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GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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Abstract

The drug delivery system enables the release of the active pharmaceutical ingredient to achieving a desired therapeutic response. Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. Moreover, the drug has to be delivered at a specified controlled rate and at the target site as precisely as possible to achieve maximum efficacy and safety. Controlled drug delivery systems are developed to combat the problems associated with conventional drug delivery. There has been a tremendous evolution in controlled drug delivery systems over the past two decades ranging from macro scale and nanoscale to intelligent targeted delivery. The initial part of this review provides a basic understanding of drug delivery systems with an emphasis on the pharmacokinetics of the drug. It also discusses the conventional drug delivery systems and their limitations. Further, controlled drug delivery systems are discussed in detail with the design considerations, classifications, and drawings. In addition, nano-drug delivery, targeted and smart drug delivery using stimuli-responsive and intelligent biomaterials are discussed with recent key findings. The paper concludes with the challenges faced and future directions in controlled drug delivery.

Keywords: controlled release dosage forms, pharmacokinetics, nano-drug delivery, smart and stimuli-responsive delivery, intelligent biomaterials

1. Introduction

A drug (API) is a substance (recognized in official pharmacopeia) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease as per the FDA. Drug delivery is a technique of delivering medication to a patient in such a manner that specifically increases the drug concentration in some parts of the body as compared to others [1]. The ultimate goal of any delivery system is to extend, confine and target the drug in the diseased tissue with a protected interaction. Every Dosage form is a combination of drug/active pharmaceutical ingredients (APIs) and the non-drug component called excipients/additives (Figure 1). APIs are the actual chemical components used to treat diseases [2].

Dosage form = Active Pharmaceutical Ingredient (API) + Excipients/additives

1.1. Need for a Dosage Form

Generally, drug delivery systems (DDS) are preferred because direct clinical use of the active drug substances (APIs) "as they are" is very rare due to several reasons: API handling and accurate dosing can be difficult or impossible for very potent drugs (e.g., low mg and µg doses) [3]. Administration of drugs into the body cavities (rectal, vaginal) can be impractical and unfeasible as they can be degraded at the site of administration (e.g., low pH in the stomach) and may cause local irritations or injury when the drug concentration is high at the site of administration [3]. Some APIs are sensitive to the environment and can benefit from reducing their exposure to environmental factors (light, moisture, temperature, and pH), or they need to be chemically stabilized due to the inherent chemical instability. APIs mostly have unpleasant organoleptic qualities (taste, smell, and compliance), which reduce patient compliance [2].

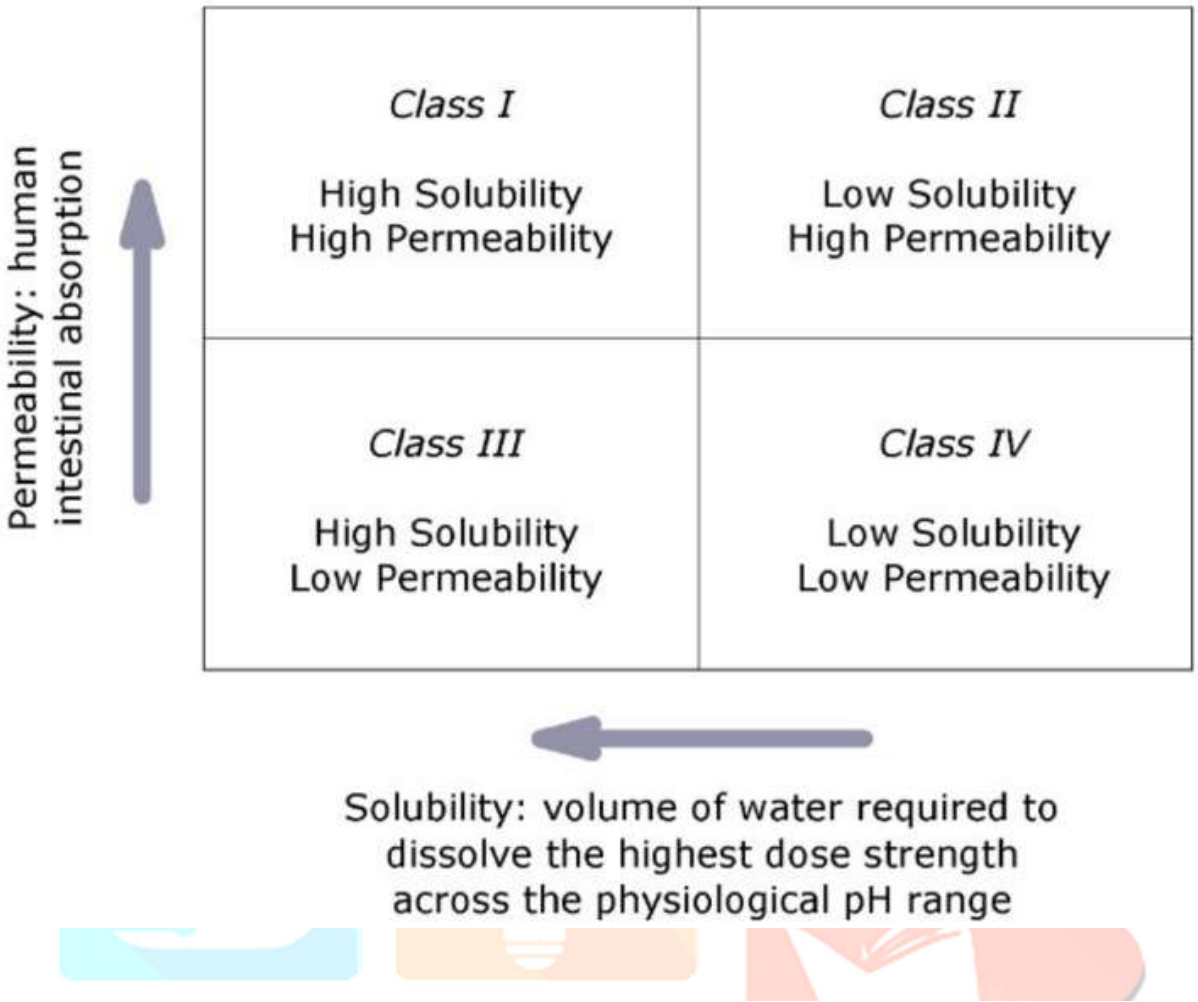
Hence APIs are always formulated along with the excipients. Excipients/Additives are used: To give particular structure and shape to the formulation, to increase stability, to mask the bitter taste and increase palatability, to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage, to aid in the handling of the active substance and to aid the manufacturing process [4]. In addition, excipients enhance the bioavailability and improve the overall safety or function of the dosage form during storage or in use with enhanced patient acceptability [5].

