

DOSAGE FORM DESIGN

Abstract

Drugs are almost always provided as prepared formulations or medicines rather than as pure chemical compounds. These might range from simple solutions to complicated drug delivery systems. To create an effective dosage form, it is important to consider the medication, method of administration, and specific requirements for drug absorption. To successfully synthesize a pharmacological ingredient into a dosage form, several parameters must be addressed. These can be broadly divided as biopharmaceutical considerations, drug factors, and clinical considerations. There are also significant sections on dosage form design in this chapter. That includes different delivery methods, dose forms to guarantee that the medication is administered in an appropriate form that can be efficiently absorbed and biological variables that may influence how quickly drugs are absorbed by the body. There are notable differences in the body's absorption of medication between different drug compounds and drug administration techniques. Dosage form is also significantly influenced by pre-formulation parameters involving physicochemical characterization, stability analysis, and solubility study. In order to set an environment for product development and develop a structure to guide its information, it is required to identify the desired product type as accurately as possible, just as before putting a medication substance into a dosage form.

Keywords: Biopharmaceutical considerations, drug factors, physicochemical characterization, stability analysis, and solubility study

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I. PRINCIPLE

Drugs are almost never given out in the form of prepared preparations or medications, and they are hardly ever 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.

Giving a medication a predictable therapeutic response when it is part of a formulation that can be mass produced with consistent product quality is the main goal of dosage form design. Dosage formulations are designed to achieve this purpose. A lot of qualities need to be present in order to guarantee the product's quality. These qualities include uniformity in medicine dosage, acceptability to users (including prescribers and patients), proper packaging and labelling, chemical and physical stability, and appropriate preservation against microbial contamination, if needed. While it is not feasible to achieve complete independence between dosage forms and patient variance, in an ideal world this would be the case. On the other hand, recent advances are starting to consider this requirement. These include implants that react to external sound or magnetic fields to initiate a drug delivery function, as well as drug delivery systems that depend on the unique metabolic activities of individual patients.

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 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 essential since various pharmacological treatments are typically required for different illnesses or diseases. While creating dosage forms for the medication, issues pertaining to the

route of administration and its particular requirements that affect drug absorption must also be taken into account.

Table 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

Many drugs are offered in a variety of dose forms and concentrations, each having special pharmacological qualities appropriate for a certain use. Prednisolone, a glucocorticoid used to treat allergy and inflammatory diseases, is one such drug. With the use of various chemical forms and formulation additives, a number of efficient anti-inflammatory formulations, including tablet, enteric-coated tablet, injections, eye drops, and enema, are available. The soluble sodium phosphate salt allows the preparation of a soluble tablet as well as solutions for eye and ear drops, enema, and intravenous injection. In contrast, the base prednisolone and acetate salts have very low aqueous solubility, making them useful in tablet and slowly absorbed intramuscular suspension injection forms. To suit the individual needs of the user, the analgesic paracetamol is also offered in a range 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, the development of biotechnology-based medicines and the increasing value of these therapeutic agents coincide with the discovery of several novel medications based on low molecular weight organic compounds that are still being explored and turned into finished products. 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.

II. BIOPHARMACEUTICAL VARIABLES

The study of how the physical, chemical, and biological sciences relate to medications, dose forms, and pharmacological effects is known as biopharmaceutics. It is essential that dosage form designers possess a basic understanding of pharmaceutical absorption, distribution, metabolism, and excretion. A medicine needs to be in solution in order for the absorbing membranes and epithelia of the gastrointestinal system, lungs, and epidermis to allow it to be absorbed into bodily fluids. Drug absorption can occur through either carrier-mediated transport routes or passive diffusion. The concentration gradient that exists across the cellular barrier drives the mechanism of passive diffusion, which is thought to affect the absorption of many drugs. Drug molecules migrate from regions of high concentration to regions of low concentration. The substance's lipid solubility and the level of ionisation at the absorption site both influence the rate of diffusion. A plethora of knowledge and insights have been obtained through recent research on carrier-mediated transport pathways, some of which have aided in the development of innovative medicinal drugs. Several specialised transport methods, such as aided and active transport, are proposed. After being absorbed, the drug may exert its therapeutic effects nearby or far from the place of delivery. If the latter case applies, the drug needs to be given through physiological fluids (Fig. 1.1).

