

INTRODUCTION TO DOSAGE FORMS

Abstract

Dosage form design is a multidiverse field which involves pathways from selection of drug and excipients to designing the formulation, manufacturing procedures, and quality assurance for the drug product. Prior to the development of any dosage form, it is important to understand the physical description of both the drug and excipients individually and in blend. Compatibility studies will results into stable dosage form throughout the shelf life. Thus before formulating a dosage form, a pharmacist should create the framework for product development by keeping in mind various factors like disease, the manner by which disease is treated (locally or through systemic), age and physiological conditions of the patient which could be helpful in pilot plant scale-up studies leading to desired drug release profile with improved bioavailability, and clinical effectiveness.

Keywords: Dosage form design; Drug; Excipients; Bioavailability

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I. INTRODUCTION

Pharmaceutical drugs, usually referred to as medicines, are chemicals that are used to treat a disease condition was previously obtained from the extraction of medicinal plants but now it has been obtained from organic synthesis [1]. The need for designing a dosage form is to protect the drug from external environment, improve its therapeutic activity and patient compliance. The dosage form is the physical form of the medication, where an active pharmaceutical ingredient (drug) and excipients (non-drug) are converted into suitable forms for administration [1]. Active pharmaceutical ingredients, API are chemical compounds with pharmacological activity intended for use in diagnosis, treatment or prophylaxis of diseases. Excipients or additives are inactive pharmaceutical ingredients including diluents/fillers, binders, lubricants, coatings, preservatives, colorants, flavouring agents and disintegrants. The pharmaceutical components transform medicinal materials into effective and appealing dosage forms by solubilizing, suspending, thickening, diluting, emulsifying, stabilising, and flavouring them. Each dosage form type has distinct physical and pharmacological properties. The medication is effective only when the drug in its desired form reach its site of action irrespective of its different routes of drug administration used according to the treatment. The proper formulation and designing of any dosage forms are important consideration focused by the product manufacturers. The nature of the disease or illness for which the drug substance should be formulated and sold depends on the type of illness it is meant to treat. Commercially, a variety of different dosage forms available, according to the mode of treatment and depending on the characteristics and advantages [2].

1. Ideal characteristics of a dosage form

- It should be safe and simple to administer
- It should be economical for the patient
- It should be physically and chemically stable in environmental conditions
- It should be easy to reproduce and formulate
- It should maintain its therapeutic activity throughout the shelf life
- It should provide high patient compliance
- It should be easy to handle for all kind of patients
- It should be biocompatible

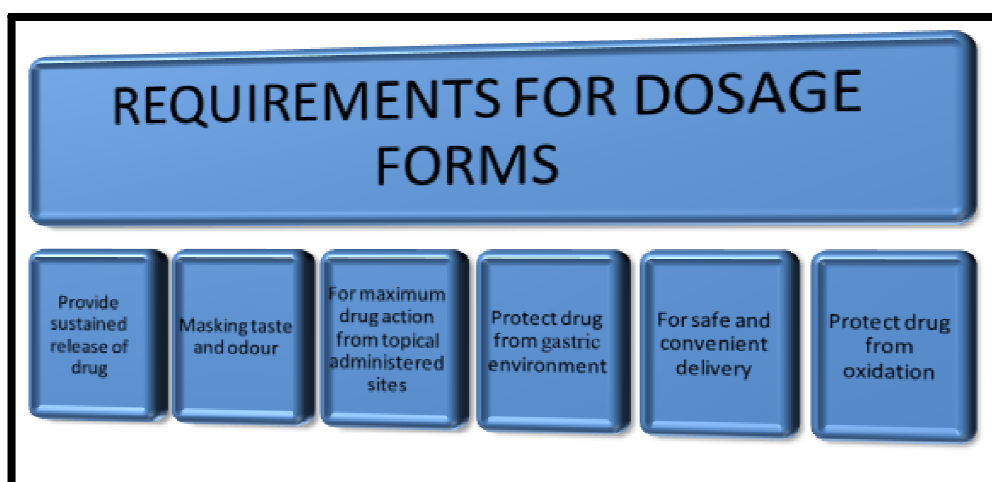


Figure 1: Ideal requirements of Dosage forms

The drug and excipients must be compatible with each other besides providing a dosage form that is stable, efficacious, easy to administer, and convenient delivery of accurate dosage. There can be no assumption that the general people could receive a medicine in a safe manner from bulk material due to the potency and low dosage of the majority of drugs now in use. Pharmaceutical dosage forms are needed for the following additional reasons [3]:

- To offer drug products that could avoid first-pass metabolism, such as parenterals, topical formulations, etc.
- To protect drug from the effects of external environment such as humidity or ambient oxygen, such as with coated tablets.
- To safeguard drugs against the effects of gastric acid pH after oral administration.
- To cover up the noxious smell or bitter taste of drugs, such as flavoured syrup, coated tablets, suspensions, and capsules.
- To offer an effective dosage form for the administration of drugs those are insoluble or unstable in the desired vehicle, such as suspensions.
- To deliver pharmacological activity that is rate-controlled, such as with different controlled-release tablets, capsules, and suspensions.
- To offer medication that, when stored according to the ICH guidelines, are stable, efficient, and safe for consumption, such as lyophilized powders for reconstitution.
- To deliver the best possible drug action from topical administration sites, including creams, transdermal patches, ointments, and preparations for the eyes, ears, and nose.
- To deliver liquid dosage forms of medications, such as injections and eye drops, that is sterile, transparent, and particle-free.
- To offer site-specific drug delivery, such as vaginal and rectal suppositories.
- To direct the medication to the intended site of action, such as with liposomes or nanoparticulate systems.
- Using inhalation therapy such as aerosols, to produce quick onset of action

Broadly, dosage form design is a multidiverse field which involves selection of drug and excipients to design the formulation, manufacturing procedures, and finally assuring the quality for the dosage form and drug. Today, most of the drugs substances appear in solid materials either have crystalline or amorphous nature. Therapeutically, drugs exist as solid, liquid, or gases forms. Today, liquid drugs are less frequently used as they pose more difficulties while handling than solid drugs. Because many liquids are volatile and they need to be kept in sealed containers to prevent evaporation loss to the atmosphere. Another additional issue arise with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form without chemical modification. Nitroglycerin is an exception, since it is formulated in such a way that when it is kept underside of tongue, it disintegrates in few seconds and provide rapid bioavailability. However, it is preferred that the tablet be kept in cool, dry place. When a liquid drug is to be administered orally and a solid dosage form is desired, it must be packed in a soft gelatin shell capsule, such as vitamins A, D, and E, cyclosporin (Neoral, Sandimmune), and ergoloid mesylates (Hydergine LC), among others. Second, it could be converted into a solid ester or salt form which is suitable for tablets or drug capsules. [2, 3].