1.2. Excipients

One or more of the excipients that are generally utilized in formulations include: colouring agents, suspending agents, binding agents, solvents and lubricants, perfumes, sweetening agents, flavoring agents, solubilizing agents, and antioxidants [4]. A filler is included to increase the size of the tablet (e.g., lactose) as often the amount of "active ingredient" is so small that the dosage form would be too tiny to handle without filler. Binders are added to hold the tablet together after it has been compressed, and prevent the break-down into separate pieces (e.g., starch, HPMC, etc.) [6]. Disintegrants help the dosage form to break down into small fragments after ingestion, which allows the medicine to dissolve and be absorbed by the body so that it can act more rapidly [6]. The glidants prevent lump formation by reducing the friction between particles and improving the flowability of the tablet granules or powder. Anti-adherents stop the powder from sticking to the machines during manufacturing. Lubricants ensure the smooth surface of dosage form, by reducing the friction between the walls of the tablets and the die cavity during ejection. Flavoring agents help to mask the unpleasant odor and colourants are added to aid in recognition and aesthetics [7].

1.3. Biopharmaceutics Classification System (BCS) Classification of Drugs

The Biopharmaceutics Classification System classifies drugs into four types based on their permeability (intestinal) and solubility (Figure 2) [8]. Class, I drugs possess high permeability and high solubility, and are well absorbed; their absorption rate is greater than excretion (e.g., metoprolol, paracetamol, etc.). Class II drugs have high permeability but low solubility and the bioavailability is restricted by their rate of solvation (e.g., glibenclamide, aceclofenac, etc.) Class III drugs possess low permeability but high solubility where the drug solvates quickly; nevertheless, absorption is limited by the rate of permeation. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied (e.g., cimetidine). Class IV drugs have low permeability and low solubility and are poorly absorbed through the intestine; thus, they have poor bioavailability with high variability (e.g., Bifonazole) [8].



1.4. Different Routes of Drug Administration

Dosage forms can be administered through different routes based on the target site, duration of treatment, and the physicochemical attributes of the drug [9]. The most common dosage forms comprise tablets, capsules, pills, ointments, syrup,s and injections. Various routes of drug administration are tabulated in Table 1 and Figure 3. The preferred route of drug administration depends on three main factors: The part of the body being treated, the way the drug works within the body,y and the solubility and permeability of the drug. For example, certain drugs are prone to destruction by stomach acids after oral administration resulting in poor bioavailability. Hence, they need to be given by the parenteral route instead. Intravenous administration of drugs gives 100% bioavailability [9].

