**DOSAGE FORM DESIGN**

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 **ABSTRACT**

Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and delivery system to prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed pharmaceutics. The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe.

**Keywords -** dosage form, efficacious, administer, compatible

1. **INTRODUCTION**

Drugs are practically never provided as prepared preparations or medicines; they are directly never administered as pure chemical compounds alone. Through the addition of suitable additives or excipients in the formulations, these can range from simplest solutions to complex drug delivery systems. The pharmacological roles performed by the excipients are numerous and specialized pharmaceutical functions. In order to create different medications or dosage forms, formulation additives like solubilize, suspend, thicken, preserve, emulsify, modify dissolution, increase the compactability, and flavour pharmacological components.

The primary goal of dosage form design is to provide a predictable therapeutic response to a drug included in a formulation capable of mass production with reproducible product quality. Numerous features are required to ensure product quality: chemical and physical stability, with appropriate preservation against microbial contamination if appropriate, uniformity of drug dose, acceptability to users, including both prescriber and patient, as well as appropriate packaging and labelling. Dosage forms should ideally be independent of patient-to-patient variance, but in practice, this is difficult to achieve. Recent improvements, however, are beginning to accommodate this necessity. These include drug delivery systems that rely on the distinct metabolic activities of individual patients, as well as implants that respond to externally delivered sound or magnetic fields to trigger a drug delivery function.

Differences in medication bioavailability and catabolic reaction in patients across apparently identical formulations, as well as probable causal factors, should be considered. As it is recognized that formulation factors can influence therapeutic performance, increasing attention has been directed in recent years towards eliminating variation in bioavailability characteristics, particularly for medicinal products containing an equivalent dose of a drug substance. To improve the bioavailability of medicinal substances, it is often important to carefully pick the most appropriate chemical form of the medicine. For example, such selection should evaluate solubility requirements, drug particle size and physical shape, as well as relevant additives and manufacturing aids, in addition to selecting the most acceptable administration route(s) and dosage form(s). Additionally, appropriate production techniques, labelling, and packaging are required.

A drug substance can be put into a variety of dosage forms for the effective and convenient treatment of a condition. To maximize therapeutic response, dosage forms might be developed for administration via alternative delivery routes. Preparations can be administered orally, intravenously, topically, or inhaled, and Table 1.1 summarizes the many dose forms that can be employed to deliver pharmaceuticals via the various administration routes. However, because each disease or sickness typically demands a specific type of pharmacological therapy, it is essential to relate the drug substance to the clinical indication being treated before the most effective combination of drug and dosage form can be created. Furthermore, while creating dosage forms, issues regulating the choice of administration route and the unique requirements of that route that affect drug absorption must be considered.

**Table 1.1 Dosage forms available for different administration routes**

|  |  |
| --- | --- |
| **Administration route** | **Dosage forms** |
| Oral | Solutions, syrups, suspensions, emulsions, gels, powders, granules, capsules, tablets |
| Rectal | Suppositories, ointments, creams, powders, solutions |
| Topical | Ointments, creams, pastes, lotions, gels, solutions, topical aerosols, foams, transdermal patches |
| Parenteral | Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions |
| Respiratory | Aerosols (solution, suspension, emulsion, powder forms), inhalations, sprays, gases |
| Nasal | Solutions, inhalations |
| Eye | Solutions, ointments, creams |
| Ear | Solutions, suspensions, ointments, creams |

Many medications are packaged into a variety of dosage forms with varied strengths, each with unique pharmacological properties that are appropriate for a certain application. Prednisolone, a glucocorticoid used to treat inflammatory and allergy conditions, is one such medication. A variety of effective anti-inflammatory formulations, including tablet, enteric-coated tablet, injections, eye drops, and enema, are accessible through the use of various chemical forms and formulation additions. Because of the extremely low aqueous solubility of the base prednisolone and acetate salts, these forms are useful in tablet and slowly absorbed intramuscular suspension injection forms, whereas the soluble sodium phosphate salt allows for the preparation of a soluble tablet form as well as solutions for eye and ear drops, enema, and intravenous injection. To meet the specific needs of the user, the analgesic paracetamol is also available in a variety of dosage forms and strengths, including tablets, dispersible tablets, paediatric soluble tablets, paediatric oral solution, sugar-free oral solution, oral suspension, double-strength oral suspension, and suppositories.

Furthermore, while many new pharmaceuticals based on low molecular weight organic compounds are still being found and developed into medicinal goods, the creation of drugs based on biotechnology is expanding, as is the value of these therapeutic agents. These active substances are macromolecular and have a relatively large molecular weight, and they comprise peptides, proteins, and viral components. Because of their diverse biological, chemical, and structural features, these pharmacological compounds provide unique and significant obstacles in their formulation and processing into medications. However, the fundamental concepts of dosage form design remain applicable. These therapeutic compounds are now prepared primarily for parenteral and respiratory administration, however other modes of administration are being investigated and researched. The delivery of these biotechnologically based therapeutic compounds via these routes of administration places additional limits on the selection of suitable formulation excipients.

As a result, it is clear that numerous criteria must be considered before a drug substance may be successfully synthesised into a dosage form. These are broadly classified into three categories:

1. **Biopharmaceutical considerations (including factors influencing drug substance absorption via various administration methods)**
2. **Drug factors (drug substance's physical and chemical properties)**
3. **Therapeutic considerations**

Only when all of these elements are considered and interconnected will high-quality and efficacious medicines be designed and manufactured. This is the fundamental idea behind dosage form design.

1. **BIOPHARMACEUTICAL CONSIDERATIONS**

Biopharmaceutics is the study of the link between physical, chemical, and biological sciences as they apply to medications, dosage forms, and drug action. Understanding the basics of this subject is clearly crucial in dosage form design, particularly in terms of medication absorption, distribution, metabolism, and excretion. A drug substance must be in solution before it can be absorbed into body fluids via absorbing membranes and epithelia of the skin, gastrointestinal system, and lungs. Drugs are absorbed in two ways: through passive diffusion and through carrier-mediated transport pathways. The mechanism of passive diffusion, which is assumed to influence the absorption of many medications, is driven by the concentration gradient that exists across the cellular barrier, with drug molecules flowing from high to low concentration regions. The rate of diffusion is influenced by the drug's lipid solubility and degree of ionisation at the absorbing site. Recent study on carrier-mediated transport pathways has provided an array of information and knowledge, guiding the design of novel therapeutic compounds in some cases. Several specialised transport systems, including active and aided transport, are proposed. Once absorbed, the drug can have a therapeutic impact either locally or at a distant site of action from the site of delivery. The medicine must be delivered in bodily fluids in the latter situation (as indicated in Fig. 1).

