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Review Article

SIGNIFICANCE OF PREFORMULATION STUDIES IN DESIGNING, FABRICATING FOR PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Prior to development of any formulations the physiochemical properties of drug should be known to the developer. Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical path in liquid, semisolid and solid dosage form technology. The need for adequate drug solubility cannot be over emphasized. Stability studies in solution will indicate the feasibility of parental or other liquid dosage form and can identify methods of stabilization. In parallel solid-state stability by DSC, TLC and HPLC in the presence of tablet and capsule excipient will indicate the most acceptable vehicles for solid dosage form. Prior to the development of pharmaceutical dosage forms, it is essential that be valid fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. Preformulation is to make available and realize information regarding:1) the degradation process 2) any adverse conditions relevant to the drug 3) bioavailability 4) pharmacokinetics and formulation of similar compounds 6) toxicity. Preformulation influences a) selection of the drug candidate itself b) selection of formulation components c) API and 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 API h) toxicological strategy i) to establish its compatibility with common excipients by observing caking, liquefaction, colour change, odour formation. It also gives directions for the development of formulation in choice of drug form, excipients, composition, physical structure, helps in adjustment of pharmacokinetics and bio pharmaceutical properties. In this review article we basically consider the various parameters should be keep in mind before to the fabrication of any formulations.

Key Words: Preformulation studies, physiochemical properties, dosage form factors, formulation optimization

INTRODUCTION

Preformulation may be described as the process of optimizing a drug through determination of those physical and chemical properties considered important in the formulation of a stable, effective and safe dosage form. The possible interactions with the various components intended for use in the final drug product are also considered. It is an effort that encompasses the study of such parameters as dissolution, polymorphic forms and crystal size and shape, pH profile of stability, and drug – excipient interactions, which may have a profound effect on a drug's physiological availability and physical and chemical stability [1-2]. In this review article we basically consider the various parameters should be keep in mind before to the fabrication of any formulations.

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Before beginning the formal preformulation programs the preformulation scientist must consider the following factors[1-4]:-

- The amount of drug available.
- The physicochemical properties of the drug already known.

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- Therapeutic category and anticipated dose of compound.
- The nature of information, a formulation should have or would like to have.

Why is Preformulation Important?

There are critical differences between companies at the detailed level of knowledge and their ability to learn before doing [1-5]

- Knowledge of the underlying variables and their relationship to performance.
- Knowledge of the future manufacturing environment and the new variables introduced by that environment.
- Part of the New Drug Development Process.

Preformulation development studies are conducted to determine the physical and chemical characteristics of the compound of interest be it a small organic molecule, peptide or protein. These studies generate the data that are a prerequisite to dosage form development and the data required for submission of the Chemistry, Manufacturing and Controls (CMC) section of the Investigational New Drug application (IND). Characterization of drug molecules is very important step at the preformulation phase of product development. Following studies are conducted as basic preformulation studies; special studies are conducted depending on the type of dosage form and the type of drug molecules[2-6]-

- Solubility determination
- pKa determination
- Partition co-efficient
- Crystal properties and polymorphism
- Practical size, shape and surface area.
- Chemical stability profile.

Solubility Determination

Drug absorption requires that molecules be in solution at the absorption site. Polar solution is more soluble in water than in organic phases, while the reverse is true for non-polar solutes. Ionized species have a greater aqueous solubility than their un-ionized counterparts for drugs absorbed by passive diffusion; those exhibiting low aqueous solubility tend to have a slower oral absorption rate than those exhibiting high aqueous solubility. For drugs intended for topical application (e.g. vaginal, rectal, dermal), the solubility of the drug in the vehicle is important. For a given vehicle, the highest driving force for absorption is obtained when the drug concentration in the vehicle equals its solubility. Concentrations below saturation decrease the absorption efficiency, while concentrations exceeding drug solubility serve as reservoirs to maintain a saturated solution [4-6].

Classification

–Class I-High Permeability, High Solubility
–Class II-High Permeability, Low Solubility
–Class III-Low Permeability, High Solubility
–Class IV-Low Permeability, Low Solubility

Class Boundaries

Highly soluble: The highest does is soluble in <250 ml water over a pH range of 1 to 7.
Highly permeable: >90% dose absorbed in humans.
Rapidly dissolving: >85% of labeled amount of drug substance dissolves within 30 min.

