

PHARMACEUTICAL PREPARATIONS AND DRUG DELIVERY SYSTEM: A BASIC ELEMENT FOR PHARMACEUTICAL INDUSTRY

Abstract

Starting with different drug administration methods, Here is a summary of medication delivery methods. (DDS). The descriptions of different medication formulations, drug delivery systems, and targeted drug delivery systems follow. Delivering proteins and peptides has unique difficulties. The delivery of drugs is thought to be improved by nanoparticles, which can be both pharmacological and diagnostic in nature. The advancement of personalised medicine, which encompasses pharmacogenomics, pharmacogenetics, and pharmacoproteomic, will be made easier by improvements in medication administration. The ideal DDS, commercial considerations, present successes, difficulties, and possibilities are also covered.

The pharmaceutical active component can be released via the drug delivery method to produce the desired therapeutic effect. The low bioavailability and erratic plasma drug levels of conventional drug delivery methods (tablets, capsules, syrups, ointments, etc.) prevent them from delivering sustainable delivery. The entire therapy procedure may be ineffective without a reliable delivery mechanism. To achieve optimal efficacy and safety, the medicine must also be administered at a precisely regulated rate and at the intended spot. The issues with traditional medication delivery are addressed by the invention of controlled drug delivery systems. Over the last 20 years, controlled drug delivery systems have seen a significant change, progressing from large- and nanoscale to intelligent focused delivery. The first section of this study offers a fundamental overview of drug delivery methods with a focus on the medication's pharmacokinetics. It also talks about the limits of traditional medication

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delivery methods. Drug delivery systems are also covered in detail, along with design factors, categories, and illustrations. Additionally, the use of stimuli-responsive and intelligence materials for targeted and smart medication administration is presented together with recent key discoveries. The obstacles and potential prospects for regulated medication distribution are discussed in the paper's conclusion.

Keywords: Drug Delivery System, Pharmaceutical Industry, Active Pharmaceutical ingredient, Excipients, Solid, Semi Solid, & Liquid Dosage Forms

I. INTRODUCTION

According to the FDA, an API is a substance that has been approved to be used in the official pharmacopoeia and is intended to be used in the diagnosis, treat, mitigation, or prevention of illness. Giving a patient their medicine in a way that exactly increases the concentration of the drug in some bodily parts over others is known as drug delivery. [1]. Any delivery method should aim to extend, contain, and target the medicine with a safe interaction in the sick tissue. Every dosage form consists of both a drug's active pharmaceutical components (APIs) and excipients or additives, which are substances that aren't actually drugs (Figure 1). The actual chemical elements utilised to cure illnesses are known as APIs [2].

II. NEED FOR A DOSAGE FORM

Drug delivery systems (DDS) are often favoured since it is extremely unusual to employ active pharmaceutical ingredients (APIs) "as they are" in clinical settings. For particularly powerful medications (such as low mg and g dosages), API storage and accurate dosing might be challenging or unattainable [3]. Drugs may deteriorate where they are administered. (for example, low pH in the stomach), and they may cause local inconveniences or damage when the drug concentration is very high at the location of administration, making prescribed medication Entering the bodily cavities (vaginal, rectal) is impossible and impractical [3]. Some APIs can benefit from less exposure to external elements (light, humidity, temperatures, and pH), or they need to be chemically modified because they are environment sensitive. due to the intrinsic uncertainty increases, stabilised. Patients are less likely to comply with APIs because they often have undesirable organoleptic (taste, odour, and adherence) [2].