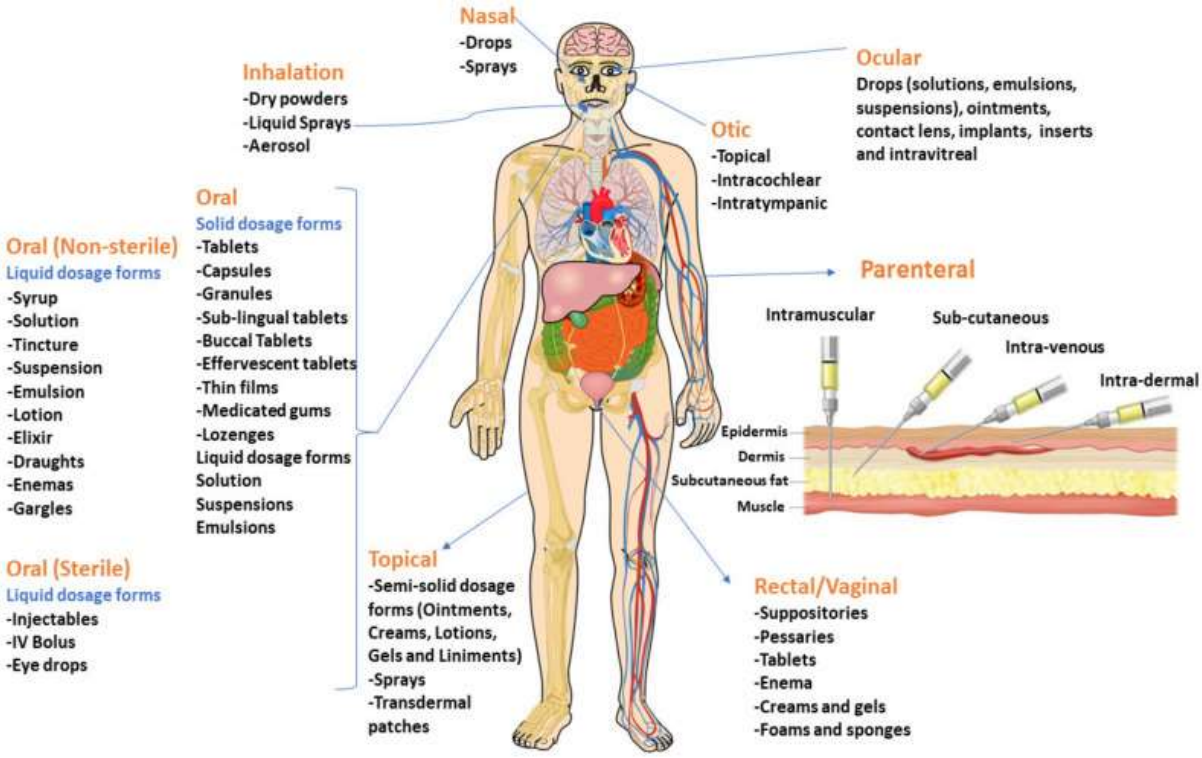


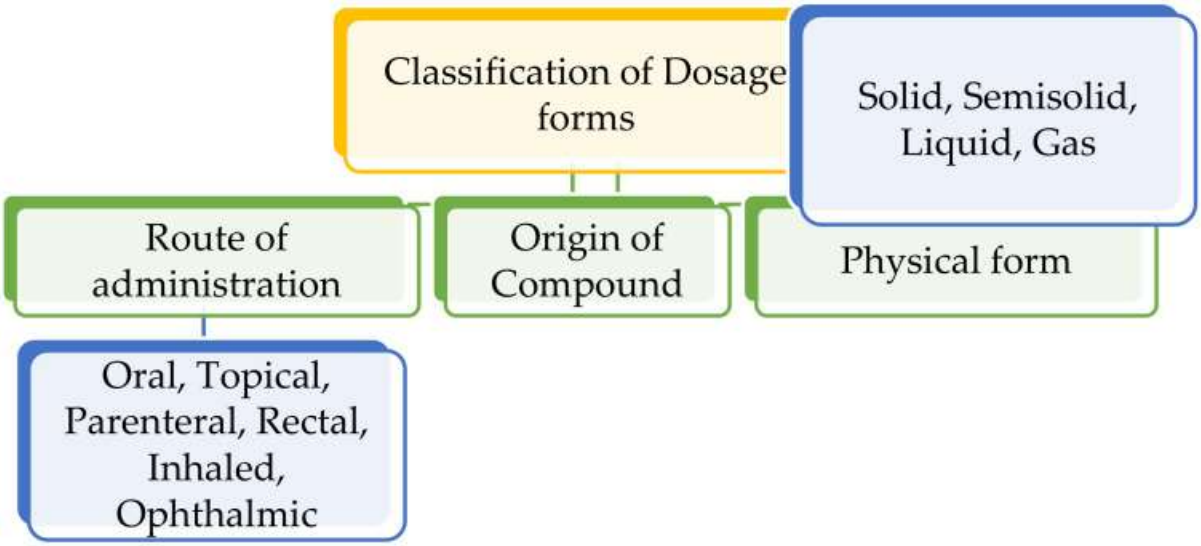
Table 1

Routes of drug administration.