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**Fig. 1. Pathways a drug may take following the administration of a dosage form by different routes.**

The medicine goes directly into the circulation blood from absorbing tissues when the dosage form is designed to deliver drugs by the buccal, respiratory, rectal, intramuscular, or subcutaneous routes, whereas the intravenous route provides the most direct route of all. The beginning of medication action will be delayed when administered orally due to the required transit time in the gastrointestinal tract prior to absorption, the absorption process, and factors linked with hepatoenteric blood circulation. The physical shape of the oral dosage form influences absorption rate and onset of action, with solutions acting faster than suspensions, which act faster than capsules and tablets. Dosage forms can thus be listed in order of therapeutic effect onset time (see Table 1). However, regardless of delivery route, all drugs remain foreign substances to the human body, and distribution, metabolic, and elimination processes begin immediately following drug absorption and continue until the drug is eliminated from the body in unchanged or metabolised form via the urine, faeces, saliva, skin, or lungs.

**Table 1. Variation in time of onset of action for different dosage forms**

|  |  |
| --- | --- |
| **Time of onset of action** | **Dosage forms** |
| Seconds | Intravenous injections |
| Minutes | Intramuscular and subcutaneous injections, buccal tablets, aerosols, gases |
| Minutes to hours | Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets |
| Several hours | Enteric-coated formulations |
| Days to weeks | Depot injections, implants |
| Varies | Topical preparations |

**1.1. ROUTES OF DRUG ADMINISTRATION**

The absorption pattern of drugs varies considerably between individual drug substances as well as between the different administration routes. Dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration. The following discussion considers briefly the routes of drug administration.

1. **Enteral Route of Medication**

Oral administration of medication is a convenient, cost-effective, and most commonly used medication administration route. The primary site of drug absorption is usually the small intestine, and the bioavailability of the medication is influenced by the amount of drug absorbed across the intestinal epithelium. The first-pass effect is an important consideration for orally administered medications. It refers to the drug metabolism whereby the drug concentration is significantly diminished before it reaches the systemic circulation, often due to the metabolism in the liver.

A sublingual or buccal route is another form of the enteral route of medication administration that offers the benefit of bypassing the first-pass effect. By applying the drug directly under the tongue (sublingual) or on the cheek (buccal), the medication undergoes a passive diffusion through the venous blood in the oral cavity, which bypasses the hepatic portal vein and flows into the superior vena cava. Compared to sublingual tissue, which has highly permeable mucosa with rapid access to the underlying capillaries, buccal tissue is less permeable and has slower drug absorption.[1]

A rectal route is another enteral route of medication administration, and it allows for rapid and effective absorption of medications via the highly vascularized rectal mucosa. Similar to sublingual and buccal routes, rectally administered medications undergo passive diffusion and partially bypass the first-pass metabolism. Only about half of the drug absorbed in the rectum directly goes to the liver.[2]

1. **Parenteral Route of Medication**

Intravenous injection is the most common parental route of medication administration and can bypass the liver's first-pass metabolism. Given their superficial location on the skin, peripheral veins provide easy access to the circulatory system and are often utilized in the parenteral administration of medications. The upper extremity is usually the preferred site for intravenous medication as it has a lower incidence of thrombophlebitis and thrombosis than the lower limbs. The median basilic or cephalic veins of the arm or the metacarpal veins on the hand's dorsum are commonly used. In the lower extremity, the dorsal venous plexus of the foot can be used.

An intramuscular medication route can be administered in different body muscles, including the deltoid, dorsogluteal, ventrogluteal, rectus femoris, or vastus lateralis muscles. Although the dorsogluteal site, or the buttock's upper outer quadrant, is a common site chosen traditionally for intramuscular injections by healthcare professionals, it poses a potential risk of injury to the superior gluteal artery and sciatic nerve.[3] On the other hand, the ventrogluteal site, or the anterior gluteal site, targets the gluteus medius muscle and avoids these potential complications; thus, it is recommended.

Subcutaneous injections are another form of the parental route of medication and are administered to the layer of skin referred to as cutis, just below the dermis and epidermis layers. Subcutaneous tissue has few blood vessels; therefore, the medications injected undergo absorption at a slow, sustained rate. Subcutaneous medication can be administered to various sites, including the upper arm's outer area and abdomen, avoiding a 2-inch circle around the navel, the front of the thigh, the upper back, or the upper buttock area behind the hip bone.

The intraarterial route is not commonly used for drug administration. Injection of contrast material after an arterial puncture is done for angiography. The other uses of this route are for administering regional chemotherapeutic agents and treating malignant tumors of the brain.

1. **Other Routes of Medication**

A trans nasal drug route facilitates drug absorption by passive diffusion across the single-layered, well-vascularized respiratory epithelium directly into the systemic circulation.

An inhaled medication is delivered rapidly across the large surface area of the respiratory tract epithelium. Drugs absorbed into the pulmonary circulation enter directly into the systemic circulation via the pulmonary vein, bypassing the first-pass metabolism. The particle size of the inhaled medication is usually 1 to 10 µm for effective delivery. The efficacy of drug delivery to the lungs depends not only on the drug particle size and morphology but also on the patient's respiratory physiology, such as tidal volume and tracheal inspiration velocity.[4]

A vaginal route is an underexplored drug delivery route that is not commonly used but has the advantage of bypassing the first-pass effect and can serve as an effective method for local and systemic therapy. The venous plexuses from the vagina communicate with the vesical, uterine, and rectal venous plexuses and drain into the internal iliac veins. The veins from the middle and upper vagina drain directly into the inferior vena cava and bypass the hepatoportal system.

The transdermal route can deliver drugs through the skin. This route uses common administration methods: local application formulations like transdermal ointments and gels, drug carriers like nanoparticles and liposomes, and transdermal patches.[5]

The intraosseous route is useful, especially in neonates, for administering fluids and drugs when both peripheral and central venous accesses have failed.[6] Clinical trials are now being conducted on its usefulness in administering medications in out-of-hospital cardiac arrest.[7] It is also used for the administration of prophylactic antibiotics for regional surgeries.[8]

**1.2. BIOLOGICAL FACTORS CAN ALSO INFLUENCE THE ABSORPTION OF DRUGS**

**1.2.1. MEMBRANE PHYSIOLOGY**

The wall of GIT is almost similar throughout its length with four distinct histological layers. On the inner side, GIT is covered with varying thickness of mucus over the length. This viscoelastic gel acts as a protective layer and mechanical barrier to the GI mucosa. Major content of mucus is water and mucins. Mucins are glycoproteins that make up the structure of the mucus. Mucus is constantly removed and is supplemented for the loss continuously. [9] This mucus and water content in it forms an unstirred water layer on the inner side of the GIT lumen. There will be an unstirred water layer on the other side as well which makes the actual barrier as a triple barrier of unstirred water layer-membrane-unstirred water layer. Unstirred mucosal layer diffusion is the rate limiting step for many neutral and ionic drugs in absorption through GIT.

