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7. Preformulation Studies: Physical Properties and Chemical Properties

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7.1 Introduction:

The process of turning a drug candidate into a drug product is called formulation. At the beginning, there might be several possible therapeutic candidate molecules, each exhibiting action towards a specific biological target and possessing a distinct set of physicochemical features.

In the end, only one—at most—will be turned into a pharmaceutical product. The decision of which promising drug candidate to pursue further development is not solely based on pharmacological efficacy.

In actuality, a material's physicochemical characteristics influence its stability, interaction with excipients, transfer to solution, and bioavailability.

These features also impact how a material is handled pharmaceutically.

Therefore, early in the development process, defining the physicochemical features of drug candidates would provide the essential knowledge.

The fact that a novel drug candidate's physicochemical qualities are typically unknown and must be determined through a mix of experimental and scientific analysis of the molecule's structure is a simple but important point regarding the task at hand.

During this phase of research and development, the novel therapeutic candidate is frequently relatively unrefined and scarce. This situation necessitates modifying standard formula.

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During this phase of research and development, the novel therapeutic candidate is frequently relatively unrefined and scarce. This situation requires a modification to standard formulation research.

One can categorize physicochemical features into two groups: bulk behavior (such as that of the powder or crystals) and intrinsic molecular properties.

While derived attributes are the outcome of a molecule's alteration, intrinsic features are inherent to the molecule and can only be changed chemically.

7.2 Classification:

Preformulation Consideration

Physical Characteristics	**Chemical Characttistics**
A.BULK CHARACTERISTIC	1. Oxidation
1. Particle Size & Surface Area	2. Hydrolysis
2. Polymorphism	3. Photolysis
3. Crystallinity	4. Racemization
4. Hygroscopicity	5. Polymerization
5. Flow properties & Bulk density	6. Isomerization
6. Compressibility	
7. Drug-Excipient Compatibility	

B. Solubility Analysis

1. Aqueous Solubility

2. Solubilization

3. Partition Coefficient

4. Thermal Effect

5. pH Solubility Profile

6. Dissolution

C. Stability Analysis

1. Stability Study in Toxicology Formulation

2. Solution Stability

3. Solid stability

7.3 Physical Characteristics

7.3.1 Bulk Characteristics:

Preformulation investigations and the synthesis process are often developed together. At this point, a drug candidate frequently hasn't had all of its solid forms identified, and additional polymorphs might yet arise. During process development, bulk parameters for the solid form, such as surface morphology, bulk density, and particle size, are also likely to change. As a result, thorough characterization of every preformulation bulk lot is required to prevent inaccurate solubility or stability forecasts that rely on a specific crystalline structure.

A. Particle Size and Surface Area:

Particle size- The simplest method of determining particle form is visual inspection under a microscope (some common shapes of particles). Unless the material is a spray-dried or micronized powder, in which case scanning electron microscopy could be a preferable choice, a light microscope will often suffice. It is challenging to determine precisely which dimension should be utilised to describe the particle size if the particles have irregular shapes rather than being spherical. A number of semiempirical measurements, such as Martin's and Feret's diameters, have been proposed.

The sizes and forms of pharmacological compounds' particles have an impact on a range of their chemical and physical characteristics. The impact extends beyond the physical characteristics of solid pharmaceuticals to occasionally include their biologic behaviour as well. For instance, the particle size distributions of griseofulvin and phenacetin are closely correlated with their bioavailability. It is now well acknowledged that when provided in a finely subdivided form rather than as a coarse substance, poorly soluble medications exhibiting a dissolving rate-limiting stage in the absorption process would be more readily accessible. finished tablet's homogeneity is also influenced by its size.

