION DEVELOPMENT

Sunisha Kulkarni*, Shyam Bihari Sharma, Anisha Agrawal

SOS in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh, India.

ABSTRACT

Activities done prior to formulation development are called as preformulation studies. It provides the scientific basis for formulation development. Preformulation studies can be broadly classified into two classes – (i) fundamental properties and (ii) derived properties. Fundamental preformulation properties are specific to the drug molecule and are dependent on the chemical structure of the drug molecule. In contrast, derived preformulation pre-formulation properties are carried out to learn about the issues related to development of a particular dosage form like solid oral, liquid oral or parenteral. Fundamental preformulation properties include – Solubility, dissociation constant (pKa), salt formation, partition or distribution coefficient, pH solubility profile and dissolution kinetics, permeability, solid state properties like polymorphism, stability profile etc. Derived preformulation properties are specific to the intended dosage form to be developed. The last activity performed in pre-formulation studies is the compatibility studies, wherein the physical and chemical stability of the drug molecule is studied in presence of excipients. Obviously, the choice of excipients is dictated by the type of dosage form to be developed. By comparing the physicochemical properties of each drug candidate with in a therapeutic group, the preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

Keywords: Fundamental properties, derived properties, physicochemical properties, etc.

INTRODUCTION

Preformulation is defined as a stage of development during which the physicochemical properties of the drug substance is characterised and established. A complete knowledge of the relevant therapeutic and physicochemical properties of the drug enables determination of its proper formulation and delivery method¹.

Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drug's combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of Preformulation study is to develop the elegant (stable, effective, and safe) dosage form by establishing kinetic rate profile, compatibility with the other ingredients & establish Physico-Chemical parameter of new drug substance. Among these properties, drug

solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in Preformulation study. Polymorphism having crystal and amorphous forms shows different chemical physical and therapeutic description of the drug molecule. Preformulation begins after literature search of similar type of compounds to provide and understand (i) the degradation process, (ii) any adverse conditions relevant to the drug, (iii) bioavailability, (iv) pharmacokinetics and formulation of similar compound and (v) toxicity. Preformulation influences (a) selection of the drug candidate itself, (b) selection of formulation components, (c) API & drug product manufacturing processes, (d) determination of the most appropriate container closure system, (e) development of analytical methods, (f) assignment of API retest periods (g) the synthetic route of the API, (h) toxicological strategy².

Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, facilitate policy development and regulatory decision making. Preformulation studies give directions for development of formulation in choice of drug form, excipients, composition, physical structure, helps in adjustment of pharmacokinetic and biopharmaceutical properties, support for process development of drug substance support for PAT (Process Analytical Technology) (critical process parameters), produce necessary and useful data for development of analytical methods.

Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrants evaluation in man. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rational for formulation design, or support the need for molecular modification³.

Need of Dosage forms^{4,5}

Formulation development is required at various stages during drug development. As we have discussed earlier, drugs are rarely administered alone. Incorporation of the drug into a formulation provides various advantages like ease of handling, ease of administration, better stability or better bioavailability. Different stages of clinical trials as described above require different formulations. Preclinical stage is performed in animals and requires simple liquid formulations that can be easily administered to animals.

A comprehensive preformulation study helps in understanding the physico-chemical properties of the drug molecule. It provides the foundation for development of a robust dosage form that can sustain the rigors of processing and shelf life. Efforts spent on preformulation provide cost savings in the long run, by reducing challenges during formulation development⁹.

- To provide mechanism for the safe & convenient delivery of accurate dose.
- To protect from environment i.e. destructive effect of oxygen or humidity.
- To protect from the destructive effect of gastric acid after oral administration Ex. Enteric coated tablet.

- To conceal the bitter, salty, nauseous odor of drug substance. Ex. Capsule, Coated tablet.
- To provide liquid preparation which are unstable or insoluble in vehicle. Ex. Suspension
- To provide clear dosage forms of substance. Ex. Syrups, Solutions
- To provide rate controlled drug action. Ex. Sustained Release & Controlled release Tablets
- To provide optimal drug action from topical administration. Ex. Ointments, Creams, Patches.

Objectives^{4,5}

- To develop the elegant dosage forms (stable, effective & safe)
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is 1st step in rational development of a dosage form of a drug substance before dosage form development.
- It generates useful information to the formulator to design an optimum drug delivery system.

MAJOR AREA OF PREFORMULATION RESEARCH^{4,5,6,7}

Bulk characterization

The first requirement of any preformulation study is the development of a simple analytical method for quantitative estimation in subsequent steps. Most of drugs have aromatic rings and/or double bonds as part of their structure and absorb light in UV range, UV spectroscopy being a fairly accurate and simple method is a performed estimation technique at early preformulation stages. Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, x-ray diffraction patterns and solubility even though they are chemically identical. Differences in the dissolution rates and solubilities of different polymorphic forms of a given drug are very commonly observed. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving form may be utilized to improve the rate and extent of bioavailability. In general, the stable polymorph exhibits the highest melting point, the lowest solubility, and the maximum chemical stability. Various techniques are available for the investigation of the solid state. These include microscopy (including hot stage microscopy), infrared

spectrophotometry, single-crystal x-ray and x-ray powder diffraction, thermal analysis, and dilatometry.

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. It is generally recognized that poorly soluble drugs showing a dissolution-rate limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state rather than as a coarse material. In case of tablets, size and shape influence the flow and the mixing efficiency of powders and granules. Size can also be a factor in stability: fine materials are relatively more open to attack from atmospheric oxygen, the humidity, and interacting excipients than are coarse materials.