1. **Nature of cell membrane**

Cell membranes are lipid bilayers. Thus any drug that needs to cross the cell membrane has to possess lipophilicity to be able to cross the membrane or it has to have a special mechanism like carrier-mediated diffusion, through which the drug can be absorbed. [10]

1. **Transport Processes**

Specific drugs are absorbed through specific transport processes depending upon their molecular structure and chemical nature. Basic transport mechanisms are passive diffusion, active transport, and endocytosis. [11]

**1.2.2 GASTROINTESTINAL PHYSIOLOGY**

Anatomical barrier, physiological functionalities, and gastric contents are major factors that directly affect the orally administered drugs. Processes like secretion, digestion, and absorption take place in the GIT. The GIT or alimentary canal starts from the oral cavity and ends at the anus. Oral cavity secrets saliva with a pH around 7. It contains amylase and mucin enzymes that help in digestion and lubrication, respectively. These enzymes can interact with drugs. After the oral cavity is the esophagus that joins the pharynx and the cardiac orifice. The pH here drops to 5-6. However, drug dissolution here is negligible. After the esophageal sphincter is the stomach, which secretes acid to digest food. [12] This acidity is the cause of degradation in many compounds. The pH here is about 1.5 and an enzyme called pepsin is secreted here which digests proteins. This enzyme is responsible for the digestion and degradation of peptide drugs, due to this reason peptide drugs are not given orally. Weakly acidic drugs are generally absorbed through the stomach. After the stomach starts the small intestine which is divided into three main parts, namely duodenum, jejunum, and ileum. Small intestine is the major site of absorption for majority of the drugs due to the large available surface area. Next is the colon and it lacks the villi that increase the surface area of the small intestine, for this reason, it has limited help in absorption. Some drugs like theophylline and metoprolol are absorbed from the colon. The colon is also a place for aerobic and anaerobic bacteria. The enzymes from these bacteria sometimes metabolize some drugs like L-dopa and lactulose. The last part of the intestine is the rectum ending at the anus. Drugs can be absorbed well here as this site is perfused well with blood. [13] Some of the physiological processes of GIT that affect drug absorption are discussed in the following subsections.

**1.2.2.1 GASTRIC EMPTYING TIME**

The medicine given by oral route can reach the stomach very quickly. However, it cannot stay for long in the stomach as the stomach contents are emptied into the small intestine. Mostly the drugs are absorbed through duodenum and delay in entry into duodenum will affect the onset time and possible extent of absorption. Various factors affect the gastric emptying time. Some important factors like fat content in meal, anticholinergic drugs delay stomach emptying. Particles with sizes lesser than 1 mm could not be effectively retained in the stomach due to the high basal pressure of the stomach when compared to duodenum. [14] Larger starting volume facilitates initial faster gastric emptying, later on it slows down. Reduction in emptying rate happens with food containing fatty acids, triglycerides, carbohydrates, and amino acids. At lower concentrations of salts and nonelectrolytes that affect the osmotic pressure, the rate of emptying will increase, and higher concentrations decrease the rate of emptying. Solutions and suspensions are emptied rapidly when compared to solid material that must be size reduced before emptying. [15] Lower molecular weight acids reduce the rate of emptying more effectively than the higher molecular weight acids. Bases like sodium bicarbonate will increase the emptying rate at lower concentrations and decrease the rate at higher concentrations. Drugs like anticholinergics, narcotic analgesics, and ethanol reduce the rate of emptying and metoclopramide increases the rate of emptying. Emptying rate is minimal in the case of patient lying on the left side. Aggression increases and depression reduces the rate of emptying. Bile salts and exercise reduces the rate of emptying. [16]

**1.2.2.2 Gastrointestinal pH**

The pH of GIT differs throughout. The pH turns very acidic in the range of 1 to 3.5 in fasted state. With the assimilation of food, the gastric juice turns less acidic in the pH range of 3 to 7. Thus, drugs administered with or just after meals will experience the higher pH of the stomach which can last up to 2 - 3 hours after food intake. This can affect the stability and dissolution of the drugs in the stomach. The intestinal pH is higher than stomach due to the bicarbonate ions released from pancreas into the small intestine. Distal duodenum will have a pH of around 5, jejunum around 6.5, and ileum around 7. In the colon, the pH drops due to the breakdown of undigested carbohydrates by the bacterial enzymes to short chain fatty acids to around 6.5. Examples of drugs that are affected by the GI pH are penicillin G, erythromycin, and omeprazole. [17]

**1.2.2.3 SURFACE AREA OF GIT**

Drugs can be absorbed from all parts of the GIT through passive diffusion. However, the major site of drug absorption is the duodenum due to enormous surface area for the absorption of drugs. Larger area of the duodenum is due to the presence of small projections known as villi. These villi contain even small projections known as microvilli. These microvilli appear as brush border on the luminal side of the intestine. Apart from this, the duodenum is supplied with a greater capillary network which can be beneficial in maintaining the concentration gradient for the diffusion of drugs into blood. [18]

**1.2.2.4 GASTROINTESTINAL MOTILITY AND INTESTINAL TRANSIT TIME**

GI motility helps in the movement of dosage form from the oral cavity to the lower parts of the intestine. There may be an anatomic absorption window for drugs that are given orally, through which the drug gets absorbed efficiently. It is highly important for drugs intended for sustained or controlled release. Drugs should have efficient transit time for good extent of absorption. Normal average small intestine transit time is about 34 hours in fasting state. In fed state, the transit time would be around 812 hours. It was found that there is no effect of high caloric food on the intestinal transit time. Colonic transit time is highly variable with a tendency for smaller particles to be transported at a slower rate than the larger particles. [19] A greater capillary networks and lymphatic vessels perfuse the duodenum and peritoneum. The splanchnic circulation which serves the GIT receives 28% of the cardiac output and it increases after ingestion of food. Drugs absorbed through the upper GIT enter the mesenteric vessels and the portal vein to reach the liver before entering the systemic circulation. Any decrease in mesenteric blood flow like in the case of heart failure will affect the drug absorption. Absorption of lipidic drugs bypasses this portal vein and avoids hepatic first-pass metabolism as these drugs enter the lymph through the lacteals present in the microvilli. [20]