B. Polymorphism:

A compound is referred to as polymorphic when it has the ability to crystallise into multiple unit cells, each of which has its molecules arranged in a unique pattern. All other forms are metastable, and the form with the highest melting temperature and, consequently, the lowest volume is referred to as the stable polymorphic form. Various polymorphs possess distinct physicochemical characteristics, making it crucial to choose the optimal form for growth. Being the only form that can be said to be in a thermodynamic state of equilibrium meaning that all metastable forms will eventually transition to the stable form is one of the stable form's distinguishing features. is one of the stable form's distinguishing features.

Therefore, it is tempting to think about formulating a drug in only its stable polymorph since this guarantees that the polymorph cannot change while being stored. However, the stable form may have the lowest bioavailability (for example, the presence of the B or C forms of chloramphenicol palmitate dramatically reduces bioavailability) or the worst process-ability (for example, the metastable form I of paracetamol has poor compressibility, while the

metastable form II has good compressibility). Although choosing a polymorphic form is not always simple, the stable polymorph is undoubtedly the best choice for development if it exhibits sufficient bioavailability.

Stable and Metastable Polymorphism:

There is only one configuration of molecules that produces the strongest intermolecular interactions and the most effective packing at a given temperature. In other words, one polymorph will be more stable than the rest. All other potential polymorphs are referred to as metastable, meaning they are less stable than the most stable form, and this is known as the stable form. Numerous materials display monotropic polymorphism, meaning that the most stable form is always the same polymorph at all temperatures, while all other polymorphs are always metastable. As for paracetamol, forms I, II, and III are metastable, with form III being the least stable. Form I is the most stable polymorph. Because of their weaker intermolecular interactions, metastable forms have lower lattice enthalpies. The energy barrier to dissolution will be lowered with a lower lattice enthalpy, increasing solubility and accelerating the rate of dissolution. The order of solubility and dissolution rate in a polymorphic system will therefore be inversely related to the relative polymorph stabilities. The solubility of paracetamol is found in order III. The antipsychotic medication olanzapine is one example of how this tendency is consistently observed: the metastable form IV of the drug dissolves more quickly than the stable polymorph form I.

Screening: Preformulation polymorph screening is carried out in a manner largely similar to that previously discussed for salt screening. A 96-well plate is filled with 0.5 mg of drug per well, and basic screening is accomplished by crystallising the drug candidate from several solvents or solvent mixtures of different polarity. A tiny amount of each solvent or solvent mixture is added to each well. Following a suitable amount of time, the presence of crystals in each well is examined using an optical device and the salt screening techniques previously discussed to aid in crystallisation.

The structural information provided by X-ray powder diffraction (XRPD) helps distinguish and identify polymorphs. It's clear right away that each has a distinct set of intensity peaks. It is immediately clear that each has a distinct set of intensity peaks, resulting in qualitative differences between the forms. A 'fingerprint' for every form is provided by the 20 angles for each peak, and each form's intensities can serve as the foundation for a quantitative assay.

Thermodynamic information is obtained by differentiating polymorphs based on their melting points and heats of fusion using differential scanning calorimetry (DSC) data. This implies that DSC is able to distinguish between stable and metastatic polymorphs. Furthermore, ideal solubility can be calculated using the heat of fusion.

C. Crystallinity:

The final crystallisation process and solvent used can result in a variety of shapes or forms (referred to as "habits") for crystalline polymorphic materials. This can include more spherical habits, needle-like crystals, flat plate-like forms, and extremely angular crystals

with an elongated shape. Their form may have an impact on the bulk powder's "flowability," for example, when it is being discharged from hoppers or containers, because of cohesion or mechanical and physical interactions between the particles.

Every kind of crystal can have distinct degrees of internal structure, which can occasionally result in extremely porous structures, or it can exist as well-formed, solid structures. Because of the variations in surface area exposed to the solvent, these variations can have a significant impact on the rates of dissolution. Therefore, it is helpful to crystallise the compound under various conditions (temperature, solvent, crystallisation speed, etc.) in preformulation studies in order to assess the potential criticality of the crystalline form and recommend ideal crystallisation conditions for additional optimisation.