Before formulating a dosage form, a pharmacist should create the framework for product development and consider factors like nature of the disease, the manner by which disease is treated (locally or through systemic), age and physiological conditions of the

patient. Pilot plant scale-up studies of the dosage forms are carried out to study the desired properties of a product e.g., release of drug from the delivery system, drug availability in the systemic circulation, and efficacy. On the basis of results obtained from pilot plant studies, formulation that best meets the goals for the product is selected and considered to be its master formula. Each batch of product subsequently prepared must meet the specifications established in the master formula record. If the medication is intended to be delivered for systemic use, tablets and/or capsules are created as oral/solid dosage forms because they are the most user-friendly and easy for self-administration of medication. A medication may be prepared in an injectable or parenteral dosage form if it can be used in an emergency situation where the patient is unable to take oral medication. Pharmaceutical liquid dose forms rather than solid dosage forms are the preferred method of administration for children under the age of five. Commercial versions of these formulations come in the form of flavoured syrups, aqueous solutions, or suspensions that are fed to children's mouths with a dropper, spoon, or oral dispenser [3].

II. CLASSIFICATION OF DOSAGE FORMS

Based on the physical state of the dosage form, oral dosage forms are classified into two types: solid oral dosage forms (tablets, capsules, or powders) and liquid oral dosage forms (solutions, syrups, emulsions, and powders for suspensions) [4].

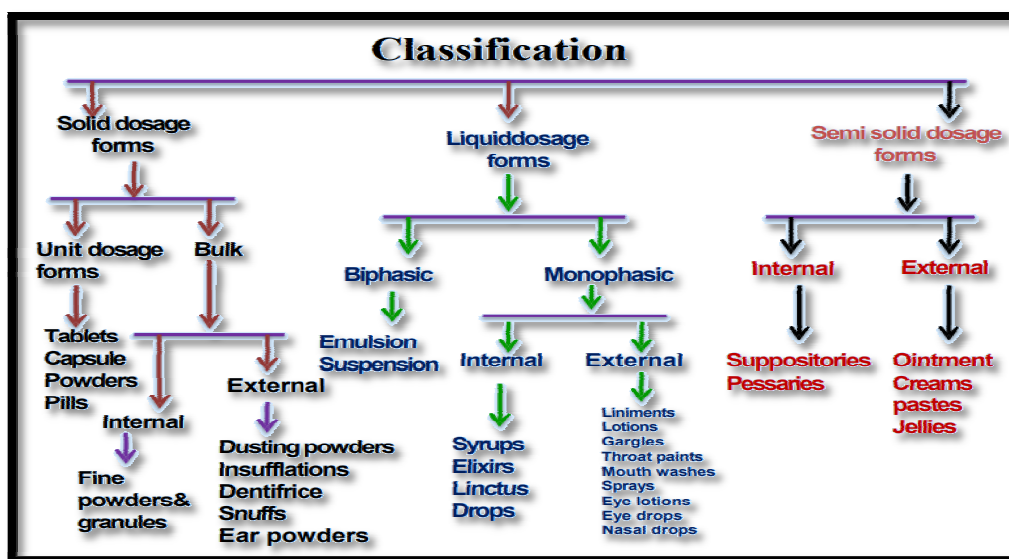


Figure 2: Classification of Dosage Forms

1. Solid oral dosage forms: The solid dosage forms are solid by nature and contain excipients like binders, sweeteners, colouring agents, etc. as well as one or more medicines for therapeutic effects [4]. These dosage forms are taken by patients orally and intended to deliver the drug to the site of action without any time delay. Out of the mentioned solid dosage forms, tablets and capsules are the preferred first choice of medication that a doctor prescribed. Because of its ease of availability and patient compliance. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules [4].

- **Tablets:** A tablet is a solid dosage form that contains one or more medications in a specific quantity, with or without appropriate excipients. To enable flexibility in dosing, manufacturers commonly make available various tablet or capsule strengths of a given medication. Tablets can be chewed or consumed whole. Before administration, some are dissolved or distributed in water. Some are placed in the mouth, where the active substance releases at a set rate. Tablets are typically solid, right-angled cylinders with flat or convex end surfaces and bevelled edges. [5] Most of the tablets are manufactured using wet granulation technique followed by compression method. The content uniformity, low cost, product identification makes compressed tablets ideal formulations [5, 6]. Types of Tablets dispensed by pharmacist:

Multiple layered tablets: These tablets are made by multiple times compressing the powder/granules. As a result, a multiple layered tablets are created. Initially these are used for incompatible drugs/chemicals such as phenylephrine hydrochloride with ascorbic acid in combination with Acetaminophen. One layer contains acetaminophen with phenylephrine hydrochloride, while the other contains acetaminophen with ascorbic acid.

Sugar coated tablets: These compressed tablets are covered in a coloured or clear sugar covering. Sugar coats are water soluble. These coats protect the medicine from the outside environment and act as a barrier for substances with unpleasant tastes or odours.

Film coated tablets: Compressed tablets also known as "film coated tablets" have a lean coating of a polymeric material on top of the tablet. As the tablet enters the GIT tract, polymeric coats get rupture in the presence of GIT fluid and the drug is exposed for further therapeutic action.

Enteric coated tablets: These formulations are designed by the use of enteric coated polymers in such a way that they are unaffected in the presence of stomach pH and are going to release the content of the dosage form in the intestine only. The tablet breaks down in the intestine and the medicine dissolves there. As a result, medications that can irritate the gastric mucosa and drug molecules that are prone to breakdown in stomach acid are better protected. In order to improve absorption, it can also be utilised to regulate the administration of specific medications to the intestines.

