**DOSAGE FORM DESIGN**

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**Principle**

Drugs are almost never given out in the form of prepared preparations or medications, and they are hardly never given out on their own as chemical compounds in their purest form. These might range from the most straightforward solutions to the most intricate drug delivery systems thanks to the inclusion of appropriate additives or excipients in the formulations. The excipients are responsible for a wide variety of specific medicinal actions in addition to their pharmacological effects. Additives used in formulation can perform functions such as solubilizing, suspending, thickening, preserving, emulsifying, modifying dissolving, increasing compactability, and flavoring pharmacological components. These functions allow for the creation of a variety of drugs and dosage forms.

The basic objective of dosage form design is to give a predictable therapeutic response to a medicine that is included in a formulation that is capable of mass production with reproducible product quality. This goal is accomplished through designing dosage forms. To ensure the quality of the product, a number of characteristics must be present. These characteristics include chemical and physical stability, appropriate preservation against microbial contamination, if necessary, uniformity of drug dose, acceptability to users (including prescribers and patients), and appropriate packaging and labelling. In an ideal world, dosage forms would be independent of the variance that exists between patients, but in reality, this independence is impossible to accomplish. Recent developments, on the other hand, are beginning to take into account this prerequisite. These include drug delivery systems that rely on the specific metabolic activities of individual patients, as well as implants that respond to sound or magnetic fields that are provided from the outside in order to start a drug delivery function.

It is important to take into account differences in the bioavailability of medications and the catabolic reactions of patients across apparently identical formulations, in addition to possible circumstances that were the cause. In recent years, an increasing amount of focus has been placed on the elimination of variance in bioavailability characteristics, particularly for medical goods that contain an equivalent dose of a pharmacological substance. This is due to the fact that it has become common knowledge that aspects related to the formulation can have an effect on the therapeutic performance of a drug. In order to make medical compounds more readily available to the body, it is frequently necessary to select the chemical form of the medication that is most suited to its intended purpose. For instance, the selection process must to take into consideration solubility requirements, drug particle size and physical shape, pertinent additives and manufacturing aids, in addition to selecting the most appropriate administration route(s) and dosage form(s). In addition to this, the production methods, labelling, and packaging must be proper.

The treatment of an illness can be made more successful and convenient by administering a pharmacological material in one of the many different dosage forms that are available. It may be necessary to develop dose forms that may be given via alternative delivery channels in order to provide the greatest possible therapeutic benefit. Table 1.1 provides a summary of the several dose forms that can be utilized to deliver pharmaceuticals via the various administration routes. Preparations can be taken orally, intravenously, topically, or inhaled. Before developing the most efficient combination of drug and dosage form, it is necessary to tie the drug substance to the clinical indication that is being treated. This is necessary since each disease or sickness normally calls for a different kind of pharmacological therapy. In addition, problems governing the choice of administration route and the specific requirements of that route that influence drug absorption need to be taken into consideration while formulating dose forms for the medication.

**Table 1.1 Available dosage formulations for various 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 |

Numerous medications are available in several dosage forms and concentrations, each with unique pharmacological properties that are suited to a particular application. One such medication is prednisolone, a glucocorticoid used to treat inflammatory and allergic conditions. Several effective anti-inflammatory formulations, such as tablet, enteric-coated tablet, injections, eye drops, and enema, are available through the use of diverse chemical forms and formulation additives. Due to 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, while the soluble sodium phosphate salt permits the preparation of a soluble tablet as well as solutions for eye and ear drops, enema, and intravenous injection. The analgesic paracetamol is also available in a variety of dosage forms and strengths, such as tablets, dispersible tablets, paediatric soluble tablets, paediatric oral solution, sugar-free oral solution, oral suspension, double-strength oral suspension, and suppositories, in order to meet the specific needs of the user.

Moreover, while many novel pharmaceuticals based on low molecular weight organic compounds are still being discovered and developed into medicinal products, the creation of biotechnology-based drugs and the value of these therapeutic agents are increasing. These macromolecular substances have a relatively high molecular weight and consist of peptides, proteins, and viral components. Due to their diverse biological, chemical, and structural properties, formulation and processing of these pharmacological compounds present unique and significant challenges. However, the fundamental principles of dosage form design continue to apply. Currently, these therapeutic compounds are predominantly prepared for parenteral and respiratory administration, but other modes of administration are being investigated and studied. The delivery of these biotechnologically derived therapeutic compounds via these routes of administration imposes additional restrictions on the choice of appropriate formulation excipients.

Therefore, it is evident that numerous criteria must be considered prior to effectively synthesising a drug substance into a dosage form. These can be roughly classified into three groups:

**1. biopharmaceutical considerations (including factors affecting the metabolism of the drug substance via various administration methods).**

**2. drug factors (physical and chemical properties of the drug substance)**

**3. clinical considerations**

Only when all of these factors are considered and interconnected can high-quality and effective pharmaceuticals be designed and produced. This is the underlying principle of dosage form design.

**1. biopharmaceutical variables**

Biopharmaceutics is the study of the relationship between the physical, chemical, and biological sciences as they pertain to drugs, dosage forms, and drug action. In terms of medication absorption, distribution, metabolism, and excretion, it is imperative that dosage form designers have a fundamental understanding of this subject. Before a drug can be absorbed into body fluids through the absorbing membranes and epithelia of the epidermis, gastrointestinal tract, and lungs, it must be in solution. There are two methods for drug absorption: passive diffusion and carrier-mediated transport pathways. The mechanism of passive diffusion, which is believed to influence the absorption of numerous medications, is driven by the concentration gradient that exists across the cellular barrier, with drug molecules migrating from regions of high concentration to regions of low concentration. The rate of diffusion is affected by the lipid solubility of the substance and the degree of ionisation at the site of absorption. Recent research on carrier-mediated transport pathways has yielded a wealth of information and knowledge, in some instances guiding the development of novel therapeutic compounds. Proposed are numerous specialised transport systems, including active and assisted transport. Once absorbed, the substance can have a therapeutic effect either locally or at a distant location from the site of administration. In the latter scenario, the medication must be administered via physiological fluids (as depicted in Fig. 1.1).

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**FIG. 1.1 Drug pathways after dosage form administration by different routes.**

When the dosage form is designed to deliver pharmaceuticals through the buccal, respiratory, rectal, intramuscular, or subcutaneous routes, the absorbed medicine travels straight into the circulation blood from the absorbing tissues. However, the intravenous route gives the most direct way of all the methods. Because of the required transit time in the gastrointestinal tract prior to absorption, the absorption process, and other elements related with hepatoenteric blood circulation, the commencement of the medication's action will be delayed when it is taken orally rather than being given intravenously. The physical structure of the oral dosage form has an effect on the rate of absorption as well as the beginning of action. Solutions have a quicker effect than suspensions, which have a quicker effect than capsules and tablets. Therefore, dosage forms can be listed in the order of the time it takes for the therapeutic effect to start taking effect (see Table 1.2). However, regardless of how they are administered, drugs are still foreign substances to the human body. The distribution, metabolic, and elimination processes begin as soon as the drug is absorbed into the body and continue until the drug is expelled from the body in an unchanged or metabolised form through the urine, faeces, saliva, skin, or lungs. This can take anywhere from a few minutes to several hours.

**Table 1.2 The differences in onset of action for various 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. Methods For the Administration of Drugs**

The way in which medications are absorbed by the body differs significantly not just between different drug compounds but also between the various methods of drug administration. To ensure that the medicine is delivered in a form that can be effectively absorbed through the various routes of administration, dosage forms have been developed. In what follows, a quick look will be taken at the various ways drugs can be taken by the patient.