Aqueous Solubility

The availability of a drag is always limited and the preformulation scientist may only have 50 mg. Solubility is generally estimated by visual observation. The solubility of a compound is initially determined by weighing out 10 mg (or other suitable amount) of the compound. To this is added 10 mL of the solvent of interest. If the compound does not dissolve, a further 40 mL of the solvent is added, and its effect is noted.

Successive amounts of the solvent are then added until the compound is observed to dissolve. This procedure should give an approximate value of the solubility. This method does not take into account the kinetic aspects of the dissolution processes involved in solubility measurements. To determine more accurately the concentration of a saturated solution of a compound, the following procedure can be used. A known volume of the solvent, water or buffer is taken into a scintillation vial, and the compound is added until saturation is observed. The solution is then stirred or shaken and the experiment restarted. It is recommended that the experiment be conducted at least overnight or longer, for low solubility compounds. Depending on the amount of the compound available, replicate experiments should be carried out. After stirring or shaking, the solvent should be separated from the suspension by centrifugation or by filtration using poly tetra fluoro ethylene

(PTFE) filters. The filtrate is then assayed preferably by HPLC; however, ultraviolet (UV)-visible spectroscopy can also be used to determine the solubility, if compound stability or impurities are not an issue. This is termed as the thermodynamic solubility. It is also useful to measure the pH of the filtrate, and to characterize any undissolved material by DSC to detect any phase changes that might have occurred [4-7].

Intrinsic Solubility (Co)

An increase in solubility in acid compared to aqueous solubility suggests a weak base and an increase in alkali, a weak acid. An increase in acidic and alkaline solubility suggests either impotence or zwitter ion behaviour. In this case there will be two pKa's, one acidic & one basic. When the purity of the drug sample can be assured the solubility obtained in acid for a weak acid or alkali for a weak base can be assured to be the intrinsic solubility (Co.) i.e. the fundamental solubility when completely unionized. The solubility should ideally be measured at two temperatures [6-8].

1)4°C to ensure physical stability and entered short term storage and chemical stability unit more definitive data are available. The minimum density of water occurs at 4°C. This leads to a minimum aqueous solubility.
2)37°C to support biopharmaceutical evaluation.

Dissolution rate limited absorption [8-9]

–The absolute amount of drug absorbed increases with the increasing of the dose
–Reduce particle size and using solution formulation should enhance absorption
Solubility limited absorption
–The absolute amount of drug absorbed does not increase with the increasing of the dose
–Increasing dissolution rate does not increase absorption

Solvents for Solubility Studies
For develop ability assessment:

- Simulated gastric fluid (SGF)
- Simulated intestinal fluid (SIF)
- pH 7.4 buffer
- Intrinsic solubility to estimate pH-solubility profile

For Formulation Development:
–pH solubility profile
–Solubility in solubilizing agents/systems

Examples of drugs with dissolution rate limited absorption [8-9]:
–Digoxin
–Penicillin
–Phenytoin
–Quinidine
–Tetracyclines
The solubility of drug is an important physicochemical property because it effects the bioavailabilty of the drug, the rate of drug resale 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 is developing a formulation. Solubility is usually determined in variety of commonly used solvents and some oils if the molecules are lipophillic. 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 achieved.

Common solvents used for solubility determination are-

Water, Polyethylene Glycols, Propylene Glycol, Glycerin, Sorbitol, Ethyl Alcohol, Methanol, Benzyl Alcohol, Isopropyl Alcohol, Tweens, Polysorbates, Castor Oil, Peanut Oil, Sesame Oil, Buffer at various pHs.

pKa Determination

Critical variables that should be considered when making formulation decisions are pKa, lipophilicity, and solubility. The pKa and lipophilicity can be measured using Sirius GLpKa and a pION pSOL instrument is used to measure the intrinsic solubility of the compound. The pKa value is the pH at which acidic or basic groups attached to molecules exist as 50% ionized and 50% nonionized in aqueous solution. The pKa value provides valuable data on the interaction of an ionizable drug with charged biological membranes and receptor sites and information on where the drug may be absorbed in the digestive tract. Knowing the pKa also enables the scientist to know how much to alter the pH to drive a compound to its fully ionized or nonionized form for analytical

and other purposes, such as formulation, solubility, and stability. Formulators need to know where a drug will dissolve in the digestive tract and whether that corresponds to the optimal region for absorption, especially if they are planning to create a dosage form that will be taken orally. If the drug dissolves too early, it may re precipitate in a form that is poorly absorbed. Determination of the dissociation content for a drug capable of ionization within a ph rang of 1 to 10 is important since solubility and consequently absorption, cab be altered by orders of magnitude with changing pH. The Henderson – Hasseslebach equation provides an estimate of the ionized and un ionized durg concentration at a particular pH [5-8].