Laryngeal tablets: These formulations are designed to be kept underside of tongue to bypass the liver metabolism. Nitroglycerin tablet is a proper example of this category since; these tablets are administered through laryngeal route to achieve rapid bioavailability of drug. Many times it is also called as fast dissolving tablets. As per there design is concerned these dosage forms are small in size and horizontal in shape. Sometimes sweetening agents are also incorporated in such type of formulations so as to improve taste masking and patient compliance.

Chewable tablets: These formulations are meant to be swallowed, results in an aftertaste that is pleasing to the mouth and which is not bitter or unpleasant. These

dosage forms have been utilised for children, particularly to give multivitamin formulations, antacids, antibiotics and so on. Formulations are formulated using the direct compression method, with the addition of excipients like sorbitol, mannitol, as well as tastes and colours to improve their flavour and appearance. Furthermore, a nice, pleasant taste formulation is offered which can hide disagreeable taste of medicines. Mannitol is occasionally used as a chewable base diluent.

Effervescent tablets: These formulations before prescribing, when added to a glass full of water, resulted into a flavoured, bubbling drink. In addition to the active components, these also contain sodium bicarbonate and one of the effervescent substances. Because of acid-base process, carbon dioxide is emitted from solutions in water. The granules are formed when the water of crystallisation is released, which also makes the powder coherent. Salty or bitter drugs are disguised by the effervescence caused by the emission of carbon dioxide leading the active component in the tablet dissolves quickly in water. This improves palatability of the dosage form.

Immediate release tablets: These formulations are designed in such a way that they can release the drug without delaying.

Extended release tablets: These formulations are meant for regulating the release of drug in specified way over an extended period of time. [7].

- **Powders:** - Powders are one of ancestral kind of solid dosing. However, these have mostly been replaced by capsules and tablets as a result of the usage of highly strong substances, problem in their handling and patient incompliance. In powders, mixtures of medications or chemicals along with excipients have been finely grinded, mixed and dispensed. Powders still offer advantages in some circumstances, despite the fact that tablets and capsules have supplanted them as a dose form in modern medicine, and as a result, they still make up a minor percentage of the solid dosage forms currently in use. Powders, for instance, can dissolve and disperse more easily than compacted dose forms because of their larger specific surface area. Similar to how kids and adults who struggle to swallow tablets or capsules could find powders easier to take. Oral powders are blended with a liquid just prior to usage. [5, 6, 7]

Types of powder

Oral powders: These are dosage forms of medicament available either in the form of granules or fine powders. Before administration these finely grounded powders are blended with soft meals like applesauce or suspended or dissolved in water. This is a common way of administering antacids and laxative powders. For use in childrens, sachets of powdered antibiotic unit dose are reconstituted prior to its administration. Multidose bottles are also used to administer powders after reconstitution into an oral solution or suspension dosage forms. Herbal medicines, such as laxatives, are commonly dispensed in bulk powder containers for dose dispensing and administration by the patient. Dentifrices are manufactured as bulk powders; consist of mild abrasive, soap or detergent, and an anticariogenic ingredient Since ancient times, dentifrices (toothpastes) have been used, but recently, formulations that provide active ingredients intended to cure and/or prevent oral disorders have been produced.

Depending on the claims made and the concentration of specific ingredients, toothpaste may fall under the cosmetic or medicinal categories. The main purpose of toothpaste is to clean teeth, which is seen as an aesthetic advantage. Cosmetic claims include the use of terms like "protects," "cleans," "freshens breath," "fights microorganisms that may cause gum issues," "whitens," or "fights tartar" [8].

Dusting powders: These dosage forms are intended to be applied externally to the skin in a fine state of subdivision, to avoid local irritation. To enhance their effectiveness, dusting powder should always be passed through an 80 no. sieve. They are of two types: - (1) Medical dusting powders (2) Surgical dusting powders. Former was used in superficial skin infections whereas latter was used in body cavities and burns. It must be sterilized before use whereas medical dusting powders must be free from dangerous pathogenic micro-organisms.

Insufflations: Insufflations are finely divided medicated powders introduced into body cavities such as nose, throat, ears and vagina with the help of an apparatus called 'Insufflator'. An insufflator (powder blower) is usually employed to administer these products. The powder blower sprays the finely divided medication in the form of stream at the site of delivery. Nowadays, the insufflations are available in the form of pressure aerosols. An example is the Norisodrine Sulfate Aerohaler Cartridge (Abbott). When the patient inhales the aerohaler, a small ball strikes a cartridge containing the drug. The force of the ball shakes the appropriate amount of powder free, allowing it to be inhaled. Another device, commonly known as Spinhaler turboinhaler, it deposits lactose together with finely divided cromolyn sodium into lungs for bronchial asthma treatment. Insufflations dosage forms are used for both local and a systemic effect. However, the difficulty in obtaining a uniform dose is a challenge that has restricted its general use.

Dry powder inhalers: These are devices that are used to deliver medicament directly to the lungs to provide local action.

Cachets: Cachets are unit solid dosage forms of medicaments meant for administering nauseous or disagreeable powders in tasteless form and a large dose. e.g. Sodium amino salicylate cachets and Sodium amino salicylate and isoniazid cachets. They are moulded from rice paper, a material made by pouring a mixture of rice flour and water between two, hot, polished, revolving cylinders; the water evaporates and sheet of wafer is formed. Two types of Cachets (1) Wet seal cachet:- Upper half (moisten with water) which is pressed over Lower half (contains drug). (2) Dry seal cachets: - Upper half is pressed over Lower half which contains the drug material. It's just like a capsule [5, 6, 7].

Lozenges: Lozenges are flavoured medication dose forms that are meant to be retained in the mouth or throat while being sucked. They typically include one or more medications in a sweetened foundation. Lozenges are used to treat oropharyngeal symptoms, which are frequently brought on by local infections. If the medication is adequately absorbed via the buccal linings or when it is eaten, they may also have a systemic impact. Lozenges are classified as (1) According to site of

action: local effect and systemic effect. (2) According to texture and composition: Chewy or caramel based medicated lozenges; compressed tablet lozenges; soft lozenges and hard lozenges [9].