**1.1.1 Administration of Medication Via the Enteral Route**

Oral administration of medication is the most prevalent route of pharmaceutical administration since it is the most practical, economical, and widely used route. The small intestine is typically the major site of drug absorption; the bioavailability of the medication is affected by the amount of drug that is absorbed across the intestinal epithelium at the primary site of drug absorption. When considering oral administration of medication, the first-pass impact is an essential factor to take into account. The term "drug metabolism" refers to the process by which the concentration of the drug is greatly reduced before it enters the systemic circulation. This is often the result of the metabolism taking place in the liver.

Another version of the enteral route of medicine administration is known as the sublingual or buccal route. This form of the enteral route provides the advantage of avoiding the first-pass effect. If the medication is placed immediately beneath the tongue (known as sublingual administration) or on the cheek (known as buccal administration), it will undergo a process known as passive diffusion through the venous circulation in the oral cavity. This will allow the medication to avoid entering the hepatic portal vein and instead enter the superior vena cava. Buccal tissue is less permeable and has delayed medication absorption as compared to sublingual tissue, which has highly permeable mucosa and rapid access to the underlying capillaries.[1]

Rectal medication administration is another type of enteral medication administration. Rectal medication administration is advantageous because it enables quick and efficient medication absorption via the highly vascularized mucosa of the rectal tract. Medication that is taken via the rectum goes by passive diffusion and partially sidesteps the first-pass metabolism, just like medication that is administered sublingually or buccally. It is estimated that only about half of the medicine that is absorbed in the rectum actually makes its way directly to the liver.[2]

**1.1.2. Administration of Medication Through the Parenteral Route**

The intravenous injection is the most usual route of medicine administration for parents, and it allows medication to avoid the first-pass metabolism of the liver. Peripheral veins are frequently used for the parenteral administration of medication because of their superficial location on the skin, which allows for simple access to the circulatory system. Peripheral veins are located at the periphery of the body. Because it has a lower incidence of thrombophlebitis and thrombosis than the lower limbs, the upper extremity is typically the chosen site for intravenous medicine because it is administered there. The median basilic or cephalic veins of the arm, as well as the metacarpal veins on the dorsum of the hand, are the veins that are most frequently used. It is possible to employ the dorsal venous plexus of the foot when working on the lower extremities.

It is possible to deliver medication using the intramuscular route in a variety of body muscles, such as the deltoid, dorsogluteal, ventrogluteal, rectus femoris, or vastus lateralis muscles. Although the dorsogluteal location, also known as the upper outer quadrant of the buttocks, is a typical site used traditionally for intramuscular injections by medical experts, there is a possibility of harm to the superior gluteal artery and the sciatic nerve if the injection is given there.[3] The ventrogluteal site, also known as the anterior gluteal site, on the other hand, targets the gluteus medius muscle and avoids these potential issues; as a result, it is recommended.

Injections given subcutaneously are still another form of the parental route of pharmaceutical administration. These injections are given to the layer of skin known as the cutis, which is located just below the dermis and epidermis layers of the skin. As a result of the low number of blood arteries found in subcutaneous tissue, the injected drugs are absorbed at a pace that is both slow and consistent. It is possible to inject subcutaneous medication in a variety of locations, such as the outside region of the upper arm, the belly (while avoiding a circle that is 2 inches in diameter and centres on the navel), the front of the thigh, the upper back, or the upper buttock area behind the hip bone.

The delivery of drugs via the intraarterial route is not as common as other methods. In the process of angiography, a contrast agent is injected after an arterial puncture has been performed. Other applications of this method include the administration of regional chemotherapeutic drugs and the treatment of cancerous tumours that are found in the brain.

**1.1.3. Alternative Methods of Medication Administration**

When a medicine is administered through the nose, it is more easily absorbed into the body because it is able to diffuse passively over the single-layered, well-vascularized respiratory epithelium and into the systemic circulation.

When a drug is inhaled, it is quickly distributed throughout the enormous surface area of the epithelium that lines the respiratory system. The first-pass metabolism is skipped over by medications that are absorbed into the pulmonary circulation and instead go directly into the systemic circulation via the pulmonary vein. In order to ensure efficient delivery, the particle size of inhaled medications is typically between 1 and 10 micrometres. Not only does the effectiveness of medication administration to the lungs depend on the particle size and shape of the drug, but it also depends on the patient's respiratory physiology, such as tidal volume and tracheal inspiration velocity.[4]

The vaginal route is a technique of drug delivery that has not been thoroughly researched and is not widely utilised. However, it does have the benefit of avoiding the first-pass effect and has the potential to be an efficient way for both local and systemic therapy. The venous plexuses that drain into the internal iliac veins originate from the vagina, the vesical veins, the uterine veins, and the rectal veins, and they all connect with one another. The veins that drain the middle and upper vagina do not connect to the hepatoportal system because they instead drain directly into the inferior vena cava.

Through the use of a transdermal patch, it is possible to provide medication. This approach employs standard methods of administration, including transdermal patches, transdermal ointments and gels, drug carriers such as nanoparticles and liposomes, and local application formulations such as transdermal ointments and gels.[5] The intraosseous route is beneficial for giving fluids and medications, especially to infants, when both the peripheral and central venous approaches have failed. This is especially true in neonates.[6] Medications are currently being tested in the context of out-of-hospital cardiac arrest in the context of clinical trials that are currently being carried out.[7] Additionally, it is utilised in the administration of preventative antibiotics prior to localised surgical procedures.[8]

**1.2. The rate at which medications are absorbed by the body can also be affected by biological factors.**

**1.2.1. The Physiology of Membranes**

Along its entire length, the wall of the GIT consists of four histological layers that are easily distinguishable from one another. On the interior of the GIT, the mucus layer can range in thickness from thin to thick along its length. This viscoelastic gel serves both as a protective layer and a mechanical barrier to the mucosa of the gastrointestinal tract. The majority of mucus is composed of water and mucins. Mucins are a type of glycoprotein that are responsible for mucus's structural integrity. Mucus is eliminated in a continuous process, and it is continuously replaced as it is lost. This mucus, along with the water that is contained inside it, creates a layer of unmixed water on the inner surface of the GIT lumen. On the opposite side of the barrier, there will also be a layer of water that has not been stirred, which will make the actual barrier into a triple barrier consisting of a layer of water that has not been stirred, a membrane, and a layer of water that has not been stirred. The rate limiting stage in the absorption of many medications, both neutral and ionic, occurs during the process of mucosal layer diffusion without stirring.

**1.2.1.1 The Characteristics of the Cell Membrane**

Lipid bilayers make up the structure of cell membranes. Therefore, any medicine that needs to be able to cross the cell membrane either needs to contain lipophilicity in order to be able to cross the membrane, or it needs to have a specific mechanism such as carrier-mediated diffusion in order to be able to absorb the drug.

**1.2.1.2 Processes Involved in Transport**

Because of the unique molecular structure and chemical composition of individual medications, particular transport pathways are required for their absorption. Passive diffusion, active transport, and endocytosis are the three fundamental transport mechanisms.

