Dosage Form Design

Dr. Suchitra S. Mishra (Corresponding Author)

(M. Pharm, Ph.D.)

Assistant professor and Research Associate (Pharmaceutics)

Dadasaheb Balpande College of Pharmacy, Besa, Nagpur. 440037

(M.S.) India

9146945512

suchitramishra36@yahoo.com23

Mrs. Rohini Kharwade(M. Pharm)

Assistant professor (Pharmaceutics)

Dadasaheb Balpande College of Pharmacy, Besa, Nagpur. 440037

(M.S.) India

9730968187

rohinismore1@gmail.com

ABSTRACT

The best drug in the treatment of any disease is one that immediately meets the need for the drug in the blood (or site of action) and remains constant throughout the recovery period. This can be done by administering the dosage at a certain dose and a certain frequency. Therefore, a drug can be used in different ways for different types of drugs. Information about various drugs has changed and evolved rapidly over the past few years with the advent of new technologies. Recently, new ideas and government regulations regarding bioavailability, bioequivalence and validation are affecting the design, development and production of drug formulations. The physicochemical properties of drug molecules have a significant impact on safety and efficacy. Poor physical properties often lead to difficulties in establishing dose-response relationships (SARs) and a lack of efficacy in clinical and clinical trials. This could lead to further changes in capacity throughout the development process, higher medical costs, and worst of all, the abandonment of late diagnostic tests. Knowing the basic physicochemical properties makes it possible to isolate and eliminate probes so that molecular defects can be modified or corrected at the design stage. This chapter aims to focus on the production of quantitative data, the important physical properties of selected molecules and how these properties can be analyzed and incorporated into research, the visualization and development of the final dose.

Keywords: structure-activity relationship, conventional drug delivery, novel drug delivery, new chemical entities, generics, biopharmaceuticals

I. INTRODUCTION

Medications are rarely given alone; instead, they are given as part of a formulation with specific drugs and one or more non-drugs with specific functions. The choice to use over-the-counter drugs called medicinal ingredients or supplements leads to different types of medical uses. Chemical ingredients can dissolve, remove, thicken, dilute, emulsify, stabilize, protect, colour, flavour and transform chemicals into attractive and attractive forms. The physical and chemical properties of each recipe are unique.

These different systems present challenges for pharmacists to select the drug to fill and the delivery system, as well as for pharmacists to manufacture and composition. The general study of the design, manufacture, safety and efficacy of medicinal products is called pharmacy. In the design and manufacture of suitable dosage forms, the physical, chemical and biological properties of all drugs and pharmaceutical products used in the manufacture of the products should be taken into account. Medicines and pharmaceutical products must be combined to create drugs that are stable, effective, attractive, easy to administer, and safe. The product must be produced with quality control and packaged in containers that control the durability of the product. Products should be labelled to encourage correct use and stored in conditions suitable for maximum shelf life. Methods for preparing dosage forms and delivery systems are described in the following sections. This section explains some general considerations regarding physical agents, pharmaceutical formulations, and pharmaceutical ingredients. Pharmaceutical formulation is a multi-step process in which active drugs are mixed with all other ingredients, including factors such as particle size, polymorphism, pH and solubility, to become the final drug product. A drug formulation consists of medicinal products containing the chemical properties of the drug, its formulation and details of the treatment regimen to be used in medical practice[1, 2, 3].

II. CHARACTERISTICS OF IDEAL DOSAGE FORMS [3, 4]

Dosage forms are non-reusable drugs and pharmaceutical products that contain a combination of excipients and other materials. Medicines need to be in the right form so that they can reach the needs of the order, which depends on how many forms are created. The ideal formula should be:

- Easy to apply and safe
- Easy to use
- Easy to repeat and manufacture
- Patient performance
- Effective
- Physical and chemical stability
- Biocompatible
- Affordable
- Maintains treatment throughout shelf life
- Ease of transportation, use and storage
- Resistant to freezing during storage and use
- Prevents mechanical shock during transportation
- Ease of use of different drugs
- Provides medical needs
- Drug release, initiation, process effort and working time

III. NEED FOR CONVERT DRUG TO DOSAGE FORMS [4, 5,7, 8]

When raw materials are taken, they are rarely added with supplements, because it is difficult to take the drug correctly and the expected treatment cannot be provided. Drugs and excipients need to be mixed to turn into different types of drugs. The basic rules of prescribing are:

- Correct dose
- Protection Eg. Coated tablets, and sealed ampoules.
- To mask taste and odour (to make it delicious)
- Place the medicine in body tissue.
- It is a sustained-release drug
- Manage drug delivery

- Injecting drugs into the body cavity (breech, genitals)
- Carriers must use insoluble drugs
- Ease of transportation, use and storage
- Stability during storage and use
- Prevents mechanical shock during transportation
- Ease of use of different chemicals
- Meets medical needs
- Predictable effect duration, release, onset, power
- Economical and elegant
- Reduce discomfort and immediate relief and improve patient compliance

IV. TYPES OF DOSAGE FORM [6,8,9]

Drugs enter the human body through various routes of administration, depending on their absorption and therapeutic effects. Medicines can be classified in different ways according to different bases such as administration, physical properties and uses.

A. Based on the physical state

a. Solid Dosage Form: Conventional and modified release Tablets, Capsules, Powder, Lozenges, Films, Chewingum, Pallets, Suppositories etc.

b. Liquid Dosage Form: SolutioSuspensionsions, Elexirs, Syrup, Linctus, Parentrals, Eye and ear drops, Aromatic water, Tincture, Mouth wash, Gargles etc.

c. Semisolid Dosage Form: Generally used for topical applications or on mucous membranes. Cream, Ointment, Gel, Liniments, Lotions, Pastes etc.

d. Gaseous Dosage Form: Combination of solid fines wth liquid or gas or combination of liquid and gas. Nebulizers, Aerosol, Inhalers, Sprey etc.

B. Based on the route of administration

a. Oral Dosage form

Tablets

Tablets are a dosage form that is administered orally to the body. Tablets may contain one or more compressed medicines along with other ingredients such as antibiotics, fragrances and binders. Tablets come in many shapes and colours. It can be controlled, supported or released immediately.

Effavescent tablet: This tablet dissolves by producing gas when it comes into contact with water. The oil obtained from the reaction of bicarbonate with citric or tartaric acid facilitates drug therapy. For example: Vitamin C tablets.

Chewable Tablet: This tablet should be chewed in small pieces. This will increase the surface area exposed during detonation and allow the released drug to be absorbed faster. These tablets are usually given to patients who have difficulty swallowing, such as the elderly and children. It can also be used if the dose is too high. Example: Chewable multivitamins.
Sublingual Tablet: This tablet is designed to be placed under the tongue for absorption through the mucous membranes directly into the bloodstream. This method results in faster recovery than oral administration. For example trinitrate tablets.

Enteric Coated Tablets: Tablets with a special coating that prevents dissolution in the stomach but does not dissolve in the intestine. It is used so that the drug can be broken down by the juice in the stomach and absorbed into the intestines.
Powder: The oral powder is usually dissolved in water for the patient to drink for therapeutic purposes. Most are available in sachets such as oral saline.

Lozenges : Lozenges are prescription medications that must be inhaled by mouth until they dissolve. Lozenges are often used to relieve cough and sore throat.

Capsule: A capsule is an oral formulation, usually made of gelatin, containing active ingredients and additives. Gelatin capsules are generally more expensive than tablets, but they do have some advantages. For example, the particle size rarely changes during capsule production, and the capsule encapsulates the flavour and odour of the active ingredients and protects the photosensitive ingredients.
Hard gelatin capsules: for solid-filled preparations

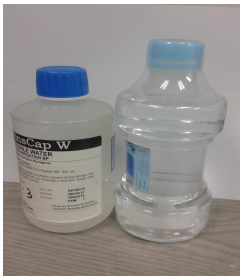
Soft gelatin capsules: Soft gelatin capsules for liquid-filled or semisolid-filled preparations. Soft gelatin capsules are suitable for the production of drugs with low water solubility as they provide good drug release and easy digestion.

Mixtures: Mixtures are liquid preparations containing medicated active ingredients dissolved in a suitable solvent medium and to be taken according to the dose prescribed. For example syrup, suspension, emulsion, etc.

b. **Topically Applied**

Cosmetics Chemicals used for cosmetic purposes on the skin include antibiotics, antiseptics, anti-inflammatory agents, and skin softeners. The amount of drug released from ointments, creams and pastes in most of the semi-solid matrix used.

Irrigation Solution: Sterile, sterile solution for cleaning the body cavity, surgical site, wound, or genitourinary system. Example: saline solution.



Emulsion: The emulsion cannot be taken orally, it can only be used externally and applied to the skin. Example: sunscreen.
Gargles: Mouthwash is used to rinse and treat mouth infections. Example: Chlorhexidine mouthwash.

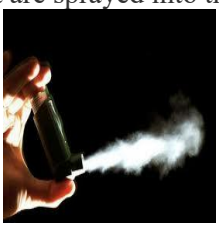
Drops: They are liquids containing some drugs placed in body cavities such as eyes, nose and ears to provide the desired therapeutic effect.

Ointment: An ointment is an oily preparation containing certain medicines. It can be used topically, such as the skin, eyes, or rectum, to reduce itching. Cosmetics are not easily removed from the body with water, sweat and other substances, so they stay on the skin for a long time. Therefore, ointments are also used as moisturizers and follow the protective mechanisms of the skin.

Cream: Cream is a semi-medical form containing one or more drugs for external use.Example: itching cream.

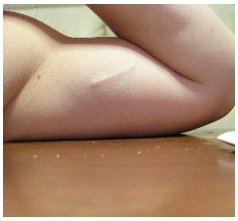
c. **Injections (sterile dosage forms)**
Injections are sterile drugs containing drugs that are injected into the blood vessels, tissues, and organs of the body using needles and syringes. Injections are classified according to the method of injection into the body.