Oral	**Swallowed by Mouth as a Tablet, Capsule, Lozenge, or Liquid**
Buccal	Held inside the cheek
Sub-lingual	Placed below the tongue
Enteral	Delivered directly into the stomach or intestine
Inhalable	Breathed in through a tube or mask
Nasal	Given into the nose by spray or pump
Ophthalmic	Given into the eye by drops, gel, or ointment
Otic	Given by drops into the ear
Rectal	Inserted into the rectum
Vaginal	Inserted into the vagina
Topical	Applied to the skin
Transdermal	Given through a patch placed on the skin
Infused	Injected into a vein with an IV line and slowly dripped in overtime
Intramuscular	Injected into the muscle with a syringe
Intravenous	Injected into a vein or an IV line
Subcutaneous	Injected just under the skin

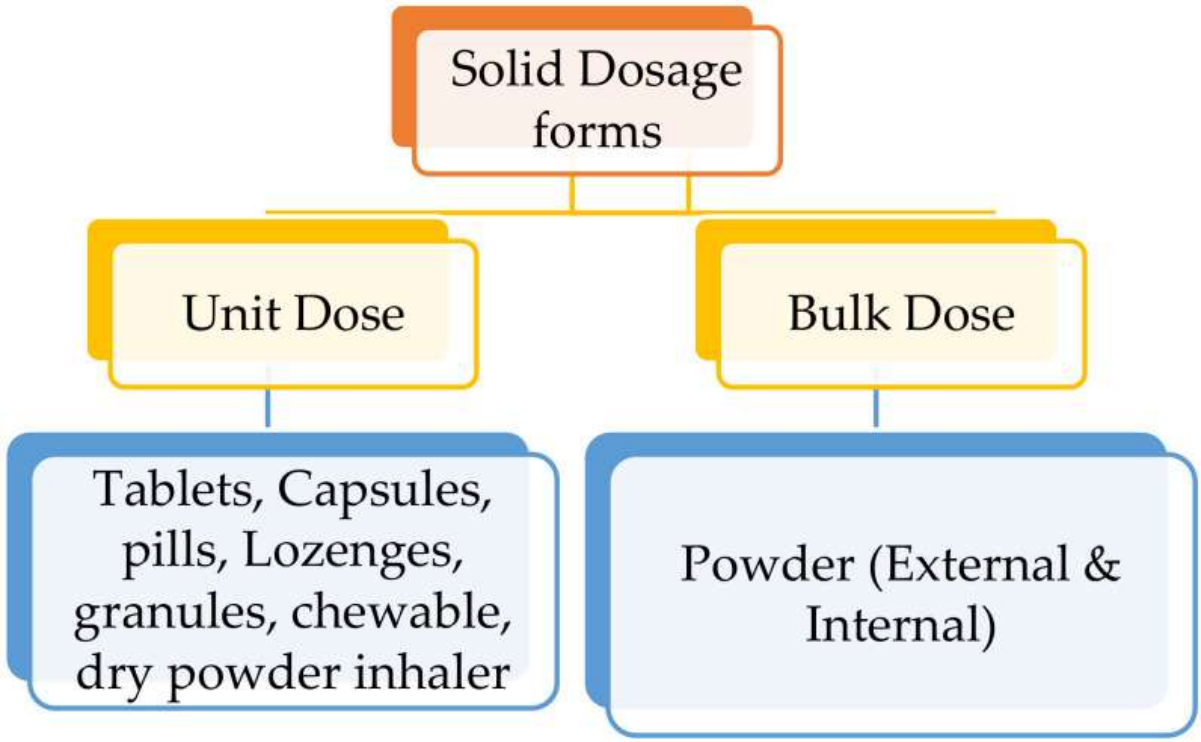
2. Classification of Dosage Forms

The dosage forms are classified based on the route of administration, the origin of the compound (natural/synthetic), and the physical form of the final delivery systems (Figure 4).



2.1. Classification of Solid Dosage Forms

Solid dosage forms are further classified into two main categories based on the type of dose, i.e., unit dose and bulk dose. (a) Unit dose: Each dose is fixed and formulated as a separate dosage form and the patient needs to take a single unit of a specific dose at a time. Examples of unit dosage forms include tablets, capsules, pills, lozenges, chewable tablets, effervescent tablets, and dry powder inhalation in metered-dose containers. (b) Bulkdoese: As the name itself says, it is a bulk solid powder where the individual dose is not formulated (Figure 5) [10,11]. Dose dumping is a major problem with bulk powders. However, bulk powders are generally used as dressing powder for surgical and injury wounds. Examples of bulk dosage forms include insufflation powder, dressing powder, etc. [10].



2.1.1. Tablets

A tablet is a solid unit dosage form that is manufactured by compression and wet/dry granulation into different shapes (round, oval, or square shape). For efficient tableting, binders, glidants, and lubricants are often added as excipients. To enhance the easy breakdown of tablets in the digestive tract, disintegrants are added. The tablet coating with pigments, sweetener, and san-flavoring ngg agents helps to mask the taste of other ingredients and makes the tablet smoother and easier to swallow. Tablet coating also offers environmental protection and extends the shelf life [10,12].