**1.2.2 The Physiology of the Gastrointestinal System**

Major aspects that have a direct impact on the effectiveness of orally delivered medications include the anatomical barrier, the physiological functions, and the contents of the stomach. The GIT is the part of the body that is responsible for functions such as digestion, secretion, and absorption. The digestive and gastrointestinal tract, also known as the alimentary canal, extends from the oral cavity to the anus. The oral cavity produces saliva with a pH that is approximately 7. It has digestive enzymes called amylase and lubricating enzymes called mucin. Both of these enzymes help break down food. These enzymes have the potential to react with several medications. Following the mouth cavity comes the oesophagus, which is the tube that connects the pharynx to the heart's opening. The pH level falls to between 5 and 6. On the other hand, there is hardly no drug dissolution taking on here. The stomach comes next, which is responsible for acid production and the digestion of food after the esophageal sphincter. The breakdown of many different substances can be traced back to this acidity. This area has a pH of roughly 1.5, and it is the secretion site for an enzyme known as pepsin, which is responsible for the digestion of proteins. Because of the fact that this enzyme is responsible for the digestion and breakdown of peptide medicines, oral administration of peptide medications is not recommended. In most cases, medications that are only mildly acidic are absorbed through the stomach. The next component of the digestive tract after the stomach is the small intestine, which is made up of three primary sections: the duodenum, the jejunum, and the ileum. Due to the high amount of accessible surface area, the small intestine serves as the primary site of absorption for the vast majority of medicines. Following that is the colon, which does not have villi like the small intestines do, which means it does not contribute as much to the process of absorption as the small intestines do. The colon is the site of absorption for certain medications, including theophylline and metoprolol. Both aerobic and anaerobic bacteria can be found in the colon at the same time. L-dopa and lactulose are two of the substances that can be metabolised by the enzymes that are produced by these bacteria. The rectum, which is the final section of the gut and terminates at the anus. Because this area receives a sufficient amount of blood flow, it is ideal for the absorption of pharmaceuticals.

**1.2.2.1 Gastric Emptying Time**

When taken orally, the medication has a much better chance of reaching the stomach in a timely manner. However, because the contents of the stomach are constantly being discharged into the small intestine, it is impossible for it to remain there for an extended period of time. The duodenum is the primary site of drug absorption; therefore, any delay in the medication's passage into the duodenum will affect both the onset time and the possible degree of drug absorption. The time it takes for the stomach to empty is contingent upon a number of things. Stomach emptying is slowed down by a number of critical factors, such as the amount of fat in the meal and the use of anticholinergic medicines. Because of the higher basal pressure in the stomach compared to the pressure in the duodenum, it was impossible for particles with a size less than 1 millimetre to be successfully retained in the stomach. A greater starting volume makes the first, faster stomach emptying possible, but after that, the rate of emptying slows down. Foods that are high in fatty acids, triglycerides, carbs, and amino acids have been shown to slow the rate at which the stomach empties. The rate of emptying will rise when salts and nonelectrolytes that alter the osmotic pressure are present in lower amounts, whereas it will decrease when salts and nonelectrolytes are present in larger concentrations. When compared to solid material, which needs to have its size reduced before it can be emptied, solutions and suspensions can be emptied much more quickly. Acids with a lower molecular weight are more effective than acids with a greater molecular weight at slowing the rate at which the stomach is emptying. The rate of emptying will speed up when bases such as sodium bicarbonate are present in lower concentrations, but it will slow down when the base is present in higher concentrations. Metoclopramide speeds up the emptying process, in contrast to other medications including anticholinergics, narcotic analgesics, and ethanol, which slow down the rate at which the stomach is emptied. When the patient is positioned so that they are laying on their left side, the emptying rate is very low. The rate at which one empties their bladder can be sped up by aggression, while slowing down by depression. The rate of emptying is slowed down by bile salts as well as activity.

**1.2.2.2 The pH of the Gastrointestinal Tract**

The pH of the GIT varies from beginning to end. During the fasting state, the pH falls into a range that is between 1 and 3.5 and becomes highly acidic. The digestion of food results in a decrease in the acidity of the gastric juice, which has a pH ranging from 3 to 7. Therefore, medications that are taken with or shortly after meals will experience the elevated pH of the stomach, which can persist for as long as two to three hours after the consumption of food. Because of this, the medications' capacity to remain stable and dissolve in the stomach may be compromised. The bicarbonate ions that are sent into the small intestine by the pancreas cause the pH of the intestines to be higher than that of the stomach. The pH of the distal duodenum will be approximately 5, that of the jejunum approximately 6.5, and that of the ileum approximately 7. The breakdown of undigested carbohydrates into short chain fatty acids by the bacterial enzymes in the colon causes the pH to drop to roughly 6.5. This occurs because of the process described above. Penicillin G, erythromycin, and omeprazole are some examples of medications that are impacted by the pH of the gastrointestinal tract.

**1.2.2.3 Surface Area of GIT**

Through a process known as passive diffusion, drugs are able to be absorbed from all areas of the GIT. The duodenum, on the other hand, has a huge surface area for the absorption of medications, making it the primary location where pharmaceuticals are absorbed. Because of the presence of villi, the surface area of the duodenum is significantly larger. villi are tiny projections. Even smaller projections, known as microvilli, can be found within these villi. On the luminal side of the intestine, these microvilli have the appearance of a brush border. In addition to this, the duodenum is provided with a more extensive capillary network, which can be advantageous in maintaining the concentration gradient necessary for the absorption of medicines into the blood.

**1.2.2.4 Intestinal Transit Time and the Motility of the Gastrointestinal Tract**

The passage of dose form from the oral cavity to the lower portions of the gut is aided by the motility of the gastrointestinal tract. It is possible that medications that are taken orally have an anatomic absorption window, which is a period of time during which the drug is absorbed most effectively. It is of the utmost significance for pharmaceuticals designed for a sustained or controlled release. In order to ensure adequate absorption, pharmaceuticals ought to have a rapid transit time. When a person is fasting, the normal average transit time for the small intestine is approximately 34 hours. The time spent in transportation within the Fed State would be around 812 hours. It was discovered that consuming foods high in calories has no impact on the amount of time it takes for meals to pass through the intestines. The length of time it takes for particles to pass through the colon is very variable, with a tendency for smaller particles to be transported at a slower rate than bigger particles. The duodenum and the peritoneum are both perfused with a significant number of lymphatic vessels and capillary networks. The splanchnic circulation, which is responsible for providing blood to the GIT, receives 28% of the cardiac output, and this percentage rises after eating. When drugs are absorbed in the upper GIT, they travel through the portal vein and the mesenteric arteries on their way to the liver. Only then do they enter the general circulation. In the event that there is a reduction in mesenteric blood flow, such as in the case of heart failure, the drug absorption will be affected. Because these medications enter the lymph through the lacteals that are present in the microvilli, the absorption of lipidic pharmaceuticals skirts around the portal vein and avoids the first-pass metabolism that occurs in the liver.

**1.2.2.5 Contents of the Gastrointestinal Tract**

Along with the medications of interest, the GIT may also contain food, fluids, enzymes, and sometimes even other drugs. All of these things have the potential to affect how well the medicine is absorbed by the GIT.

**1.2.2.6 Impact of Consuming Food**

Consuming food can increase or decrease the pace at which medicines are absorbed from the gastrointestinal tract. It is possible for medications to form complexes with the components of meals that are not efficiently absorbed by the GIT. When a complex that cannot be undone or broken apart is developed, this is a very real concern. Tetracycline, for instance, produces complexes with calcium and iron that are incapable of absorption; as a result, consuming milk or an iron supplement at the same time will prevent the body from absorbing the medication. Additionally, the pH of the GIT can be changed by food. In most cases, eating something raises the pH of the stomach by acting as a buffer. This can speed up the rate at which a medicine that is only slightly acidic is dissolved and absorbed by the body. The emptying of the stomach can be affected by the food that is eaten, particularly those that are high in fat content. Food causes a delay in the emptying of the stomach, which can impede the rate of absorption of certain medications like zidovudine and lamivudine; however, this delay is not clinically relevant. Food has the ability to trigger the release of enzymes, and if the medications in question are susceptible to enzymatic breakdown, this will have an effect on how well they are absorbed. The fact that food components and pharmaceuticals compete for the same transporters could possibly have an effect on absorption.

**1.2.2.7 The Impact of the Fluid**

The presence of a significant quantity of fluids within the stomach makes rapid breakdown of the dose form and rapid gastric emptying more likely, which ultimately results in higher absorption. When compared to the absorption that occurs during a fed state, the erythromycin is absorbed more effectively when the stomach is empty and when it is taken with a full glass of water.