Intramuscular: Local or systemic injection by injection into the muscles, particularly the deltoid (shoulder), gluteus maximus (butt), and quadriceps (front of the thigh).
Subcutaneous injection: Inject drugs into the body by injecting them into the subcutaneous fat layer in the skin and muscles. This method is often used to administer insulin, antibiotics, opioids, and hormones.
Intravenous: Intravenous administration of drugs by intravenous injection (intravenous). This method is often used to administer saline infusions and parenteral nutrition.
d. **Inhalation**s
Inhaler: Inhaler usually consists of two types: aerosol or powder.
Aerosol: The term "aerosol" refers to sprays that result from a highly pressurized pressurised system/tool. This spray contains certain medications that are sprayed into the mouth.



Powder: There are also medicated powders that are supplied in capsules. Patients will place the capsule into a special inhaler that is capable of breaking the capsules so that the medicine can be inhaled into the respiratory tract through the mouth.

e. **Miscellaneous Implant:** An implant is a medicine delivery device planted in the body (most commonly under the skin) to enable the administration of medicine slowly and steadily over some time. This device is usually used to deliver hormones or contraceptives. For example Implanon



Suppository: A suppository is a type of dosage form introduced into the body through the anus. It is made from a material that can easily melt at body temperature. It is used for patients with difficulty taking oral medications, such as infants and the elderly. Example: Paracetamol suppository.

V. GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Before formulating a drug substance into a dosage form, the desired product type must be determined, then various initial product formulations are developed and investigated for desired properties (e.g., drug release profile, bioavailability, clinical efficacy) and pilot studies and scale-up production. The formulation that best meets the product objectives is selected as the master formulation. Each batch of subsequently prepared product must meet the specifications laid down in the master recipe. There are many different forms in which the medicine can be placed for convenient and effective treatment of the disease. Most often, the manufacturer prepares the medicinal substance in several dosage forms and strengths for effective and convenient treatment of the disease. Before a drug is formulated into one or more dosage forms, among the factors considered are such therapeutic issues as [4,7,8].

A. Drug Consideration In Dosage Form Design

a. Characteristics of Drug Substances

b. Drug and Formulation Stability

B. Therapeutic Considerations In Dosage Form Design

a. Route of Administration

b. Nature of the illness

c. The age and anticipated condition of the patient.

C. **Biopharmaceutics Considerations**

A. Drug Consideration In Dosage Form Design

a. Characteristics of drug substances

To achieve the goals of drugs and dosage forms, pre-formulation testing is the first step in the development of dosage forms before formulation. Preformulation is defined as the examination of the physical and chemical properties of the drug itself and together with the excipients before formulation. The main goal of preformulation testing is to obtain information useful for the formulator in the development of stable and bioavailable dosage forms before formulation development. Pre-formulation research is designed to provide all the necessary data, especially the physicochemical, physicomechanical and biopharmaceutical properties of medicinal substances, excipients and packaging materials [10].

Organoleptic properties

Organoleptic properties of a new preformulation of a chemical entity start with a detailed description of the organoleptic properties of medicinal substances including colour, smell, taste, texture and taste, and these properties should be recorded at the preformulation stage and also described using expressive

terminology. These properties change with vendor changes and are therefore evaluated against reference standards to confirm API purity. Furthermore, once these organoleptic properties are determined, they can analyze the consistency of individual batches [12,13].

Solid state properties

They include crystallization, salt formation, polymorphisms, and solvates, which profoundly affect solubility, stability, permeability, and ultimately bioavailability. These are the most fundamental drug parameters that are necessary for the effective development of drug candidates for patients [14]. For example, powders are masses of solid particles enclosed in air (or another fluid), these two systems significantly affect the bulk properties of powders. Liquid content and other variable parameters are associated with powder formulations that can affect the flow, which is affected by particle physical properties such as shape, size, size inconsistency, angularity, and stiffness. Some external factors including humidity, aeration, vibration and traffic environment amplify this problem [15].

Flow properties

The flow properties of powders are critical to successful tabletting operations. For effective mixing and tolerable mass consistency of compressed tablets, an optimal flow of granules/powders is required. Suppose that at the preformulation stage, the drug is categorized as "poorly liquid", so the right choice of excipients can solve this problem. For powdered drugs, pre-compression and granulation methods are used to improve their flow behaviour. A pre-formulation test of the granule mass to measure flow properties is carried out using the angle of repose, orifice flow, Hausner ratio, bulk and shock density, interparticle porosity, Carr index and ideal fluidity. In general, a uniform shape or a large crystal exhibits a narrower deposit angle and a low Carr index resulting from changes in particle size and shape [16]. The angle of incidence can be understood as the maximum angle formed between the free-standing surface of the powder pile and the horizontal plane of the powder at the base. It can be used to evaluate the interparticle force of powder particles and bulk characterization of solids. The range of the pouring angle can vary from 0° to 90°, the pouring angle below 25° represents excellent flow properties, on the other hand, if the pouring angle is between 25° and 45°, the flow is considered poor. The formula for calculating the angle of repose is as follows [17].

Angle of repose $\tan \theta = h/r$

h is the height of the pile and r is the radius of the horizontal base.

Particle size distribution

The size of the particles of the dosage form affects the physicochemical properties and biopharmaceutical behaviour of medicinal substances. Drug solubility is often inversely proportional to particle size; for example, a dosage form with a smaller particle size has a large surface area, and so does the surface area to volume ratio. A stronger contact between the surface and the solvent increases the solubility. Particle size reduction methods such as grinding and milling often subject the drug product to high levels of physical stress that could lead to degradation [21]. In addition, micronization is a common technique used to reduce the size of particles and increase the surface area of drugs, thereby increasing solubility and dissolution.

Compressibility

Compressibility is the ability of drug powders to reduce volume under pressure and compress into tablet dosage forms with a specific tensile strength. It is calculated using Hausner's ratio and Carr's index to determine the flow behaviour of powder-based drugs for density calculation in preformulation stages [23].

Crystallinity and polymorphism

The polymorphism and crystalline behaviour of drugs in the solid state are important to formulators because most drugs exist in the solid state and are suitable for their intended use. In the solid state, drugs can exist as salts, co-crystals, hydrates, polymorphs, amorphous forms, solid solutions, and eutectics. Medicines in liquid form such as valproic acid and general anaesthetics in the gas phase. In a crystal, the lattice atoms are arranged in a unique pattern and are highly ordered based on this arrangement and are classified as crystalline or amorphous. Both forms exhibit different physical and chemical properties and

therefore have different solubility and stability properties that affect the delivery system and drug activity [16]. Crystals and polymorphs are analyzed by advanced techniques such as X-ray diffraction, FTIR, NMR, optical crystallography, thermal microscopy, SEM/TEM, and differential scanning calorimetry [24, 25]. Polymorphism and crystal behaviour affect solubility [22].

Hygroscopicity and Deliquescence

Hygroscopicity can be viewed as the ability of a substance or salt to absorb moisture or water vapour. Chemicals can interact with moisture by storing them in bulk or absorbing them from the surface, capillary condensation, and chemicals. Atmospheric conditions and API area determine the amount of moisture absorbed. Changes in moisture content affect stability, compressibility and flow properties, so these properties should be carefully studied. Moisture content is measured by Karl Fischer titration, thermogravimetric analysis (TGA) and gas chromatography methods [29].

Pseudopolymorphism

Pseudopolymorphism refers to the incorporation of chemical molecules into a crystal lattice. The material can be found in different types of crystals called pseudopolymorphism and this process is pseudopolymorphism. These materials have secondary heterostructures with the same chemical composition (water, solvents, co-formers, etc.) in the lattice. These materials have other names such as hydrates, solvates, and co-crystals, which the FDA recognizes as polymorphs [28].

Pseudopolymorphism Pseudopolymorphism refers to the incorporation of chemical molecules into a crystal lattice. The feature can be found in different types of crystals called pseudopolymorphism and this process is pseudopolymorphism. These materials have secondary heterostructures with the same chemical composition (water, solvents, co-formers, etc.) in the lattice. These materials have other names such as hydrates, solvates, and co-crystals, which the FDA recognizes as polymorphs [28].

Solubility Parameters

An important issue in production is solubility. Poor drug solubility is a common cause of drug discovery and development failure. Insufficient solubility affects the ability to generate molecules because it can complicate testing and adversely affect in vivo combinations. Therefore, insufficient solubility will affect the development of therapy. In general, drug solubility is affected by many factors such as lattice energy, molecular arrangement, bond strength, weak bond, lipophilicity, ionization potential, pH, co-solvent, and additives. , dielectric constant, surfactant solubility, hydrophilicity, complexation, temperature, pressure and molecular volume. If these factors are adequately explored during preliminary research, they can be used in the final formulation and reduce the risk of drug failure [30].

Measurement of pH in the Preformulation Step

The negative logarithm of the hydrogen ion concentration of the solution is called pH. pH is calculated as pH = − Log [H+] depending on the pH range, pH 1-7 for acidic solutions, ± 7 for neutral solutions, and pH 7-14 for alkaline/neutral solutions. Most chemicals contain salts, weak bases or acids. Therefore, a good understanding of the molecular ionization behaviour at a given pH is important. Therefore, the effects of ionization, ionic strength, pH, and temperature are simultaneously studied to understand the form stability, solubility, bioavailability, and activity results of drug molecules during the pre-formulation phase [31].

Dissociation Constant (pKa) Analysis

pKa is the dissociation constant of a substance that exists in solution as a weak base or weak acid, so the substance can exist in ionized or non-ionized form at any pH. The solubility of the drug in water depends on the ionization of the drug and the ratio of the ionized form to the ionized form. The nonionic form of the drug is lipophilic and therefore able to pass through the bilayer membrane, however, the ionized form is oil-insoluble and therefore penetrates slowly. The three parameters for absorption are stable ionization, the non-ionized form of the drug available for absorption in the gastrointestinal tract region to see its effect [32].