Characterization approaches in drug discovery and preformulation of solid dosage forms

Drug discovery

1. Nuclear Magnetic Resonance (NMR)
2. Mass Spectra
3. Elemental Analysis

Preformulation

1. Karl Fischer
2. pKa, Log P/log D
3. Initial Solubility
4. Crystal Structure
5. Hygroscopicity
6. Stability in solution and HPLC
7. Other spectroscopical data⁸.

Solubility analysis

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents is determined as a first step. This information is valuable in developing a formulation. Solubility is usually determined in a variety of commonly used solvents and some oils if the molecule is lipophilic. The solubility of material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged until equilibrium is achieved.

1. Ionization constant –Pka,
2. pH solubility profile,
3. Common ion effect-Ksp,
4. Solubilization,

5. Dissolution,
6. Partition co-efficient.

Stability analysis

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include both solution and solid state experiments under conditions typical for the handling, formulation, storage, and administration of a drug candidate as well as stability in presence of other recipients. Factors effecting chemical stability critical in rational dosage form design include temperature, pH and dosage form diluents. The method of sterilization of potential product will be largely dependent on the temperature stability of the drug. Drugs having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by another means, e.g., filtration. The effect of pH on drug stability is important in the development of both oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for potential dosage forms will be largely based on the stability characteristic of the drug.

- Solid state stability
- Solution phase stability
- Compatibility studies: stability in the presence of excipients
- Typical stability protocol for a new Chemical Entity.

Before beginning the formal preformulation programs the preformulation scientist must consider the following factors

- The amount of drug available.
- The physicochemical properties of the drug already known.
- Therapeutic category and anticipated dose of compound.
- The nature of information, a formulation should have or would like to have⁹.

Drug development

Pre-clinical phase is preceded by human clinical trials, consisting of phase I, II and III. Formulations used for phase I clinical trial are called as 'first time in human' or 'first time in man' formulations. These can be simple solid or liquid formulations and include formulations like 'chemical in capsule' and 'chemical in bottle'. Sometimes Phase I CTs can also be initiated using the proposed commercial formulation. The sophistication of the formulation increases as the stage of clinical trial progresses. It is desirable to initiate late phase 2 or phase 3 clinical trials with the proposed commercial formulation. Drug development involves investigations on 'lead

molecules or candidate molecules identified in drug discovery stage. These investigations mainly involve clinical evaluation. Clinical trials (CTs) are conducted in human subjects and involve phase I, II and III. Phase IV trials involve post-marketing surveillance of the new drug.

Phases of CTs

Phase I

These trials involve initial safety trials on a new chemical entity (NCE), to establish the dose range tolerated by human volunteers for single and for multiple doses. These are usually carried out on healthy subjects and sometimes on severely ill patients (e.g., in the field of cancer). They provide information on safety and pharmacokinetics of the molecule.

Phase II

Phase II trials are carried out to establish evidence of efficacy and generate more information on safety of the NCE. They are further classified as phase IIA and IIB. Phase IIA is specifically designed to assess dosing requirements and phase IIB is specifically designed to study efficacy in the prescribed doses.

Phase III

This phase of CT is also categorized into IIIA and IIIB. Phase IIIA includes trials conducted after efficacy of the medicine is demonstrated, but prior to regulatory submission of a New Drug Application (NDA) or other dossier. These trials are randomized, multi-centric and focus on generating definitive evidence of efficacy of the NCE against the current 'gold standard' treatment. Phase IIIB includes trials that continue after submission of the NDA and continue till marketing approval is obtained. These trials may supplement earlier trials, complete earlier trials, or may be directed toward new types of trials (e.g., quality of life, marketing).

Phase IV

Studies or trials conducted after a medicine is marketed to provide additional details about the medicine's efficacy or safety profile¹⁰.

CONCLUSION

The preformulation phase is a critical phase in establishing the properties that will allow suitable risk assessment for development of a formulation. Decisions made on the information generated during this phase can have a profound effect on the subsequent development of those compounds. Therefore, it is imperative that preformulation should be performed as carefully as possible to enable rational decisions

to be made. The quantity and quality of the drugs can affect the data generated as well as the equipment available and the expertise of the personnel conducting the investigations. This knowledge can be useful in developing various types of formulations of any drug. By comparing the physicochemical properties of each drug candidate with in a therapeutic group, the preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

REFERENCES

1. Preformulation - Almac, www.almacgroup.com/api-services-chemical.../solid.../preformulation-2/
2. Gopinath R and Naidu RAS. Pharmaceutical Preformulation Studies – Current Review, International Journal of Pharmaceutical & Biological Archives. 2011;2(5):1391-1400.
3. Lachman L, Liberman HA and Kanig JL. The Theory and Practice of Industrial Pharmacy, Lea &Febiger, Philadelphia. 1986;171-195.
4. Ansel CH, Popovich GN and Allen VL. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams and Wilkins, New York, 2005;42-111.
5. Preformulation in: Aulton ME (Ed). Pharmaceutics -The Science of Dosage form Design. Churchill Livingstone; 1996;113-138.
6. Absorption of drugs in: Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics A treatise.1st ed. VallabhPrakashan; 1995;5-75.
7. Vilegave K, Vidyasagar G and Chandankar P. Preformulation Studies of Pharmaceutical New Drug Molecule & Products: An Overview, Am J Pharm Health Res. 2013;1(3)ISSN: 2321–3647(online)
8. Habiburrahman SM. Preformulation - Solid Dosage Form, Pharmainfo.net.
9. Garg R. Preformulation: A need for Dosage Form Design, Wed, 02/20/2008Pharmainfo.net
10. Bansala.lab-training.com/.../role-of-preformulation-studies-in-drug-development/.