Sublingual and Buccal tablets are also solid unit dosage forms administered by placing them under the tongue and between the gum and cheek, respectively. Advantages of sublingual/buccal delivery systems include: The medications dissolve rapidly and are absorbed through the mucous membranes of the mouth into the systemic circulation. This avoids the acid and enzymatic environment of the stomach and the drug-metabolizing enzymes of the liver [10,12].

Effervescent tablets are designed to evolve carbon dioxide when in contact with water and disintegrate within a few minutes. These are uncoated tablets consisting of acids (citric or tartaric acid) and carbonates or bicarbonates which react rapidly in water and release carbon dioxide. They are intended to be either dispersed or dissolved in water before intake to offer very rapid tablet dispersion and dissolution and release of the drug. It tastes similar to a carbonated drink (e.g., antacids). Chewable tablets are chewed before swallowing. They are designed for administration to deliver the drug by

mastication. They are very useful for children and the elderly (e.g., vitamin products) [10,12].

2.1.2. Capsules, Lozenges, Pills, and Granules

A capsule is a unit solid dosage form where the drug components are enclosed in a soluble shell. Capsules help to mask the unpleasant taste of its contents and the drug has limited interaction with the excipients. Capsules are classified into two types: Hard-shelled capsules, which are used to encapsulate dry, powdered components; soft-shelled capsules, principally used for hydrophobic drugs and oily active substances that are suspended or dissolved in oil. Lozenges are chewable solid unit dosage forms, where the drug is loaded in a caramel base made up of sugar and gum; the latter provides cohesiveness and strength to the lozenge and enables slow release of the drug. Lozenges are traditionally used for local slow release of demulcents, anesthetics, and cough remedies in the mouth/pharynx. Pills are solid unit dosage forms made by compressing API with adhesives and other excipients into rounded masses for oral administration. Granules are solid, dry aggregates provided as a single dose in sachets which can either be placed on the tongue and consumed with water or dissolved in water before taking (Figure 6h). Effervescent granules evolve carbon dioxide similar to effervescent tablets when added to water. Figure 6 represents the examples of solid unit dosage forms [10].

2.1.3. Bulk Solid Dosage Forms

Bulk Powders are multidose formulations comprising loose, solid, and dry particles of variable fineness. One or more active ingredients are present with or without excipients and, if needed, colouring and flavoring agents are added. These are packed in wide-mouthed, air-tight, bulk containers made of glass or plastic, and are intended for either internal or external administration. There are two kinds of bulk powders intended for internal use.

Bulk powders are often limited by inaccurate dosage since the patient measures each dose varyingly. Hence, they are usually formulated with non-potent drugs such as laxatives, antacids, purgatives, etc., The powder is then typically dispersed in water or dissolved before taking. Divided powders are single-dose of powder (for example, a small sachet) with more accurate control on dosage than bulk powder [10].

2.2. Semisolid Dosage Forms

Semisolid dosage forms are of semisolid consistency intended to apply onto skin/mucous membranes (nasal, vaginal, or rectal cavities) for therapeutic, protective,e or cosmetic applications. Semisolid dosage forms include ointments, creams, gel/jelly, lotions, pastes, suppository,ies, and transdermal patches (Figure 7 and Table 2) [13]. Semisolid dosage forms are used externally and locally at the target site, which reduces the probability of side effects. It is convenient for unconscious patients or patients who have difficulty in oral administration. It is a suitable dosage form for bitter drugs and more stable than liquid dosage forms [14].

Table 2

Differences between ointment, paste, cream, and gel.

Ointment	Cream	Paste	Gel
Hydrocarbon based greasy semisolid	Mostly water-based where drugs are loaded in O/W or W/O emulsion	It is an ointment where a high percentage of insoluble solids are added	The liquid phase is trapped within a three-dimensional polymeric matrix
Translucent to opaque	Opaque	Opaque	Transparent
Greasy	Less greasy	Less greasy	Non-greasy

2.2.1. Ointments

Ointments are oil-based semisolid formulations where the base is usually anhydrous and immiscible with skin secretions. These are made of less than 20% water and volatile substances, and more than 50% of hydrocarbons (waxes, or polyols) as the vehicle, due to which retention time for ointments is high and spreadability is less. Hence, ointments may be used as emollients or to apply suspended or soluble drugs to the smaller portions of skin for a longer duration [14,15].

2.2.2. Creams

Creams are relatively soft, easy to spread, semisolid dosage forms which often contain more than 20% water and volatile substances and less than 50% hydrocarbons (waxes or polyols) as the base for the drugs. Cream bases are emulsions that are classified into two types: Oil-in-water (O/W) creams and water-in-oil (W/O) creams. Oil-in-water (O/W) creams are comprised of small oil globules dispersed in a continuous aqueous phase stabilized by surfactants [15]. Oil-in-water creams are more cosmetically tolerable as they are less greasy and simply washed off using water. Water-in-oil (W/O) creams are comprised of small droplets of water dispersed in a continuous oily phase. Hydrophobic drugs can easily be incorporated into W/O creams and, are also more moisturizing than O/W creams as they offer an oily barrier to prevent moisture loss from the outermost layer of the skin, the stratum corneum [14].