Capsules: The word capsule is derived from the Latin word Capsula, meaning “a small box or packet.” Capsules are characterised as a unit solid dose form of medications and inert substances that come in the shape of tiny gelatin capsules (shells) containing precisely calculated drugs. Depending on their formulation, the gelatin capsule shell may be hard or soft. Hard shell capsules can be regarded as containers for delivery of formulated drug substances that are generally designed for oral administration, although non-oral products for rectal or vaginal administration are available. Capsules as a platform for delayed or controlled-release delivery offer numerous advantages and adaptabilities over tablets. Because of the way they are manufactured, till now they are considered as the primary oral dosage form because they can easily accommodate a variety of special excipients, formulations, and pre-fabricated systems to target specific regions of the GI tract. Depending on their formulation, the gelatin capsule shell may be hard or soft. Hard shell capsule sizes range from number 5, the smallest, to number 000, which is the largest, except for veterinary sizes. However, size number 00 generally is the largest size acceptable to patients. Hard gelatin capsules are used for enclosing solid medicaments while soft gelatine capsules are used for liquid and semi solid medicaments [10, 11].

- 2. Liquid oral dosage forms:** Liquids are homogenous or biphasic formulations containing active medicinal agents dispersed in a suitable liquid vehicle. They are produced either this way or after dilution for oral delivery. Additionally, they contain antibacterial compounds for preservation along with the proper solubilizing, emulsifying, stabilising and suspending agents. Apart from this, formulation also contains colouring, flavourings, and appropriate sweeteners to enhance the aesthetic properties of the dosage form. If potassium or sodium saccharin is used to sweeten foods for children, the content in those foods shouldn't exceed 5 mg per kg of body weight. They include:- Syrups; Oral suspension; Oral solution; oral drop; oral emulsions; Mixtures; Elixirs; Linctus. During manufacturing, packaging, storage and distribution process of oral liquids, microbial quality should be maintained and microbial count should be within the acceptance criteria. Oral Liquids should not be diluted and stored after dilution unless the individual monograph directs for dilution. Diluted oral liquids may not be stable for long period physically and chemically so it should be diluted freshly or should be used within the period as stated on the label.

Syrups: The syrup is a saturated sugar solution. It is a viscous oral liquid that contains one or more active ingredients in solution. The base generally contains large amounts of saturation concentration of 67% weight per weight of sucrose to inhibit crystallization or to modify solubilization, taste and other base properties. In exceptional cases, other sugars (such glucose/dextrose) or non-sugars may be used to replace it completely or in part (e.g., sorbitol, glycerin, and propylene glycol). Nonmedicated syrups are those that contain flavouring ingredients but no medicines. Sugarless syrups may contain other sweetening agents as saccharin and thickening agents. Syrups may contain ethanol (95%) as a preservative or as a solvent for flavors. Antimicrobial agents may also be added to syrups to maintain the microbial quality of preparation. Drugs that dissolve in water

should be taken as syrups. The most popular types of medicinal syrups are those used to treat colds and coughs. In addition to purified water and drug(s), most syrups also include the following ingredients: (a) Sugar, often sucrose or other sugar substitutes, (b) antimicrobial preservatives, (c) flavorants, and (d) colourants are employed to produce sweetness and viscosity. Additionally, thickeners, stabilisers, and solubilizing chemicals may be present in syrups.

Oral Suspension: Because of their intrinsic structural instability, issues with manufacturing and packing, and importance as a class of pharmaceutical formulation, suspensions pose several difficulties for those responsible for formula development. Suspensions may be intended for parenteral usage, external application, or oral delivery. They typically consist of a finely split solid suspended in a liquid or semi-solid medium that makes up the continuous phase, with individual particles ranging in size from 0.5 to 5.0. Nowadays, a lot of suspensions are sold as dry powders that must be "constituted" before usage by adding a certain quantity of a vehicle. Such "suspensions" are created mostly due to stability issues.

Types of suspension

- According to the route of administration:- oral, topical, parenteral and ophthalmic.
- According to the nature of dispersed phase and method of preparation:- diffusible solid and indiffusible solids etc.
- According to nature of sediment:-Floculating and Deflocullatingsuspension.
- **Oral Solution:** Oral Solution is an oral liquid that contains one or more active ingredients dissolved in a suitable base.
- **Oral Drop:** Oral Drop is an oral liquid that is prepared to take in small quantity with the help of a suitable measuring device such as a dropper.
- **Oral Emulsions:** A biphasic system with two immiscible liquids, of which one (the dispersed phase) is finely and evenly scattered as globules throughout the second phase, is known as an emulsion (the continuous phase). Emulsifier, a third agent, is introduced to stabilise the system since emulsions are a thermodynamically unstable system.

Types of emulsions are

- **Type1**, in which oil acts as a dispersed phase and water, is in continuous phase. This type of emulsion is mostly preferred for internal use. Natural, cellulose derivatives and soaps are used as emulsifying agent.
- **Type2**, in which water is in dispersed phase, where as oil is continuous phase. This type of formulations is mainly used externally like cosmetics, applied topically. Fat, resin, beeswax etc are some examples of emulsifying agent.
- **Type3**, are emulsion in emulsion e.g., O/W/O (oil in water in oil emulsion) and W/O/W (water in oil in water emulsion). These are also known as complex emulsion, normally developed when controlled release is required.
- **Type4**, are microemulsion composed of water, oil and surfactant, that is optically isotropic and thermodynamically stable.

Mixtures: An appropriate base is used to suspend or distribute one or more active components in the combination, which is an oral liquid. When kept for a while, suspended solids may separate, but shaking quickly brings them back to suspension.

Elixirs: These are transparent, aromatic oral liquid forms that contain potent (antibiotics, sedatives etc.) and nauseous drugs dispersed in ethanol (4-40%), glycerine, and an appropriate syrup base. They are more stable than mixtures.

Linctuses: These are viscous formulations, prescribed for the relief of cough. They contain therapeutic agents which have demulcent, sedative or expectorant action diluted in syrup that is acceptable and has a greater concentration of sucrose or sometimes glycerine, sorbitol which apart from providing sweetening tastes on taste buds, also provides soothing action on the oral cavity. Typically, linctuses are produced to cure a cough, should be prescribed in small doses, so that it can be swallowed gradually in the absence of water to have prolonged effect of therapeutic agents. Linctuses are coloured with coal tar dyes and tartrazine solution.