**1.2.2.5** **GASTROINTESTINAL CONTENTS**

GIT contains food, fluids, enzymes and sometimes other drugs along with the drugs of interest. These all can influence the absorption of the drug from GIT. These are discussed in the following text. [21]

**1.2.2.6 EFFECT OF FOOD**

Food can also affect the rate and extent of absorption of drugs from the GIT. Drugs can form complexes with the food components that are not absorbed well from the GIT. This is a real issue when an irreversible or insoluble complex is formed. Tetracycline for example forms nonabsorbable complexes with calcium and iron, thus concomitant intake of milk or iron preparation will prevent the drug’s absorption. [22] Food can also alter the pH of the GIT. In general, food increases the stomach pH by acting as a buffer. This can increase the dissolution and absorption rate of a weakly acidic drug. Gastric emptying can be altered by the food particularly those containing high fat content. Food slows the rate of absorption due to delayed gastric emptying of some drugs like lamivudine and Zidovudine but it is not clinically significant. Food can stimulate the secretion of enzymes and if the drugs are prone to enzymatic degradation their absorption will be affected. Competition between food components and drugs for transporters might also affect the absorption. [23]

**1.2.2.7 EFFECT OF FLUID**

Large amounts of fluids in the stomach favor rapid dissolution of the dosage form and rapid gastric emptying resulting in increased absorption. The absorption of erythromycin is better in an empty stomach and when taken using a glass of water compared to the absorption under fed state. [24]

**1.2.2.8 EFFECT OF OTHER NORMAL GI CONTENTS**

Regular GI contents like mucin, bile salts, and enzymes can affect the drug absorption. Mucin interacts with streptomycin to hinder its absorption. Mucin acts as a barrier in drug diffusion to other drugs as well. The bile salts help in solubilization and absorption of lipophilic drugs like griseofulvin and vitamins A, D, E, and K. Bile salts sometimes can also inhibit the absorption of certain drugs like neomycin and kanamycin by forming water-insoluble complexes. Enzymes can influence the absorption drastically of drugs that are susceptible. The metabolism by these enzymes is known as pre systemic metabolism. [25]

**1.2.2.9 DRUG STABILITY IN GIT**

Drug stability in the GIT can be influenced by extreme acidic pH and enzymes. Drugs that are unstable in acidic environment are generally coated with protective materials that protect the drug from acidic environment. This is called an enteric coating. Drugs that undergo metabolism by the enzymes cannot be given orally and need to be administered via other routes of drug administration, generally. This is true in the case of proteinous and peptide drugs. These drugs are administered by other routes to avoid degradation by the proteolytic enzymes in the GIT. [26]

**1.2.2.10 EFFECT OF PRE-SYSTEMIC METABOLISM**

Drugs absorbed from GIT will reach the liver initially through portal vein except for the drugs that are absorbed from colon. During the absorption process simultaneously, metabolism starts. The metabolizing enzymes are present in the lumen, gut wall, and liver. In colon there are enzymes that are being produced by the bacteria that can also to some extent metabolize the drugs. The drugs absorbed from upper GIT will pass through the liver and if they are highly sensitive to metabolism in liver some amount of the unchanged form reaching the blood circulation is lost. This metabolism is termed as first-pass metabolism or effect and affects the absorption of many drugs given orally. Other than liver luminal enzymes, gut wall enzymes can also metabolize the drug to some extent. The metabolism that is taking place before the drug is termed as presystemic metabolism including first-pass metabolism. [27]

1. **LUMINAL ENZYMES**

Luminal enzymes are the enzymes secreted into the GIT lumen by various types of cells and organs of the body. Pancreas secretes various luminal enzymes such as lipases, amylases, and proteases. Apart from that gastric juice contains pepsin. Lipases, amylases, and proteases are secreted by the pancreas into the small intestine. Mostly, degradation of high molecular weight peptides and proteins occur through these luminal enzymes. Several nucleotides and fatty acids are also degraded by these enzymes. [28]

1. **GUT WALL ENZYMES**

Gut wall enzymes contribute to the presystemic metabolism of the drugs. These enzymes can degrade the drugs before they can reach the blood circulation which is called as presystemic metabolism. The major enzyme CYP3A belonging to the cytochrome family is present in the intestinal mucosa, thus absorption of substrates to this enzyme is affected. CYP levels are higher in the intestine than in the colon. [29]

1. **BACTERIAL ENZYMES**

Bacteria in the colonic region secrete certain enzymes and can also affect the drug absorption. Sometimes these enzymes are used in designing drugs that target the colon. Sulfasalazine is an example of a prodrug in which 5-ASA connected to sulfapyridine through azo linkage. This sulfapyridine moiety makes the drug too large for absorption in the upper GIT. In the colon bacterial enzymes reduce the azo bond and release the active drug, 5-aminosalicylic acid, for local action in colonic diseases such as inflammatory bowel disease. [30]

1. **HEPATIC ENZYMES**

Liver is the primary site of drug metabolism. It can also be a barrier to drug absorption as the drugs that are absorbed through the GIT go directly to the liver before going anywhere else. So if the drug is metabolized to a great extent in the liver then the amount of drug reaching the site of action is very limited. This metabolism is known as first-pass metabolism. Propranolol is absorbed well through the GIT but due to first-pass metabolism only 30% of the oral dose is available to the systemic circulation. Other examples include atorvastatin, lidocaine, imipramine, diazepam, pentazocine, and morphine. [31]

1. **DRUG FACTORS: PREFORMULATION**

Each type of dosages forms requires careful study of the physical and chemical properties of drug substances to achieve stable, officious product.

Before formulating a drug substance into a dosage form, the desired product type must be determined insofar as possible to establish the framework for product development. Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up. The formulation that best meets the goals for the product is selected to be its master formula. Each batch of product subsequently prepared must meet the specifications established in the master formula. There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease. Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are such therapeutic matters as the nature of the illness, the manner in which it is treated (locally or through systemic action), and the age and anticipated condition of the patient. If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are usually prepared because they are easily handled by the patient and are most convenient in the self-administration of medication. If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment. The age of the intended patient also plays a role in dosage form design. For infants and children younger than 5 years of age, pharmaceutical liquids rather than solid forms are preferred for oral administration. These liquids, which are flavoured aqueous solutions, syrups, or suspensions, are usually administered directly into the infant’s or child’s mouth by drop, spoon, or oral dispenser or incorporated into the child’s food. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When a young patient has a productive cough or is vomiting, gagging, or simply rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instances, injections may be required. Infant-size rectal suppositories may also be employed, although drug absorption from the rectum is often erratic. During childhood and even adulthood, a person may have difficulty swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant-tasting creamy material. Newly available tablets dissolve in the mouth in about 10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water. Also, a teaspoonful of gelatine dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, if a person has difficulty swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed. Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance. Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and colour of solid dosage forms, the easier is proper identification of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. [32] Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous. In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the preformulation work needed before actual product formulation begins.