The equations for basic and acidic compounds are mentioned below:

For acidic drugs: pH=log pKa+ratio of un-ionised to ionised drug

For basic drugs: pH=log pKa+ratio of ionised to unionised drug

Distribution Coefficient (Log P) Analysis

The ratio of non-ionized solution dispersed in the aqueous and organic phases is called the dispersion coefficient. This helps predict the drug's ability to cross the bilayer. Lipinski's 5 rule was used to estimate solubility and transmittance. log P can be determined from the equation log P = oil/water. The lipophilicity of the compound is indicated by the Log P value, with a log P value of 0 indicating that the drug has a solubility in n-octanol and water. A Log P value of 2 indicates the hydrophilicity of the drug and 5 indicates its lipophilicity. While the fit curve of Log P values is between 1 and 3, Log P values less than 1 and greater than 6 indicate weak permeability. Currently, software tools such as Molecular Modeling Pro™ 6.27 software [33] are useful for Log P determination.

Thermal Effect (solution enthalpy)

The effect of heat on the solubility of a solution can be measured in terms of the temperature of the solution. The heat released or absorbed when one mole of solute is dissolved in a large amount of solvent is called the heat of solution. The optimum temperature ranges are 5°C, 25°C, 37°C and 50°C. Solution temperature is considered good for endothermic processes and bad for exothermic processes. Effectively heating the drug increases the solubility of the drug when the temperature is increased, so that optimal drug solubility can be determined during preformulation using the temperature of the drug formulation. A heat of dissolution between 4 and 8 kcal/mol indicates that weak and acidic substances dissolve in water in an unionized state [14].

Common Ion Effects (Ksp)

Pretests to determine solubility should not avoid ion effects because ions often reduce the solubility of salts. Le Chatelier's principle states that when equilibrium is disturbed, the response changes to bring it back into equilibrium. The balance of mixed ions with a weak acid or base will shift in favour of the reactants. Most ions suppress the ionization of weak acids in the presence of weak bases or weak acids, producing more comparable product ions [34]. Therefore, the addition of mixed ions to the solution can change the reaction to the reactants to remove excess products from the solubility-reducing precipitates.

Dissolution

Dissolution is defined as the amount of solute per unit time of a liquid or compound under specified conditions of temperature and pressure. This process is called dissolution. The separation ratio can be determined with the aid of the Noyce-Whitney equation. The dissolution rate is the rate-limiting step at the point of absorption of the drug in solution. At the formulation stage, scientists understand how excipients, surface area, and particle size affect the dissolution behaviour of the drug and determine the rate-limiting behaviour mediated by dissolution. The drug is soluble in the body and depends on the type of drug, for example oral (pill, capsule and suspension) and intramuscular (tablet or suspension) training; The price limit determines which drug is used correctly. recommended for dosage form [35, 12].

b.Stability analysis of Drugs and Formulations as per ICH guidelines

According to ICH (International Conference on Harmonization) Q1A (R2) guidelines, the purpose of these guidelines is to test the drug under various stress conditions, such as longs. -period stability test, at least three stability tests at different times and sometimes intermediate tests for some properties. Tests include the effects of pH, temperature, humidity and photolysis under stress. Studies on pre-process stability are most important for controlling the chemical stability and degradation of solid and liquid materials. Physical inspection to check for clumping, liquefaction, discolouration, odour and gel formation during manufacture. After physical analysis, the degradation can be analyzed by mass spectrometry, HPLC or DSC, NMR, FTIR or other advanced analytical methods [36].

Photostability

Photostability criteria are fully addressed in the ICH-Q1B guidelines. The photostability of drugs and pharmaceutical products should be clearly understood for the evaluation of transport, packaging, labelling, negative drug analysis and new formulation strategies. The best simulation during drug development is usually 1.2 million lux, according to the Working Group of Experts of the European Pharmaceutical Industry Federation.

Solid State Stability

In terms of solid state, in addition to environmental factors such as temperature, light and humidity, packaging materials that come into contact with the drug are in the first place for drug stability. If not chosen correctly, additives can affect the different effects of the drug/drug. Lack of binding or moisture from excipients, pH and microclimate can affect the quality of the medicinal product. Therefore, excipients with low moisture content and low hygroscopicity are preferred for chemical degradation by hydrolysis[37].

Solution State Stability Studies

Liquid-state reactions are easier to detect than solid-state reactions. The method of checking for fluid incompatibilities is the same as for medical supplies. Research for suspension and resolution of the drug includes high nitrogen and oxygen ambient circulation, alkaline/acid pH conditions and the availability of chelation, mixtures and stabilizers conditions specified and which must be evaluated by FDA safety guidelines [38].

Drug-excipients Compatibility

The drug is closely related to one or more excipients in the dosage form of tablets; which will affect the stability of the drug. Therefore, understanding how drugs and excipients interact helps manufacturers select the best excipients. Binders, disintegrants, lubricants and fillers are usually found in tablets [39]. Interaction analysis of new drugs should consider adding two or more in each class. Preformulation researchers have a lot of control over the drug-to-excipient ratio used in these studies. Various techniques used to detect the composition of substances with materials include differential FT-IR spectroscopy, scanning calorimetry, fluorescence spectroscopy, differential thermal analysis, osmometry, diffuse reflection spectroscopy, high-pressure liquid chromatography, and radiolabeling [40]. Stability tests were performed at different temperatures and times, according to ICH guidelines.

Table 1: Stability Study

Type of Study	Conditions	Period
Long Term Testing	25±2°C/60±5%RH	12 Months
Accelerated Testing	40±2°C/75±5%RH	6 Months

For the design of sustainability, as a minimum, three groups should be examined and analyzed for their physicochemical and microbiological properties.

B. Therapeutic Considerations In Dosage Form Design [4,7]

a. **Route of Administration**

If the drug is intended for physical use and has to be administered orally tablets and/or capsules are usually prepared by the patient as they are easy to use and suitable for self-monitoring. In cases where the patient may forget the medicine or cannot take it orally if emergency medicine is used, injection records are also arranged.

b. **The nature of the illness**

Examples of the treatment of many other medical conditions, including abdominal pain, nausea, and vomiting, that affect formulation using tablets and skin for protection, suppositories and injections. for prophylaxis treatment.

c.The age and anticipated condition of the patient.

For infants and children under 5 years of age, liquid solutions are preferred over oral administration forms. When the patient coughs, vomits or simply revolts, questions may arise about how much medicine was swallowed and how much was coughed up. In this case, a shot is required. In childhood and even in old age, a person may have difficulty swallowing large amounts of information, especially uncoated tablets, which is why some medications are formulated as chewable tablets. Freshly sold tablets dissolve in the mouth in about 10 to 15 seconds; this allows patients to take the tablets but be able to swallow the liquid.

C. **Biopharmaceutical considerations [4,7]**

The route of administration varies with pharmacokinetic parameters such as absorption, distribution, metabolism and elimination (ADME). Drugs enter the body through a variety of routes, including oral, topical, parenteral, inhalation, rectal, nasal, ear and eye. The preferred route of administration is based on candidate pharmacokinetic profile (ADME) and disease type (disease).

VI. METHOD FOR CHARACTERIZATION OF SOLIDS

Solid dosage forms, such as tablets and capsules, are used to administer the majority of active pharmaceutical ingredients (API). Processing of the API with the excipients in dry form or granulating mass was necessary for the formulation of these dosage forms. This procedure entails milling, blending, and granulation which are impacted by the physicochemical characteristics of the solids. It affects the overall performance, processability, stability, and appearance of solid dosage forms. Along with this, the physicochemical status of the API and excipients used in formulations also impact on characteristics of the dosage form [41].

The pharmacological behaviour of a drug can also be altered by a little modification to its structure or particle size. Polymorphism of API is the most important factor to consider in the preparation of a pharmaceutical dosage form. These polymorphs exhibit different physicochemical properties that may also have an impact on the biopharmaceutical behaviour of drugs. Therefore, solid-state characterization is crucial to understand the physicochemical features of API and excipients to produce safe and effective dosage forms [42].

According to the United States of Pharmacopeia (USP), various characterization tests have been performed to determine physicochemical characteristics of drugs such as particle shape and size distribution, surface area, porosity, moisture or solvent content, solubility, pH, solid state stability, thermal properties, and crystal morphology. Additional solid-state characterization includes drug-excipient compatibility and nano-particles confirmation and encapsulation efficiency. The structural characterisation is achieved by applying infrared spectroscopy (FTIR), UV-Visible spectroscopy, nuclear magnetic resonance (NMR) and ^{1}H, ^{13}C mass spectroscopy[43].

A. Types of solid [44,45]

a. Crystalline and amorphous phases

Morphology, solubility, dissolution rate, and ultimately the properties of tablets are depends on the crystalline or amorphous nature of API as well as excipients. The crystalline materials are characterized by a regular, well-defined, and long-range periodicity arrangement of the constituent atoms, ions, or molecules with sharp melting points. Besides this, poor solubility is one of the leading challenges due to the crystalline nature of drugs in drug development. Therefore, most of the new APIs fail to show their potent pharmacological effect in the solid dosage form. Therefore, the design and delivery of crystalline API in solid dosage form has become a significant research area. particularly for those drugs which show poor solubility or permeability and are eventually related to poor bioavailability. The issue is most common in the case of oral formulations and approaches such as cocrystallization and salt formation, stabilized amorphous and amorphous forms, lipid formulations, nanocarriers, and other advanced formulation methods are used to enhance its solubility. Therefore, it's a need to study both molecular pharmaceutics as well as crystal growth and design crystalline of the new chemical moiety.

Amorphous materials show a lack of long-range order in their molecular arrangement. They do not have sharp melting points. Rapid cooling of a melt below its melting point where the structural characteristics of the liquid are maintained but the viscosity is much higher is the most common method to obtain the amorphous solid. This form of solid chemical moiety is considered a supercooled liquid. Amorphous solids possess higher free energy than their crystalline complements. Therefore, amorphous entities have good solubilities, dissolution rates, and chemical reactivities with bioavailability as compared to crystalline forms.

b. Polymorphic forms

Polymorphism is the ability of a compound exists in more than one crystalline form. The most critical aspect of the pharmaceutical dosage form is to ensure the optimal physical form of API because it can exist in polymorphs. Polymorphs of a given drug are chemically identical but, different in structural and physical properties including dissolution rates, melting point, density, hardness, and crystal shape which affect its biopharmaceutical properties. It can be prepared by crystallizing the drug in different solvents under diverse conditions. In addition to polymorphs, the term molecular adduct nowadays is more famous in association with solvents (solvates). Molecules that form solids at room temperature are called co-crystals or with salts called ionic co-crystals. It is important to say that all these crystal forms are polymorphic. The existence of polymorphs can be determined by optical crystallography, X-ray diffraction (XRD), and differential scanning calorimetry (DSC).