Drug and excipients solubility in pharmaceutical solvent are essential concerns as these are required to be present in solution over the shelf-life of the formulated product. One of the major challenges faced by the pharmaceutical scientist is the attainment of homogeneity of the formulation, due to the limited aqueous solubility of the drug. The difference between the aqueous solubility of the drug and the required concentration is bridged by the use of co-solvents or surfactants. Commonly used co-solvents are glycerol, propylene glycol, ethanol and poly (ethylene glycol). Because of the effects of many variables direct or indirect on solubility, predicting drug solubility in mixed solvent systems (the vehicle, water, and chosen co-solvent) is difficult. In regular practise, the pharmaceutical scientist must evaluate the solubility of the active pharmaceutical agent in a series of mixed solvents so as to select the best solvent system for achieving the set objective. Furthermore, apart from taking into account the solubility of the therapeutic agent in the vehicle, it is also important to evaluate the toxicity of the selected vehicle, and the cost of the formulation. Indeed, it should be noted that the range of concentrations of each co-solvent used in oral formulations is primarily constrained by toxicity concerns. Excipients that are incorporated in pharmaceutical solutions for oral drug delivery must be physiologically inert, physically and chemically stable and be able to enhance the solubility of the therapeutic agent. A wide range of excipients discussed below can be utilized in liquid dosage forms.

The vehicle: The preferred and most commonly used vehicle in solutions for oral drug administration is Purified Water USP, due to the low cost and low toxicity of this ingredient. Under normal circumstances tap (drinking) water should not be used due to the possibility of chemical incompatibilities within the formulation. The main features of Purified Water USP are:

- It is prepared by distillation, ion exchange methods or by reverse osmosis.
- The solid residue (obtained after evaporation) is less than 1 mg per 100 ml of evaporated sample.
- It must not be used for the preparation of parenteral formulations. In the case of parenteral formulations Water for Injections BP must be used.

Cosolvents: These are solvents primarily used to improve the solubility of the active pharmaceutical agent in the formulation. Examples of co-solvents that are added in the oral formulations are: Glycerol, commonly known as glycerine, is an odorless, sweet liquid that is miscible with water and contains three hydroxyl groups, or triols. It has similar cosolvency properties to ethanol. Alcohol, ethyl alcohol (also known as ethanol) used between 94.9 and 96.0% of Alcohol USP, is frequently used as a co-solvent both alone and in combination with other co-solvents, such as glycerol. The use of alcohol in medicinal formulations has been restricted by the toxicological and pharmacological consequences of this co-solvent. As a result, there are guidelines for the labelling of preparation that contain alcohol as well as restrictions on the maximum content of alcohol that may be used in formulations. Another co-solvent, propylene glycol, it is a thick liquid diol with no colour, odourless, having two hydroxyl groups. In pharmaceutical formulations, it is used instead of glycerin. PEG stands for poly (ethylene glycol), which is made up of ethylene oxide repeating units (in parenthesis). The polymer's molecular weight (W) and the number of repeat units (n) both affect its physical state. PEG 200 and PEG 400 are recommended as co-solvents in medicinal solutions because of their lower molecular weight. Further, apart from these cosolvents, there are several other substances that can increase the medicinal medicines' solubility. Therefore the pharmaceutical chemist should explore other options besides using co-solvents to improve the solubility of therapeutic compounds in the preferred vehicle.

Surface-active agents: These are the molecules and ions that are adsorbed at the interface and reduce the interfacial tension. In chemical sense, surface active agents are defined as polymer like substances which have both polar and nonpolar groups so that they remain at the interface. At low concentrations, they adjust at the interface of two immiscible phases (e.g., water/oil, water/air), with its polar and nonpolar group of the molecule positioned towards the hydrophilic and hydrophobic phases of the liquid, respectively. Similarly, at high concentration, the interface of the liquid phases becomes saturated with surface-active agent, and the molecules in the bulk aqueous phase orient themselves to protect the surface-active agent's hydrophobic regions. This positioning is known as a micelle, and the concentration of surface-active agent is known as the critical micelle concentration (CMC). Surface-active agents are used as pharmaceutical adjuvants to improve the solubilisation of poorly soluble drugs in the presence of micelles, and thus at concentrations above the CMC. The core of the micelle represents a hydrophobic region into which the poorly water-soluble drugs may partition. The chemical structure of the drug is related to its location in the micelle. For example, if the pharmaceutical therapeutic agent is poorly soluble, the molecule will orient exclusively within the micelle, whereas if the drug is water-insoluble but contains polar groups, the molecule will orient within the micelle, with the polar groups at the micelle's surface and the hydrophobic region of the molecule within the micelle's hydrophobic core. In this way, the drug is solubilised within the colloidal micelles, and the resulting solution appears homogeneous to the naked eye due to their small size. The functional groups such as alcoholic (-OH), carboxylic acid (-COOH), sulphate (-SO₄) and quaternary ammonium (NH₄) contribute to the hydrophilic portion and alkyl chains contribute to the lipophilic nature of the molecules.

Complication: Complexes constitute a separate class of compounds which result from some type of interaction among different chemical species. They possess properties such as solubility, partition behaviour which are different from those of its components. The

complexation method involves interaction of poorly soluble drug with hydrophilic polymers or surface active agents to form a soluble drug-polymer complex. If solubility is enhanced, the dissolution rate also increases. While developing the pharmaceutical formulations, numerous excipients such as buffers; sweetening agents; and viscosity-improving agents are added to improve the physicochemical performance of the product. Buffers role in the pharmaceutical formulation is to control the pH of the final product.

Regulation of pH is typically done: Firstly, control the solubility of the drug. As large number of currently available medications depend on pH for solubility enhancement, even little pH changes may have an adverse effect on the drugs solubility.

Secondly, to improve the chemical extent of active drug in products as variation in pH affects the chemical stability of the product. The concentration of buffer salts used in the formulation should be chosen to provide adequate pH control while yet being able to withstand the action of biological fluids after administration. For parenteral formulations to prevent irritation after injection, this factor is very crucial. It should be noted that the solubility of the therapeutic agent should not be adversely affected by the buffer system employed in the formulations, for example, in case of phosphate salts; the solubility of pharmaceuticals may be disturbed.

