Pre-formulation Studies

Introduction:

The pre-formulation is the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients. Certain fundamental physical & chemical properties of drug powder are determined. This information may dictate many of subsequent event & approaches in formulation development. This first learning phase is called as pre-formulation.

- Introduction, objectives & organoleptic properties: Taste, Color, odor and purity.
- Bulk Characterization: Crystallinity and Polymorphism, Hygroscopicity, Fine Particle Characterization, Bulk density and Powder flow properties.
- Solubility Analysis: Temperature, pH, co-solvency, solid dispersion, Ionization constant – pKa, pH solubility profile, Solubilization, Particle size, shape, surface area and Dissolution. Thermal Analysis: Differential scanning calorimetry, thermo gravimetric analysis, differential thermal analysis, X-ray diffraction studies.
- Stability studies: Analytic data from studies as HPLC, TLC, Florescence, or UV/Visible spectroscopy may be required to determine precisely the kinetics of decay product.
- Chemical Properties: hydrolysis, oxidation, reduction, recemization, polymerization etc and their influence on formulation and stability of products.

Objective: It is first step in rational development of a dosage form of a drug substance before dosage form development.

- To establish the physico-chemical parameters of new drug substance.
- To establish the physical characteristics, kinetic rate profile, compatibility with the common excipient.
- To choose the correct form of a drug substance.

Module: 01 Introduction & objectives of pre-formulation studies

Pre-formulation is branch of Pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form new drug, it is essential that certain fundamental physical & chemical properties of drug powder are determined. This information may dictate many of subsequent event & approaches in formulation development. The pre-formulation is the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients. A typical pre-formulation program should begin with the description of the drug substance. The color, odor and taste of the new drug must be recorded using descriptive terminology. The color, odor and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property.

Questions:

1. Explain introduction and objectives of pre-formulation studies.

Module: 02 Bulk Characterizations

Crystalline forms have fixed internal structure. These are more stable than its amorphous forms. Such form has lesser solubility than its amorphous form; crystalline form has lesser tendency to change its form during storage. Amorphous forms do not have any fixed internal structure. It has higher thermodynamic energy than its crystalline form; these are less stable than its crystalline forms. Amorphous forms have greater solubility than its crystalline forms; Amorphous tend to revert to more stable forms during storage.Tendency of drug molecule to adsorb atmospheric moisture is called hygroscopicity. Adsorption and Equilibrium moisture content can depend upon:-Atmospheric Humidity, Temperature, Surface Area Exposure, Analytical methods: Gravimetric, TGA, Karl Fisher titration, gas chromatography. Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. Size also plays a role in the homogeneity of the final tablet. When large differences in size exist between the active components and excipients, mutual sieving (de- mixing) effects can occur making thorough mixing difficult or if attained difficult to maintain during the subsequent processing steps. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. "Compressibility" of a powder can be defined as the ability to decrease in volume under pressure and "compactability as the ability of the powdered material to be compressed into a tablet of specified tensile strength.

Module: 03 Solubility Analysis

An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility. A drug must possess some aqueous solubility for therapeutic efficacy in the physiological P H range of 1 to 8. For a drug to enter into systemic circulation, to exert therapeutic effect, it must be first in solution form. If solubility of drug substance is less than desirable, than consideration must be given to increase its solubility. Many drugs are either weakly acidic or basic compounds and, in solution, depending on the pH value, exist as ionized or un-ionized species. The un- ionized species are more lipid-soluble and hence more readily absorbed. The gastrointestinal absorption of weakly acidic or basic drugs is thus related to the fraction of the drug in solution that is un- ionized. In many instances, dissolution rate in the fluids at the absorption site is the rate limiting steps in the absorption process. This is true for the drug administered orally in the solid dosage forms such as tablet, capsule, and suspension as well as drug administered I.M. in form of pellets or suspension. The lipophilicity of an organic compound is usually described in terms of a partition coefficient; log P, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases.

Module: 04 Chemical Properties

In aqueous solution, water is in excess so the reaction is 1st order. Conditions that catalyze the breakdown are Presence of hydroxyl ion, hydride ion, divalent ion and heat, light, ionic hydrolysis, solution polarity and ionic strength, high drug concentration. Hydrolysis can be prevented by adjusting the pH. As most of the potent drugs are weakly acidic or weakly basic in nature. Formulate the drug solution close to it's pH of optimum stability or by Addition of water miscible solvent in formulation or by Using Optimum buffer concentration to suppress the ionization. Reaction of any material with molecular oxygen producing free radicals by hemolytic bond fission of a covalent bond. These radicals are highly unsaturated and readily accept electron from other substance causing oxidation is called Auto- oxidation. Reduction of prednisolone and cortisone results in the formation of their active metabolites hydrocortisone. Azo dyes used as coloring agents in pharmaceutical products or foods are reduced to form amines in the liver and by the intestinal flora. The phenomenon where molecules or excipients which absorb energy but do not participate themselves directly in the reaction but transfer the energy to others which cause cellular damage by inducing radical formation is known as photosensitization.

Module: 05 Stability studies

When we mix two or more API and / or excipients with each other & if they are antagonistic & affect adversely the safety, therapeutic efficacy, appearance or elegance then they are said to be incompatible. In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipients interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the pre-formulation scientist must generate the needed information. A typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipients used in these tests is very much subject to the discretion of the pre-formulation scientist.

References:

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