Dosage form = Active Pharmaceutical ingredient (API) + Excipient/ Additives

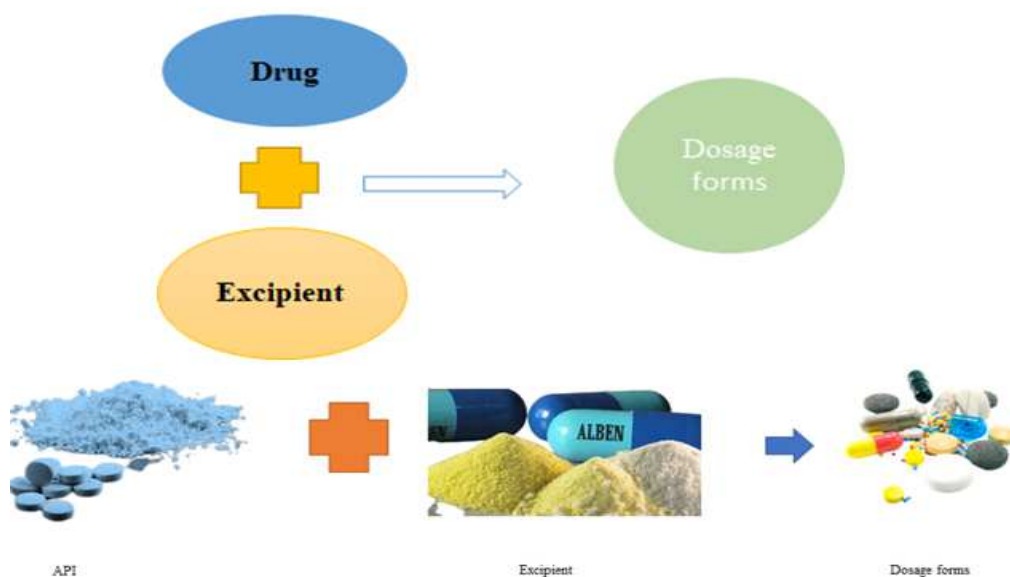


Figure 1: Dosage form composition

III. THE PERMEABILITY OF DRUG DELIVERY SYSTEMS AND PACKAGING

Drug research and development are becoming more interested in cell-free permeation systems as instruments to achieve a trustworthy prediction of passive intestinal absorption without the drawbacks connected with cell- or tissue-based permeability profiling. Cell-free permeation systems are divided into two categories based on the nature of the barrier, including (i) biomimetic barriers made of (phospho) lipids and (ii) non-biomimetic barriers made of dialysis membranes. In this review, the various cell-free permeation methods—such as Parallel Artificial Membrane Permeability Assay (PAMPA), Phospholipid Vesicle-based Permeation Assay (PVPA), Pereopod®, and artificial membrane-based systems (such as the artificial membrane insert system (AMI-system))—are analysed in terms of the nature of their barriers and their ability to predict results in comparison to well-studied intestinal permeation methods. Given the possible integrity loss higher resilience of cell-free barriers makes them appropriate for the combined dissolution/permeation assessment of formulations when compared to cell-based permeation barriers in the presence of food components or medicinal excipients. Cell-free permeation systems are often used to study intestinal absorption, but by changing the membrane's composition, they may also be used to assess non-oral medication delivery.

Class I greater solubility increased permeation	Class II minimal solubility increased permeation
Class III greater solubility minimal permeation	Class IV minimal solubility minimal permeation

Solubility: Volume of water required to dissolve the highest dose strength across the physiological pH Range

Figure: 2 Biopharmaceutics Classification System

IV. EXCIPIENTS

Table 1: Common excipients used in tablets [4-7]

Excipient	Function	Examples
Diluents	supplying in bulk and enabling precise dosage of powerful substances	Lactose, dextrin, glucose, sucrose, and sorbitol are examples of sugar compounds. Silicates, calcium and magnesium salts, potassium or sodium chloride, and other inorganic materials
Binders, compression aids, granulating agents	Combine the materials for the tablet to give it shape and mechanical strength.	mostly composed of manufactured or natural polymers, including sugars, starches, sugar alcohols, and derivatives of cellulose
Disintegrants	Help the tablet's active component to be released and increase the surface	substances that expand or dissolve in water, such as crospovidone, alginates, and derivatives of

	area for disintegration in the digestive system.	cellulose
Glidants	By lowering friction and adhesion between particles, improve the flow of powders during tablet production. utilized as anti-caking agents as well	Silicon and other silica compounds in colloidal form
Lubricants	They may, however, impede disintegration and dissolution in a manner like glidants. Even though some substances, such starch and talc, have both effects, the characteristics of glidants and lubricants are different.	Sea salts and stearic acid (e.g., magnesium stearate)
Tablet coatings and films	Protect the pill from the elements (air, light, and moisture), boost the mechanical strength, cover the flavour and odour, make swallowing easier, and help customers identify the product. can be used to alter how the active substance is released. flavoring and colorings possible	film coating made of natural or manmade polymers has now supplanted sugar (sucrose). Enteric coatings employ insoluble in acid polymers, like cellulose acetate phthalate, to postpone the release of the active substance.
Colouring agents	Enhance patient acceptance, facilitate identification, and stop counterfeiting. Boost the stability of medications that are light-sensitive.	mostly manufactured colours and natural pigments. It is also possible to employ substances that are natural food pigments themselves.