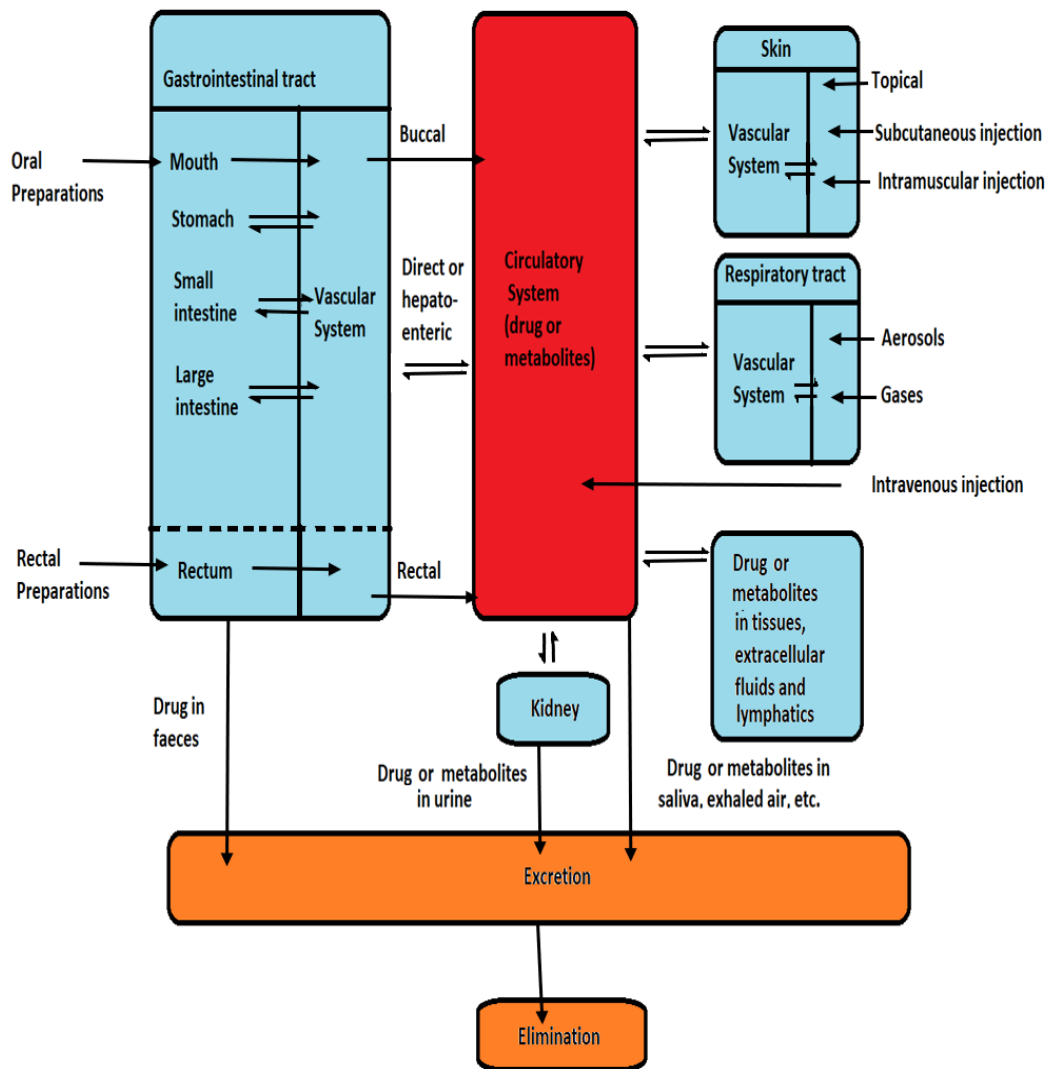


Figure 1: Drug pathways after dosage form administration by different routes.