A drug can exist in different polymorphic forms but only one of them is thermodynamically stable at a given temperature and pressure, while the others are metastable. The metastable polymorphs have higher free energies, apparent solubilities, and dissolution rates than their stable counterparts.

Therefore, the choice of the polymorphic form determines the physical and chemical stability, compressibility, and bioavailability of the drug. For example, chloramphenicol palmitate is available in three polymorphic forms A, B, and C. From these, the B form shows the best bioavailability and the A form is biologically inactive.

c. Solvates and hydrate

The crystalline drug can either be a polymorph or molecular adduct. Solvates are molecular adduct that contains solvent molecules within the crystal in either stoichiometric or nonstoichiometric proportions. If a water molecule is incorporated into a crystal then the solvate is called a hydrate. The different crystalline forms of solvates are called pseudo polymorphs. The incorporation of the solvent molecule in the crystal lattice results in different physical and pharmaceutical, and biopharmaceutical properties. Differences in solubility of the hydrated and anhydrous phases may result in a difference in bioavailability. On another hand, organic (nonaqueous) solvates have greater aqueous solubility than hydrates.

B. Molecular level properties

These properties are defined as those that can be measured at a molecular level. Molecular properties can be determined at the earliest stage of drug development as well as in the formulation of the dosage form by using the minimum amount of material. It includes properties such as molecular interactions and molecular bonds that can be characterized by spectroscopic techniques. These studies provide information regarding crystallinity, amorphism, polymorphic form, and solvates [46].

a. Ultraviolet (UV) /visible spectroscopy

UV–visible spectroscopy is a primary tool for functional characterization of drugs and excipients used in solid oral dosage. Although this technique is widely used for the analysis of solutions, it can be adapted for the characterization of solids [47].

The performance of UV-visible spectroscopy is based on diffuse reflectance techniques and it measures the fraction of radiation that penetrates the molecule and then emerges. The instrumentation of UV-spectroscopy consists of a light source, a monochromator, an integrating sphere, and a detector. The instrumentation and dilution of the sample can be optimized to minimize the undesirable specular reflectance. Several diffuse reflectance theories have been proposed for UV-spectroscopic characterization of drugs but the Kubelka–Munk theory is the most generally accepted. According to this theory, diffuse reflectance can be expressed by equation (1).

$$\frac{K}{S} = \frac{(1-R_\infty)}{2R_\infty} \qquad (1)$$

Where,

K and S = The molar absorption and the scattering coefficients, respectively,

R_∞ = The reflectivity of an infinitely thick sample.

UV visible spectroscopy has been used to evaluate solid–solid interactions in formulations, the effect of formulation composition and processing variables and the physicochemical nature of the formulation in the solid state.

b. Vibrational spectroscopy[48,49]

infrared (IR) and Raman spectroscopy techniques are widely used for the characterization of pharmaceutical solids. The IR region in the electromagnetic spectrum can be divided into three regions; the near-IR (4000–14,000 cm^{-1}), mid-IR (400–4000 cm^{-1}), and far-IR (100–400 cm^{-1}). Generally, near and mid-IR ranges are used for analysis. Five forms of tranilast (three polymorphs and two solvates) were characterized by using IR and Raman spectroscopes. Polar groups such as C=O and NH are likely to be IR active, and bonds such as C=C and SS are more likely to be Raman active. These techniques are also used for the analysis of drugs with different degrees of crystallinity. Spectrometers usually consist of an electromagnetic source, a sample chamber, and a detector. For IR analysis, sample preparation can be carried out using different methods including

(i) Alkali halide pellet method: In this method, the analyte is pulverized with either KBr or KCl and compressed into discs;

(ii) Mull preparation: In this method, the analyte is mixed with ∼1 mg of mineral oil;

(iii) Use of a neat powdered sample in diffuse reflectance Fourier transform infrared spectroscopic technique (FTIR).

The FTIR method uses all frequencies from the source and provides a signal-to-noise ratio. The infrared spectra can be obtained in the solid state using diffuse reflectance, and compilation of group vibrational frequencies which provide an observed band. When a sample is irradiated, absorption of IR energy results in transitions between molecular vibrational and rotational energy levels. The molecular vibrations depend on the structure of the analyte and thus it can be used for the identification of functional groups of molecules.

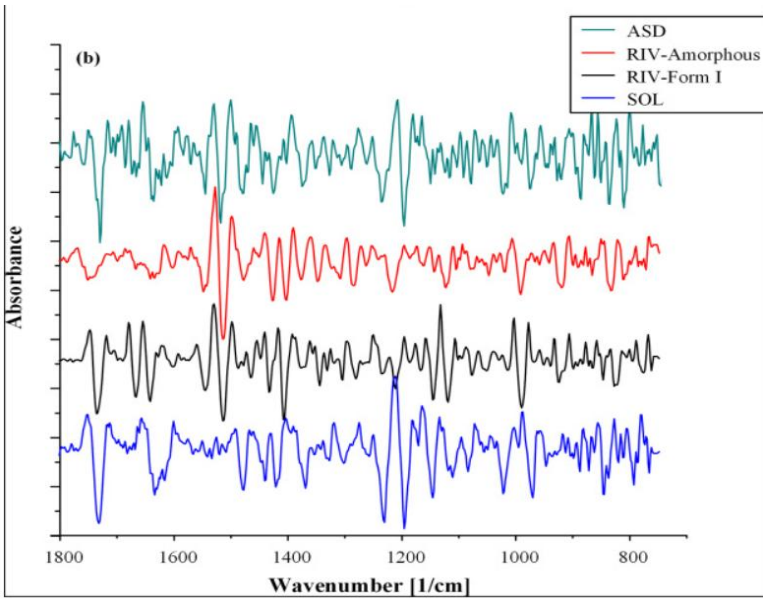


Figure No. 1: Comparative FTIR spectra of RIV of crystalline and the amorphous, as well as its matrix (SOL) and its amorphous solid dispersion (ASDs)

Afroditi et al. determine the physical state of Ritonavir (RIV) of crystalline and the amorphous RIV, as well as its matrix (SOL) and its amorphous solid dispersion (ASDs) by the FTIR spectra. Crystalline RIV showed several characteristic peaks but the ATR-FTIR spectrum obtained by amorphous RIV showed several significantly different peaks as compared to crystalline RIV. Concerning the amorphous RIV, the peak corresponding to the NH stretching of the amide group is significantly broadened and shifted in lower wavenumbers (from 3350 to 3313 cm^{-1}, respectively), while the peak corresponding to the -C=O stretching from the ester group of the RIV shows a shift from 1733 to 1745 cm^{-1}. In addition, there is a significant change in other groups. The ATR-FTIR spectrum of SOL shows two characteristic peaks at 1635 and 1736 cm^{-1}, attributed to the -C=O stretching of the polyvinyl acetate group and the stretching of the -C(O)N or the tertiary amide of the polyvinyl caprolactam group, respectively. Finally, in the case of RIV-SOL ASDs the obtained spectrum showed that the peak corresponding to the secondary amide (-NH) stretching vibration of the RIV is now completely missing, probably due to the formation of significant RIV-copolymer hydrogen bonding [50].

c. Solid-state nuclear magnetic resonance

The chemical environment of each atom in the API was obtained by nuclear magnetic resonance (NMR). It has been extensively used to analyze molecules in the solution phase. However, its use for the study of polymorphs or solvates is now being widely used for the qualitative and quantitative characterization of solids or in the amorphous state.

It showed various interactions such as the magnetic moment of the nucleus and the external magnetic field, magnetic coupling of two nuclei through space, magnetic shielding by surrounding electrons called chemical shift, andspin–spin couplings. In a solid sample, the anisotropy reflects the chemical shift which is dependent on chemically identical nuclei on their spatial arrangement with respect to applied field. High-power proton decoupling is also used simultaneously to eliminate additional line-broadening effects due to ^{13}C-^{1}H dipolar interactions. Generally, it is observed that the NMR spectra of polymorphs or pseudo polymorphs are nonequivalent. This effect arises due to differing crystal structures of the various types that can bother the chemical environment of each nucleus under investigation. In considering the NMR spectra of polymorphs, certain resonance bands are observed at identical chemical shifts, while others are significantly shifted. Solid-state NMR spectra can be used to deduce the nature of polymorphic variations [51,52].

d. X-ray powder diffractometry [53,54]

X-ray powder diffractometry (XRPD) is a potential technique for the characterization of the different crystalline states of a solid including hydrates and polymorphs. Every crystalline solid form has its unique X-ray pattern which can use for its identification. In a powder mixture, each crystalline phase produces its independent X-ray pattern with respect to other constituents in the mixture. Thus, XRPD allows the identification of API in the presence of excipients. It is also used to identification of more than one API in formulations.

An X-ray diffractometer exposes the sample to electromagnetic radiation positioned between the ultraviolet and γ - rays in the electromagnetic spectrum. When the X-rays are incident on the crystalline solids, diffraction occurs and the X-rays are scattered in all directions. A peak in the X-ray pattern is observed when these scattered beams are in phase and reinforce each other, and this is quantified by Bragg's law as shown in equation 2.

$$n\lambda = 2d \sin \theta \qquad (2)$$

Where,
d is the distance between the planes in the crystal (angstrom units)
n is the order of reflection.