V. DIFFERENT ROUTES OF DRUG ADMINISTRATION

Depending on the target location, length of therapy, and physicochemical characteristics of the medication, different dosage forms can be delivered by different routes [9]. Tablets, capsules, pills, ointments, syrups, and injections make up the bulk of dosage forms. Table 1 and Figure 3 list several medication delivery methods. The body part being treated, the medication's action inside the body, and the solubility and permeability of the drug are the three key elements that determine the best route of drug administration. For instance, the oral delivery of some medications might cause stomach acids to break them down, resulting in low bioavailability. As a result, they must be administered intravenously. 100% bioavailability is achieved when medicines are administered intravenously [9].

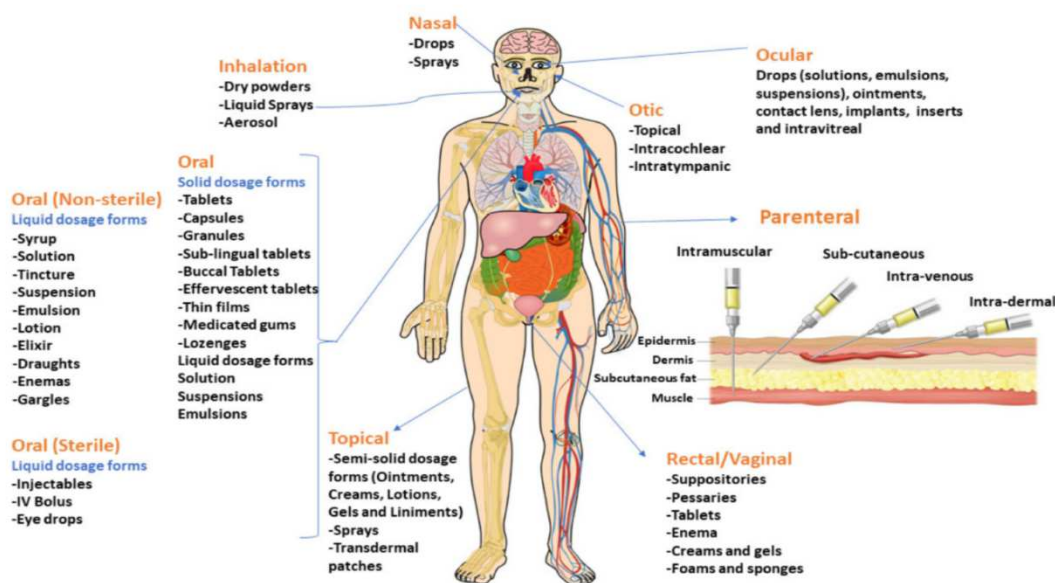


Figure 2: Various routes of drug administration.

1. **Solid dosage forms:** (Solid dosage forms are further divided into the two main categories of single dose and bulk dosage based on the type of dose.

- **Unit dose:** Every dosage is predetermined and prepared as a distinct dosage form, and the patient must take one unit at a time. of each prescribed dose. Tablets, capsules, pills, lozenges, chewable effervescent tablets, and powder form inhalation in metered-dose containers are a few examples of unit pharmaceutical formulations.
- **Bulk dose:** As the name implies, this is a solid powder in bulk, not individually dosed, (Figure 3). With bulk powders, dose dumping is a significant issue. Bulk powders, on the other hand, are typically used as dressing powder for surgical and wound wounds. Insufflation powder, dressing powder, etc. are a few instances of bulk dosage forms [10].
- **Tablets:** Compress and granulating are used to generate tablets, which can be produced in a variety of forms (round, oval or square shape). Binders, gelling agents, and lubricants are commonly added as active ingredients to enhance tableting. Excipients are added to pills to facilitate their simple digestion. The tablet's coating of colours, sweeteners, and flavourings makes the pill smoother and simpler to swallow while also helping to hide the taste of the other components. Additionally extending shelf life and providing environmental protection, tablet coating [10,12] Tablets that are placed under the tongue or between the mouth and cheek, respectively, are known as buccal tablets and are solid unit dose forms. Sublingual/buccal delivery methods have several benefits, including: The oral mucous membranes allow for quick drug dissolution and absorption into the bloodstream. By doing this, the liver's drug-metabolizing enzymes and the acid and enzymatic milieu of the stomach are avoided [11,12]. Effervescent tablets are made to release carbon dioxide when they meet

water and dissolve quickly afterward. These uncoated tablets contain carbonates or bicarbonates that quickly react in water to release carbon dioxide and acids (citric or tartaric acid).