D. Hygroscopicity:

The term "hygroscopicity" describes a substance's propensity to absorb or adsorb water from its surrounding environment. Physicochemical characteristics typically alter as water content rises. Wet powders will usually become less flowable and more cohesive. An increase in water content can frequently accelerate the rate of chemical degradation of the active ingredient or interaction with any excipients because water mediates many solid-state reactions. If the substance is amorphous, then water absorption results in matrix plasticization, which essentially increases the molecules' molecular mobility, and ultimately causes a significant structural change. When water absorbs into an amorphous matrix that is a freeze-dried powder, structural collapse frequently results. Particularly, salts typically have a higher proportionality to absorb water than the corresponding free acid or base, so it is important to ensure that salt forms are stable in relation to environmental humidity. Certain salts, like magnesium chloride and potassium hydroxide, are so hygroscopic that they will dissolve in the water they absorb and form solutions. Deliquescence is the term for this process. In any case, the drug candidate or drug product needs to be protected if water absorption is likely to result in a negative change in physicochemical properties. Usually, this entails choosing appropriate packaging and advising the patient on how to store it. Karl Fischer titration, Thermogravimetric analysis (TGA), and gas chromatography techniques are used to measure the moisture uptake. Four distinct grades of hygroscopicity are defined by the European Pharmacopoeia for drug substances that are stored for twenty-four hours at a temperature of twenty-five degrees Celsius and 80% relative humidity. These for mentioned storage conditions are used to describe the four classes of hygroscopicity.

E. Flow property and bulk density:

Effective tabletting operations depend on the flow properties of powders. An ideal granule flow is needed for efficient mixing and a manageable weight consistency for the compressed tablets. A medication is categorised as "poor flowable" during the preformulation stage; this issue can be fixed by carefully choosing the excipients. For powder drugs, precompression and granulation techniques are used to enhance the flow characteristics. The ideal flowability, bulk and tapped density, Hausner ratio, inter-particle porosity, Carr's index, angle of repose, and flow through an orifice are used to perform a preformulation test of the granule mass for the measurement of flow properties.

A large crystal or uniform shape exhibits a low Carr's index and a narrower angle of repose due to variations in particle size and shape. The greatest angle that forms between the powder heap's free-standing surface and the horizontal plane of powder at its base is known as the angle of repose.

It can be applied to bulk solid characterization and the assessment of the interparticle force between powder particles. Angle of repose values can range from 0° to 90°; a value below 25° indicates excellent flow characteristics; on the other hand, a value between 25° and 45° indicates poor flow properties.

Bulk density: It is defined as total volume occupied by entire powder mass. It can be determined by placing previously sieved powder bulk into a graduated cylinder and measuring the volume in milliliters. Division of original weight and attended volume gives idea about bulk density.

F. Compressibility:

The ability of medicine powders to compress into tablet dosage forms with a particular tensile strength and reduce in volume under pressure is known as compressibility. Carr's index and the Hausner ratio are used to calculate it.

The drug's cohesion and compression properties lead to compaction. Although most drug powders have very poor properties, drugs alone are rarely used to make tablets. It adds excipients with good compaction qualities. Since excipients make up the majority of tablets containing low-dose medications, the drug's actual characteristics are less significant. However, the drug's compressibility features will significantly affect the tablet's overall qualities as the dose rises above 50 mg.

During the preformulation phase, knowledge about a drug candidate's compaction characteristics is extremely helpful. The ideal property for a material to be tabled is plasticity that is, once it is deformed, it should stay that way.

However, brittleness is also advantageous because it promotes bond formation by generating new surfaces during fragmentation. Since water frequently acts as a plasticizer, changing mechanical properties, its content may also be significant. A helpful practical rule of thumb is that the excipients should fragment if a high dose medication exhibits plastic behaviour. If not, the excipients undergo plastic deformation.

G. Drug Excipient Compatibility:

One of the most crucial stages of the pre-formulation phase of drug development is the investigation of drug-excipient compatibility.