**PREFORMULATION**

For the achieving goals of drug and dosage forms, preformulation testing is a first step in the development of dosage forms before the formulation. Preformulation is defined as an investigation of physical and chemical properties of a drug substance alone and along with excipients before the formulation. The main objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms before formulation development. Pre-formulation investigations are designed to deliver all necessary data, especially physicochemical, physico-mechanical, and biopharmaceutical properties of drug substances, excipients, and packaging materials.

**2. PRE-FORMULATION PARAMETERS (Physicochemical characterization)**

**2.1. Organoleptic properties**

**2.2. Bulk characteristics**

* 1. Assay development
	2. Melting point
	3. Solid state characteristics: Particle size, surface area
	4. Flow properties
	5. Densities
	6. Compressibility
	7. Crystalline and amorphous
	8. Polymorphism
	9. Hygroscopicity.

**2.3. Solubility analysis**

* 1. Ionization constant (pKa)
	2. Partition coefficient
	3. Dissolution
	4. Solubilization
	5. Thermal effect
	6. Common ion effect (Ksp).

**2.4. Stability analysis**

* 1. Solid-state stability
	2. Solution-state stability
	3. Drug-excipients compatibility

**2.1. Organoleptic properties**

This includes appearance, color, odor, and taste of the new drug substances must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties to avoid confusion among scientists using different terms to describe the same property.

**2.2. Bulk characteristics**

**a. Assay development**

The strength of a drug substance may be its concentration (quantity of the drug per unit measure), its potency, or both. The potency of a drug is a measurable amount of therapeutic active constituents of drug per unit weight or volume of the drug preparation. No relevant physicochemical property can be measured without an assay. Assay development is a first step of preformulation. [33]

Percent purity (assay) of drug is determined using different techniques. In this method, development for particular drug substance is necessary, and this can be developed by ultraviolet (UV) spectrophotometer or for better accuracy high-performance liquid chromatography (HPLC).

Assay development determines the approximate values if these are acceptable to make a “go/no go” decision in respect of a particular drug candidate. The assays that may be used to quantify them and as function of molecular structure.[34] Absorption maxima (λmax) also used to determine purity of drug substance using UV-spectrophotometer.

**b. Melting point**

The melting point of a pure solid substance is defined as the temperature at which solid and liquid exist in equilibrium. A melting point or range of a drug can be used as an indicator of purity of drug substances (characterized by very sharp melting peak in differential scanning calorimetry [DSC]). A change in a peak or peaks at different temperature may indicate an adulterated or impure drug. Melting point of a drug substance can be measured using three techniques, (1) capillary melting, (2) hot stage microscopy, and (3) DSC.[35]

**c. Solid state characteristics**

Powders are masses of solid particles or granules surrounded by air (or other fluid). Means it is the solid plus fluid combination, which significantly affects the bulk properties of the powder. Physical characteristics of the particles, such as size, shape, angularity, size variability, and hardness will all affect flow properties. External factors affect during handling such as humidity, conveying environment, vibration, and perhaps most importantly aeration will change the properties of solid.

* **Particle size, size distribution and surface areas**

Particle size distribution and shapes are affected on various chemical and physical properties of drug substances. These changes in properties may affect on their biopharmaceutical behaviour. For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distributions of these drugs. Size also plays a role in the homogeneity of the final tablet. When ununiform size exists between the active components and excipients, mutual sieving (demixing) effects can occur making thorough mixing difficult or if attained difficult to maintain during the subsequent processing steps.

Washington (1992) has reported the concepts and techniques of particle size analysis.[36] There are many different techniques available for particle size analysis. The techniques most readily available include sieving, optical microscopy in conjunction with image analysis, electron microscopy, the coulter counter, and laser diffractometry. Table 2 lists particle size measurement methods commonly used and the corresponding approximate useful size range.

The particle size distribution of a micronized powder determined by scanning electron microscopy and laser light scattering. The Malvern mastersizer is an example of an instrument that measures particle size by laser diffraction. The use of this technique is based on light scattered through various angles, which is directly related to the diameter of the particle. Thus, by measuring the angles and intensity of scattered light from the particles, a particle size distribution can be deduced.

The surface areas of drug particles are important because they alter the rate of dissolution (as predicted by the NoyesWhitney equation).[37] Surface area can also be quoted if the particle size is difficult to measure. Surface areas are usually determined by gas adsorption technique (nitrogen or krypton) and Brunauer, Emmet and Teller (method) describe this phenomenon. Singh, 1992 have been reviewed in detail gas adsorption methods for surface area determination.

**Table 2: Particle size techniques and size range**

|  |  |
| --- | --- |
| **Method** | **Size range (µm)** |
| Sieving (woven wire) | 20‑125,000 |
| Sieving (electroformed) | 5‑120 |
| Sieving (perforated plate) | 1000‑125,000 |
| Microscopy (optical) | 0.5‑150 |
| Microscopy (electron) | 0.001‑5 |
| Sedimentation (gravity) | 1‑50 |
| Sedimentation (centrifugal) | 0.01‑5 |
| Electrical zone sensing (e.g., Coulter) | 1‑200 |
| Laser light scattering (Fraunhofer) | 1‑1000 |
| Laser light scattering (quasi‑elastic) | 0.001‑1 |

**d. Powder flow properties**

For efficient tableting, flow properties of powders are critical. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and uniform weight of the compressed tablets. If a drug is identified at the preformulation stage to be “poorly flow” the problem can be solved by selecting appropriate excipients. In some cases, improve flow properties of drug powders by precompression or granulation. Some of these methods used to measure flow properties are angle of repose, flow through an orifice, compressibility index, shear cell, etc. Changes in particle size and shape are generally very apparent; an increase in crystal size or a more uniform shape will lead to a smaller angle of repose and smaller Carr’s index. [38]

* **Angle of repose**

Maximum angle which is formed between the surface of powder pile and horizontal surface called as angle of repose. For most pharmaceutical powders, the angle of repose values range from 25° to 45°. The angle ≤30° indicate free-flowing material while ≥40° indicate poor flowing material. Angle of repose can be determined using fixed funnel method, fixed cone method, rotating cylinder method, and tilting box method.