- **Capsules, lozenges, pills and granules:** A capsule is a dose form that is solid, that contains the medication ingredients inside of a soluble shell. The flavour of the medication's ingredients is covered up by the capsules, and the medicine seldom interacts with the active ingredients. There are two categories for capsules: Soft-shelled capsules are mostly utilised when hydrophobic medicines and oily active ingredients that are suspended or dissolved in oil. Hard-shelled capsules are used to encapsulate dry, powdered components. Lozenges as chewy solid unit dose form that include the medication filled with caramel -flavored foundation comprised of sugar and gums. The gum gives the lozenge cohesion and strength while also allowing for a delayed release of the medication. Common applications of chewable tablets include the localised gradual release of demulcents, medications, and cough medicines in the mouth/pharynx. Using polymers and other additives to compress API into rounded masses for oral delivery, pills are solid unit dosage forms. Crystals are solid, dry aggregates that come in single-dose sachets and can be swallowed whole or before being dissolved in water use (Figure 3). When introduced to water, effervescent granules produce carbon dioxide in a manner like effervescent pills.[10].



Figure 3: Solid unit dosage forms: (a) Tablets, (b) Effervescent tablets, (c) Chewable tablets, (d) Pills, (e) Hard-gelatin capsules, (f) Soft-gelatin capsules, (g) Lozenges. (h). Granules.

2. **Bulk solid dosage forms:** Large powder are transdermal patches compositions made up of free, dry, solid particles with varying degrees of fineness. With or without excipients, one or more active substances are present, and if necessary, coloration and flavored agents are added. This is prepared for interior or exterior administration and stored in widemouthed, airtight bulk glass or plastic containers. There are two categories of internal usage bulk powders. Since each dose is measured differently by the patient, bulk powders are frequently constrained by erroneous dosage. As a result, they are frequently made using non-potent medications including enemas, antacids, purgatives, etc. The

powder is then commonly dissolved into water before consumption. Single-dose powders are divided powders. (such as a little sachet) that have a more precise dosing control than bulk powder [10].

3. **Semisolid dosage forms:** To utilise to skin or mucous membranes (in the nasal, vaginal, or rectal cavities) for medicinal, preventative, or aesthetic purposes, tablet and capsule forms are of a semisolid consistency. Ointments, creams, gel/jelly, lotions, pastes, suppositories, and transdermal patches are examples of semisolid dose forms (Figure 4) [13]. By applying semisolid dosage forms locally and externally to the target site, the likelihood of adverse effects is decreased. It is practical for individuals who are asleep or who have trouble receiving medication orally. It is more stable than liquid dose forms and an appropriate dosage form for bitter medications^[14].



Figure 4: Semisolid dosage forms

- **Ointments:** To apply to skin or mucous membranes (in the nasal, vaginal, or rectal cavities) for medicinal, preventative, or aesthetic purposes, semisolid dosage forms are of a semisolid consistency. Ointments, creams, gel/jelly, lotions, pastes, suppositories, and transdermal patches are examples of semisolid dose forms (Figure 4 and Table 2) [13]. By applying semisolid dosage forms locally and externally to the target site, the likelihood of adverse effects is decreased. It is practical for individuals who are asleep or who have trouble receiving medication orally. It is more stable than liquid dose forms and an appropriate dosage form for bitter medications [14].
- **Creams :** Skincare products are semisolid dosage forms that are relatively soft, simple to spread, and frequently include more than 20percentage water and volatile chemicals and less than 50% hydrocarbons (waxes or polyols) as the drug's foundation. Oil-in-water (O/W) and water-in-oil (W/O) cream bases are two different types of emulsifications that are utilized as the foundation for cream products. Small oil globules spread in a continuous aqueous phase stabilised by surfactants make up oil-in-water (O/W) creams [15]. Because they are less oily and may be easily removed with water, petroleum creams are more aesthetically pleasant. Small droplets

of water are spread across a continuous oily phase in water-in-oil (W/O) creams. Hydrophobic medications are easily integrated into W/O creams and provide greater moisture than O/W creams barriers to stop moisture loss from the cytoplasm, the skin's outermost layer.[14]