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 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

III. 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. Administration of Medication via the Enteral Route: Since oral administration is the most practical, affordable, and frequently used method of pharmaceutical administration, it is also the most common. The amount of medication that is absorbed across the intestinal epithelium at the principal site of drug absorption, which is usually the small intestine, determines the medication's bioavailability. The first-pass effect is a crucial consideration when thinking about oral medicine administration. "Drug metabolism" describes the process via which a drug's concentration is drastically lowered prior to it entering the bloodstream. This is frequently the outcome of the liver's metabolism.

The sublingual or buccal route is an alternative to the enteral method for administering medication. One benefit of using this enteral route type is that it does not cause the first-pass effect. The drug will undergo a process called passive diffusion through the venous circulation in the oral cavity whether it is injected right under the tongue (sublingual administration) or on the cheek (buccal administration). By doing this, the drug will be able to enter the superior vena cava rather than the hepatic portal vein. Compared to sublingual tissue, which has a highly permeable mucosa and quick access to the underlying capillaries, buccal tissue is less permeable and has a delayed medication absorption time. (Source:)

Another form of enteral medicine administration is rectal medication administration. Because the highly vascularized mucosa of the rectal tract facilitates rapid and effective medicine absorption, rectal medication administration is favourable. Similar to medication supplied sublingually or buccally, medication taken via the rectum bypasses

the first-pass metabolism partially by passive diffusion. Only over half of the medication that is absorbed through the rectum is thought to reach the liver directly.[2]

- 2. Administration of Medication through the Parenteral Route:** The most common method of administering medication to parents is intravenous injection, which enables medicines to bypass the liver's first-pass metabolism. Because of their easy access to the circulatory system due to their superficial placement on the skin, peripheral veins are commonly employed for parenteral medicine delivery. The body's periphery is home to peripheral veins. When administering intravenous medication, the upper extremity is usually chosen because it has a lower incidence of thrombophlebitis and thrombosis than the lower limbs. The most commonly used veins are the metacarpal veins on the dorsum of the hand and the median basilic or cephalic veins of the arm. When treating the lower limbs, the dorsal venous plexus of the foot might be utilised.

Numerous bodily muscles, including the rectus femoris, ventrogluteal, dorsogluteal, and vastus lateralis muscles, can receive medication via the intramuscular method. Medical professionals typically administer intramuscular injections in the dorsogluteal position, which is the upper outer quadrant of the buttocks. However, if the injection is administered there, there is a risk of damage to the sciatic nerve and the superior gluteal artery.[3] However, the ventrogluteal site, also called the anterior gluteal site, avoids these possible problems by targeting the gluteus medius muscle; for this reason, it is advised.

Another way to administer medication through the parental route is by subcutaneous injections. The cutis, a layer of skin that lies immediately beneath the skin's dermis and epidermis, is the target of these injections. The injectable medications are absorbed gradually and consistently because subcutaneous tissue has fewer blood vessels than other types of tissue. Subcutaneous medication can be injected subcutaneously in a number of areas, including the outside of the upper arm, the belly (avoid the 2-inch-diameter circle centred on the navel), the front of the thigh, the upper back, and the upper buttocks 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.

- 3. Alternative Methods of Medication Administration:** A medication supplied by the nose diffuses passively over the single-layered, well-vascularized respiratory epithelium and into the systemic circulation, making it easier for the body to absorb.

A medication that is breathed spreads swiftly over the vast surface area of the respiratory system's lining epithelium. Medication absorbed into the pulmonary circulation bypasses the first-pass metabolism and enters the systemic circulation straight through the pulmonary vein. The normal particle size of inhaled drugs is between 1 and 10 micrometres to ensure effective delivery. Medication administration to the lungs is dependent on the patient's respiratory physiology, including tidal volume and tracheal inspiration velocity, in addition to the drug's particle size and shape.[4]

The vaginal route is a less commonly used and less well studied method of medication delivery. It does, however, offer the advantage of not having the first-pass impact and has the potential to be a productive method for both systemic and local therapy. The vagina, vesical veins, uterine veins, and rectal veins are the sources of the venous plexuses that drain into the internal iliac veins, and they are all connected to one another. The inferior vena cava is where the veins that drain the middle and upper vagina go directly, bypassing the hepatoportal system.