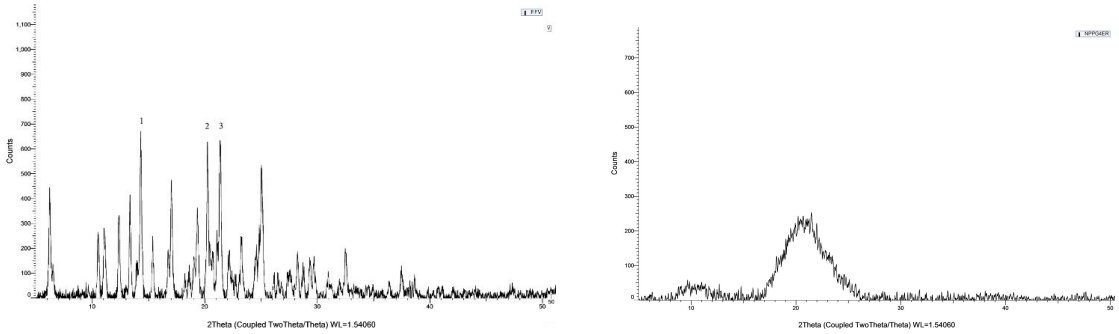


Figure No. 2: X-ray diffractogram of crystalline EFV and its formulation.

Kharwade et al. explored the transformations and changes in crystallinity of Efavirenz (EFV) by the X-ray diffraction pattern after being loaded into PAMAM G4 dendrimers as shown in **Fig. 2.**
The result showed that the diffractogram of pure EFV showed sharp and intense crystalline peaks at 2θ of 11.04° (peak 1),21.77(peak 2), and 23.77° (peak 3) with % crystallinity 78.5%. It confirms that the unprocessed pure EFV was crystalline. However, all of the mentioned sharp and intense peaks of pure EFV were changed to broad peaks with mild intensity after entrapment into PAMAM G4. The absence of sharp and extreme peaks of pure crystalline EFV was indicating the complete amorphization of the free EFV.

e. Differential Scanning Calorimetry (DSC)

DSC is widely used for the characterization of API, including melting point, crystallization, desolvation, and glass transitions. The DSC thermogram of the drug, compensated power of the drug and its heat flux were measured. In compensated power DSC thermogram, the sample and the reference are kept at the same temperature and in heat flux DSC the temperature differential between the sample and the reference is monitored [55].
In modulated DSC, controlled temperature modulation is overlaid on the conventional linear heating or cooling rate to produce a continuously changing nonlinear sample temperature. This helps in separating overlapping thermal events such as enthalpic recovery and glass transition. In pressure DSC the sample is subjected to different pressures and thus used to separate overlapping endotherms [56,57].

f. Particle morphology

The solid particle morphology and powder properties offer the application in the performance of solid particles in dosage form. Optical and electron microscopy methods are used to study the purest API consisting of small aggregated microcrystals. These methods are used to determine the nature of aggregated species, shape and average particle size.
If the stability of a drug is related to the degree of crystallinity, therefore it is important to identify the crystalline form of the drug and identify the most stable one. Optical microscopy can be used to determine the crystalline form of the drug (polymorphs) either enantiotropic or monotropic. The crystal habit of the solid can also be determined by scanning electron microscopy (SEM) examination. In SEM characterization the surface is scanned by a focused electron beam and the intensity of the secondary electron is monitored. It gives an excellent picture of the solid particle surface as shown in **Fig. 3.** It showed the SEM photograph of Tofacitinib citrate uncoated pellets which are homogenous and quite rough [58,59].

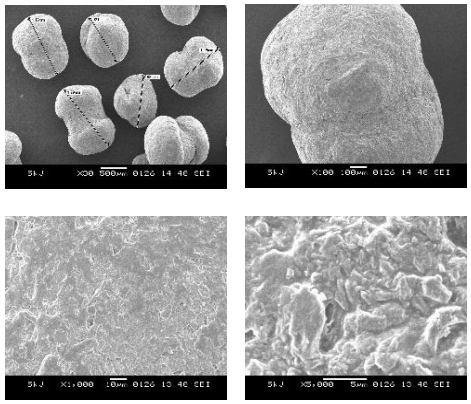


Figure 3: SEM image of Tofacitinib citrate uncoated pellets which are homogenous and quite rough.

g. Bulk characterization of solid particles[60,61]

These include all the bulk properties of drugs including size distribution, flow property, compressibility, dispersibility, porosity, and density. These bulk properties can strongly influence various processes during manufacturing. The surface area per unit weight or volume can influence the dissolution, chemical reactivity, and bioavailability of the API. In the case of excipients, flowability is a major factor that is influenced by the surface area and surface morphology for example, grades of lactose and avicel with larger size of particles have a smaller surface area and better flow properties. Surface area can be determined by the air permeability method or the Adsorption method. The Kozeny–Carman equation can be used to determine the surface area using equation (3):

$$V = \frac{A}{nSw^2} \cdot \frac{\Delta Pt}{Kl} \cdot \frac{\varepsilon^3}{(1-\varepsilon)^2} \qquad (3)$$

Where,

A = the cross-sectional area of the plug,

K = a constant,

ε = the porosity,

V = volume of air flowing through the capillary of length l in t seconds, and

η = the viscosity of air

The porosity of a solid is defined as the ratio of the void volume to the bulk volume (total sample volume) and is frequently represented in percentage porosity. Porosity influences the dissolution of both powders and tablets. It is measured by mercury porosimetry. In this method, the sample is placed in a sample holder with a tapered calibrated stem. The sample holder and stem are then filled with mercury and pressure is applied to force the mercury into the pores. The amount of mercury that penetrates the sample can be determined from the decrease in volume in the calibrated stem, which is indicative of sample porosity.

Material transfer, blending, and flow can be significantly influenced by the density of the solid particle. There are three types of densities such as true density, granule density and bulk density. True density is the density of the solid material itself exclusive of voids and intraparticle pores and measured by gas pycnometer and liquid displacement. Granule density is the weight of the particles per unit volume as determined by the mercury displacement method. The volume occupied by a powder is referred to as the bulk volume including void spaces. The bulk density depends on the size, shape, porosity, and cohesiveness of powders. For smaller particles (<10 μm), the flow may be restricted because the cohesive forces are equal to the gravitational forces. Flat particles such as needles and flakes tend to pack loosely to give powders with high porosity. Poor flow may also arise due to high moisture content and surface roughness [62,63].

These powder characteristics such as the density, particle size distribution, and shape can significantly influence the flow of powders or granules. It can be measured by the angle of repose and compressibility. Generally, values lower than 15% indicate good flow, whereas values above 35% indicate poor flowability [58].

VII. PHARMACEUTICAL INGREDIENTS AND EXCIPIENTS

Pharmaceutical excipients are the approved ingredients that are considered “inactive” and generally recognized as safe (GRAS) for human consumption. Excipients are used to produce bulk dosage forms, ensure accuracy and precision, homogenous blending, mask bitter taste, improve flowability, bioavailability, patient compliance, and stability and reduce the toxicity of API [64,65]. Excipients are classified depending on the (1) origin of the source such as plant, animal, mineral, and synthetic-based, (2) The functional role they play in the formulation such as binders, diluents, disintegrants, bulking agents, glidants, lubricants, colouring agents, preservatives, etc. and (3) chemical constituents (functional group) present in the excipients such as alcohols, acids, esters, carbohydrates, glycerides, halogenated derivatives, mercury salts, etc.

Application of pharmaceutical aids [66,67]:

- ➢ It helps to mask the unpleasant odour, taste, colour etc.
- ➢ It reproduces a safe, efficient, and convenient manner of drug delivery.
- ➢ It increases the stability and shelf life of the drugs.
- ➢ It protects the drug as well as dosage form from chemical and microbial degradation, it includes antibacterial agents, preservatives and antioxidants.

➢ It helps to design the different forms of shape and size with maintaining the uniformity of the dosage form.

➢ It improves the patient's compliance and helps in manufacturing and designing the attractive dosage form.

Ideal characteristics of the pharmaceutical aids

➢ It does not change the chemical nature of the drug.

➢ It does not cause any toxic effects.

➢ It masks the unpleasant colour, odour, and taste.

➢ It does not cause any allergic reactions during administration.

➢ It improves patient compliance.

➢ It prevents microbial contamination of pharmaceutical products and improves its shelf life.

➢ It can be low-cost and easily available [68,69,70].

A. Flavouring pharmaceuticals

Flavouring pharmaceuticals enhances the mixed sensation of taste, smell, touch, sight, and sound. According to USP, a flavouring agent is a single chemical entity or a blend of chemicals of synthetic or natural origin that can produce a taste or fragrance when consumed orally or smelled [71,72].

Flavouring agents can be classified into two categories

A. Natural flavouring agents: Citrus fruit (lemon, orange), spice (cinnamon, peppermint, ginger, onion), fruits (apple, banana).
B. Synthetic flavouring agents: Alcohols, esters, ketones, terpenoids [73,74].

It improves flavours as well as tastes of different dosages. It also helps to improve the patient compliance or palatability of pharmaceutical dosage forms. The taste buds are sensitive to several basic tastes i.e. sweet, sour, bitter, salt and possibly, metallic and alkaline, but their response is altered by some other factors such as temperature, physical nature and some special characteristics like astringency and pungency of the flavoured material. The acceptance of flavour also depends upon the drug as well as age as shown in **Table 2.** Generally, children like fruit-flavoured, while adults prefer mint or wine flavours. Response to the flavour may be changed according to health and disease conditions. Flavour acceptance for a long time may become objectionable if the treatment is prolonged. Flavours are also selected based on the taste of the drug as shown in **Table 3**.

Table 2: Preferable flavours according to the category of drug [35].

Sr. No	Drug	Preferred flavour
1	Antibiotics	Cherry, maple, pineapple, orange, raspberry, banana-vanilla, butterscotch, coconut-custard, fruit-cinnamon, strawberry, vanilla
2	Antihistamines	Apricot, cherry, cinnamon, grape, honey, lime, peach-orange, peach rum, raspberry, wild cherry
3	Barbiturates	Banana-pineapple, banana-vanilla, cinnamon-peppermint, orange, peach-orange, grenadine-strawberry
4	Decongestants and expectorants	Anise, apricot, butterscotch, cherry, coconut-custard, custard-mint strawberry, grenadine-peach, strawberry-lemon, gooseberry, orange lemon, coriander, pineapple, raspberry.
5	Electrolyte solution	Cherry, grape, lemon-lime, raspberry, wild cherry syrup, grenadine strawberry, lime, port wine, cherry wine, wild-strawberry.