- **Liquids (Gels) and lotions:** Gels are semisolid systems in which the liquid phase is contained in 3-dimensional polymer matrices with a high level of physical or chemical cross-linking (made from natural or synthesised gums) [16]. They are utilised in lubrication products, cosmetics, medicine, and even as a delivery system for spermicides injected into the vagina [14]. An aqueous fluid preparation for friction-free external usage is a lotion. To lessen evaporation, they are immediately applied to the skin or poured onto an appropriate dressing before being covered by a waterproof dressing [14].
- **Pastes:** In essence, a paste is an ointment that has had a significant number of insoluble materials added. The system stiffens when there is a lot of particle debris present. Paste has less penetration, less maceration, and less heat than ointment. They create a strong perimeter of protection when applied to the skin [15]. Before certain toxic chemicals reach the skin, the solids they contain can absorb and, as a result, neutralise them. The paste, like the ointment, creates a seamless coating that is largely water-impermeable [16]. The film may be used as an effective sunscreen since it is opaque, unlike the ointment. The paste is less oily because the fluid hydrocarbon percentage is absorbed by the particle [14].
- **Transdermal patches:** An adhesive medicinal patch used to apply a particular amount of medication to the skin to enter the bloodstream is known as a transdermal patch or skin patch. Transdermal patches are a highly advised therapy choice for people who are unable to take oral dose forms or oral drugs that have unbearable side effects [17]. However, this cannot be used to manage severe pain or in clinical settings when a quick medication titration is necessary. The transdermal patch is composed of two layers a backing film and a medication enclosed in a film or adhesive on the second layer. The membrane, which is a thin film, regulates how quickly the medicine diffuses from the patch to the skin. The patch's sticky coating aids in its adhesion to the skin [18]. The film-coated tape is immediately included into the patch design as a useful layer or outer lining. Before placing the patch to the skin, the release liner is removed to protect the sticky side of the patch that will come into touch with the skin. [19]. Based on the method of drug loading, transdermal patches are divided into four categories: matrix, reservoir, multilaminate, and drug-in-adhesive. The first type is a single-layer/multilayer drug-in-adhesive transdermal patch, in which the medication is directly incorporated into the adhesive; the second type has a separate drug-containing layer that is thought of as a drug reservoir; the third type, known as matrix transdermal patches, have a drug layer made up of a semisolid matrix that contains a medication solution or suspension; and the fourth type is multilaminate with various drug layers (Figure 4). To be formulated as a transdermal patch, the drug's molecular weight must be less than 500 Daltons. The medication has to have enough lipophilicity to easily penetrate the skin. The length affects the drug's dose.

- **Suppositories:** A tiny, round or cone-shaped semisolid dosage form called an suppository is put into a bodily orifice (such as the vaginal cavity), where it dissolves or melts to release the medication and have either systemic or local therapeutic effects. Natural fat (cocoa butter) or polyethylene glycol (Carbowax) and glycerol serve as the major excipients in suppositories. The rectum is highly vascularized; thus, they function quickly and avoid the liver first-pass metabolic [14,22]. They are only meant to be injected in the anus.
- **Liquid dosage forms:** A suitable solvent or solvents are used to dissolve or disperse the API and excipients in liquid dosage forms, which are pourable pharmaceutical formulations. These are meant to provide an immediate therapeutic response in patients who have difficulty ingesting solid dose forms. There are two types of liquid dosage forms: dry powders that need to be reconstituted and ready-to-use liquids. These can be delivered parenterally (injectable, ocular, nasal, optic, and topical) or orally (syrups, suspensions, etc.). While parenteral liquid dosage forms are available in both sterile and non-sterile formulations, oral liquids are typically non-sterile (Figure 5). Based on the number of phases present, liquid dosage forms are divided into two categories: monophasic (solutions) and biphasic (suspensions and emulsions) [23].