Medication can be administered by means of a transdermal patch. Standard delivery methods such as transdermal patches, transdermal ointments, and gels, drug carriers including liposomes and nanoparticles, and formulations for local application like transdermal ointments and gels are all used in this strategy. When peripheral and central venous methods have failed to deliver fluids and medication, the intraosseous route is helpful, especially for newborns. This is particularly valid for newborns.[6] In the framework of ongoing clinical trials, medications are presently being investigated in the context of non-hospital cardiac arrest.[7] It is also employed in the prophylactic administration of antibiotics before localised surgeries.[8]

IV. THE RATE AT WHICH MEDICATIONS ARE ABSORBED BY THE BODY CAN ALSO BE AFFECTED BY BIOLOGICAL FACTORS.

- 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.
- 2. 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.
- 3. 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.
- 4. 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.

- 5. 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.

- 6. 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.
- 7. 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.
- 8. 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 lipodic pharmaceuticals skirts around the portal vein and avoids the first-pass metabolism that occurs in the liver.

- 9. 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.
- 10. 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.
- 11. 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.
- 12. 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 as 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.

13. 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.

14. 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.

- **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.
- **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.
- **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.

- **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 anywhere 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.

V. 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. Many therapeutic factors are taken into account as part of the formulation process before a pharmaceutical agent is formulated into one or more dosage forms. These factors include the nature of the ailment, the method of treatment (locally or through systemic action), the patient's age and expected condition, and more. When a medicine is intended for oral administration and is intended for systemic use, tablets and/or capsules are usually produced. This is because the most practical alternative for self-administration of medication is in the form of pills or capsules, which the patient can easily handle. If a drug substance proves beneficial in an emergency situation where the patient is unable of taking oral medication or may be unconscious, an injectable version of the treatment may also be created. Motion sickness, nausea, and vomiting can be prevented with tablets and skin patches; to cure these symptoms, suppositories and injections are utilised. One may list countless such examples of therapeutic circumstances that could influence how a dose form is designed. An additional

consideration considered in the development of the dose form is the age of the intended patient. For infants and children under five years old, oral medication administration is best done with liquid forms rather than solid ones. These liquids are usually given directly into the mouth of the baby or child using a dropper, spoon, or oral dispenser. They can be flavor-infused aqueous solutions, syrups, or suspensions. As an alternative, you might incorporate them into the child's meal. For babies and children of all ages, a single liquid paediatric preparation can be used; the medication's dosage is changed based on the patient's volume. A young patient may not have eaten all of the medication that was administered to them; some may have been expectorated instead, especially if they are coughing up blood, vomiting, gagging, or acting defiantly. You could be required to receive injections under such conditions. 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 dissolve into a creamy substance with a palate-pleasing flavour, and their consistency is similar to that of an after-dinner mint. Newly developed tablets dissolve in the mouth in ten to fifteen seconds, allowing the patient to swallow a beverage while seeming to take a pill. Many people have found that swallowing capsules is much easier than swallowing whole tablets. A tablet that has been allowed to get moist in the mouth before consumption will become slick and easier to pass down the throat when there is water present. To aid in the swallowing process, one can also put a teaspoonful of a gelatine dessert, liquid candy, or syrup in the mouth and half drink it before placing the solid dose form in the mouth. This is carried out prior to the solid dose form being ingested. Moreover, if a person finds it difficult to swallow a capsule, the contents can be transferred onto a spoon and mixed with jam, honey, or any other food item that shares a taste with the medication before being ingested. This is to cover up the taste of the drug. The most common way for senior patients to receive their prescriptions is in the form of oral liquids; however, chemists can also make tablets or capsules on the spot for oral administration. It is not advised to crush or chew any tablets and capsules meant for controlled release as this may damage the medication's integrity and make it act differently from how it was intended 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. In order to answer the challenge of formulating a medicinal ingredient into the proper dosage form, research chemists gather knowledge from experience with other chemically comparable pharmaceuticals and through the appropriate application of the physical, chemical, biologic, and pharmaceutical sciences. The process of solving the issue of creating a drug substance in the appropriate dose form then makes use of this knowledge. The initial phases of developing any novel formulation must include studies to gather basic data on the chemical and physical characteristics of the medication component. Before beginning work on the actual product formulation, these fundamental studies serve as the necessary preformulation work.