Drug-excipient interactions may have an impact on the dosage form's stability, bioavailability, physical characteristics, and chemical makeup. Studies on the compatibility of drugs and excipients to offer information on interactions between these two, which can aid in choosing the excipient for the creation of a stable dosage form.

Excipients are substances that are added to dosage forms in addition to the active pharmaceutical ingredient (API). The majority of excipients don't directly affect pharmacokinetics, but they are still necessary to make administration easier, control how the active component releases, and stabilise API against deterioration.

Inappropriate excipients, however, can also result in unintended effects that may impact the stability, bioavailability, and chemical makeup of the API, thereby compromising its safety and therapeutic efficacy. Drug-excipient compatibility studies are a crucial step in determining how possible formulation excipients and the API interact during the dosage form development process.

a. Three Different Kinds of Incompatibility:

Physical incompatibility: We evaluate how the formulation's physical form changes, such as color changes, immiscibility, dissolution, solubility, sedimentation rate, liquefaction, and phase separation.

Chemical incompatibility: To determine if compounds experience hydrolysis, oxidation, reduction, precipitation, decarboxylation, and racemization, we evaluate unfavorable reactions between API and excipients.

Therapeutic incompatibility: We evaluate the interactions that arise following drug administration. Premature breakdown of the enteric coat, interactions resulting from adjunct therapy, and an increase in gastrointestinal motility are a few examples of biopharmaceutical interactions.

I. Drug-Excipient Compatibility Analytical Methods:

- Thermal Analysis Techniques: Thermal analysis is widely used to quickly assess physicochemical incompatibility and plays a crucial role in compatibility studies. We offer three distinct categories of thermal analyses.
- DSC (differential scanning calorimetry)
- Thermochromic microcalorimetry
- 4)HSM, or hot stage microscopy

II. Techniques for Spectroscopy:

- Vibrational spectroscopy:
  - Diffuse Reflectance Spectroscopy (DRS)
  - FT-IR Spectroscopy
- X-ray powder diffraction:
- Nuclear magnetic resonance spectroscopy in solid state (ss NMR)

III. Techniques Used in Microscopy:

- Scanning electron microscopy (SEM)

IV. Chromatography:

- Thin-layer chromatography (TLC),
- high-performance liquid chromatography (HPLC),
- self-interacting chromatography (SIC).

7.3.2 Solubility Analysis:

The solubility profile of a potential drug is one of the methods for preformulation analysis that has been studied the most. The performance of the developed formulation is determined by the fundamental study of the preformulation stage. The biopharmaceutics classification system (BCS), which can serve as a framework for the design of various drug delivery systems, is based on the scientific principles of solubility and permeability. A drug's molecule needs to be well soluble in water in order to be better absorbed and transformed into an oral formulation that is effective. Solubility depends on a number of factors, including molecular structure, temperature, pH, complexation, and crystal characteristics. It is not an independent parameter.

Techniques to Improve Solubility:

- Chemical modification of drug
- Addition of cosolvent or surfactant
- Particle size reduction
- Hydrotropy
- Complexation

A. Aqueous Solubility:

One essential quality is aqueous solubility. A drug cannot achieve its ultimate therapeutic goal unless it is first dissolve in solution. As a result, it has been determined to be the first physicochemical parameter.

Poor aqueous solubility has been estimated to have led to the abandonment of up to 40% of drug candidates in the past, and between 35 and 40% of compounds currently in development have an aqueous solubility below 5 mg mL^3 at pH 7. Concentration-based definitions of solubility are provided by the USP and PhEur.

a. Intrinsic solubility
b. Dissolution constant

a. Intrinsic Solubility (Absolute Solubility):

To attain equilibrium and maximum absolute (saturated) solubility, the drug or excipient is vigorously stirred at a constant temperature, such as 37 °C, using standard aqueous buffers. The equilibrium solubility of the unionised form for compounds containing ionisable groups is referred to as the intrinsic solubility.