**1.2.2.8 The Impact of Other Normally Occurring GI Contents**

The drug absorption can be affected by normal gastrointestinal contents such as mucus, bile salts, and enzymes. Mucin has an interaction with streptomycin that reduces the effectiveness of the antibiotic. Mucin is a barrier that prevents drug diffusion, not only for one drug but also for others. Solubilization and absorption of lipophilic medicines like griseofulvin and vitamins A, D, E, and K are both aided by the bile salts. By creating compounds that are water insoluble, bile salts can occasionally also prevent some medications, such neomycin and kanamycin, from being absorbed by the body. It is possible for enzymes to have a significant impact on the absorption of medications that are sensitive. The metabolism that takes place as a result of these enzymes is referred to as pre systemic metabolism.

**1.2.2.9 Stability of Drugs in the GIT**

The stability of a drug in the GIT is susceptible to changes brought on by an extremely acidic pH and enzymes. In general, drugs that become unstable when exposed to acidic environments are covered in protective materials that shield the medicine from the effects of the acidic environment. This type of coating is known as an enteric coating. Drugs that are metabolised by the enzymes cannot be given orally and must normally be taken through one of the other modes of drug administration. This holds true for both protein-based and peptide-based pharmaceuticals. These medications are given through different pathways so that the proteolytic enzymes found in the gastrointestinal tract won't break them down.

**1.2.2.10 The Influence of the Pre-systemic Metabolism**

With the exception of the medications that are absorbed in the colon, drugs that are absorbed in the GIT will arrive at the liver through the portal vein. Simultaneously with the beginning of the process of absorption, the metabolic process begins. The lumen, the gut wall, and the liver all contain metabolising enzymes in varying amounts. The bacteria in the colon create enzymes, which also have the ability to metabolise medications to some extent, and these enzymes are located in the colon. The pharmaceuticals that are absorbed from the upper GIT will make their way through the liver, and if they are particularly susceptible to the metabolism that occurs in the liver, then a portion of the drugs in their original form will not make it into the blood circulation. This metabolism, which has the effect of affecting the absorption of many medications that are administered orally, is known as the first-pass metabolism or effect. In addition to the luminal enzymes found in the liver, the enzymes found in the intestinal walls are also capable of metabolising the medication. The metabolism that happens before the drug is referred to as presystemic metabolism, and it includes the metabolism that happens during the first pass.

**1.2.2.10.1 LUMINAL ENZYMES**

Luminal enzymes are the enzymes that are secreted into the lumen of the GIT by the many different kinds of cells and organs found in the body. The pancreas is responsible for the secretion of a number of different luminal enzymes, including lipases, amylases, and proteases. Pepsin is also present in the juice that comes from the stomach. The pancreas, which is located in the abdomen, sends digestive enzymes called lipases, amylases, and proteases into the small intestine. These luminal enzymes are responsible for the majority of the peptide and protein breakdown that occurs at high molecular weights. These enzymes are also responsible for the degradation of a number of nucleotides and fatty acids.

**1.2.2.10.2 ENZYMES OF THE GUT WALL**

Enzymes found in the intestinal lining participate in the presystemic metabolism of the medicines. This process, known as presystemic metabolism, refers to the degradation of pharmaceuticals by these enzymes before they enter the systemic circulation of the body's blood. As a result of the presence of the main enzyme CYP3A, which is a member of the cytochrome family, in the mucosa of the intestinal tract, the absorption of substrates for this enzyme is altered. Intestinal CYP levels are significantly greater than colonic CYP levels.

**1.2.2.10.3 BACTERIAL ENZYMES**

Certain enzymes are secreted by the bacteria that live in the colon, and these enzymes can also influence how well a medicine is absorbed. These enzymes are frequently used into the formulation of medications with a colonic focus. One example of a prodrug is sulfasalazine, which contains an azo bond connecting 5-ASA to sulfapyridine. Because it contains sulfapyridine, the medicine cannot be absorbed in the upper part of the gastrointestinal tract. Bacterial enzymes in the colon weaken the azo bond, which results in the release of the active medication 5-aminosalicylic acid. This allows the drug to exert a local effect on colonic disorders such as inflammatory bowel disease.

**1.2.2.10.4 HEPATIC ENZYMES**

The liver is the principal organ involved in the metabolism of drugs. It is also possible for it to act as a barrier to the absorption of medications, because pharmaceuticals that are taken through the GIT are sent straight to the liver before being sent anyplace else in the body. Therefore, if the drug is metabolised to a significant degree in the liver, then the quantity of drug that reaches the site of action is going to be extremely low. The term "first-pass metabolism" refers to this type of metabolism. Propranolol is absorbed quite efficiently by the GIT; nevertheless, as a result of first-pass metabolism, only thirty percent of the oral dose is made available to the systemic circulation. Morphine, atorvastatin, lidocaine, imipramine, diazepam, and pentazocine are some other examples.

**2. Drug factors: Preformulation**

In order to create a stable and effective product, all of the different types of dosage forms need to be carefully studied in terms of the chemical and physical properties of the pharmacological ingredients.

Before putting a drug substance into a dosage form, it is necessary to specify the desired product type as precisely as possible in order to set the stage for product development and create a structure to guide its creation. Next, a number of initial formulations of the product are generated and tested to see whether or not they possess the necessary characteristics (such as drug release profile, bioavailability, and clinical effectiveness), in addition to being used for pilot plant studies and the scaling-up of production. The product's "master formula" will always be the formulation that provides the greatest degree of success in meeting the product's objectives. In successive iterations of the product's production, each batch must be prepared in accordance with the master formula's predetermined parameters. A medicinal substance can be introduced into a variety of different forms in order to provide treatment that is both convenient and effective for the treatment of disease. A producer would typically prepare a drug ingredient in a number of different dosage forms and intensities for the purpose of providing a disease treatment option that is both effective and convenient (Fig. 4.1). Before a pharmaceutical agent is formulated into one or more dosage forms, a number of therapeutic considerations, including the nature of the ailment, the method by which it is treated (locally or by systemic action), as well as the age and anticipated condition of the patient, are taken into account as part of the formulation process. Tablets and/or capsules are typically made when the drug is meant for systemic use and oral administration is sought. This is due to the fact that tablets and/or capsules may be readily handled by the patient and are the most convenient option when it comes to the self-administration of medication. In the event that a drug substance is useful in the event of an emergency in which the patient may be comatose or otherwise unable to take oral medication, a form of the medication that is administered via injection may also be developed. Tablets and skin patches are used for the prevention of motion sickness, nausea, and vomiting; suppositories and injections are used for the treatment of these conditions. There are many additional instances of therapeutic scenarios that can affect the design of a dosage form, and they could all be cited. The age of the person who is going to take the medication is another factor that goes into the formulation of the dose form. Oral administration of pharmaceuticals is best performed with liquid forms rather than solid forms for infants and children younger than five years of age. These liquids, which can be flavoured aqueous solutions, syrups, or suspensions, are typically supplied directly into the mouth of the infant or kid using a dropper, spoon, or oral dispenser. Alternatively, they can be mixed into the child's food. It is possible to utilise a single liquid paediatric preparation for newborns and children of all ages, with the dosage of the medication being adjusted according to the volume that is given to the patient. When a young patient has a productive cough, is vomiting, gagging, or is simply being defiant, there is a possibility that not all of the medication that has been given to them has been swallowed, and that some of it may have been expectorated instead. In such circumstances, you could be forced to get injections. It's also possible to use infant-sized suppositories for the rectal area, although medicine absorption through the rectum is notoriously unreliable. It is possible for a person to have trouble swallowing solid dose forms, particularly uncoated pills, at any age, including childhood and even maturity. Because of this factor, certain medicines come in the shape of pills that can be chewed. Many of these tablets have a consistency that is analogous to that of an after-dinner mint and dissolve into a creamy substance that has a flavour that is pleasing to the palate. Tablets that have recently become available dissolve in the mouth in around ten to fifteen seconds; this enables the patient to appear to take a pill but actually swallow a liquid. Many people have discovered that it is far simpler to swallow capsules than it is to swallow full tablets. If a pill is allowed to become wet within the mouth before it is consumed, it will become slippery and will go more easily down the throat when water is present. Additionally, placing a teaspoonful of a gelatine dessert, liquid candy, or syrup in the mouth and partially swallowing it before inserting the solid dose form in the mouth helps with the process of swallowing them. This is done before placing the solid dosage form in the mouth. In addition, if a person has trouble swallowing a capsule, the contents can be poured onto a spoon, combined with jam, honey, or another food that has a flavour similar to the drug, and then consumed. This is done to hide the taste of the medication. Oral liquid forms of medications prescribed to senior patients are the most typical delivery method, while a chemist may also impromptu create tablets or capsules for oral administration. Crushing or chewing some tablets and capsules that are intended for controlled release is not recommended since doing so could compromise the integrity of the medication and cause it to behave differently than it was designed to. Numerous people, especially senior patients, are required to take multiple drugs on a regular basis. Correctly identifying pharmaceuticals in solid dose forms is made much simpler when those forms' sizes, shapes, and colours are more easily distinguishable from one another. It is common for older people to make mistakes when taking their drugs due to the various medications they take and their diminished ability to see well. It is especially beneficial to have dosage forms that can lessen the amount of times the medication needs to be taken without compromising its effectiveness. Research chemists obtain knowledge from experience with other chemically similar pharmaceuticals and through the appropriate application of the physical, chemical, biologic, and pharmaceutical sciences in order to solve the problem of formulating a drug substance into the appropriate dosage form. This knowledge is then applied in the process of dealing with the problem of formulating a drug substance into the suitable dosage form. Studies to collect fundamental information on the physical and chemical features of the drug component are an integral part of the preliminary stages of any new formulation's development. Before beginning work on the actual product formulation, these fundamental studies serve as the necessary preformulation work.