Sweetening agents: These are used to improve unpleasant taste of the medicinal agents delivered through oral route. Natural sugars and artificial sugars are few of the common sweeteners mostly used in oral formulations. Saccharin sodium can be used as the sole sweetener or in conjunction with sugars or sorbitol to reduce the sugar concentration in a formulation. Sugars are not recommended in oral formulations for children or patients with diabetes mellitus.

Viscosity-enhancing agents: For the volume to be dispensed to be measured accurately, the formulation's viscosity needs to be appropriately controlled. Additionally, some pharmaceutical formulations palatability may be improved by increasing viscosity of the external phase. Typically with the help of a syringe, a small, metered cup, or 5-ml spoons, a conventional oral dose can be provided to the patients. In order to make these procedural steps of dispensing easier, the formulation viscosity has to be controlled up to a certain range. Some liquid formulations due to their innate viscosity don't necessarily need the incorporation of viscosity increasing adjuvants, like syrups. In case of pharmaceutical suspensions, by adding non-ionic or ionic hydrophilic polymers, the viscosity of the formulation can be easily enhanced. Sodium carboxymethylcellulose (anionic), polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, and non-ionic (neutral) polymers are some of the few examples of cellulose derivatives which are used as viscosity enhancers.

Antioxidants: Antioxidants are those chemical agents which when added into the formulation; improve the stability of drug for the reason that they are prone to chemical breakdown by oxidation. These substances typically gets oxidised (and subsequently destroyed) in aqueous solutions rather than the medicinal agent, preserving the drug molecules from breakdown. Ascorbic acid, Sodium sulphite, Sodium meta bisulphite, Sodium formaldehyde sulphonylate, and Sodium sulphite are some of the commercially available antioxidants utilized in different formulations but the choice of particular antioxidant depends on the type of formulation and its application and compatibility with

therapeutic agent. Butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and propyl gallate are few other examples of antioxidants that can be employed in oil-based formulations. Antioxidants are used at low concentrations of 0.2% w/w, and its concentration in the drug product should always kept lower than the original concentration because of the oxidative degradation during fabrication of the dosage form. Additionally, chelating compounds such as citric acid and ethylenediamine tetraacetic acid that act to form complexes with heavy-metal ions, and are involved in the oxidative destruction of therapeutic agents, may be used in combination with antioxidants to enhance their chelating effects. Along with chelating compounds like citric acid and ethylenediamine tetraacetic acid, which act to form complexes with heavy-metal ions typically involved in the oxidative destruction of medicinal medicines, antioxidants may also be used.

Preservatives: These are incorporated into pharmaceutical drug products to manage the formulation's microbial bioburden. It should possess characteristics like low toxicity, broad spectrum of antibacterial activity against bacteria and fungus and last but not the least should be chemical and physical stable during the product's manufacturing to expiry period. Furthermore, products delivered through oral route can use selected preservatives with permissible concentration range, such as benzoic acid and its salts (0.1-0.3%), sorbic acid and its salts (0.5%-0.2%), and alkyl esters of parahydroxybenzoic acid (0.001-0.2%). Formulators often use combination of preservatives, typically methyl and propyl parahydroxybenzoates (in a ratio of 9:1) for best results. The antibacterial spectrum is improved by combining these 2 preservatives. Unfortunately, the pH of the formulation and the presence of other excipients may have an impact on the concentration of preservative inside the formulation. Utilizing acidic preservatives, such as sorbic acid and benzoic acid, can be challenging in some aqueous formulations.

Flavours: The flavour concentration in oral liquid dosage form is the amount required to effectively mask taste. These are used when the unpalatable taste of a therapeutic agent is noticeable, even when sweetening agents are present. Natural flavours such as peppermint, lemon, herbs and spices are broadly available in the form of oils, extracts, spirits, and aqueous solutions. Alternatively, varieties of synthetic flavours are also commercially available, with advantages over natural origin in terms of purity, availability, stability, and solubility. Certain flavours possess mild therapeutic properties. For example, carminative properties of mint because of this property many antacids formulation contain it. Other flavours possess taste-masking effect by bring out a mild local anaesthetic effect on taste receptors. Peppermint oil, chloroform, and menthol are some of the examples of flavours in this category.

Colours: These are water soluble additives, obtained from natural or synthetic, added to enhance the aesthetic properties of the drug formulation. Colours are chosen based on the product flavour. For instance, drug product with mint flavours is typically green, while those with banana flavours are yellow in colour. Ideally, colour as an additive should be physically or chemically inert and cannot interfere with the properties of other formulation ingredients throughout the shelf life. Titanium dioxide used as opacity agent for capsules dosage forms, due to its high reflectance. It also finds application in tablet coating and semisolid dosage forms. Due to its high reflectance, titanium dioxide is also included in sunscreen preparations as it protects from harmful ultra-violet rays. Similarly,

ferric oxides both red and yellow varieties as colourant are preferred by formulators in topical preparations such as calamine lotions.

- 3. Semi-solid dosage forms:** This category of dosage forms are meant to be applied on the upper surface layer of the skin, despite the fact that they are unit dosage forms. These preparations are characterised as topically applied drugs that have local and systemic effects when applied through outer layer of skin and mucous membranes. They usually contain complex structure, comprising of two phases—oil and water—with the exterior phase being continuous and the inside phase being dispersed. In semi-solid dosage forms, a three-phase system is frequently created by dissolving the active ingredient in either one or both phases. This 3-dimensional structure is strong enough to give an undisturbed system a solid-like quality, but is also easily deformed and realigned in response to an external force. It include: - Ointments, Creams, Pastes, Jellies and Suppositories.

Ointments: When shear force is applied, ointments, which are semisolid systems, often act like viscoelastic materials. They often contain medications and are meant for application on skin outer epidermal layer so as to penetrate inside and release into the physiological fluids. Non-medicated ointments, also known as ointment bases, are used to make medicated ointments or can be used directly for lubricating or emollient properties. While selecting an ointment base for formulating ointments, many factors should be taken into consideration such as action desired, physicochemical nature of drug and stability. An ointment base should be inert, stable, and compatible, should have good spreading coefficient and should not interfere with the pharmacological action of the drug. There is no single ointment base available that possessed all the above properties, so it is always suggested to incorporate combination of ointment bases for better outcomes.