2.2.3. Gels (Jellies) and Lotions

Gels are semisolid systems in which the liquid phase is confined in a 3D polymeric matrix (made up of natural or synthetic gums) with a high degree of physical or chemical cross-linking [16]. They are used in medicine, cosmetics, for lubricating purposes an,d also as a drug carrier for spermicides used in the vagina [14]. A lotion is an aqueous fluid preparation for external use without friction. They are applied to the skin directly or pored on a suitable dressing and covered with a waterproof dressing to reduce evaporation [14].

2.2.4. Pastes

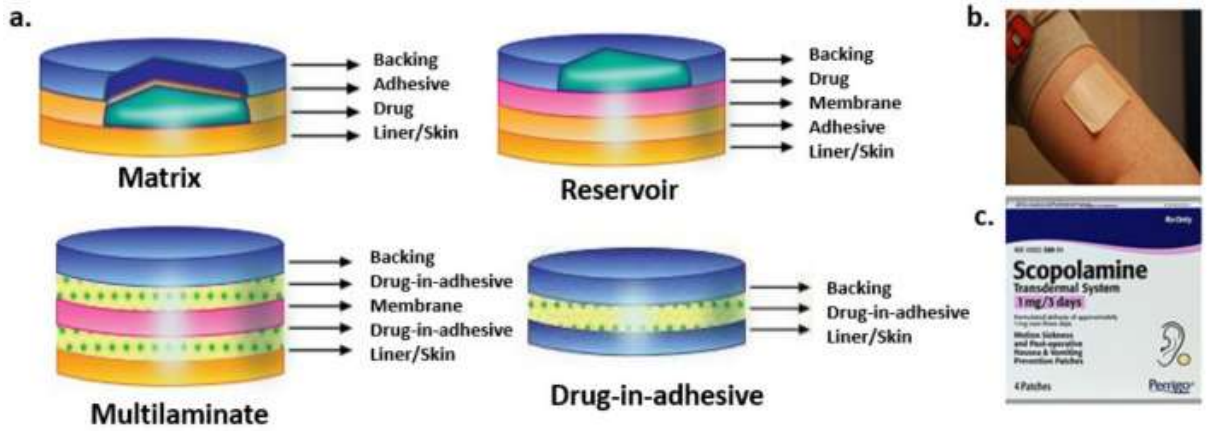
A paste is an ointment with a high percentage of insoluble solids added. A large amount of particulate matter stiffens the system. As compared to the ointment, paste has lower permeability, lower maceration, and lower, heat. When applied to the skin, they form a good protective barrier [15]. The solids they contain can absorb and therefore neutralize certain harmful chemicals before they reach the skin. Like the ointment, the paste forms a complete film that is relatively

impermeable to water [16]. Unlike the ointment, the film is opaque, so it can be used as an effective sunscreen. Since the fluid hydrocarbon fraction is absorbed by the particles, the paste is less greasy [14].

2.2.5. Transdermal Patches

A transdermal patch or skin patch is an adhesive drug patch that is placed on the skin to deliver a specific dose of drug into the blood through the skin. For patients who are unable to take oral dosage forms or oral medications that cause intolerable side effects, the use of transdermal patches is strongly recommended as a treatment option [17]. However, this is not an appropriate method to control acute pain or clinical situations that require rapid titration of the drug. The transdermal patch is made up of a backing film, which is the outermost layer of the patch and provides protection for the drug components. The second layer consists of a drug contained in a film or adhesive. The membrane is a thin film that controls the diffusion rate of the drug from the patch to the skin. The adhesive layer helps the patch adhere to the skin [18]. As a functional layer or outer lining, the film-coated tape is directly integrated into the patch design. The release liner protects the sticky side of the patch which is going to be in contact with the skin and is removed before applying the patch to the skin [19].

Transdermal patches are classified into four types based on the drug loading type: Matrix, reservoir, multilaminate and drug-in-adhesive. The first type is a single-layer/multi-layer drug-in-adhesive transdermal patch, in which the drug is directly incorporated into the adhesive; the second type has a separate drug-containing layer, which is considered to be a drug reservoir; the third, called matrix transdermal patches, have a drug layer comprising a semisolid matrix containing a drug solution or suspension; and the fourth one is multilaminate having different layers of drugs (Figure 8). The molecular weight of the drug should be less than 500 Daltons to formulate as a transdermal patch. The drug should be sufficiently lipophilic for easy permeation through the skin. The dosage of the drug depends on the duration for which the patch is worn. The first commercially available patch was scopolamine for motion sickness [20].



2.2.6. Suppositories

A suppository is a small, round, or cone-shaped semisolid dosage form that is inserted into a body orifice (rectum, vagina) where it dissolves or melts to release the drug and exerts local or systemic therapeutic effects. Suppositories are made up of natural fat (cocoa butter) or polyethylene glycol (Carbowax) and glycerol as main excipients. They are exclusively intended to be introduced in the anus and show a rapid onset of action since the rectum is highly vascularized; besides, they bypass the hepatic first-pass metabolism [14,22].