**PREFORMULATION**

Preformulation testing is the initial phase in the process of developing dosage forms before formulation. This testing is done with the intention of ensuring that the aims of the drug and its dosage forms are met. An assessment of the physical and chemical properties of a pharmacological material both on its own and in combination with excipients is called preformulation. Preformulation comes before the formulation step. The primary goal of pre-formulation testing is to create information relevant to the formulator in producing stable and bioavailable dosage forms before formulation development. This information is generated before formulation development. Investigations conducted prior to the formulation of a drug are intended to provide all of the relevant data, particularly information regarding the physicochemical, physico-mechanical, and biological properties of drug ingredients, excipients, and packaging materials.

**[2] PRE-FORMULATION PARAMETERS Physicochemical characterization**

**2.1. Organoleptic properties**

**2.2. Bulk characteristics**

a. Assay development

b. Melting point

c. Solid state characteristics: Particle size, surface area

d. Flow properties

e. Densities

f. Compressibility

g. Crystalline and amorphous

h. Polymorphism

i. Hygroscopicity.

**2.3. Solubility analysis**

a. Ionization constant (pKa)

b. Partition coefficient

c. Dissolution

d. Solubilization

e. Thermal effect

f. Common ion effect (Ksp).

**2.4. Stability analysis**

a. Solid-state stability

b. Solution-state stability

c. Drug-excipients compatibility

**2.1. Organoleptic properties**

This means that the new drug substances' look, colour, odour, and taste must all be described using descriptive terms. Also included in this category is the terminology used. It is essential to settle on a word that will be used consistently to describe these features in order to minimise confusion among scientists who use different phrases to refer to the same property.

**2.2. Bulk characteristics**

**a. Assay development**

The strength of a drug substance can refer to either its concentration (the amount of drug present in a given unit of measurement) or its potency, or it can refer to both. A drug's potency is defined as the amount of its therapeutically active ingredients that may be measured as a percentage of the total weight or volume of the drug preparation. Without an appropriate assay, it is impossible to test any relevant physicochemical characteristic. The initial stage of preformulation is the development of the assay.

A variety of methods are utilised in order to ascertain the percentage of the drug's purity (assay). In this procedure, it is important to develop for a specific pharmacological substance. This can be done using an ultraviolet (UV) spectrophotometer or, for greater accuracy, high-performance liquid chromatography (HPLC).

The process of developing an assay involves estimating the relevant values and determining whether or not they can be used in a "go/no go" judgement about a particular drug candidate. The tests that can be done to quantify them, as well as how their quantitative results are affected by the molecular structure.[2] Using an ultraviolet spectrophotometer, one can also utilise the absorption maxima (max) to determine the purity of the pharmacological ingredient.[3]

**b.  Melting point**

The temperature at which a pure solid substance reaches a state of equilibrium between its solid and liquid states is known as the melting point of the substance. When determining the purity of drug compounds, a very sharp melting peak in differential scanning calorimetry (DSC) can be used as a sign of purity. A drug's melting point or range can also be utilised as an indicator. A sign that a medicine has been contaminated or is impure is when there is a change in one or more peaks at different temperatures. Capillary melting, hot stage microscopy, and differential scanning calorimetry (DSC) are the three methods that can be used to determine the melting point of a drug substance.[2]

**c.  Solid state characteristics**

Granules or solid particles that have been compressed into a mass and then encased in air to form a powder. This indicates that it is the mix of the solid and the fluid that has a substantial impact on the bulk characteristics of the powder. All of the particles' physical features, including their size, shape, angularity, size variability, and hardness, will have an effect on the flow properties of the mixture. Changes in the characteristics of a solid can occur during its handling due to the influence of external elements such as humidity, the atmosphere in which it is conveyed, vibration, and possibly most significantly aeration.

**Dimensions of the particles, their size distribution, and their surface areas**

Many different chemical and physical properties of medicinal compounds are influenced by the particle size distribution and morphologies of the particles. These alterations in characteristics might have an impact on the biopharmaceutical behaviour of the substance. For instance, the particle size distributions of griseofulvin and phenacetin are strongly connected to the bioavailability of these medications. The homogeneity of the finished tablet can also be affected by the size of the particles. When there is a difference in size between the active components and the excipients, a phenomenon known as mutual sieving (demixing) can take place. This makes it difficult to achieve thorough mixing, and even if it is achieved, it is difficult to keep during the subsequent processing steps.

According to Washington (1992), the principles and methods of particle size analysis have been documented.[4] When it comes to particle size analysis, there are a wide variety of methods to choose from. Sieving, optical microscopy in conjunction with image analysis, electron microscopy, the coulter counter, and laser diffractometry are some of the methods that are most widely available. The most prevalent methods for measuring particle size are outlined in Table 1, along with the approximate size ranges that correspond to each approach.[5] By using scanning electron microscopy and laser light scattering, researchers were able to determine the particle size distribution of a micronized powder. Laser diffraction is one method that can be used to measure the size of particles. One equipment that does this is called the Malvern mastersizer. The application of this method is predicated on the scattering of light at a variety of angles, the measurement of which is directly proportional to the particle's diameter. It is therefore possible to determine the distribution of particle sizes by taking measurements of the angles and intensities of the scattered light produced by the particles.