Tan θ = (h/r)

Where, h = height of pile, r = radius of base of pile.

**e. Densities**

It may be affect on the floe properties of material and tableting operation. The ratio of mass to volume is known as density.

**Types of density:**

1. Bulk density: It is obtained by measuring the volume of known mass of untapped powder that passed through the screen
2. Tapped density: It is obtained by measuring the volume of known mass of powder after tapping the measuring cylinder
3. True density: It actual density of the solid material
4. Granule density: May affect compressibility, tablet porosity, disintegration, dissolution, and settling of particles in diffusible mixtures or suspension. [39]

**f. Compressibility**

“Compressibility” of a powder can be defined as the ability to reduction in volume under pressure and compatibility as the ability of the powdered material to be compressed into a tablet of specified tensile strength (plastic deformation). It can be used to predict the flow properties of solids based on density measurement.



**g. Crystalline**

The external shape of a crystal is termed the habit whereas the internal structure is the molecular arrangement within a solid. Crystal morphology or habit is important since it can influence many properties of the compound. For example, powder flow properties, compaction, and stability have all been found to be dependent on crystal morphology. A single internal structure for compound has several different habits, depending on environment for growing crystal. Crystallization is invariably employed as the final step for the purification of a solid. The use of different solvents and processing conditions may alter the habit of recrystallized particles, besides modifying the polymorphic state of the solid. Crystallinity is determined by X-ray diffraction technology, estimate the degree of crystallinity was based upon the measurement of the total scattering [40]

**h. Amorphous forms**

Amorphous forms mean non-crystalline nature of materials, i.e. they possess no long range order. Their structure can be prepared by rapid precipitation, lyophilization, or rapid cooling (supercooling) of liquid melts and milling and compaction of crystals.

One consequence of a disordered structure is that they are the most energetic form, thermodynamically unstable; therefore, the tendency of amorphous forms is to revert in a more stable form, this is particularly true when the formulation is in an aqueous suspension. Another consequence for some compounds with a low degree of crystalline can be a decrease in chemical stability. Because of these problems with physical and chemical stability, attempts to crystallize the amorphous phase should always be undertaken; however, it should be borne in mind that amorphous phases, if chemically and physically stable, can have some advantages over the crystalline phase. For example, a stabilized amorphous form of novobiocin was found to be 10 times more soluble and therapeutically active compared to the crystalline form.[41]

**i. Polymorphism**

Many drug substances can exist in more than one crystalline form with different internal lattice arrangements. This property is known as polymorphism. The different crystal forms are called polymorphs. When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal; either they may be packed differently in the crystal lattice or there may be differences in the orientation or conformation of the molecules at the lattice sites.

In general, polymorphs of a given compound have different physicochemical properties, such as melting point, solubility and density, so that the occurrence of polymorphism has important formulation, biopharmaceutical, and chemical process implications. In addition to polymorphs, solvates (inclusion of the solvent of crystallization), hydrates (inclusion of water of crystallization), and amorphous forms (where no long-range order exists) may also exist (e.g., polymorphism shown by estrone). Solvates has also termed as pseudopolymorphs.[42]

**j. Hygroscopicity**

Many pharmaceutical compounds and salts are sensitive to water vapor or moisture. When compounds come in contact with moisture, they retain the water by bulk or surface adsorption, capillary condensation, chemical reaction and, in extreme cases, a solution (deliquescence). Deliquescence is where a solid dissolves and saturates a thin film of water on its surface. It has been shown that when moisture is absorbed to the extent that deliquescence takes place at a certain critical relative humidity, the liquid film surrounding the solid is saturated. This process is dictated by vapor diffusion and heat transport rates.

Moisture is also an important factor that can affect the stability of drugs candidate and their formulations. Sorption of water molecules onto a candidate drug (or excipient) can often induce hydrolysis.[43] In this situation, by sorbing onto the drug-excipient mixture, the water molecules may ionize either or both of them and induce a reaction.

**2.3. Solubility analysis**

The solubility of solid is defined as the concentration at which solution phase is equilibrium with a given solid phase at stated temperature and pressure. The solubility of a candidate drug may be the critical factor determining its usefulness, since aqueous solubility dictates the amount of compound that will dissolve; therefore, the amount available for absorption. If a compound has a low aqueous solubility, it may be subject to dissolution rate-limited absorption within the gastrointestinal residence time. Solubility expression given in Table 2.

Recently, the importance of solubility, in biopharmaceutical terms, has been highlighted by its use in the Biopharmaceutical Classification System. In this system, compounds are defined in terms of combinations of their solubility and permeability [Figure 3]

• Class I: High solubility, high permeability

• Class II: Low solubility, high permeability

• Class III: High solubility, low permeability

• Class IV: Low solubility, low permeability.

**Table 2: Solubility classification**

|  |  |
| --- | --- |
| **Descriptive term** | **Parts of solvent (in ml) required for 1 part (per gram) of solute** |
| Very soluble | <1 |
| Freely soluble | From 1 to 10 |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30 to 100 |
| Slightly soluble | From 100 to 1000 |
| Very slightly soluble | From 1000 to 10,000 |
| Practically insoluble | 10,000 and over |



**Figure 2: Biopharmaceutical Classification System**

High solubility is defined as the highest dose strength that is soluble in 250 ml or less of aqueous media across the physiological pH range. Poorly soluble drugs can be defined as those with an aqueous solubility of <100 g/mL. If a drug is poorly soluble, then it will only slowly dissolve, perhaps leading to incomplete absorption.[44]

The importance of solubility (and permeability) in drug discovery and development has been discussed by Lipinski et al. 1997.[25] The “rule of 5” states that poor absorption or permeation more likely when there are more than 5 H-bond donors (expressed as the sum of OHs and NHs); the MWT is over 500; the Log P is over 5 (or M LogP is over 4.15); there are more than 10 H-bond acceptors (expressed as the sum of Ns and Os); James et al., 1986 has provided some general rules regarding solubility.[26]

i. Electrolytes dissolve in conducting solvents

ii. Solutes containing hydrogen capable of forming hydrogen bonds dissolve in solvents

iii. Capable of accepting hydrogen bonds and vice versa

iv. Solutes having significant dipole moments dissolve in solvents having significant dipole moments

v. Solutes with low or zero dipole moments dissolve in solvents with low or zero dipole moments.