2.3. Liquid Dosage Forms

Liquid dosage forms are pourable pharmaceutical formulations comprising API and excipients either dissolved or dispersed in a suitable solvent/s. These are intended to offer a fast therapeutic response to people with trouble swallowing solid dosage forms. Liquid dosage forms are available as ready-to-use liquids or dry powders for reconstitution. These can be administered by oral (syrups, suspensions, etc.) and/or parenteral (injectable, ophthalmic, nasal, otic,d topical) routes. Oral liquids are generally nonsterile, while the parenteral liquid dosage forms are offered as sterile and non-sterile formulations (Figure 9). Liquid dosage forms are classified based on the number of phases present into two types: Monophasic (solutions) and biphasic (suspensions and emulsions) [23].

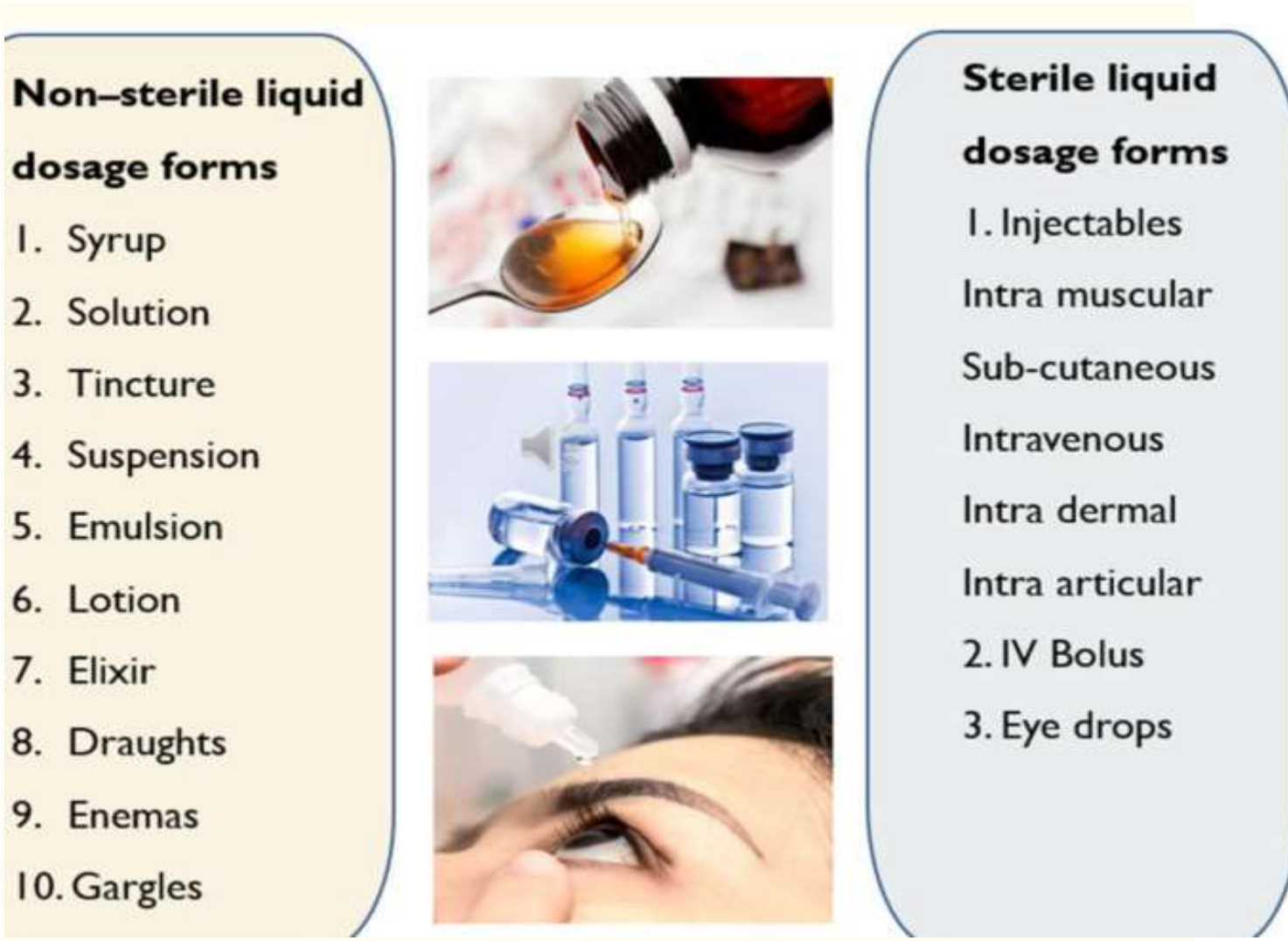


Figure 9

Sterile and non-sterile liquid dosage forms.

a. Oral solutions are monophasic clear liquids for oral use comprising of one or more active ingredients dissolved in a suitable solvent system [24].