According to the results of the Noyes-Whitney equation, the surface areas of drug particles are significant factors that influence the rates at which the particles dissolve.[6,7] If it is difficult to accurately determine the particle size, another option is to quote the surface area.[8] Surface areas are typically calculated using the gas adsorption technique (using either nitrogen or krypton), and the method developed by Brunauer, Emmet, and Teller describes this phenomenon. Singh, 1992 have been studied in detail for their contribution to gas adsorption method determinations of surface area.[9]Table 1: Particle size techniques and size range [5]

|  |  |
| --- | --- |
| 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**

The flow characteristics of powders are extremely important for the effectiveness of tableting. It is vital to have a proper flow of the powder or granulation that is going to be compressed in order to ensure that the mixing will be effective and that the compressed tablets will have a uniform weight. The problem can be fixed by choosing suitable excipients if it is discovered that a medicine would "poorly flow" during the preformulation stage of the manufacturing process. When working with medication powders, precompression or granulation can sometimes help improve their flow characteristics. The angle of repose, the flow through an orifice, the compressibility index, the shear cell, and other similar methods are all examples of flow property measurement techniques. An increase in crystal size or a more uniform shape will lead to a reduced angle of repose and a smaller Carr's index. Particle size and shape changes are often extremely noticeable. [10,11]

**Angle of repose**

The term "angle of repose" refers to the maximum angle that can be established between the surface of a powder pile and a horizontal surface. The angle of repose values for the majority of medicinal powders fall somewhere between 25 and 45 degrees. If the angle is less than thirty degrees, the material flows easily, however if it is less than forty degrees, the material flows poorly. There are four different methods that can be used to calculate the angle of repose: the fixed funnel technique, the fixed cone method, the rotating cylinder method, and the tilting box method.[12]

Tan equals height of pile divided by base radius, where h is height of pile and r is base radius.

**e. Density**

It is possible for it to have an effect on the floe characteristics of the material as well as the tableting process. The term "density" refers to the proportion of mass to volume.

**Types of density:**

I. Density in bulk: This is determined by determining the volume of a known mass of untapped powder that was able to pass through the screen.

II. Tapped density: This is the density that is acquired by measuring the volume of a known amount of powder after tapping the measuring cylinder III.The actual density of the solid material is referred to as its true density.

IV.Density of the Granules: It is possible that this ingredient will impact the compressibility, tablet porosity, disintegration, dissolution, and settling of particles in diffusible mixes or suspension. [13,14]

**f. The ability to be compressed**

"Compressibility" of a powder can be defined as the ability to reduce in volume under pressure, while "compatibility" of a powdered material can be defined as the ability to be crushed into a tablet of specified tensile strength (plastic deformation). Both definitions can be used interchangeably. On the basis of density measurements, it can be utilised to make predictions about the flow properties of solids.[12]

**g. Crystalline**

The exterior form of a crystal is referred to as its habit, while the internal structure of a solid is defined as the arrangement of molecules within the crystal itself [Figure 1]. Crystal morphology, also known as crystal habit, is significant because it can have an effect on many of the properties of the material. It has been discovered, for instance, that the flow properties of powder, as well as compaction and stability, are all dependent on the morphology of the crystal. The environment in which the crystals are grown can impart a variety of distinct behaviours on a compound's otherwise identical internal structure. When it comes to the final stage of the purification process for a solid, crystallisation is almost always used. Altering the polymorphic state of the solid can be accomplished by utilising distinct solvents and adjusting the processing parameters. This can result in a change in the habit of the recrystallized particles. X-ray diffraction is the method that is used to determine crystallinity; an estimate of the degree of crystallinity was derived from a measurement of the total scattering [Figure 2].[12]

**h. Amorphous forms**

Materials that have amorphous shapes have a non-crystalline character, which indicates that they lack any kind of long-range organisation. The preparation of their structure can be accomplished through the processes of rapid precipitation, lyophilization, or rapid cooling (supercooling) of liquid melts, in addition to milling crystals and compacting them.[12]

The most energetic and thermodynamically unstable forms are those that have disordered structures. As a result, amorphous forms have a propensity to revert into more stable forms. This is especially true when the formulation is in the form of an aqueous suspension.[15] A decline in chemical stability is yet another effect that may be brought about by the low degree of crystallinity present in certain molecules. Because of these issues with chemical and physical stability, attempts should always be made to crystallise the amorphous phase. However, it is important to keep in mind that amorphous phases, provided they are chemically and physically stable, can have some advantages over the crystalline phase. For instance, it was discovered that an amorphous version of novobiocin that had been stabilised was 10 times more soluble and had the same level of therapeutic activity as the crystalline form.[16]

**i. Polymorphism**

Numerous pharmacological compounds are capable of taking on multiple crystalline forms, each of which can have a distinctive set of internal lattice configurations. Polymorphism is the name given to this characteristic. The many crystalline configurations are referred to as polymorphs. When polymorphism takes place, the molecules in the crystal rearrange themselves in two or more distinct ways; either they are packed in a different manner within the crystal lattice, or there are changes in the orientation or conformation of the molecules at the lattice sites. Polymorphism can occur in a wide variety of crystals, including those that are common in nature.[12,17]

Because polymorphs of a given molecule in general have various physicochemical properties, such as melting point, solubility, and density, the presence of polymorphism has significant consequences for formulation, biopharmaceutical, and chemical process. In addition to polymorphs, it is possible for there to be solvates (inclusion of the solvent of crystallisation), hydrates (inclusion of water of crystallisation), and amorphous forms (where there is no long-range order) [18] (for example, the polymorphism exhibited by estrone). Solvates are also known as pseudopolymorphs in some circles.[19,20]

**j. Hygroscopicity**

A significant number of pharmaceutical chemicals and salts are unstable when exposed to water vapour or moisture. When compounds come into contact with moisture, the water is retained by the compounds through a variety of mechanisms, including bulk or surface adsorption, capillary condensation, chemical reaction, and, in the most extreme situations, a solution known as deliquescence. When a solid dissolves and saturates a thin layer of water that is present on its surface, this phenomenon is known as deliquescence. It has been demonstrated that the liquid layer that is surrounding the solid will become saturated when it absorbs enough moisture to the point that deliquescence occurs at a specific relative humidity that is required for that humidity. The rates of vapour diffusion and heat transmission are the primary determinants of this process.

Additionally, moisture is a significant component that plays a role in the stability of medication candidates and the formulations of those drugs. It is not uncommon for hydrolysis to be induced when water molecules are adsorbed onto a prospective medication (or excipient).[21] By sorbing onto the medication and excipient mixture, the water molecules have the potential to ionise either one of them or both of them, which will then cause a reaction.

**2.3. Solubility analysis**

The concentration at which the solid phase is in equilibrium with the solution phase at a given temperature and pressure is the definition of what is known as the solubility of the solid. Because a substance's water solubility determines the amount of that chemical that will dissolve and, consequently, the amount that is available for absorption, the therapeutic candidate's solubility may be the most important determinant in determining whether or not it will be beneficial. When a substance has a low aqueous solubility, there is a greater chance that its rate of dissolution will limit the amount of time it spends in the gastrointestinal tract before being absorbed. Table 2 provides an expression of the solubility.

The incorporation of solubility into the Biopharmaceutical Classification System recently brought to light the significance of this property with regard to the biopharmaceutical industry. [Figure 3] illustrates how this method classifies substances according to the various permeation and solubility combinations that they exhibit.[22,23]

* 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 3: Biopharmaceutical Classification System**

The greatest dose strength soluble in 250 ml or less of aqueous fluid throughout physiological pH is called high solubility. Drugs having water solubility <100 g/mL are considered poorly soluble. A poorly soluble medication will dissolve slowly, perhaps preventing absorption. [22,24]

Solubility and permeability are crucial to drug discovery and development, according to Lipinski et al. 1997. The “rule of 5” states that poor absorption or permeation is 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), and more than 10 H-bond acceptors. James et al., 1986 has provided some general solubility rules.[26]

* Electrolytes dissolve in conductive liquids
* Solutes with hydrogen bonding ability dissolve in solvents.
* Accepts hydrogen bonding and vice versa
* Solutes with high dipole moments dissolve in high-dipole solvents
* Solvents having low or zero dipole moments dissolve low- or zero-dipole solutes.