VI. PREFORMULATION

The process of generating dosage forms begins with preformulation testing, which is the first step in the process before formulation. Testing like this is carried out with the purpose of ensuring that the goals of the drug and the dosage forms it comes in are achieved. The evaluation of the pharmacological material's physical and chemical properties, both on its own and in combination with excipients, is referred to as preformulation. This evaluation can take place either before or after the formulation process. The phase known as "preformulation" comes before the step known as "formulation." Before formulation development takes place, the primary objective of pre-formulation testing is to generate information that is useful to the formulator in the process of developing dosage forms that are stable and bioavailable. 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.

1. Pre-Formulation Parameters Physicochemical Characterization

- Organoleptic properties
- Bulk characteristics
 - Assay development
 - Melting point
 - Solid state characteristics: Particle size, surface area
 - Flow properties
 - Densities
 - Compressibility
 - Crystalline and amorphous
 - Polymorphism
 - Hygroscopicity.

2. Solubility analysis

- Ionization constant (pKa)
- Partition coefficient
- Dissolution
- Solubilization
- Thermal effect
- Common ion effect (Ksp).

3. Stability analysis

- Solid-state stability
- Solution-state stability
- Drug-excipients compatibility

4. 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 vital to choose a word that will be used consistently to describe these traits in order to limit confusion among scientists who use different phrases to refer to the same quality. This word will be used in a consistent manner to explain these features.

5. Bulk characteristics

- **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 accomplished by the use of an ultraviolet (UV) spectrophotometer or, for a higher level of precision, through the use of 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]

- **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. A very sharp melting peak in differential scanning calorimetry (DSC) can be used as an indicator of purity for measuring the purity of medicinal compounds. This can be done by using the DSC technique. A drug's melting point or range is another property that can be used as a diagnostic tool. 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]
- **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.

VII. 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. Methods such as sieving, optical microscopy in conjunction with image analysis, electron microscopy, the coulter counter, and laser diffractometry are among the most common that can be used. 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 This phenomenon can be described using the methodology that Brunauer, Emmet, and Teller devised. Singh, 1992 have been investigated in great detail for the purpose of determining the extent to which they contribute to surface area calculations using the gas adsorption method. [9]

Table 1: Methods for determining particle size 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

1. Powder Flow Properties: Tableting efficiency is directly related to the flow properties of powders. Flow parameters of powders are particularly essential. It is quite necessary to have an adequate flow of the powder or granulation that is going to be compressed in order to make certain that the mixing will be successful and that the compressed tablets will have a weight that is consistent across all of them. 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]

2. 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.

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

Types of Density

- **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.
- **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.
- **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]

- 4. The ability to be compressed:** The "compressibility" of a powder is described as its capacity to decrease in volume when subjected to pressure, whereas the "compatibility" of a powdered material is defined as its capacity to be crushed into a tablet with a particular tensile strength (plastic deformation). Both of these definitions are interchangeable with one another. It is possible to use it to make predictions about the flow properties of solids by basing those predictions on the results of density measurements. [12]

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} * 100$$

- 5. 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]
- 6. Amorphous forms:** Materials that have amorphous shapes have a non-crystalline character, which indicates that they lack any kind of long-range organisation. In addition to milling crystals and compacting them, other methods of preparing their structure include rapid precipitation, lyophilization, or rapid cooling (supercooling) of liquid melts. All of these methods can be used to produce the same result: the production of their structure. [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]

- 7. 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]

The presence of polymorphism has important repercussions for formulation, biopharmaceutical, and chemical process since polymorphs of a particular molecule in general have a variety of physicochemical properties, such as melting temperature, solubility, and density. In addition to polymorphs, it is conceivable 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 instance, the polymorphism that is demonstrated by estrone). Solvates are also referred to as pseudo polymorphs in certain scientific communities. [19,20]