Measurements of intrinsic solubility in neutral, acidic, and alkaline environments—typically 0.1 M HCl, water, and 0.1 M NaOH at 4 ℃, 25 °C, 37 ℃, and an elevated temperature, such as 50 °C will be the first step in preformulation studies. These data can be compared to data on known and related compounds by recording the absolute (intrinsic) aqueous solubility at each pH. Furthermore, the type of aqueous solvent can be inferred from the solubility profile at various pH values.

b. Dissolution Constant:

The dissociation constant (pKa), like the partition coefficient, is the characteristic that establishes the degree of ionisation and solubility in a pH-dependent environment.

Since only the unionised form can be absorbed, the degree of ionisation controls absorption, making the molecule's pKa value crucial to ascertain. Determining the pKa value provides information about the absorption site.

Since weakly acidic drugs are primarily found in unionised form, the stomach is the best place to absorb them. Their pKa value is approximately 4. Since the majority of strong bases and acids are found throughout the GIT in ionised form, they are not well absorbed. However, it is also true that most pharmaceutical substances are made of weak bases and acids, so absorption is not a problem.

B. Solubilization:

The process of solubilization involves adding surface-active agents to a poorly water-soluble substance to increase its solubility. The process involves molecules being trapped in micelles, either dissolved or adsorbed, and surfactants' propensity to form colloidal aggregations at critical micelle concentration levels. The lowest surfactant concentration at which the insoluble molecule starts to become soluble is therefore known as the critical micelle concentration. The solubility of drugs increases with an increase in micelle concentration.

The FDA has approved the use of several commonly used surfactants for parenteral products, including polysorbate 20, 40, and 80; sodium deoxycholate; monopalmitate; and polyoxyethylated fatty acid, castor oil, and sorbitan compounds.

Solubilization is a crucial tool in preformulation studies for the selection of surfactants in liquid dosage forms of water-insoluble drugs.

C. Partion Coefficient:

A partition coefficient, or log P, is typically used to characterise the lipophilicity of an organic compound. It is the ratio of the unionised compound's concentration at equilibrium between organic as well as aqueous phases:

logP = (Unionised Compound) organic/(Unionized compound) aquaous

- The most popular technique for determination of distribution and partition coefficient It is the shake flask method of coefficients.
- This method involves shaking the medication between octanol and water layerExperimental conditions influence the partition coefficient value in this type of experiment, with factors like temperature, insufficient mutual phase saturation, pH, buffer ions, their concentrations, solvent nature, and the examined solute. Compounds with log P values between 1 and 3 demonstrate favorable absorption, while those with log P greater than 6 or less than 3 often exhibit poor transport characteristics. Highly non-polar molecules tend to reside in lipophilic membrane regions, whereas very polar compounds face challenges in penetrating membrane barriers, leading to poor bioavailability. A balanced relationship between log P and transport is crucial, suggesting that candidate drugs with this balance are likely to have optimal oral bioavailability.

D. Thermal Effect:

A set of methods known as the "thermal method of analysis" measure how a substance's physical and/or chemical properties change with temperature while the material is exposed to controlled temperature programmers. Numerous uses in preformulation and formulation development have been shown for thermal analysis and calorimetric methods. These methods are essential for salt form screening, characterization of polymorphs to ascertain the thermodynamic relationships between the different crystal forms, and physical-chemical screening of early discovery leads.

Preformulation applies biopharmaceutical principles to characterize the physicochemical parameters of a drug substance, aiming to design an optimal drug delivery system.

Thermal analysis plays a crucial role in this process, providing fundamental information on material properties for research, development, and quality control in both industry and academia.

Thermal analytical methods encompass measurements such as weight, loss on drying, enthalpy, glass transition temperature, gas evolution, electrical conductivity, optical characteristics, magnetic properties, changes in dimension, and viscoelastic properties of substances.