**The pKa determinations**

Most medication candidates are weak acids or bases, hence the pKa or ionisation constant is important before development. [25] Medium pH determines acidic and basic chemical solubility. Strong acids, like HCl, are ionised at all pH levels, but weak acids rely on pH. The extent to which a molecule is ionised at a given pH affects solubility, stability, medication absorption, and activity. [12,27]

For basic compounds:



**b. The partition and distribution coefficients**

The oil/water coefficient is a measure of the chemical structure's lipophilicity and its capacity to pass through biological cell membranes. These consist of volume of distribution, renal and hepatic clearance, solubility, absorption potential, membrane permeability, and plasma protein binding.

An organic compound's lipophilicity is typically expressed in terms of its partition coefficient, log P or K o/w, which is the ratio of the unionised compound's concentration between the organic and aqueous phases at equilibrium:



Keeping in mind that this is a logarithmic scale, a log P = 0 indicates that the component is equally soluble in the partitioning solvent and in water. A molecule is 100,000 times more soluble in the partitioning solvent if its log P value is 5.

A log P = –2 indicates that the substance is very hydrophilic, or 100 times more soluble in water. Stated otherwise, a chemical is lipophilic if the log P value is greater than 1, and hydrophilic if the log P value is less than 1. [28,29, 12]

c. Disintegration

When a medicine is sparingly soluble, the absorption process is mostly determined by the dissolving rate rather than saturation solubility. Therefore, it is crucial to determine the dissolution rate experimentally. Evaluation of various solid drug forms (such as salts, solvates, polymorphs, amorphous, stereoisomers), as well as the impacts of particle size, are the primary areas of focus for dissolving rate investigations.In [12] The following methods can be used to calculate the dissolving rate for a constant surface:

* **Intrinsic dissolution:** The Noyes-Nernst equation provides a sufficient description of a solid's rate of dissolving in its own solution. In a fixed volume of solvent, the intrinsic dissolution rate is commonly represented as mg dissolved × (min−1 cm−2). The pre-formulation scientist can estimate if absorption would be limited by the rate of dissolution by knowing this value.
* **Particulate dissolution:** This measures the drug's dissolution at various surface areas. It is employed to investigate how surface area, mixing with the excipient, and particle size affect dissolution. Therefore, alternative techniques such the use of surfactant will be taken into consideration if particle size has little effect on dissolving.

**d. Dissolution**

When a medicine dissolves into a solution, it is said to be soluble. The bioavailability of a medicine is influenced by its solubility. Limited studies to investigate potential mechanisms of solubilization for improved solubility should be included in the pre-formulation research if the solubility is poor or insufficient for the predicted solution dosage form. Changes in pH, cosolvency, dielectric constant, surfactant solubilization, complexation, hydrotropy, and chemical alteration of the drug are some of the techniques utilised to promote solubility.(26]

**e. Thermal effect**

The basic rule is that increasing solubility of solids with a rise in temperature applies to dissolution, which is typically an endothermic process. As a result, the majority of solubility graphs plotted against temperature exhibit a continuous rise, with a few exceptions. For example, sodium chloride's solubility is nearly constant, but calcium hydroxide's solubility significantly decreases from 0.185 g/mL at 0°C to 0.077 g/mL at 100°C.[29, 31]

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

The common ion effect is a frequent interaction with solvent that is frequently disregarded. The solubility of a marginally soluble electrolyte is frequently decreased by the addition of common ions. When competing ions hydrate, the water molecule is removed as the solvent, a process known as "salting out." Because of this, weakly basic drugs administered as HCl salts are less soluble in acidic (HCl) solutions.In [12]

**2.4. Drug substances' physicochemical stability**

Pre-formulation stability studies are often a novel drug's initial quantitative evaluation of its chemical stability. Both solution and solid state stability are examined in these investigations when additional recipients are present. Temperature, pH, and dosage form diluents are factors that substantially impact chemical stability and are crucial in the sensible design of dosage forms. The drug's ability to withstand changes in temperature will have a significant impact on the sterilisation process for any possible product. Autoclaving is not a suitable method for sterilising drugs that lose their stability at high temperatures; instead, they need to be sterilised using filtration or another method. Drug stability is influenced by pH, therefore both oral doses must be shielded from the stomach's extremely acidic environment during development. The stability feature of the medication will play a major role in the buffer selection process for prospective dosage forms. [32, 12]

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

Changes in the physical characteristics of active pharmaceutical ingredients (APIs), such as their colour, odour, identity, specific gravity, and optical rotation, are considered to be part of their physical stability. The acceleration phase may follow zero, first, or higher orders, depending on the temperature and humidity to which the solid is exposed. Classes of surface moisture have been described using the following in terms of the chemical stability of substances with respect to moisture uptake.[49]

**i. Limited water**

The degradation reaction uses up all of the water, thus not enough remains to fully break down the molecule. Sufficient water: There's enough water for the compound to break down entirely. Too much water This is a volume of water that is either the same as or more than the moisture content required to dissolve the medication. This means that the medicine may eventually break down.

**ii. Loss of volatile constituents**

Products containing iodine, camphor, menthol, ethyl alcohol, anaesthetic, and chloroform may experience evaporation. Tablets containing nitroglycerine may become less effective due to medication vitalization. Colour shifts: One kind of instability that occurs frequently is colour fading.

**iii. Water loss**

Loss of fluids causes weight loss, increases medicine dosage, and boosts potency. For instance, substances like quinine sulphate, caffeine, and borax naturally tend to lose water.

**iv. Water absorption**

causes the drug's weight to rise and its potency to be diluted. Amorphous transformation: At high temperatures, amorphous materials can easily melt into crystalline states due to their high energy. Also, moisture quickens the transition of amorphous matter. The growth and polymorphic transition of crystals occur when moisture is absorbed, causing a shift in the crystal's crystal habit from a metastable to the most stable polymorphic form. Drug compounds become less soluble as a result of this.[34, 33]

**V. Precautionary actions**

The product is airtight and light-resistant. As additions, reducing chemicals (like dextrose) are avoided. For the medication product, choose excipients with low moisture or water content.

**b. Liquid-state stability, or chemical stability**

Chemical stability research encompasses a wide range of mechanisms that lead to drug instability via reducing potency through chemical reactions. [35]

**i. Hydrolysis**

The term "hydrolysis" refers to the dissolution of drug molecules in the presence of acid or water. Many factors influence hydrolysis-induced degradation, but the most significant ones are ionic strength, buffer salts, and solution pH. This kind of degradation can also be impacted by the presence of complexing agents, surfactants, and cosolvents. As mentioned, one of the key factors influencing a compound's stability is its pH in the solution.

Drugs containing amide groups and esters hydrolyze when they interact with a single water molecule. Hydroxyl groups hydrolyze more quickly than amide groups.

Medications are weak bases or acids. Consequently, the could be offered in neutral or ionic form. Ionic form hydrolysis reactions move more quickly than those involving neutral molecules.

Examples

• Esters atropine, procaine, and aspirin.

• Amide: Barbituric acid, ampicillin, and chloramphenicol. [36–34]

**ii. Countermeasures against the hydrolysis process**

The following measures can be taken to stop hydrolysis processes, which are caused by the presence of moisture, the catalytic species H+, and (OH).

**a. Buffer:** Using a buffer to stabilise the product

**b. Complexation:** The drug forms a complex with the complexing agent, which prevents hydrolysis and extends the drug's shelf life.

**c. Solubility suppression:** Reduced solubility lowers medication concentration in solution phase and slows down hydrolysis rate.

**d. Elimination of water:** Water causes hydrolysis, which is best avoided by storing drugs dry and utilising water-impermeable containers.

**iii. Oxidation**

Oxidation is the second most frequent way that a molecule breaks down in solution. Heat, light, or trace metal ions that form organic free radicals can start reduction/oxidation reactions, which include the transfer of either oxygen or hydrogen atoms. The oxidation reaction is accelerated by these radicals and continues until the radicals are eliminated by inhibitors or the chain is eventually broken by side reactions.