Table 3: Preferable flavours according to the taste of the drug [48].

Sr. No.	Taste	Masking flavour
1	Salt	Butterscotch, maple
2	Bitter	Wild cherry, walnut, chocolate-mint, liquorice
3	Acid	Citrus
4	Sweet	Fruit, berry, vanilla

B. Sweetening Pharmaceuticals[70]

Sweetening pharmaceuticals or sweeteners are mainly used for masking the undesirable or bitter taste of any drug formulation and increasing the patient acceptance of pharmaceutical dosages form. In pediatric dosages form it is widely used because children prefer the sweet taste.

Sugar is the most widely used sweetening agent. Due to its viscosity-enhancing nature, it is also used as a preservative in syrup.
sweetening agents are divided into two categories:
A. Natural sweetening agent-Glucose, fructose, sucrose, dextrose, sorbitol.
B. Artificial colouring agent-Sucralose, aspartame, saccharin.

a. Saccharin

According to the Academy of Nutrition and Dietetics, saccharin is considered a synthetic or non-nutritive sweetener. It does not have a carbohydrate value and hence produces minimal or no energy. Daily intake of saccharin has been recommended to be 0.2–0.9 mg/kg for the adult population, while that number is 3 times in diabetics.
Saccharin is an o -toluene sulfonamide that causes "sulfa" type of hypersensitivity reaction in children including wheezing, urticaria, pruritis, nausea, vomiting, diarrhoea, tachycardia, headache, diuresis and sensory neuropathy. Therefore, it induces insomnia, irritability, and hypertonicity in children. Therefore, American Medical Association recommends limited intake of saccharin in infants and pregnant women.

b. Aspartame

Similar to saccharin, aspartame is also a non-nutritive sweetener with no carbohydrate value but is recommended as safe by the FDA. Therefore, it is increasingly used in sugar-free and chewable formulations. It is an aspartic acid and phenylalanine derivative. It significantly increases the serum levels of phenylalanine hence, the content of phenylalanine should be clearly mentioned in the drug product label and its consumption should be closely monitored in children with autosomal recessive phenylketonuria. Daily intake of aspartame can be 5 and 10 mg/kg for children who do not have any dietary restrictions. Several adverse effects have been reported by aspartame such as headaches, panic disorders, mood changes, and seizures due to high doses (>30 mg/kg/day) or long-term ingestion. However, none of the adverse effects could be verified by a single randomized double-blind clinical trial. Aspartame can be replaced by some natural sweetening agents such as stevia, date sugar, maple sugar, maple syrup molasses, and agave nectar in pediatric formulations [71].

c. Sucralose

Sucralose is a non-nutritive chlorine derivative of sucrose and 600 times more sweeter. It is recommended as safe by the FDA in pediatric formulations, food and beverages. It is slowly absorbed from the gastrointestinal tract and has a greater impact on the gut bacteria. Recent data suggest a link between increased intake of saccharin and sucralose to the prevalence of irritable bowel syndrome in children and the adult population.

d. Sorbitol

Sorbitol is a hexahydric polyol and a nutritive sweetener that produces sweetness with less energy intake (2.6 vs 4 kcal/g of energy for sucrose). Therefore, it is labelled as "sugar-free" by the Academy of Nutrition and Dietetics. Ingestion of sorbitol at doses of 0.5 g/kg body weight has caused gastrointestinal distress, bloating, diarrhoea, and abdominal pain in children. Because it is metabolized to pyruvic acid and lactic acid and produces a laxative effect in the intestine which shortens the transit time and decreases energy value. Newborns and infants have immature and developing epithelial barriers and drug-metabolizing enzymes which limited their absorption. However. Its absorption has been enhanced in the presence of glucose and fatty acids. Accumulation of sorbitol in the body of newborns and infants has been implicated in diabetic-like symptoms. Therefore, pediatric formulations containing sorbitol have labelling requirements that state the content of sorbitol in the drug product.

C. Preservative [72,73]

In pharmaceutical formulations, most of the natural ingredients can promote microbial growth and promote unwanted contamination. To prevent this, antimicrobial agents or preservatives need to be added to the formulation.
Preservatives protect the product from microbial degradation but should not compromise product performance
examples are methyl paraben, ethyl paraben, propylparaben, phenol, and benzoic acid.
Preservatives have the following ideal properties:

- It exerts a wide spectrum of antimicrobial activity against all possible micro-organisms at low concentration
- It maintains activity throughout product manufacture, shelf life and usage
- It should be non-toxic and compatible with other constituents of the preparation
- It should not compromise the quality or performance of the product, pack or delivery system.
- It should be safe and tolerant of the product.

There are two main types of drug preservatives.

a. Antioxidants
b. Antimicrobial agent

a. Antioxidants [74]

At low concentrations, it prevents or delays the oxidation of the pharmaceutical product. They are self-reducing agents that oxidize themselves and prevent oxidation of the components that are sensitive to oxygen. Antioxidants act by [75]several mechanisms such as hydrogen atom transfer, single electron transfer, or chelate transition of metal. Antioxidant capacity is a measure of the amount of a certain free radical captured by an antioxidant. Some example of antioxidants includes vitamin C, vitamin E, BHA (butylated hydroxy anisole), BHT (Butylatedhydroxytoulene), propyl gallate etc. They make an excellent guard against deterioration which considers two main factors oxygen and sunlight.

b. Antimicrobial agents [70,75]

The antimicrobial agents act by inhibiting microbial cell walls or cell membrane growth. Antimicrobial agents are of two types, antifungal preservative and antibacterial preservative.

The most common antifungal preservatives are benzoic and ascorbic acids and their salts, as well as phenols (parabens), such as methyl, ethyl, propyl, and butyl p-hydroxybenzoate. On the other hand, compounds such as quaternary ammonium salts, alcohols, phenols, and mercurials are antibacterial preservatives.

Sodium Benzoate: Sodium Benzoate is primarily used as an antimicrobial preservative in cosmetics, foods, and other pharmaceutical formulations. It is used as a bacteriostatic agent with fungistatic activity in many drug formulations

Alcohols: Chorobutanol is one of the most widely used alcohols which acts as a bacteriostatic agent and exhibits preservative properties.

Mercurial compounds: It is used as bacterial preservative in drug preparation and also used in topical antiseptics.

Benzyl alcohol: Peptide and protein products are commonly preserved with phenol and benzyl alcohol, while vaccines are preserved with phenoxyethanol.

Parabens: Preservatives commonly used in cosmetics include parabens. Propylparaben and methylparaben are widely used in medicines.

All the preservatives must undergo PET (Preservative Efficacy Testing). These tests involve a product with a defined number of colony-forming units of various microorganisms including bacteria, fungi, etc. The results are monitored for 28 days and if the compound passes these tests, then it proceeds for further tests and is used in different dosage forms.

D. Colouring agents [76,77]

colouring agents are mainly used to enhance the distinctive appearance of pharmaceutical dosage forms. These are cosmetics for pharmaceutical preparations because they enhance the aesthetic appearance and elegance of dosage forms. Colouring agents are needful pediatric dosage forms including tablets (either the core itself or the coating), capsule shell or coated beads, topical creams, toothpaste, ointments, and topical gel. It also helps to identify the similar-looking product of the same manufacturer or similar product of a different manufacturer [78].

The ideal properties of colouring agents are as follows

- It should be nontoxic and have no physiological activity.
- It should be free from harmful impurities
- Its colouring power will be reliable and the assay will be practicable and easier.
- Its tinctorial ability should be high so that used only in small quantities.
- It should be stable at light and tropical temperatures on storage
- It should not affected by oxidizing or reducing agents and pH changes.
- It should be compatible with medicaments and not interfere with them.
- It readily gets solubilised in water but in most cases, oil-solublity and spirit-solublity are necessary.
- Free from objectionable taste and odour.

Colouring agents are Classified as follows:

a. Organic dyes and their lakes
b. Inorganic or mineral colours
c. Natural colours or vegetable and animal colours

a. Organic dyes and their lakes

Dyes are synthetic chemical compounds that exhibit their tinctorial strength by dissolving in solvents such as propylene glycol and glycerin. They are available in a wider range of shades with higher colouring power than natural pigments at a cheaper cost. The tinctorial strength of a dye is directly proportional to its pure dye content. The dye solution should be prepared in stainless steel or glass-lined tanks with moderate mixing. This process minimises the incompatibility with the container. Examples of dyes are tartrazine and erythrosine.

Lakes

Lakes are the calcium salt of FDC water-soluble dyes extended on a substratum of alumina. They are not soluble therefore they prepare dispersion. Its particle size is very critical to its colouring capacity. Generally, the tinctorial strength of lakes is increased by smaller particle size because it increases surface area for reflating light.
The insoluble certified lakes have several advantages

- They are insoluble enabling the drying stages to be performed more quickly.
- Mottling is reduced because the opacity of the system minimizes the defect of the tablet.
- Over-colouring is not a problem because the system is opaque and only one shade of color will result.
- Full-colour development can be achieved with fewer application states.
- Raw material costs are also improved.
- FDC lakes are available in six basic colours: One yellow, One orange, two reds (pink-red and orange-red), and two blues (green-blue and royal blue).

b. Inorganic colours or mineral colours

Inorganic colours have good stability towards light and opacifying capacity. These are more useful in multinational companies in standardised formulae but the range of colours is minimal. Until the discovery of coal tar dyes, mineral pigments were often used to colour foods and drugs but due to their toxic effects, they are readily displaced by available dyes. Titanium dioxide is used to colour and opacify hard gelatin capsules.

c. Natural colours or vegetable and animal colours

This is a chemically and physically diverse group of materials. Some of these colours are the products of chemical synthesis rather than extraction from a natural source, for example, β-carotene of commerce is of synthetic origin. Generally, Natural colours are not stable to light and temperature as compared to dyes and lakes. Few colours are medicinally acceptable after dilution such as caramel, formerly called burnt sugar, cochineal (a dried insect), and carmine (aluminium lake of the colouring matter of cochineal). Other includes riboflavin and anthocyanins, paprika oleoresin, beetroot red, annatto, and curcumin. The disadvantage of these colours includes variation in colouring power and difficulty in standardisation. It has very low tinctorial power and expensive than coaltar colours [79].