Simultaneous Thermal Analysis (STA) involves the combined use of Thermogravimetric (TGA) and differential scanning calorimetry (DSC) on a single sample. Simultaneous Thermal Analysis conditions are identical for both TGA and DSC signals and Coupling Simultaneous Thermal Analysis with an Evolved Gas Analyzer (EGA) like Fourier transform infrared spectroscopy (FTIR) or mass spectrometry (MS) enhances information gathering. DSC, TG/DTA, and TG/DTA-IR are commonly employed for pharmaceutical characterization, distinguishing between polymorphic structures, investigating transformations, and determining polymorphic purity with varied heating rates. TGA is utilized for measuring residual solvents, moisture, and determining solubility of pharmaceutical materials in solvents, making thermal analysis a significant tool in pharmaceutical material analysis.

E. PH Solubility Profile:

To determine solubility at a specific temperature and pH, introduce an excess of solute into a defined amount of solvent. To maintain the solution at the targeted temperature and pH while agitating or stirring overnight to reach equilibrium.

Following the overnight agitation, either centrifuge or filter the sample, and employ spectrophotometric or alternative methods to analyze and ascertain the concentration.

The resulting concentration represents the solubility at the given temperature and pH. The pH scale, ranging from 1 to 14, quantifies acidity and alkalinity, with pH values below 7 indicating acidity, 7 representing neutrality, and values above 7 indicating alkaline or basic conditions. The formula pH = − Log [H+] captures the relationship between pH and hydrogen ion concentration in the solution.

Maintaining the appropriate pH is crucial in preformulation for various reasons:

- To avoid tissue damage and injection site pain, injections should fall within the pH range of 3-9.
- For palatability, oral syrups must not be excessively acidic in their formulation.
- Excessive alkali content can lead to glass container corrosion.
- If a drug is prone to degradation in acidic pH, a delayed-release formulation becomes necessary.
- The pH of a formulation should not cause sensitivity at the application site; for instance, the pH for buccal application should be within the range of 6.6 to 6.8.

F. Dissolution of Salts:

The enhanced dissolution rate of salts arises from their higher saturated concentration in the boundary layer compared to free acids or bases. In the case of acidic and basic drugs, solubility is influenced by pH.

The Noyes-Whitney model suggests that the dissolution rate is consequently pH-dependent, with the solute's solubility at the pH and ionic strength of the dissolution medium acting as the key parameter controlling the rate. Similarly, when the pH of the dissolution medium aligns with pHmax, the dissolution rates of the free acid or base and its salt are expected to be identical based on the same reasoning.

The pH difference between the bulk solvent and the boundary layer results from the dissolution of acids, bases, or salts, which causes a change in pH that is maximised when the boundary layer is saturated. When examining the dissolution of different theophylline salts this correlation first noticed by Nelson (1957). Salts with higher diffusion layer pH had higher in vitro dissolution rates and, more importantly, faster in vivo absorption.

The pH of a saturated solution of the dissolving solid in water is the same as the pH of the boundary layer at the surface, which is referred to as the pH microenvironment (pHmenv).

7.3.3 Stability Analysis:

Preformulation stability studies are the first quantitative assessment of chemical stability of a new drug. This may involve.

A. Stability study in toxicology formulation
B. Solution stability
C. Solid Stability

A. Stability Study in Toxicology Formulation:

A new drug is administered to animals through oral route either by

i. mixing the drug in the feed
ii. in the form of solution
iii. in the form of suspension in aqueous vehicle

- Water, vitamins, minerals (metal ions), enzymes, and other functional groups that may be present in feed could significantly impair the stability of the novel medication. Therefore, stability studies ought to be done in the feed at room temperature.
- It is important to verify the chemical stability of solutions and suspensions at various pH levels and temperatures.
- To ensure dispersibility, the drug suspension in the suspension-state is periodically shaken.