For acidic compounds

pH = pKa + log [un-ionized drug] / [ionized drug]

Partition Coefficient

The partition coefficient [8-10] is a measure of the extent a substance partitions between two phases, generally an oil phase and an aqueous phase. This ratio is often expressed as log P (logarithm of partition ratio). Both pKa and log P measurements are useful parameters for understanding the behavior of drug molecules at the Preformulation stage. The pKa will determine the species of molecules, which is likely to be present at the site of action and how quickly or completely would the species cross a large number of transport barriers in the body, regardless of the route of administration. Factors, such as absorption, excretion, and penetration of the central nervous system (CNS) are also related to the log P value of a drug and in certain cases predictions can be made; these are important in assessing the endogenous toxicity of compounds and their activity.

Partition Coefficient (oil/ water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium.

P o/w = (C oil / C water) equilibrium.

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/ hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/ hydrophilic nature of the drug. Since biological membranes are lipoidal in nature. The rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water. Drugs having values if P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect id dissolution rate, pKa and solubility on absorption must not be neglected.

Dissolution

The dissolution rate [8-10] of the drug is only important where it is the rate limiting step in the absorption process. Kaplan suggested that provided the solubility of a drug exceeded to mg/ ml at pH 7, no bioavailability or distinction related problems were to be expected. Below / mg/ ml such problems were quite possible and salt formation could improve absorption and solubility by controlling the pH of the microenvironment, independently of the drug and dosage forms position within the GI Tract.

Intrinsic Dissolution Rate

When dissolution is controlled solely by diffusion the rate of diffusion is directly proportional to the saturated concentration of the drug in solution under these conditions the rate constant K_1 is defined by

K_1 = 0.62 D2/3 V 1/6 w1/2

Where, V is the kinematic viscosity
W is the anguter velocity of a rotating disc of drug.

Common Ion Effect

A common ion [9-11] significantly reduces the solubility of a slightly soluble electrolyte. The 'selling out' results from the removal of water molecules as solvent owing to the completing

hydration of other ions. The reverse process 'salting in' qries with large anions e.g. benzoate, salivate which open the water structure. These hydro topics increase the solubility of properly water soluble compounds such as diazepam.

Melting Point

The melting point [8-12] of a drug can be measured using three techniques :-
1)Capillary Melting
2)Hot Stage Microcopy
3)Differential scanning calorinetry or thermal Anaylysis.

Capillary Melting

Capillary melting gives information about the melting range but it is different to assign an accurate melting point.

Hot Stage Microcopy

This the issued observation of melting under a microscope equipped with a heated and lagged sample stage. The heating rate is controllable and upto three transitions can e registered.

Differential Scanning Calorimeltry and thermal analysis

Differential thermal analysis (DTA) measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate differential scanning calorinetry (DSC) is similar to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference i.e. it measures the enthalpy of transition.

Crystal Properties and Polymorphism

Many drug substances can exit in more than one crystalline [8-13] from 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 from may be utilized to improve the rate and extent of bioavailability. For drugs pane to degradation in the solid state, physical form of the drug influences degradation. Selection of a polymorph that is chemically more stable is a solution in many cases. Different polymorph also leads to different morphology, tensile strength and density of power bed which all contribute of compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance as it relates to pharmaceutical processing is desirable during its Preformulation evaluation especially when the active ingredient is expected to constitute the bulk of the tablet mass. Although a drug substance may exist in two or more polymorphic forms, only one form is thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. 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 microcopy), infrared spectrophotometry, single-crystal x-ray and x-ray power diffraction, thermal analysis, and dilalometry.