VIII. CONCLUSION

Dosage form design and development involve the combination of various components and optimization processes. Excipients also play an important role in the quality of dosage form. Because any type of drug-excipient interaction or incompatibility affects the stability as well as the therapeutic efficacy of the drug. While this chapter also provides a brief introduction to some of the widely used techniques for the physicochemical characterization of pharmaceuticals. It is important to have a comprehensive understanding of the physicochemical characteristics of API earlier during product development to prevent future problems associated with its stability and bioavailability.

REFERENCES

[1] https://www.ncbi.nlm.nih.gov/books/NBK562239/

[2] Stewart KD, Johnston JA, Matza LS, Curtis SE, Havel HA, Sweetana SA, Gelhorn HL. Preference for pharmaceutical formulation and treatment process attributes. Patient Prefer Adherence. 2016;10:1385-99.

[3] Chapter 4 • Pharmaceutical And Formulation Considerations Pg n 90-142 Drug Dosage Form and Drug Delivery System Design

[4] Ansel's pharmaceutical dosage forms and drug delivery systems , tenth edition

[5] Allen LV, Popovich NG, Ansel HC. Pharmaceutical Dosage Form and Drug Delivery System. 9th ed. New Delhi: Lippincott Williams and Wilkins; 2011.

[6] R Ananthakumar. Types of dosage forms and their definitions. School of Pharmaceutical Sciences Vels Institute of Science, Technology and Advanced Studies (VISTAS)

[7] Dr. AthmarDhahirHabeeb.Presentation. Dosage Form Design Lecture 5. Industrial pharmacy and drug delivery

[8] Kamlesh.Chapter 1, Dosage Form Design 1-2 http://www.bspublications.net/downloads/05805bfacb3933_Ch-1_Pharmaceutical%20Dosage%20form_Kamlesh.pdf.

[9] B. Prathap, K. Ananth, A. Arthi, A. Arunagiri, R. Balaji, Quality Control Test for Pharmaceutical Dosage Forms: A Review, 1 (2021) 227–233.

[10] Aulton ME. Pharmaceutics: The Design and Manufacture of Medicine. 4th ed. Edinburgh: Churchill Livingstone; 2013.

[11] Sandip Mohan Honmane , Yuvraj Dilip Dange , Riyaz Ali M. Osmani , Dhanraj Raghunath Jadge. General considerations of design and development of dosage forms: Preformulation review. Asian Journal of Pharmaceutics • Jul-Sep 2017 (Suppl) • 11 (3) | S479

[12] Desu PK, Vaishnavi G, Divya K, Lakshmi U. An overview on preformulation studies. Indo American Journal of Pharmaceutical Sciences. 2015;**2**(10):1399-1407
[13] Bandopadhyay S, Bandyopadhyay N, Deb PK, Singh C, Tekade RK. Preformulation studies of drug substances, protein, and peptides: Role in drug discovery and pharmaceutical product development. Dosage Form Design Considerations. 2018;**I**:401-433
[14] Ledeţi A, Vlase G, Vlase T, Bercean V, Murariu MS, Ledeţi I, et al. Solid-state preformulation studies of amiodaronehydrochloride. Journal of Thermal Analysis and Calorimetry. 2016;**126**(1):181-187
[15] Huang LF, Tong WQ. Impact of solid-state properties on developability assessment of drug candidates. Advanced Drug Delivery Reviews. 2004;**56**(3):321-334
[16] Baldelli A, Power RM, Miles REH, Reid JP, Vehring R. Effect of crystallization kinetics on the properties of spray dried microparticles. Aerosol Science and Technology. 2016;**50**(7):693-704
[17] Harahap U, Marianne M, Yuandani Y, Laila L. Preformulation study of Pugun Tano (Curanga fel-terrae [lour.] Merr) Ethanolic extract granule mass in capsule as Hepatoprotective drug. Open access Maced. Journal of Medical Sciences. 2019;**7**(22):3729-3732
[18] Akseli I, Hilden J, Katz JM, Kelly RC, Kramer TT, Mao C, et al. Reproducibility of the measurement of bulk/tapped density of pharmaceutical powders between pharmaceutical laboratories. Journal of Pharmaceutical Sciences. 2019;**108**(3):1081-1084
[19] Antonio A, Júnior S, Carbinatto FM, Castro O. Preformulation studies of Gymnema sylvestre extract powder formulation for hard gelatin capsules. Revista de Ciências Farmacêuticas Básicae Aplicada. 2011;**32**(2):175 180
[20] Moravkar KK, Korde SD, Bhairav BA, Shinde SB, Kakulade Sv, Chalikwar SS. Traditional and advanced flow characterization techniques: A platform review for development of solid dosage form. Indian Journal of Pharmaceutical Sciences. 2020;**82**(6):945-957
[21] Szunyogh T, Ambrus R, Szabóné RP. Importance of particle size decrease in the preformulation. Acta Pharmaceutica Hungarica. 2011;**81**(1):29-36
[22] Quodbach J, Kleinebudde P. A new apparatus for real-time assessment of the particle size distribution of disintegrating tablets. Journal of Pharmaceutical Sciences. 2014;**103**(11):3657-3665
[23] Nachajski MJ, Bazela A, Zarzycka M, Broszczyk A, Kołba A, Kołodziejczyk MK. Effect of API on powder flowability, direct compression and properties of orally disintegrating tablets: A preformulation study. Indian Journal of Pharmaceutical Sciences. 2019;**81**(3):489-495
[24] Gao Z, Rohani S, Gong J, Wang J. Recent developments in the crystallization process: Toward the pharmaceutical industry. Engineering. 2017;**3**(3):343-353
[25] Burger A, Lettenbichler A. Polymorphism and preformulation studies of lifibrol. European Journal of Pharmaceutics and Biopharmaceutics. 2000;**49**(1):65-72
[26] Patel C, Suthar D, Patel H, Movaliya V, Parejiya P. Preformulation study of glimepiride: An insight for formulation and development of parenteral formulation. Journal of Pharmaceutical Research International. 2022;**34**(15b):38-49
[27] Kesharwani R, Ansari MS, Patel DK. Novel technology used in the preformulation study: A review. Journal of Drug Delivery and Therapeutics. 2017;**7**(4):20-33
[28] Bashir Alsirawan MHD, Paradkar A. Impact of the polymorphic form of drugs/NCEs on Preformulation and formulation development. In: Bachhav Y, editor. Innovative Dosage Forms: Design and Development at Early Stage. Wiley. 2019:1-47
[29] Acharya PC, Shetty S, Fernandes C, Suares D, Maheshwari R, Tekade RK. Preformulation in drug research and pharmaceutical product development. Dosage Form Design Considerations. 2018;**I**:1-55
[30] Makoni PA, Ranchhod J, WaKasongo K, Khamanga SM, Walker RB.The use of quantitative analysis and Hansen solubility parameter predictions for the selection of excipients for lipid nanocarriers to be loaded with water soluble and insoluble compounds. Saudi Pharmaceutical Journal. 2020;**28**(3):308-315
[31] Di L, Kerns EH. Drug-Like Properties. Amsterdam: Elsevier; 2016. DOI: 10.1016/ B978-0-12-801076-1.00023-X
[32] Dudzinski J, Lachman L, Shami E, Tingstad J. Preformulation studies I: Molindone hydrochloride. Journal of Pharmaceutical Sciences. 1973;**62**(4):622-624.
[33] Thumma S, Majumdar S, ElSohly MA, Gul W, Repka MA. Preformulation studies of a prodrug of Delta9-tetrahydrocannabinol. AAPS PharmSciTech. 2008;**9**(3):982-990
[34] Chikezie Ayogu P, Ezugwu MI, Ifeanyi EF. Principle of common-ion effect and its application in chemistry: A review. Journal of Chemistry Letters. 2020;**1**(2):77-83