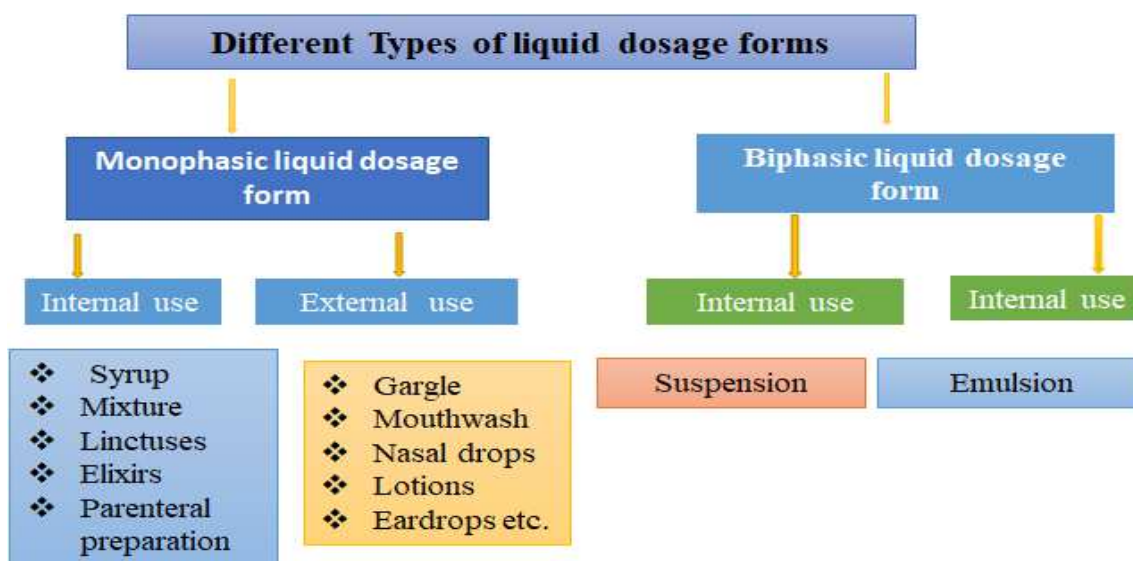


Figure 5: Liquid Dosage Forms

4. Advantages and disadvantages of solutions as dosage forms

- **Advantages:** Medication may be designed for any route of administration and is immediately ready for absorption. No need to shake the container makes swallowing easier in challenging situations.
- **Disadvantages:** Drug stability is frequently decreased in solution, making it challenging to disguise disagreeable flavours and making the containers more likely

to shatter. Technical precision is required to quantify dosage while administering medications, therefore a measurement instrument is required [24].



Figure 6: Sterile and non-sterile liquid dosage forms

5. Oral liquid pharmaceutical dosage forms : Oral fluids are homogeneous liquid preparations, often a suspension of one or more active substances in a suitable liquid basis or a solution, emulsion, or combination of those components. Either directly or after dilution, they are prepared for oral delivery. They might comprise additional ingredients including appropriate dispersing, solubilizing, wetting, emulsifying, stabilising, suspending, and thickening agents as well as antibacterial chemicals for preservation. They could also include the appropriate sweeteners, flavourings, and colourings. [25]

- **Syrup:** A second active substance is present in solution in the syrup, a poisonous oral liquid. To prevent crystallisation or alter solubilization, taste, and other base qualities, sorbitol may be added to this base, which often contains substantial amounts of sucrose or other sugars. Other sweeteners, such as saccharin, and thickening agents may be present in sugarless syrup. Ethanol 95 percent may be used in syrup as a preservative or as a flavouring solvent. In order to preserve the microbiological quality of the preparation, antimicrobial agents may be added to syrups.
- **Oral suspension:** An oral liquid that has an additional active component contained in a suitable base is known as an oral suspension. Suspended solids can segregate for a while when kept, but they are quickly re-distributed when shaken. When creating oral suspensions with suspended particles, it is important to make sure that particle size is under control for the preparation's intended purpose.
- **Solution:** An oral liquid called an oral solution is one that has one or more active components that have been dissolved in an appropriate base measurement tool, such as a dropper.

- **Drop:** With the use of an appropriate measurement tool, such as a dropper, an oral drop is a liquid that has been prepared to be ingested in small quantities.
- **Emulsion:** An oral emulsion is a liquid that is taken orally and contains an additional active component that is unstable in water. Stabilized oil-in-water dispersions may also contain dissolved particles in any or both phases of the preparation. Although the two preparatory phases can readily be combined by shaking, they can also separate. When properly shaken, the product is completely stable to deliver a homogenous dosage.
- **Mixture:** An oral liquid made up of one or more active substances that have been suspended or dispersed in a suitable base makes up the combination. While kept for a while, suspended solids may separate, shaking makes them readily re-suspended.
- **Linctus:** Linctus is a viscous oral liquid with one or more active substances mixed in a base that is acceptable and often has a greater concentration of sugar. Generally speaking, linctus are created to cure a cough, and these are taken with out inclusion of water.
- **Elixir:** This is a transparent, flavoured oral beverage with a high concentration of sucrose that may also contain ethanol (95%) or ethanol that has been diluted [26]. It comprises one or more active substances that have been dissolved in a suitable base.