Particle Size, Shape and Surface Area:-

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and Surface morphology of the drug particles. In general, each new drug candidate should be tested during Preformulation with the smallest particle size[7, 8-16] as is practical to facilitate preparation of homogeneous samples and maximize the drug' s surface area for interactions. 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 bio available 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.

Particle size Determination

Though microscopy [9-12] is the simplest technique of estimating size ranges and shapes, it is to slow for quantitative determination the material is best observed as a suspension in non dissolving fluid. Saving is less useful technique at preformulation storage due to lack of bulk material. Andreason pipette is based on the rate difference of sedimentation of different particles, but techniques like this are seldom used due to their tedious nature instruments based on light scattering, (Royco), light blockage (HIAC) and blockage of electrical conductivity path (coulter counter) are available.

Surface Area Determination

Surface area [9-12] is most commonly determined based on brunaver emette teller (BET) theory of adsorption. Most substances adsorb a mono molecular layer of gas under certain conditions of partial pressure of gas and temperature. Knowing the monolayer capacity of adsorbent and the area of absorbale molecule, the surface area can be calculated the adsorption process is carried out with nitrogen at-195 degree Celsius at a partial pressure attainable when nitrogen is in a 30% temperature with an inert gas (helium). The adsorption takes place by virtue of vander wall's forces.

Power Flow Properties

When limited amounts of drugs are available Power flow properties [10-16] can be evaluated by measurements of bulk density and angle of repose. Changes in particles size and shape are generally very important an increase in crystal size or a more uniform shape will lead to a small angle of repose and a smaller Carr's index.

Bulk Density

Knowledge of absolute and bulk density [10-13] of the drug substance is Very useful in having some idea as to the size of final dosage form the density of solids also of affects their flow Properties Carr's compressibility index can be used to predict the flow properties based on density measurement.

Carr's index (%)=[(Tapped density – Pored density)/ Tapped density] *100

A similar index has been defined by Hausner's:

Hausner's ratio = Tapped density / Pored density

Angle of repose

The maximum angle which is formed b/w the surface of a pile of powder and horizontal surface is called the angle of repose.
Relationship between flows, angle of repose, Carr's index fee power flow

Table 1:

Flow	Angle of repose	Carr's index (%)
Excellent	<25	5-15
Good	25-30	12-16
Fair to passable	30-40	18-21
Poor	> 40	23-35
Very Poor		33-38
Extremely Poor		>40

Stability studies

The regulatory authorities clearly define the protocols for the testing of drug products for stability [10-19] during the shelf life. However, testing of drug substances at the preformulation level for stability evaluation offers several advantages and opportunities once the drug substances enter the formulation stage. First, it provides a clear idea about which types of dosage forms can be used. The development of stability testing protocols start with the development of stability indicating methods, the details of which can be readily found in any pharmaceutical analysis text or through the website of the US FDA. The Q1A R2 (Stability Testing of New Drug Substances and Products) is a good starting place.
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 condition typical for the handing, formulation, storage, and administration of a drug candidate as well as stability in presence of other recipients.

Factor 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

Solid state stability

Chemical instability normally results from either of the following reaction: - hydrolysis, oxidation, photolysis and pyrolysis, Chemical structure of the drug is the determination of drug to either of these attacks. Esters and lactase and to lesser extent, amides are to prone to solvolysis. Instauration or electron rich centre in the structure make the molecule vulnerable for free radical mediated or photo-catalysed oxidation.

Physical properties of drugs: Amorphous materials are less stable than their crystalline forms. Denser materials are more stable to ambient stress.
Elevated temperature studies:-

The elevated temperatures commonly used are 40, 50, and 60 degree centigrade with ambient humidity. The samples stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control. If a substantial change is seen, samples stored at lower temperature are examined. If no changes are seen after 30 days at 60 degree centigrade, the stability prognosis is excellent.

Stability under high humidity conditions:-

Solid drug samples can be exposed to different relative humidity conditions by keeping them in laboratory desiccators containing saturated solutions of various salts. The closed desiccators in turn are kept in oven to provide constant temperature. The preformulation data of this nature are useful in determining if the material should be protected and stored in controlled low humidity environment or if non aqueous solvent be used during formulation.