- 8. Hygroscopicity:** When exposed to water vapour or moisture, a considerable number of pharmaceutical compounds and salts become unstable and lose their effectiveness. When compounds come into contact with moisture, the water is held by the compounds by a variety of mechanisms. These mechanisms include bulk or surface adsorption, capillary condensation, chemical reaction, and, in the most extreme of scenarios, a solution known as deliquescence. This process, referred to as deliquescence, is characterised by the dissolution and saturation of a very thin layer of water that is present on the surface of a solid. It has been established that the liquid layer that is surrounding the solid will become saturated when it absorbs sufficient moisture to the point where deliquescence happens at a specific relative humidity that is required for that humidity. In other words, the liquid layer will become saturated when it reaches the level of humidity that is required for that humidity. The key factors that determine how quickly this process will occur are the vapour diffusion and heat transmission rates.

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.

VIII. 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

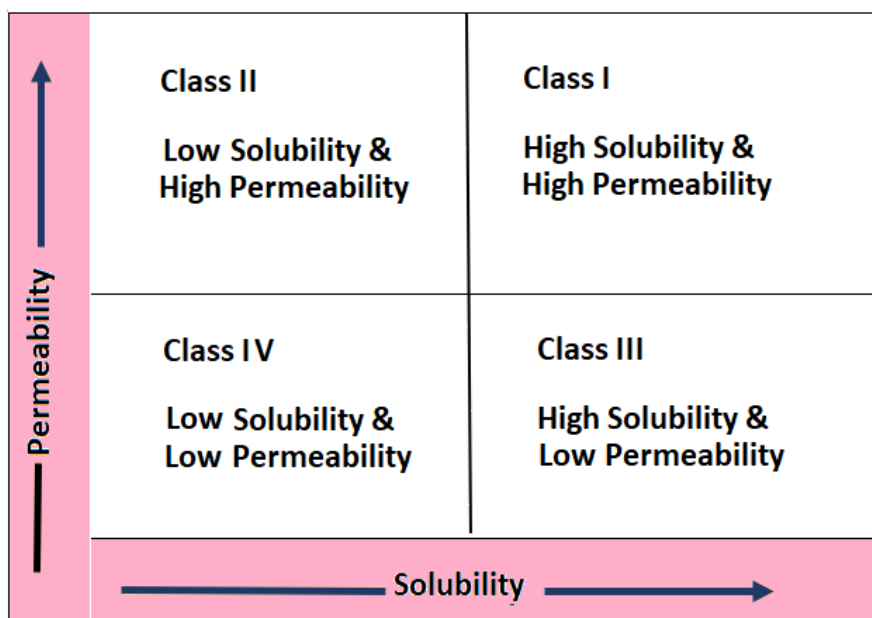


Figure 3: Biopharmaceutical Classification System

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 two characteristics that are

essential to the discovery and development of new drugs. According to the "rule of 5", poor absorption or penetration is more likely when there are more than 5 H-bond donors (represented as the sum of OHs and NHs), the MWT is greater than 500, the Log P is greater than 5 (or M LogP is greater than 4.15), and there are more than 10 H-bond acceptors. Other factors that contribute to this increased likelihood include a MWT that is greater than 500. [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.

1. The pKa determinations: Because the majority of potential medications are either weak acids or bases, determining their pKa, also known as their ionisation constant, is critical prior to development. [25] The solubility of acidic and basic chemicals is determined by a pH of medium. Strong acids, such as HCl, are ionised regardless of the pH level, whereas weak acids are dependent on the pH. The degree to which a molecule is ionised at a particular pH has an effect on its solubility, stability, and the amount of medication that may be absorbed as well as its activity. [12,27]

For basic compounds:

$$\text{pH} = \text{pKa} + \log \frac{(\text{Concentration of ionized species})}{(\text{Concentration of unionized species})} \quad (1)$$

For acidic compounds:

$$\text{pH} = \text{pKa} + \log \frac{(\text{Concentration of unionized species})}{(\text{Concentration of ionized species})} \quad (2)$$

Thus at pKa = pH, 50% dissociation (or ionization) and 50% unionization.