Creams: According to the definition Creams are viscous semi-solid preparations of either the oil-in-water or water-in-oil type whose consistency varies according to the ratio of oil to water. These preparations are used to be applied on top most layer of skin. Creams be used for protective, cleansing, beautifying, increasing appearance, and other medicinal or cosmetic purposes. These formulations deliver the medicaments to particular skin regions for targeted effects for skin disorders. They fall into two categories: Firstly, oil-in-water type creams that are made up of oil droplets spread in an aqueous continuous phase. In aqueous creams, the emulsifying anionic, cationic and non-ionic waxes, polysorbates and triethanolamine soaps are used as emulsifying agents. Secondly, water-in-oil type creams made up of water droplets spread in oily emulsifying agents such as wool fat, beeswax, calcium soaps, and wool alcohols. Due to the non-greasy nature of former have more acceptances among customers than latter. A suitable preservative is always included in water based creams compared to oil based because of their tendency to bacterial and fungal growth.

Pastes: Pastes are ointments with a high concentration of insoluble solids. The unusual amount of insoluble solids stiffens the system by adsorbing the vehicle's liquid hydrocarbon component on the particle surface and directly interacting with the scattered particles. The stiffening property of paste makes them useful as protective coating. Pastes are frequently created by directly introducing solids into a congealed system and allowing them to leech with some of the base material to form a paste-like mass. The remaining components of the base are applied after the solids have been evenly distributed

throughout the vehicle. Compared to the ointment dosage forms pastes are less greasy and finds application mainly as antiseptic and protective.

Jellies: Jellies are semisolid transparent, non-greasy preparations having a liquid phase constrained by a 3-D polymeric matrix (composed of gum such as gelatin, cellulose derivative, tragacanth etc. obtained naturally or synthetically) with a high degree of cross-linking. In this, hydrated form of insoluble drugs is suspended in water to get colloidal suspensions or gels. In addition to finding its application as carriers for spermicidal medications that are administered intravaginally with diaphragms as an another method of contraception, they are also used for lubrication, medicine, and other uses to the skin.

Suppositories: An active substance is often inserted into an inert base, which can be either stiff or semi-rigid, to create a standard suppository. For patients in comas or who are unable to take oral medications owing to recurrent bouts of nausea and vomiting or pathological disorders of the gastrointestinal tract, it provides an alternative form of oral drug for systemic action. It liquefy in the local mucosa to liberate the active ingredient from the dosage form so that it can either move to the mucosal barriers into the systemic circulation to produce a pharmacological effect.

Pessaries: Devices called pessaries, which are often made of silicone or rubber, support the uterus, vagina, bladder, and rectum structurally. The market currently offers a variety of models and sorts, increasing popular acceptability. Vaginal touch is used to choose the model. The perineal body supports the pessary, which is positioned beneath the pubic symphysis. There are several types of devices (ring, donut, gelhorn, and cube) that are divided into two categories: support and occlusive.

Bases, Preservatives, Chelating agents, Humectants, and Fragrances are some of excipients used in the formulation of semisolid dosage forms and has been discussed below.

Bases: Till date, many drugs intended for external use available in semi-solid dosage forms. In addition to acting as a carrier system for drugs, the semi-solid bases also regulate how much of the drug gets absorbed from the drug delivery system. A base for an ointment should be easy to apply, stable throughout the shelf life, must be smooth in texture, non-irritating, must be inert able to absorb water and must have the property of quickly releasing the medicament after application. Important considerations on which selection of an base depends:

- Desired release rate
- The rate and extent of medication absorbed through the skin after application
- Desirability of skin moisture occlusion.
- Removal of base after washing
- Compatibility with skin type on which base is applied

Ointment bases may be classified in several ways

- **Oleaginous bases:** This includes combination of different oleaginous components, such as hydrophobic oils and fats that are insoluble in water. In the past, ointment

bases were only oleaginous in nature, but today components from plant, animal, mineral, and synthetic sources are utilized as ointment bases. These materials can be combined to produce desired range of melting temperatures and viscosities.

- **Absorption Bases:** Fundamentally, these are hydrophobic systems made up of anhydrous components. They are referred to as emulsifiable bases because they absorb water to create water-in-oil type and oil-in-water type of emulsions even if they do not initially contain any water. Practically, absorption bases are categorised as emulsions of the water-in-oil type because of their ability to absorb large amounts of water without changing its consistency. Animal sterol and petrolatum are the main ingredients of absorption bases. Under several brand names, including Eucerin and Aquaphor, white petrolatum is combined with cholesterol and/or other appropriate lanolin fractions.
- **Emulsion Bases:** These are categorised as water-in-oil and oil-in-water type of emulsion bases. Since the oil is in the exterior phase and emulsions cannot be washed with water, therefore it has an average acceptance among the population. O/W emulsions have a good acceptance and are employed in dermatological preparations and cosmetic creams. Cold creams, Creams for the skin, hands, foundation, emollients and vanishing creams are a couple of the well-liked creams based on o/w type of emulsion.
- **Water Soluble Bases:** These are dermatological water soluble bases having both anhydrous and hydrous and devoid of an oil phase. These bases often have one or more hydrocolloids or PEGs as their foundation. Carbowaxes, also known as polyethylene glycols, are non-volatile reagents which do not hydrolyze or degrade and have a low dermal and oral toxicity and low irritant nature. Formulation developed using carbowaxes allows drugs to easily diffuse into the body tissues however their absorption is minimal. Commercially, carbowaxes various grades of are available and they are identified by their numbers that generally corresponds to their molecular weights such as 200, 300, 400, 600, 1000, 1540, 4000, and 6000. Carbowaxes 200 to 400 are transparent in appearance while those from 1000 to 60,000 are white at room temperature. Apart from this, variety of other PEGs based on their physical state are obtained depending on the type of dosage form and its application by blending. For example PEG ointment is a combination of PEG 4000 and 400.