Photolytic stability:-

For drug substances, photostability testing [12-16] should consist of two parts: forced degradation testing and confirmatory testing. The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. For development and validation purposes, it is appropriate to limit the exposure and end the studies if extensive decomposition occurs. Under forced conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. Many drugs fade on exposure light. Though the extent of degradations small and limited to the exposed surface area, it presents anesthetic problem. Exposure of drug 400 and 900 foot-candles of illumination for 4 and 2 week periods respectively is adequate to provide some idea of photosensitivity. Resulting data may be useful in determining if an amber colored container is required or if color masking bye should be used in the formulation.

Stability to Oxidation:-

Drug's sensitivity to oxidation [13-17] can be examined by exposing it to atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere allows for rapid evaluation. A shallow layer of drug exposed to a sufficient headspace volume ensures that the system is not oxygen limited. Samples are kept in desiccators equipped with three-way stop cocks, which are alternatively evacuated and flooded with desired atmosphere. The process is repeated 3 or 4 times to ensure 100% desired atmosphere. Results may be useful in predicting if an antioxidant is required in the formulation or if the final product should be packaged under inert atmospheric conditions.

Compatibility studies:-

The knowledge of drug excipients interaction [12-15] is useful for the formulation to select appropriate excipients. The described preformulation screening of drug excipients interaction requires only 5mg of drug in a 50% mixture with the excipients to maximize the likelihood of obscuring an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard heating rate on DSC, over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance one or more peaks in themograms of drug excipient mixtures are considered of indication of interaction.

Solution phase stability:

As compared with the dry form, the degradation is much rapid in solution form [12-14]. It is important ascertain that the drug doesn't degrade when exposed to GI fluid. The pH based stability study, using different stimulator GI condition can be designed. A poor solution stability of drug may urge the formulator to choose a less soluble salt form, provided the bioavailability is not compromised

Absorption behavior:

It is essential to test the in vivo behavior of the new drug for successful formulation of a dosage from good bioavailability. Partial in vivo and in vitro test [12-14] are designed to study pharmacokinetic profile of the drug.

Some Product Specific Aspects-

1) Solid dosage forms

- Effect of micronization and processing such as granulation on solid state properties and chemical stability
- Effect of excipients on crystallization/nucleation
- Powder flow properties: bulk density, compression properties and particle size and shapes

2) Parenteral Dosage Forms

- Injection site precipitation
- Pain upon injection
- Toxicity of new excipients
- Effect of excipients on crystallization/nucleation

3) Suspensions

- Effect of processing and formulation on the physical and chemical stability
- Effect of excipients on crystallization /nucleation

Dosage Form Considerations in Preformulation

Preformulation studies inevitably extend beyond the basic characterization of the lead compound, because what is considered as an acceptable characteristic of a lead compound will largely depend on the intended or anticipated dosage form. For example, the solubility [7] issues will largely determine the route of administration; if a particular route of administration is the only desired route, then preformulation studies should attempt to find out the structural changes necessary for the candidate molecule.

In most instances the choice of a prospective dosage form [7-9] will depend on a variety of factors:

1. Rate of entry to body tissues desired
2. Onset of action desired
3. Aqueous and non aqueous solubility
4. Irritability of solution of drug
5. Stability of drug at the site of administration
6. Storage and handling requirements for the dosage form
7. Shelf life desired
8. Patient acceptance vis-a`-vis the customary routes for the defined class

SOLID DOSAGE FORM CONSIDERATIONS

Most pharmaceutical companies [8, 10] would rather have their new molecule enter the market as a tablet or capsule for a variety of safety, cost, and marketing considerations. As a result, almost 70% of all drugs administered today are in solid dosage forms. When so intended, the default form should be a solid dosage form (unless it is predetermined in the case of therapeutic proteins or other drugs that must be administered by parenteral route or other specific routes for specificity of the desired activity). The typical parameter studies for solid dosage forms relate to the ability of a powder mix to flow well in manufacturing machines, and to the intrinsic characteristics that make it compressible. Some examples of properties studied include:

crystal structures (polymorphs), external shapes (habits), compression properties, cohesion,

powder flow, micromeritics, crystallization, yield strengths and effects of moisture and hygroscopicity, particle size, true bulk and tapped density, and surface area.

SOLUTION FORMULATIONS

Solution dosage forms [12-15] offer several advantages, particularly the resolution of bioavailability problems, instant administration as injectable forms (though non solution forms are also given parenterally). At the preformulation stage, more important factors are the solubility (and any pH dependence) and stability of the new compound.