2. The partition and distribution coefficients: The oil/water coefficient is a measurement of the lipophilicity of a chemical structure as well as its ability to pass through the membranes of biological cells. These characteristics include a substance's volume of distribution, its clearance in the kidneys and liver, its solubility, its absorption potential, its membrane permeability, and its binding to plasma proteins.

The lipophilicity of an organic compound is often described in terms of the substance's partition coefficient, also known as log P or K_{o/w}. This coefficient is the ratio of the concentration of the unionised molecule that exists in the organic phase to the concentration that exists in the aqueous phase at equilibrium:

$$\log P = \frac{[\text{Unionized compound}]_{\text{org}}}{[\text{Unionized compound}]_{\text{aq}}}$$

Keeping in mind that this is a logarithmic scale, a log P value of 0 implies that the component has the same level of solubility in water as it has in the partitioning solvent. If the logarithm of a molecule's P value is 5, then that molecule is 100,000 times more soluble in the partitioning solvent.

If the chemical has a log P value of -2, it means that it is extremely hydrophilic, which means that it is 100 times more soluble in water. To put it another way, a chemical is considered to have lipophilic properties if its log P value is larger than 1, while it is considered to have hydrophilic properties if its log P value is less than 1. [28,29, 12]

3. 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 $\text{mg dissolved} \times (\text{min}^{-1} \text{cm}^{-2})$. 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.

4. 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. Techniques used to improve solubility include changes in pH, cosolvency, dielectric constant, surfactant solubilization, complexation, hydrotrophy, and chemical modification of the medication. [26]

5. Thermal effect: The general rule is that dissolution, which is usually an endothermic process, is affected by an increase in the solubility of solids with temperature. Because of this, with a few notable exceptions, solubility graphs plotted versus temperature typically show a steady climb. For instance, the solubility of calcium hydroxide dramatically falls from 0.185 g/mL at 0°C to 0.077 g/mL at 100°C, whereas the solubility of sodium chloride is almost constant. [29, 31]

- 6. Common ion effect (K_{sp}):** 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]

IX. 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. Since pH affects drug stability, both oral dosages need to be protected from the extremely acidic environment of the stomach while they are being developed. The medication's stability characteristic will be a key consideration when choosing a buffer for potential dose forms. [32, 12]

- 1. Physical stability (initial solid-state stability):** Physical stability refers to alterations in the properties of active pharmaceutical ingredients (APIs), including colour, aroma, identity, specific gravity, and optical rotation. Depending on the temperature and relative humidity that the solid is subjected to, the acceleration phase may occur in zero, first, or higher orders. The following has been used to characterise classes of surface moisture in terms of the chemical stability of compounds with regard to moisture uptake. [49]
- 2. 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.
- 3. 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.
- 4. 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.
- 5. 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]

6. **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.
7. **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]
8. **Hydrolysis:** The term "hydrolysis" refers to the drug molecule disintegration in water or acidic environments. 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, they 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]

9. **Countermeasures against the hydrolysis process:** The following measures can be taken to stop hydrolysis processes, which are caused by the catalytic species H^+ , the presence of moisture, and (OH^-) .
 - **Buffer:** Using a buffer to stabilise the product
 - **Complexation:** The drug forms a complex with the complexing agent, which prevents hydrolysis and extends the drug's shelf life.
 - **Solubility suppression:** Reduced solubility lowers medication concentration in solution phase and slows down hydrolysis rate.
 - **Elimination of water:** Water causes hydrolysis, which is best avoided by storing drugs dry and utilising water-impermeable containers.
10. **Oxidation:** Oxidation is the second most frequent way that a molecule breaks down in solution. Reduction/oxidation reactions involve the transfer of either oxygen or hydrogen atoms and can be initiated by heat, light, or trace metal ions that produce organic free radicals. 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.

11. 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]

12. 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]

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

14. 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]

15. Preventative actions: Avoid exposure to light and low storage temperatures.

16. 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.

17. 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)

X. 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		

1. 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.

2. **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. **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.
4. **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.
5. **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 attapulgit 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.

XI. 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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