Molecules undergo oxidation when their electrons are removed. You may easily determine if a compound is sensitive to oxygen by adding hydrogen peroxide or bubbling air through the solution and measuring the amount of deterioration that occurs.

Autoxidation is the reaction that occurs when a chemical and molecular oxygen interact. Unsaturated fatty acids are autoxidized in fats and oils.

Examples include morphine, vitamin A, riboflavin, ascorbic acid, clove oil, and cinnamon oil.

**iv. Preventive measures against oxidation**

The presence of moisture, oxygen, trace metals, H+, and (OH)− ions causes an oxidation process. Antioxidant usage: The chelating agents, tocopherol: When there are heavy metal traces present, apply a buffer, keep the area oxygen-free, avoid light exposure, and store items at low temperatures.[35, 34]

**v. Racemization**

Drugs can break down mostly by oxidation and hydrolysis, but they can also change in solution through a process called racemization. Without altering its chemical makeup, this optically active substance loses its optical activity and transforms into a racemic mixture, which is its inert version. Levoadrenaline, for instance, has 15–20 times the activity of dextroadrenaline. Half of the pharmacological effect of the pure levo compound is exhibited by a racemic mixture of equal parts levo and dextro-adrenaline formed by the solution of levo-adrenaline.

Analysing the kinetics of racemization can be done similarly to studying hydrolytic processes. First-order kinetic principles dictate the general deterioration of racemization reactions. [36–34]

**vi. Photolysis**

A lot of medication compounds accelerate chemical reactions when they come into contact with light energy, including heat. Drugs that are photosensitive or photolablie undergo chemical breakdown brought on by light.

**v. The photodecomposition mechanism**

The drug's electronic arrangement overlaps with the spectrum of artificial light or sunshine, absorbing energy and causing excitement in the electron. Because they are unstable, they break down the medication to release the energy they have gained and go back to the ground state. Photosensitization is the process by which molecules or excipients absorb energy and pass it to other molecules or agents that cause cellular harm by causing radical production, without actually participating in the reaction themselves.

For instance, riboflavin, chlorpromazine, and tetracycline. Another example of photodegradation is colour development or fading. [36–34]

**vi. Preventative actions**

Avoid exposure to light and low storage temperatures.

**vii. Polymerization**

There is an ongoing chemical reaction going on. A polymer is created by the reaction of several monomers. For example, polymerization is thought to be the cause of the glucose solution's darkening.

**c. Drug-excipient compatibility studies**

The careful selection of excipients plays a crucial role in producing high-quality dosage forms, and it is not only the quality of the API that determines the stability and effectiveness of the dosage form development process. Excipients are chosen at this stage according to how well they work with the drug's ingredient. Making the right excipient selection requires the formulator to have a thorough understanding of drug-excipient interactions. There may already be this information available for well-known medications. For novel pharmaceuticals or novel excipients, the pre-formulation scientist needs to produce the required data. As required by regulatory filings, this study forecasts possible incompatibilities and justifies the use of excipients in formulation. The pre-formulation scientist has a great deal of control over the medication to excipient ratio utilised in these testing.[37, 35]

The following methods are employed to ascertain the compatibility of drugs and excipients. Fourier transform infrared spectroscopy is utilised in Figure 4 to examine structural alterations and the absence of a crystal structure.[39, 38] DSC looks at the melting point and decomposition depicted in Figure 5 using thin-layer chromatography, HPLC, and differential thermal analysis.(40–43)

**STABILITY TESTING**

Evidence regarding how the quality of a drug's ingredient or dosage form changes in response to environmental factors including temperature, humidity, and light is provided by stability testing. The suggested shelf life and storage conditions can be determined with the help of this information. As per the guidelines provided by ICH, stability testing was conducted under varying temperature and humidity conditions throughout a range of time periods, as indicated in Table 3.

For long-term testing, the testing frequency (intervals) are typically every three months during the first year, every six months during the second year, and subsequently once a year.

Three batches should be examined and their physicochemical and microbiological properties assessed for the stability research design minimum.

**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 |

**3. Considering the therapeutic**

Any medical therapy that is prescribed has the ultimate goal of helping the patient experience the desired results. These intended results are a crucial component of the goals for managing the illnesses or ailments. But even with the greatest of intentions and efforts on the side of the medical staff, if the patients refuse to comply, those results could not be possible. The management of diseases may also be adversely affected by this deficiency in a major way.

**3.1 Years**

The GI physiology varies depending on the age. Drug absorption varies depending on the age since distinct physiologies are seen in different age groups. Compared to adults, infants' absorption is indifferent because to their lower intestinal surface and blood flow, as well as their greater stomach pH. Drug absorption is hampered in the elderly due to altered stomach emptying.

**3.2 Gender**

There are differences in the gastrointestinal physiologies of men, women, and pregnant women. Men have a lower stomach pH than women, with pregnant women coming in second. This may impact ionizable medication absorption. The rate of gastric emptying and intestinal motility are higher in men. Women's body weight and volume of distribution are lower, which is a pharmacokinetic factor that explains how drugs are distributed. Divergences in medication absorption may also result from these factors.

**3.3 State of disease**

The gastrointestinal tract's physiological conditions and disease states may have an impact on how well medications taken orally are absorbed. The integrity of the gut wall can change under pathological circumstances. Many inflammatory illnesses cause the integrity of the gut wall to be compromised, which improves medication absorption. Drug absorption may be impacted by changes in GI pH brought on by localised GIT disorders. Patients with acquired immune deficiency syndrome (AIDS) frequently oversecrete gastrin, which raises acid output and lowers the stomach's pH. This may have an impact on how well weakly basic medications, like the antifungal ketoconazole, dissolve. The pH of the gastrointestinal tract can also be lowered by conditions such ulcerative colitis and Crohn's disease.

**3.4 Presence of other drugs**

The physiochemical or physiological absorption of the medicine of interest may be impacted by the presence of other medications in the GIT. Adsorbents such as attapulgite or kaolin-pectin used in antidiarrheal treatments can delay or stop the absorption of certain medications when taken in combination with them. Lincomycin and promazine are two examples. By forming unabsorbable complexes, antacids and mineral replacements containing heavy metals like calcium, iron, magnesium, zinc, or calcium, calcium, or zinc delay the absorption of tetracyclines. The anion exchange resins colestipol and cholestyramine bind to medications and bile salts, preventing some medications from being absorbed. When basic medications dissolve in the stomach, the pH rises, the rate of dissolution decreases, or tetracycline precipitation occurs.

**Conclusion:**

Drug substances are rarely provided on their own. Rather, they are supplied as a component of a formulation along with one or more nonmedicinal chemicals that have a variety of specific pharmaceutical uses. Dosage forms of different kinds are produced by the selective use of these non-medicinal substances, often known as pharmaceutical ingredients or excipients. The pharmaceutical components create effective and aesthetically pleasing dosage forms for therapeutic agents by solubilizing, suspending, thickening, diluting, emulsifying, stabilising, preserving colour, and flavouring them. Every kind of dosage form has distinct pharmacological and physical properties. These diverse preparations give the doctor the option of which medication and delivery method to prescribe, while also presenting formulation issues for the manufacturing and compounding chemists. Pharmaceutics is the general field of study that addresses the formulation, production, stability, and efficacy of pharmaceutical dosage forms.

All of the drug substances and pharmaceutical ingredients that will be used in the fabrication of the product must have their physical, chemical, and biologic properties taken into account in order to properly design and formulate a dosage form. For a pharmaceutical product to be stable, effective, aesthetically pleasing, simple to administer, and safe, the medicine and pharmaceutical ingredients must get along. The product must be produced using the proper quality control procedures, and it must be packaged in containers designed to maintain its stability. The product should be stored in a way that maximizes its shelf life and be labelled to encourage proper usage.

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