Solubility

In case a solution form is desired, and the compound has low solubility [2-6], there are several techniques, some very simple to some very complex, to achieve the desirable property of the lead drug, including pH manipulation, use of co-solvents, surfactants, emulsion formation, and adding complexing agents. In a more complex stage, the liposomes or similar drug delivery systems can be used. As many compounds are weak acids or bases, their solubilities become a function of pH. However, the ionic strength of the medium plays a significant role, and as a result most parenteral formulations are buffered to prevent the crystallization of drugs.

FREEZE-DRIED FORMULATIONS

The stability of the solution forms intended for parenteral administration [6-9] can be significantly improved by lyophilizing the solutions to dryness without the use of heat. The solution is frozen to a very low temperature, and vacuum is applied to remove water through sublimation. The cake left is easily dispersible, and thus offers a highly desirable dosage form that is reconstituted just prior to administration.

Examples of lyophilized drugs include erythromycin, vancomycin, bacitracin, cyclophosphamide, cefazolin, infliximab, somatropin, trimetrexate glucuronate MVI and doxorubicin.

SUSPENSIONS

When the lead compound has limited solubility [7-9], and the efforts to enhance it fail, and when there is a tendency for fast crystallization from solutions, or even when chemical stability is a problem, often formulating suspension dosage forms obviates some of these drawbacks. However, suspensions, by nature, must have higher viscosity to prevent the settling of particles, and thus create problems in pourability, syringability, and so on. Appropriate selection of a vehicle that provides an ideal compromise among all characteristics thus becomes a critical factor, because the intent is to have as little solubility in the vehicle as possible to prevent crystallization from the solution that surrounds the suspended particles.

As a result, weak acids and bases appear as poor choice for suspension formulation. In some instances, it may be possible to prepare a derivative with larger hydrophobic groups or salt formation that would have lower solubility, if preparing hydrates when in suspension state can create stability problems.

TOPICAL

Topical delivery of drugs using semisolid [6-9], controlled release patches, and many other dosage forms offers advantages, including reduced blood level fluctuation, obviating the first pass effect, and protection from gastrointestinal pH. In cases where localized action is desired, this dosage form offers remarkable opportunity for drug action. However, skin is a poor medium to deliver drugs, because by its very design it is supposed to prevent the entry of chemicals (though it fails miserably as we know from the chemical warfare agents). Generally, large polar molecules do not penetrate the stratum corneum well. The intrinsic physico-chemical properties of candidate drugs, important in expediting delivery across the skin include MW and volume, aqueous solubility, melting point, and log P. For weakly acidic or basic drugs, the skin pH will play a strong role in their transport.

Drugs that form zwitter ions can be made more penetrable by using appropriate salt forms. The formulation additives strongly impact on transdermal delivery as the variety of dosage forms, such as creams, ointments, lotions, gels, and patches offer a wide variety of formulation additives.

PULMONARY DELIVERY

The pressurized metered dose inhalers [7-10] in the use of environmentally friendly propellants means the choice of hydro fluoro alkanes, wherein the dosage form can be a suspension of the solution form. Solution dosage forms require the selection of propellants, wherein the drug can dissolve without crystallizing, and may require the addition of surfactants and co-solvents. However, there are toxicological issues with the use of surfactants. The solubility of drugs in solvents is determined by filtering the suspension in a pressurized can into another can, and then evaporating the clear solution (bringing to room temperature) followed by determination of the amount of drug in it. High solubility in propellants can lead to crystal growth as propellants evaporate. Ostwald ripening, common to suspensions, applies to inhalation suspensions. The changes in the property of suspension can be studied by using microscopy, and observing the changes in the axial ratio of crystal. Drugs for inhalation therapy in a powder form require a particular particle size, which is achieved by the process of micronization between 1 mm and 6 mm to allow deep penetration through the lung alveoli system.

Conclusion:

Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical path in both liquid and solid dosage form technology. The need for adequate drug solubility cannot be over emphasized. Stability studies in solution will indicate the feasibility of parental or other liquid dosage form and can identify methods of stabilization. In parallel solid-state stability by DSC, TLC and HPLC in the presence of tablet and capsule excipient will indicate the most acceptable vehicles for solid dosage form. 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.

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