Antimicrobial Preservatives: These are the chemical substances which are added into the dosage forms to prevent the growth of the micro-organism. Some bases used in the topical formulation, although defy the microbial growth but since they possess high content of water molecules, it always required to incorporate antimicrobial preservative during their production. Methyl hydroxyl benzoate, Propyl-hydroxybenzoate, Chlorocresol, Benzoic acid, Phenyl mercuric nitrate, Benzalkonium chloride, Chlorhexidine acetate, Benzyl alcohol and Mercurial are few examples of preservatives having antimicrobial activity.

- **Antioxidants:** These are the substances which prevents the oxidation of medicinal agent susceptible to oxidation. Butylated hydroxy toluenes, Tocopherols, Propyl gallate are few of the examples of oil soluble antioxidants whereas Cysteine, Sodium

formaldehyde sulfoxylate, Sodium sulfite are few examples of water soluble antioxidants.

- **Chelating Agents:** Citric acid, Maleic acid are few common examples of antioxidants.
- **Humectants:** Common examples of humectants are Poly Ethylene Glycol, Glycerol or Sorbitol.
- **Fragrances:** Examples are Lavender oil, Rose oil, Lemon oil, Almond oil.
- **Emulsifier:** Alkyl sulphates, Soaps, Dodecyl benzene, sulfonate Lactylates, Sulfosuccinates, Monoglyceride, sulfonates Phosphate ester, Silicones, Taurates, Quaternary, ammonium compounds Alkoxyalkylamines, Polyoxyethylene, alkyl-aryl ethers Polyoxyethylene fatty, acid ester Polyoxyethylene, sorbitan esters Sorbitan fatty acid, esters Glyceryl fatty acid, esters Sucrose fatty acid, esters Polyoxyethylene polyoxypropylene
- **Permeation Enhancers:** Skin can act as a barrier and prevent deep penetration of drug molecules. With the introduction of various penetration enhancers systemic drug delivery through the transdermal route has gained major footing.

4. Gaseous dosage forms: These include: - Inhalers; Nebulisers; Aerosols.

Inhalers: Inhalers are collections, suspensions, or emulsions of drugs kept under pressure in an airborne distributor by a combination of latent forces. Gases, vapours, solutions, and suspensions designed for oral or nasal inhalation are also considered to be forms of inhalation. The medication is delivered from the holder through a spring-stacked valve fusing a metering device in the form of beads that are 50 μm wide or fewer. The drug is subsequently inhaled by the patient via a mouthpiece. In certain types, the finger weight propels the valve, whereas in others, the patient breathes through the mouthpiece to activate the valve. It is frequently utilised to treat respiratory related problems including asthma.

Nebulisers: A nebulizer is a medicine delivery system used to inhale medication in spray form into the pulmonary. Nebulizers are frequently used to treat conditions including cystic fibrosis, asthma, Coronary obstructive diseases, and other respiratory illnesses. Another form of nebulizer is an analytical one, and they are typically utilised in lab settings. It turns a liquid drug into a vapour by pumping air or oxygen through it, which the patient then inhales.

Aerosols: A pressurised dosage form containing one or more therapeutic active substances is called an aerosol. When activated, an aerosol releases a fine dispersion of liquid and solid components in a gaseous medium with a particle size less than 50 μm . Pressurized packages, pressure packages, or pressurised dosage forms are other names for aerosol. Most of the aerosols are use topically. The component of an aerosol includes:

- Propellant
- Container
- Valve and actuator
- Product concentrates

5. **Novel dosage forms:** It has been proven that novel dosage forms are helpful for achieving precise and controlled drug therapy. These formulations are designed with an rationale to reduce drug deterioration, minimize side effects, and enhance drug bioavailability at the delivery site.

Liposomes: Bingham and his colleagues discovered liposomes in the early 1960s. Liposomes were initially employed to find out the behaviour of *in vitro* biomembrane simulations, but later on they have emerged as potent drug delivery tool for drug transport and targeting. Structurally, liposomes are made up of phospholipids (lipid vesicles) which can transport both hydrophilic and lipophilic drugs. These novel drug carriers are sometimes developed with cholesterol to change the permeability of liposomal drugs.

Nanosomes: As a substitute for liposomes, niosomes is currently subject for extensive research. Niosomes have physical characteristics that are comparable to those of liposomes, which are generated from phospholipids (lipid vesicles), despite the terminology suggesting differences between niosomes and liposomes, with the former having chemical variances in the monomers units. As implied by the name, components containing non-ionic surfactants are typically used to create non-ionic surfactants vesicles. Alkyl ether lipids predominate among the non-ionic chemicals that form vesicles. These can be polyols subunits, similar isomers, or bigger sugar molecules, and those with repeat ethylene oxide subunits. Alkyl esters, amides, fatty acids, and amino acid compounds are other vesicle-derived substances. Till date niosome formulations have not yet been used commercially, but they have shown effective response in the administration of anti-infective, anti-cancer, anti-inflammatory, and vaccine adjuvant chemicals. These systems also find application in diagnostic imaging agents because it has been demonstrated that they can target specific parts of the mammalian anatomy.

Microparticles: These are characterised as spherical particles with a core material either in solution or in crystalline form and sizes ranging from 50 nm to 2 nm. In research, terminology "microspheres" and "microcapsules" are frequently used vice-versa. However, large particles with spherical morphologies are also used to describe microparticles. The controlled-release of drugs from solid biodegradable microspheres, where the drug is distributed throughout the particle matrix has potential in drug targeting. Advantages of using microparticles as a drug carriers is: longer duration of action, controlled drug release, improved therapeutic efficacy, drug protection from external environment, Biocompatibility, targetability, water solubility, and relative stability. These novel carriers have the potential to deliver drugs that target tumours, notably those that can fight cancer. Few of the methods that can be used practically to develop microspheres such as: in situ polymerization, solvent evaporation, coacervation phase separation, sprays drying, and sprays congealing. However, choice of a particular method depends on the type of polymer incorporated in the formulation, drug and its intended use, and last not the least it depends on extent of therapy. For formulating the microspheres, variety of biodegradable and non-biodegradable materials such as modified natural compounds as well as polymers with natural synthetic origins are available. Methyl methacrylate, acrolein, lactide, glycolide, and related co-polymers, ethylene vinyl acetate copolymer, polyanhydrides are some of the synthetic polymers which can be used as carriers. Apart from this certain natural polymers like albumin, gelatin, starch, collagen, and carrageenan can also be used for developing microparticles.

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