VI. DRUG DELIVERY SYSTEMS

1. **Pharmacokinetics:** What the body "does to the medication" is what it is. Absorption, distribution, metabolism, and elimination are all included. Drug Absorption shown in figure .7

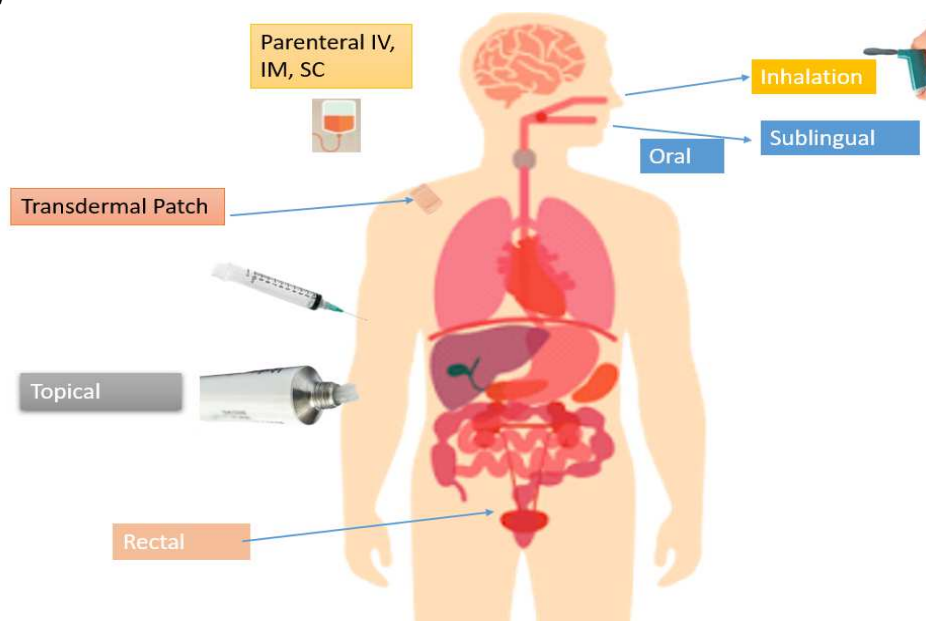


Figure 7: Drug Absorption

Drug absorption is the process by which an unaltered drug moves from the site of delivery to the systemic circulation. It is the transfer of a medication into the bloodstream from the place of administration. The way that drugs are absorbed depends on several different things.

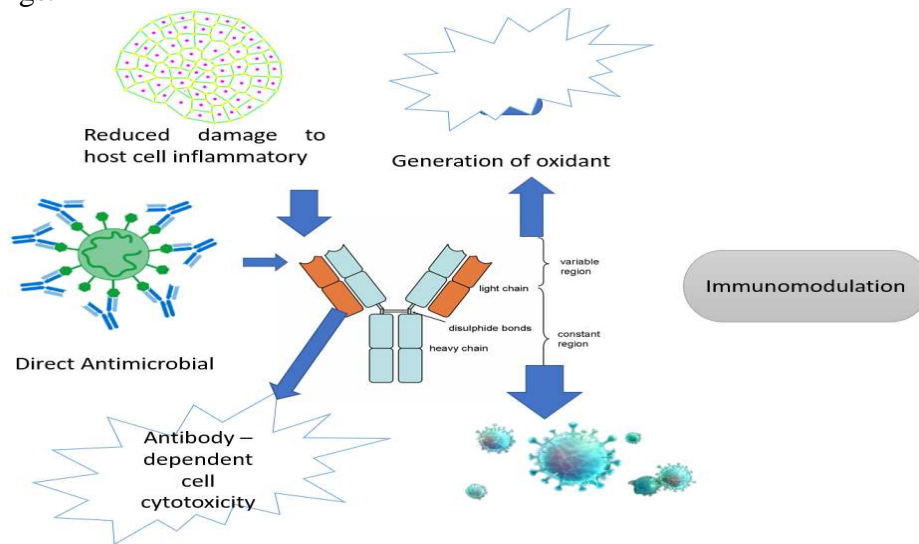


Figure 8: Factors influencing drug absorption

It contains physiological characteristics of the medication, such as how fat-soluble form is better absorbed than water soluble form. Drug administration methods, such as intravenous, allow drugs to reach the bloodstream directly. Food, such as milk and milk derivatives, reduces absorption. The absorption of oral iron is increased by the presence of other medications, such as ascorbic acid. Drug absorption is decreased by gastrointestinal and other illnesses, such as gastroenteritis.

2. Drug Distribution: The reversible transport of a medicine from the circulation to the body's extravascular fluids and tissues is referred to as drug distribution (for example, fat, muscle, and brain tissue). Drugs are absorbed and then enter the bloodstream. Drugs must first pass the capillaries barrier to reach the interstitial space from the serum before continuing through the cell membrane to reach the intracellular fluids.