**b. pKa determinations**

The majority drug candidates are weak acids or bases; therefore, one of the most pertinent determinations carried out before development is the pKa or ionization constant. pH of the medium imparts the solubility of acidic and basic compounds. Strong acids, e.g., HCl, are ionized at all pH values, whereas the ionization of weak acids is dependent on pH. It is useful to know the extent to which the molecule is ionized at a certain pH, since properties such as solubility; stability, drug absorption, and activity are affected by this parameter. [45]

For basic compounds:



**b. The partition and distribution coefficients**

The relationship between chemical structure, lipophilicity, and an indication of its ability to cross biological cell membrane is oil/ water coefficient. These include solubility, absorption potential, membrane permeability, plasma protein binding, volume of distribution, and renal and hepatic clearance. The lipophilicity of an organic compound is usually described in terms of a partition

coefficient log P or K o/w, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:



It is worth noting that this is a logarithmic scale; therefore, a log P = 0 means that the compound is equally soluble in water and in the partitioning solvent. If the compound has a log P = 5, then the compound is 100,000 times more soluble in the partitioning solvent.

A log P = –2 means that the compound is 100 times more soluble in water, i.e., it is quite hydrophilic. In other words, if log P value is more than 1 then compound is lipophilic while log P value is <1 then hydrophilic. [12,28,29]

**c. Dissolution**

The dissolution rate, rather than saturation solubility, is most often primary determinant in the absorption process of a sparingly soluble drug. Experimental determinations of the dissolution rate are therefore of great importance. The main area for dissolution rate studies is evaluation of different solid forms of a drug (e.g. salts, solvates, polymorphs, amorphous, stereoisomers) or effects of particle size.[46] The dissolution rate can either be determined for a constant surface are as follows:

1. **Intrinsic dissolution:** The dissolution rate of a solid in its own solution is adequately described by the NoyesNernst equation. The intrinsic dissolution rate in a fixed volume of solvent is generally expressed as mg dissolved × (min−1 cm−2). Knowledge of this value helps the pre-formulation scientist in predicting if absorption would be dissolution rate limited.
2. **Particulate dissolution:** It will determine dissolution of drug at different surface area. It is used to study the influence on dissolution of particle size, surface area, and mixing with excipient. Hence, if particle size has no influence on dissolution than other methods such as addition of surfactant will be considered.

**d. Solubilization**

Solubility is defined as the drug goes into solution. Solubility of drug substance affect on the bioavailability of drug. Poor water solubility or insufficient solubility for projected solution dosage form, pre-formulation study should include limited experiments to identify possible mechanism of solubilization for improves solubility. The methods used to increase solubility are change in pH, cosolvency, dielectric constant, solubilization by surfactant, complexation, hydrotropy, and chemical modification of drug, etc.[26]

**e. Thermal effect**

Since dissolution is usually an endothermic process, increasing solubility of solids with a rise in temperature is the general rule. Therefore, most graphs of solubility plotted against temperature show a continuous rise, but there are exceptions, e.g., the solubility of sodium chloride is almost invariant, while that for calcium hydroxide falls slightly from a solubility of 0.185 g/mL at 0°C to 0.077 g/mL at 100°C.[30,31]

**f. Common ion effect (Ksp)**

A common interaction with solvent, which often overlooked, is the common ion effect. The addition of common ion often reduces the solubility of slightly soluble electrolyte. Salting out is results from the removal of the water molecule as the solvent due to competing hydration of other ions. Hence, weakly basic drug which are given as HCl salts have decreased solubility in acidic (HCl) solution.[48]

**2.4. Physicochemical stability of drug substances**

Pre-formulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include solution and solid state stability in the 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 administrations 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. [12,32]

1. **Physical stability (initial solid-state stability)**

Physical stability of active pharmaceutical ingredients (APIs) includes: Change in physical appearance, color, odor, identity, specific gravity, and optical rotation of API. Depending on the conditions of temperature and the humidity to which the solid is exposed, the acceleration phase may follow zero, first, or higher orders. In terms of the chemical stability of compounds with respect to moisture uptake, the following descriptions have been used to describe classes of surface moisture.[49]

**i. Limited water**

Water is used up during the degradation reaction, and there is not enough present to degrade the compound completely. Adequate water: Sufficient water is present to decompose the compound completely. Excess water: This is an amount of water equal to or greater than amount of moisture necessary to dissolve the drug. As such, this may decomposes drug with time.

**ii. Loss of volatile constituents**

Iodine, camphor, menthol, ethyl alcohol, anesthetic, and chloroform have tendency to evaporate from product. Nitroglycerine tablets may lose their potency owing to vitalization of medicament. Color changes: Color fading is a fairly common type of instability.

**iii. Loss of water**

Loss of water leads to decrease in weight and raise the dose of drug and increase potency. For example, borax, caffeine, and quinine sulfate have a natural tendency to lose water.

**iv. Absorption of water**

Leads to increase the weight and dilute and decrease the potency of drug. Amorphous transformation: Amorphous substances have high energy and readily converted to crystalline state at elevated temperature through melting. Moisture also enhances the rate of amorphous transformation. Crystal growth, polymorphic transformation: By absorption of moisture change in crystal habit of crystal and change from metastable form to most stable polymorphic form. This leads to decreases solubility of drug substances.[50]

**V. Preventive measures**

The product is protected from light and air. Reducing substances are avoided as additives (e.g., dextrose). Select excipients at low moisture/water content for drug product.[33]

**b. Chemical stability (Solution-state stability)**

Chemical stability study includes many ways that cause instability of drug through the chemical reaction resulting in a reduction of potency.[35]

**i. Hydrolysis**

Hydrolysis means breakdown of drug molecules in presence water and or sometimes acid. Degradation by hydrolysis is affected by a number of factors of which solution pH, buffer salts, and ionic strength are the most important. In addition, the presence of cosolvents, complexing agents, and surfactant can also affect this type of degradation. As noted, solution pH is one of the major determinants of the stability of a compound.

Drug with esters and amide group react with one molecule of water and undergoes hydrolysis. Ester group hydrolyses faster than amide group.

Drugs are either weak acid or bases. Therefore, the may be available as ionic form or neutral form. Hydrolysis reaction between ionic form proceeds faster than neutral molecules.

Examples;

* Esters: Aspirin, procaine, atropine
* Amide: Chloramphenicol, ampicillin, barbituric acid.[49-50]

**ii. Preventive measures against hydrolysis**

Hydrolysis reactions are due to presence of moisture, catalytic species H+ , and (OH)− it can be prevented by following way,

* + Buffer: Use of buffer for stabilization of product
	+ Complexation: Complexing agent form complex with drug and prevent hydrolysis and shelf life of drug is prolonged
	+ Suppression of solubility: Less solubility decreases concentration of drug in solution phase and reduce rate of hydrolysis
	+ Removal of water: Presence of water is responsible for hydrolysis, so it is better to avoid by storage of drug in dry form and using water immiscible vehicle.