[35] Kumar P, Desu PK, Vaishnavi G, Divya K, Lakshmi U, Kumar DP. An overview on preformulation studies. Indo American Journal of Pharmacetical Sciences. 2015;**2**(10):1399-1407 .
[36] Jones TM. Preformulation studies. In: Tovey GD, editor. Pharmaceutical Formulation: The Science and Technology of Dosage Forms. Croydon, UK: The Royal Society of Chemistry; 2018. p. 1-19.
[37] Majee SB, Biswas GR. Computational methods in preformulation study for pharmaceutical solid dosage forms of therapeutic proteins. Physical Sciences Reviews. 2019;**2**(6):19-19.
[38] Chaudhary P. Preformulation studies for ayurveda drugs: A review. International Research Journal of Pharmacy. 2019;**10**(3):19.
[39] Egart M, Janković B, Srčič S. Application of instrumented nanoindentation in preformulation studies of pharmaceutical active ingredients and excipients. Acta Pharmaceutica. 2016;**66**(3):303-330
[40] Verma G, Mishra MK. Pharmaceutical Preformulation studies in formulation and development of new dosage form: A review. International Journal of Pharma Research & Review. 2016;**5**(10):12-20 .
[41] D. Horter, J.B. Dressman, Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract, Adv. Drug Deliv. Rev. **25** (1997) 3–14. https://doi.org/10.1016/S0169-409X(96)00487-5.
[42] J. Conceicao, M. Estanqueiro, M. H. Amaral, J. P. Silva, J.M. Sousa Lobo, Technological Excipients of Tablets: Study of Flow Properties and Compaction Behavior, Am. J. Med. Sci. Med. **2** (2014) 71–76. https://doi.org/10.12691/ajmsm-2-4-2.
[43] Z. Ahmad, N.N. Roziaizan, R. Rahman, A.F. Mohamad, W.I.N. Wan Ismail, Isolation and characterization of Microcrystalline Cellulose (MCC) from Rice Husk (RH), MATEC Web Conf. **47** (2016). https://doi.org/10.1051/matecconf/20164705013.
[44] J.A. Yáñez, D.R. Brocks, L.M. Forrest, N.M. Davies, Pharmacokinetic Behaviors of Orally Administered Drugs, 2011. https://doi.org/10.1002/9781118067598.ch13.
[45] H.G. Brittain, S.J. Bogdanowich, D.E. Bugay, J. DeVincentis, G. Lewen, A.W. Newman, Physical Characterization of Pharmaceutical Solids, Pharm. Res. An Off. J. Am. Assoc. Pharm. Sci. **8** (1991) 963–973. https://doi.org/10.1023/A:1015888520352.
[46] D. Bar-Shalom, K. Rose, Introduction, AAPS Adv. Pharm. Sci. Ser. **11** (2014) 5–8. https://doi.org/10.1007/978-1-4899-8011-3.
[47] I. Martins, H. Tomás, F. Lahoz, J. Rodrigues, Engineered Fluorescent Carbon Dots and G4-G6 PAMAM Dendrimer Nanohybrids for Bioimaging and Gene Delivery, Biomacromolecules. **22** (2021) 2436–2450. https://doi.org/10.1021/acs.biomac.1c00232.
[48] A.A. Mendhe, R.S. Kharwade, U.N. Mahajan, Dissolution enhancement of poorly water-soluble drug by cyclodextrins inclusion complexation, Int. J. Appl. Pharm. **8** (2016). https://doi.org/10.22159/ijap.2016v8i4.14156.
[49] J.B. Hall, M.A. Dobrovolskaia, A.K. Patri, S.E. McNeil, Characterization of Nanoparticles for Therapeutics: Physicochemical Characterization, Futur. Med. **2** (2007) 789–803. http://www.medscape.com/viewarticle/574912_2.
[50] A. Kapourani, V. Valkanioti, K.N. Kontogiannopoulos, P. Barmpalexis, Determination of the physical state of a drug in amorphous solid dispersions using artificial neural networks and ATR-FTIR spectroscopy, Int. J. Pharm. X. **2** (2020) 100064. https://doi.org/10.1016/j.ijpx.2020.100064.
[51] R. Kharwade, S. More, A. Warokar, P. Agrawal, N. Mahajan, Starburst pamam dendrimers: Synthetic approaches, surface modifications, and biomedical applications, Arab. J. Chem. **13** (2020) 6009–6039. https://doi.org/10.1016/j.arabjc.2020.05.002.
[52] R. Kharwade, N. Mahajan, S. More, A. Warokar, A. Dhobley, D. Palve, Effect of PEGylation on drug uptake , biodistribution , and tissue toxicity of efavirenz – ritonavir loaded PAMAM G4 dendrimers, Pharm. Dev. Technol. 0 (2023) 1–19. https://doi.org/10.1080/10837450.2023.2173230.
[53] Q. Wei, Q. Yang, Q. Wang, C. Sun, Y. Zhu, Y. Niu, J. Yu, X. Xu, Formulation, Characterization, and Pharmacokinetic Studies of 6-Gingerol-Loaded Nanostructured Lipid Carriers, AAPS PharmSciTech. **19** (2018) 3661–3669. https://doi.org/10.1208/s12249-018-1165-2.
[54] A. Suresh Rewar, Design, Development and Evaluation of Press Coated Tablets of an Eprosartan Mesylate, Bull. Pharm. Med. Sci. **23** (2014) 191–196.
[55] A. Akkewar, N. Mahajan, R. Kharwade, P. Gangane, Liposomes in the Targeted Gene Therapy of Cancer: A Critical Review, Curr. Drug Deliv. **20** (2022) 350–370. https://doi.org/10.2174/1567201819666220421113127.
[56] M. Maghsoodi, F. Kiafar, Co-precipitation with PVP and agar to improve Physicomechanical properties of ibuprofen, Iran. J. Basic Med. Sci. **16** (2013) 627–634. https://doi.org/10.22038/ijbms.2013.723.

[57] R. Kharwade, N. Ali, P. Gangane, K. Pawar, S. More, of Tioconazole-Loaded Transferosomal Hydrogel for the Effective Treatment of Atopic Dermatitis : In Vitro and, (2023).
[58] R. Kharwade, H. Nair, D. Masurkar, A. Pise, S. More, S. Pise, Formulation and Evaluation of Chronomodulated Pulsatile Drug Delivery System for Nocturnal Hyperacidity, Res. J. Pharm. Technol. **15** (2022) 1449–1454. https://doi.org/10.52711/0974-360X.2022.00240.
[59] S. Mallick, S.K. Pradhan, M. Chandran, M. Acharya, T. Digdarsini, R. Mohapatra, Study of particle rearrangement, compression behaviour and dissolution properties after melt dispersion of ibuprofen, Avicel and Aerosil, Results Pharma Sci. 1 (2011) 1–10. https://doi.org/10.1016/j.rinphs.2011.05.003.
[60] S.M. More. R.S . Kharwade, N. S . Vyavhare, Formulation of mucoadhesive tablet by using aegle marmelos, Int. J. Appl. Biol. Pharm. Technol. **2** (2011) 154–161.
[61] S. Ramteke, N. Haigune, S. More, S. Pise, A. Pise, R. Kharwade, Flaxseed Mucilage Hydrogel based Floating Drug Delivery System: Design and Evaluation, Res. J. Pharm. Technol. **15** (2022) 1549–1554. https://doi.org/10.52711/0974-360X.2022.00258.
[62] P. Decuzzi, R. Pasqualini, W. Arap, M. Ferrari, Intravascular delivery of particulate systems: Does geometry really matter?, Pharm. Res. **26** (2009) 235–243. https://doi.org/10.1007/s11095-008-9697-x.
[63] E. Hari Krishna, V. Rama Mohan Gupta, S. Jyothi, Spherical crystallisation - A modern technique for direct compression of pharmaceutical substances, Asian J. Pharm. Clin. Res. **5** (2012) 114–117.
[64] B. Sun, M. Zhang, J. Shen, Z. He, P. Fatehi, Y. Ni, Applications of Cellulose-based Materials in Sustained Drug Delivery Systems, (2019) 2485–2501. https://doi.org/10.2174/0929867324666170705143308.
[65] A. Pandit, J. Shikshan, P. Mandal, Study of disintegration properties of mucilage from linum study of disinteghation properties of mucilage from linum, (2018).
[66] C. Solas, I. Poizot-Martin, M.P. Drogoul, I. Ravaux, C. Dhiver, A. Lafeuillade, T. Allegre, M. Mokhtari, J. Moreau, G. Lepeu, N. Petit, A. Durand, B. Lacarelle, Therapeutic drug monitoring of lopinavir/ritonavir given alone or with a non-nucleoside reverse transcriptase inhibitor, Br. J. Clin. Pharmacol. **57** (2004) 436–440. https://doi.org/10.1046/j.1365-2125.2003.02020.x.
[67] S. Rodriguez-Mozaz, M. Ricart, M. Köck-Schulmeyer, H. Guasch, C. Bonnineau, L. Proia, M.L. de Alda, S. Sabater, D. Barceló, Pharmaceuticals and pesticides in reclaimed water: Efficiency assessment of a microfiltration-reverse osmosis (MF-RO) pilot plant, J. Hazard. Mater. **282** (2015) 165–173. https://doi.org/10.1016/j.jhazmat.2014.09.015.
[68] P. Kolhe, E. Misra, R.M. Kannan, S. Kannan, M. Lieh-Lai, Drug complexation, in vitro release and cellular entry of dendrimers and hyperbranched polymers, Int. J. Pharm. **259** (2003) 143–160. https://doi.org/10.1016/S0378-5173(03)00225-4.
[69] J. Fadke, J. Desai, H. Thakkar, Formulation Development of Spherical Crystal Agglomerates of Itraconazole for Preparation of Directly Compressible Tablets with Enhanced Bioavailability, AAPS PharmSciTech. **16** (2015) 1434–1444. https://doi.org/10.1208/s12249-015-0332-y.
[70] A.L. Harvey, R. Edrada-Ebel, R.J. Quinn, The re-emergence of natural products for drug discovery in the genomics era, Nat. Rev. Drug Discov. **14** (2015) 111–129. https://doi.org/10.1038/nrd4510.
[71] A.A. Saeed, A.M. Khidir, A. Awadallah Saeed, Aspartame Sweetener, World J. Pharm. Res. **9** (2020) 195. https://doi.org/10.20959/wjpps20202-15435.
[72] K.M.S. Fahelelbom, Y. El-shabrawy, Analysis of preservatives in pharmaceutical products, Pharm. Rev. **5** (2007) 1–54.
[73] S.M. Shaikh, R.C. Doijad, A.S. Shete, P.S. Sankpal, A Review on: Preservatives used in Pharmaceuticals and impacts on Health, PharmaTutor. **4** (2016) 25–34.
[74] R. Bahramsoltani, M.H. Farzaei, R. Rahimi, Medicinal plants and their natural components as future drugs for the treatment of burn wounds: An integrative review, Arch. Dermatol. Res. **306** (2014) 601–617. https://doi.org/10.1007/s00403-014-1474-6.
[75] R. Kharwade, P. Badole, N. Mahajan, S. More, Toxicity And Surface Modification Of Dendrimers: A Critical Review, Curr. Drug Deliv. **18** (2021) 1–15. https://doi.org/10.2174/1567201818666211021160441.
[76] B. Pramod K, M. Manoj K.Mishar, B. Anupam Singh, Y. Vivek Kumar, An updated review on colorants as the pharmaceutical excipients, Int. J. Pharm. Chem. Biol. Sci. **5** (2015) 1004–1017. https://www.researchgate.net/publication/322861568.
[77] M. Šuleková, M. Smrčová, A. Hudák, M. Heželová, M. Fedorová, Organic Colouring Agents in the Pharmaceutical Industry, Folia Vet. **61** (2017) 32–46. https://doi.org/10.1515/fv-2017-0025.
[78] K.V.I. Allam, G.P. Kumar, Colorants - the cosmetics for the pharmaceutical dosage forms, Int. J. Pharm. Pharm. Sci. **3** (2011) 13–21.
[79] N.M. Mahajan, R.S. Kharwade, P. Badole. Development of Pharmaceutical aid from agricultural and other

waste. 360-degree Waste Management. 1(2023)67-87.