- **Drug Metabolism:** Metabolism, sometimes referred to as biotransformation, is the chemical modification of a drug in a live body. Drug metabolism mostly occurs in the liver, although it can also occur in the GI tract, kidney, lungs, blood, skin, and placenta.
- **Drug Excretion:** Drug excretion is the process through which a drug and its metabolites are eliminated from the body. The kidney is the primary organ via which medications are excreted; other organs include the lungs, bile, faeces, perspiration, saliva, etc. [27]

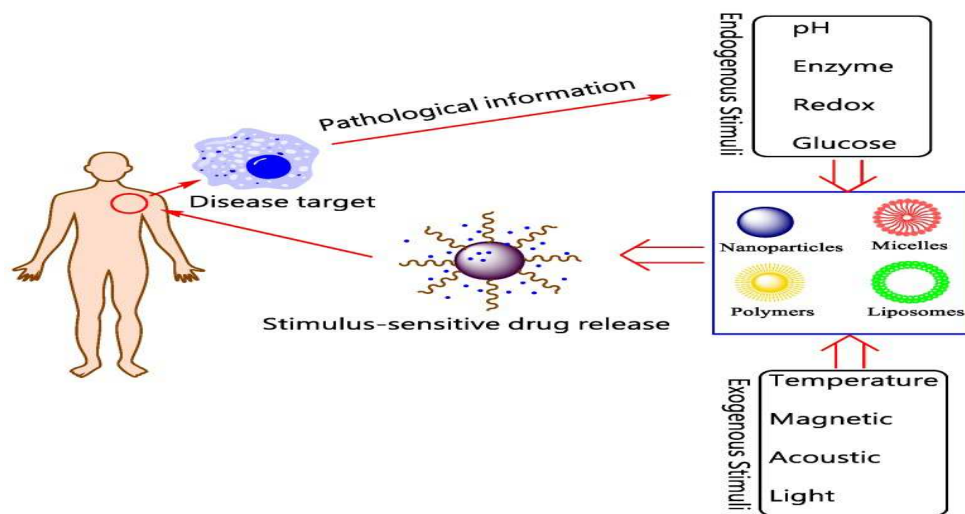


Figure 9: Schematic Illustration for Stimuli-Responsive DDSs.

Table 2: Microspheres: as Carriers used for Novel Drug Delivery System

Sr.No.	Type of microsphere	Application
1.	Bio adhesive microspheres	medication distribution through the buccal, oral, ocular, nasal, and colon GI - Glipizide, Nasal - Gentamicin, and Insulin Insulin in the colon and methyl prednisolone in the eyes
2.	Magnetic microspheres	used it for directing medications to tumour areas, protein purification, cell isolation, and DNA analysis (Doxorubicin)
3.	Floating microspheres	Carriers for drugs like antiviral, antifungal and antibiotic agents (so called absorption windows), non-steroidal anti-inflammatory drugs, Prednisolone, Lansoprazole
4.	Radioactive microspheres	in order to diagnose - Diagnostic radioembolization using human serum albumin macroaggregated to ^{99m} Tc (MAA) ^{99m} Tc-sulfur colloid for thrombus imaging in deep vein thrombosis ⁹⁰ Y microspheres are used for radioembolization of liver and spleen tumours, and ²¹² Pb-sulfur colloids are used for local radiotherapy.
5.	Polymeric microspheres	delivery of vaccines for hepatitis, influenza, pertussis, and diphtheria Easy-to-degrade medication administration via oral route: Using DNA plasmids for gene therapy, insulin and LHRH delivery medication distribution under control following local application: release of hormones, peptides, and proteins over a long period of time

Table 3: Possible advantages and disadvantages of biomaterials and extracellular vesicles as a drug delivery system.

Funding

Biomaterials	Extracellular vesicles
Advantage	Advantage
<ul style="list-style-type: none"> • Control and targeted drug release. • Scalable, cost effective. • Customized modification for personalized medicine. • Drug delivery to the intended administration route. • Temperature responsive. 	<ul style="list-style-type: none"> • Bioavailability and biocompatibility. • Better BBB permeability. • Carry biomolecules DNA, RNA, proteins, and small molecules. • Natural, safe and efficient in delivering their cargo. • Can be used for targeted drug delivery. • Delivery with or without modification.
Disadvantage	Disadvantage
<ul style="list-style-type: none"> • Strategies evolving for drug delivery across BBB • Studies indicated the degree of toxicity. (Cytotoxicity, inflammation, immunotoxicity). 	<ul style="list-style-type: none"> • Lack of controlled release mechanism. • Interaction of drug with components. • Mechanism of drugs of drugs to the target and immune clearances is understudied.

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