**iii. Oxidation**

The second most common way a compound can decompose in solution is through oxidation. Reduction/oxidation reactions involve either the transfer of oxygen or hydrogen atoms reaction can be initiated by the action of heat, light, or trace metal ions that produce organic free radicals. These radicals propagate the oxidation reaction, which proceeds until inhibitors destroy the radicals or until side reactions eventually break the chain. [46-48]

Oxidation involves removal of electrons from molecules. To test whether a compound is sensitive to oxygen, simply bubble air through the solution, or add hydrogen peroxide, and assess the amount of degradation that takes place.

Reaction between compound and molecular oxygen is called autoxidation. In fats and oils autoxidation of unsaturated fatty acid is done.

Example: Arachis oil, clove oil, cinnamon oil, Vitamin A, riboflavin, ascorbic acid, morphine.

**iv. Preventive measures against oxidation**

Oxidation reaction is due to the presence of moisture, oxygen, trace metals, H+, and (OH)− ions. Use of antioxidant: Tocopherol, chelating agents: Use when the presence of traces of heavy metals, use of buffer, prevents light exposure, oxygen free environment, and low-temperature storage.[34,35]

**v. Racemization**

Although hydrolysis and oxidation constitute the main mechanisms by which drugs can decompose; racemization is another way in which the compound can change in solution. In this optically active compound loses its optical activity without changing its chemical composition and converted into its inactive form that is racemic mixture. For example, levo-adrenaline is 15-20 times more active than dextro adrenaline. Solution of levo-adrenaline form racemic mixture of equal parts of levo and dextro-adrenaline with half of its pharmacological action over the pure levo compound.

The kinetics of racemization may be studied in a manner similar to hydrolytic reactions. Racemization reactions, in general, undergo degradation in accordance with first-order kinetic principles.[42-45]

**vi. Photolysis**

Many drug molecules enhance the rate of chemical reaction under the influence of light energy, such as heat. Drug which undergoes light-induced chemical degradation is called photolablie or photosensitive drugs.

**v. 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.

Example: Riboflavin, tetracycline, chlorpromazine. Color development or color fading is also example of photodegredation.[34-36]

**vi. Preventive measures**

Prevent light exposure, low-temperature storage.

**vii. Polymerization**

It is a continuous reaction between molecules. More than one monomer reacts to form a polymer. E.g., darkening of glucose solution is attributed to polymerization.

**c. Drug-excipient compatibility studies**

During development of stable and effective dosage form it is not only depends on quality of API but also the careful selection of excipients and selection of a good quality of excipient is also vital role in designing of good quality of dosage forms. During this stage, selection of excipients is based upon their compatibility with drug substance. Knowledge of drugexcipient 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 to generate the needed information. [35,37]

**STABILITY TESTING**

Stability testing provides evidence on how the quality of drug substance or dosage form varies with the influence of environmental conditions such as temperature, humidity, and light. This information is useful for the recommendation of storage conditions and shelf life. According to ICH guidelines, stability testing carried out in different conditions of temperature and humidity for different period shown in Table 3. [38,39]

Testing frequency (intervals) for long-term testing will normally be every 3 months, over the 1st year, every 6 months over the 2nd year and then annually.

For the stability study design minimum, three batches should be studied and evaluated for their physicochemical and microbiological characteristics

**Table 3: Stability testing**

|  |  |  |
| --- | --- | --- |
| **Type of study** | **Conditions** | **Minimum time period at submission** |
| Long‑term testing | 25±2°C/60±5% RH | 12 months |
| Accelerated testing | 40±2°C/75±5% RH | 6 months |
| RH: Relative humidity |

1. **THERAPEUTIC CONSIDERATIONS**

The ultimate aim of any prescribed medical therapy is to achieve certain desired outcomes in the patients concerned. These desired outcomes are part and parcel of the objectives in the management of the diseases or conditions. However, despite all the best intention and efforts on the part of the healthcare professionals, those outcomes might not be achievable if the patients are non-compliant. This shortfall may also have serious and detrimental effects from the perspective of disease management. [40,41]

**1. Age**

GI physiology is not the same in all ages. Owing to the different physiologies observed in different ages drug absorption is not similar in all cases. Infants have indifferent absorption as compared to adults due to higher gastric pH and lower intestinal surface and blood flow. In elderly people drug absorption is impaired because the gastric emptying is different. [51]

**2. Gender**

Men, women, and pregnant women have different gastrointestinal physiologies. Gastric pH is lower in men than in women followed by pregnant women. This can affect the absorption of ionizable drugs. Males have higher gastric emptying rate and intestinal motility. Women have smaller body weight and volume of distribution, a pharmacokinetic parameter explaining the drug distribution. These factors can also give differences in drug absorption. [52]

**3. Disease state**

Disease states and physiological disorders associated with the gastrointestinal tract are likely to influence the absorption of orally administered drugs. The absorption mechanisms discussed at the start of this chapter are true for healthy subjects. In diseased conditions, the intestinal wall integrity can be varied. Gut wall integrity is breached in many inflammatory disorders leading to enhancement in drug absorption. Local diseases of GIT can cause alterations in GI pH that can affect the absorption of drugs. Acquired immune deficiency syndrome (AIDS) patients often have oversecretion of gastrin which increases the acid secretion and thus a low pH is observed in stomach. This can affect the dissolution of weakly basic drugs such as antifungal ketoconazole. Diseases like Crohn’s disease and ulcerative colitis will also lower the pH of the GIT. [53]

**4. Presence of other drugs**

Presence of other drugs in the GIT might affect the absorption of the drug of interest physiochemically or physiologically. Antidiarrheal preparations containing adsorbents like attapulgite or kaolin-pectin retard/prevent absorption of some drugs coadministered with them. Examples include promazine and lincomycin. Antacids, mineral substitutes containing heavy metals such as aluminum, calcium, iron, magnesium, or zinc retard the absorption of tetracyclines through formation of unabsorbable complexes. Anion exchange resins cholestyramine and colestipol bind to bile salts and drugs and prevent absorption of some drugs. Basic drugs dissolving in stomach increase the stomach pH and decrease the dissolution rate or cause precipitation of tetracyclines. [54]

1. **CONCLUSION**

Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more nonmedicinal agents that serve varied and specialized pharmaceutical functions. Selective use of these nonmedicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types. The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and delivery system to prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed pharmaceutics.

The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe. The product should be manufactured with appropriate measures of quality control and packaged in containers that keep the product stable. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

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