B. Solution Stability:

Evidence on undiscovered liquid incompatibilities that could present a major obstacle throughout the drug development process is provided by solution-state stability studies. It acts as a manual for the formulation procedures as well. When conducting stability studies in the solution state, it's critical to assess.The pharmacological substance's stability at different pH values (pH 1, 2, 4, 7, and 10), both at room temperature and at higher temperatures. The effects of ICH light on photolytic stability and, ultimately, oxidative stability (peroxide oxidation) is discussed. Analysis of solution-state stability can detect API loss and any resulting increase in degradation products.

C. Solid Stability:

Solid-state stability analysis is a very important aspect of drug stability testing. It identifies the stable storage conditions for drug products and also investigates any physical or chemical properties of the drug molecule that may affect the stability of a drug product. This study requires repetitive testing of the initial bulk lot in parallel with newer bulk lots. Unlike reactions that take place when drugs are in solution, solid-state reactions are usually slower and more difficult to interpret due to a reduced number of molecular contacts between drug molecules and excipient(s) and also the occurrence of multiple phase reactions. Information generated from this analysis is influenced by temperature, pH, humidity, hydrolysis, oxidation, etc.

7.4 Chemical Characttistics:

7.4.1 Oxidation:

Many molecules can undergo oxidative degradation, which involves exposure of molecule to atmospheric oxygen or autoxidation by free radicals. However, in some cases, oxidation can be initiated in presence of light or elevated temperature. So, degree of oxidation can be controlled by avoiding exposure to lights and storage at controlled temperatures. Even the extent of oxidation can be controlled by addition of antioxidants. The extent of oxidation for a given substance can be studied by passing oxygen through the solution of substance, or it can be achieved by addition of hydrogen peroxide to the solution of substance.

7.4.2 Hydrolysis:

Hydrolysis involves reaction of a molecule with water resulting in cleavage of a chemical bond within the molecule. If readily hydrolyzable functional groups are available, then reaction proceeds even at faster rates, making the molecule ineffective. Molecules containing esters and amide functional groups are prone to hydrolysis and especially the ester derivatives, which may lead to formation of carboxylic acid or an alcohol. Effectiveness of molecule therefore depends on hydrolytic stability of molecule. For example, lidocaine is amide derivative of procaine, which is ester derivative used as local anesthetic. As ester derivative is more readily hydrolyzed; its duration of action is short while amide derivative is more stable and hence used as long-acting local anesthetic. Beta-lactam antibiotics are susceptible to hydrolysis and hence they are supplied as dry powder injection where they are reconstituted before intravenous administration.

7.4.3 Photolysis:

Mechanism of photodecomposition: Electronic configuration of drug overlaps with the spectrum of sunlight or any artificial light where energy is absorbed by the electron resulting in excitation. As they are unstable, they release the acquired energy and return to the ground state by decomposing the drug. 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. Photosentizer Convert oxygen from its ground state to singlet excited state and Generate superoxide molecule which is an anion radical and acts as a powerful oxidizing.

7.4.4 Racemization:

It is an event where optically active molecule becomes inactive without any change in molecular composition. Such study is of highest importance when racemic mixture form is used. Racemization leads to either loss of pharmacological action or toxic effect may be enhanced by severalfold. Racemization is mostly affected by the conditions like pH, type of solvents, presence of light, and temperature. So main goal in this study is to design optimum condition in which molecule can remain stable.

7.4.5 Polymerisation:

form of chemical degradation where two or more identical molecules combine to form large complex molecules known as polymers.

It can also be defined as a process in which simple monomer molecules combined to form large complex.

Polymerisation can be of mainly two types:

- Addictive polymerisation monomers with double or triple bond combine to form polymers, and the reaction does not give byproducts Condensation polymerisation monomers combine to form polymers along with the formation of by products like water, ammonia, hydrochloric acid etc.

E.g. shellac on aging undergoes polymerisation which disintegration and dissolution time.

- Glucose solution darkens due to polymerisation

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