b. Oral emulsions are biphasic liquids for oral use where the drug is present in oil-in-water emulsion either in single or dual phases [25].

c. Oral suspensions are biphasic liquid dosage forms for oral use comprising of one or more APIs suspended in a suitable solvent. They tend to sediment with time; nevertheless, they can be readily re-dispersed by shaking into a uniform suspension that remains appropriately stable to allow the accurate dose to be delivered [24].

d. Syrup is a concentrated aqueous sugar solution, usually sucrose, in which APIs are dissolved. Flavored syrups are suitable to mask the unpleasant taste of drugs [25].

e. Elixir is monophasic clear liquids for oral use for administering potent or nauseous drugs by adding pleasant flavors. The vehicle comprises a high amount of ethanol or sucrose along with antimicrobial preservatives to enhance the stability of the formulation [25].

f. Linctuses are viscous oral liquids made of a high amount of syrup and glycerol which have a demulcent effect on the membranes of the throat and are used for cough relief. These are taken in smaller doses (<5 ml) and undiluted to prolong the demulcent action [26].

g. Oral drops are either solutions, suspensions, or emulsions that are administered in very small volumes (<1 ml) into the eyes, nose, or ears [27].

h. Gargles are concentrated aqueous solutions that need to be diluted with warm water before use to wash the mouth and throat by holding the liquid in the throat and agitating with the air from the lungs [28].

i. Mouthwashes are similar to gargles but are used to maintain food oral hygiene and also to prevent infections in the mouth [23,28].

Go to:

3. Pharmacokinetics of Drug Delivery Systems

Pharmacokinetics is the movement of drugs into, through, and out of the body—the time course of drug absorption, distribution, metabolism, and excretion. In simple terms, it is what the body does to a drug [29]. A schematic illustration of pharmacokinetics is represented in Figure 10.

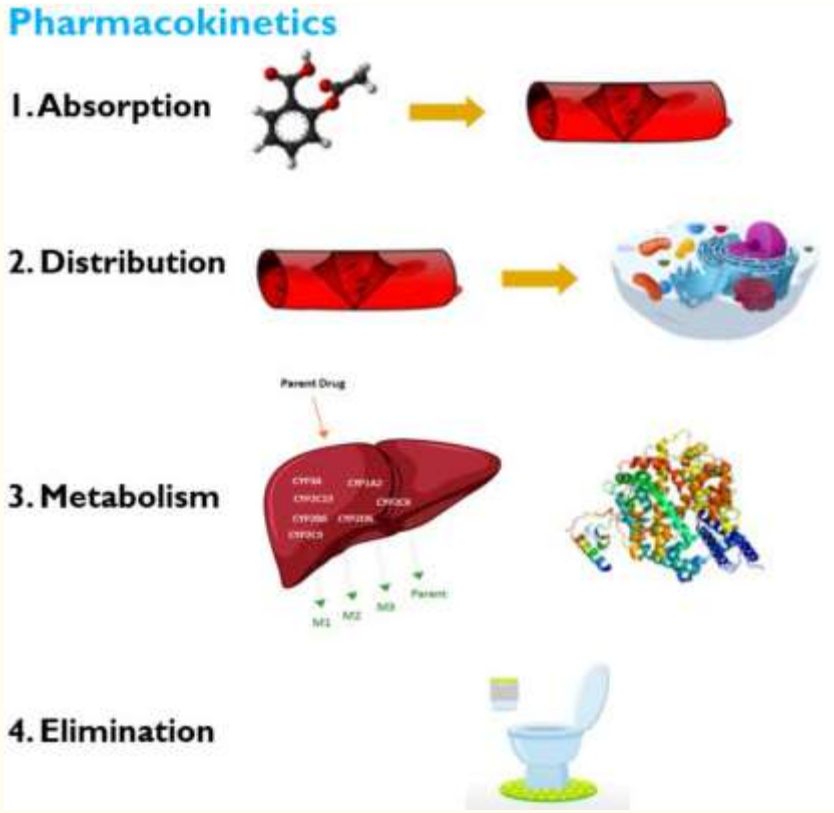


Figure 10

Pharmacokinetic phases of a drug: 1. Absorption, 2. Distribution, 3. Metabolism, 4. Excretion.

3.1. Absorption

Absorption is the movement of a drug from its site of administration to the bloodstream. The rate and extent of drug absorption depend on several factors, such as route of administration, physicochemical properties of the drug, type of formulation, and drug-food interactions [30,31]. The fraction or amount of drug (in active form) that reaches the target site through the systemic circulation is called bioavailability. Intravenous administration of the drug offers 100% bioavailability as the dosage form is directly administered into the bloodstream. Oral dosage forms suffer from poor bioavailability due to incomplete absorption and hepatic first-pass effect which metabolizes the drug in the liver, rendering it less active or inactive. Absorption of the drug through the plasma membrane occurs by either passive transport or active transport [30].

- (a)

Passive Transport involves the movement of the drug across the cell membrane from the high drug concentration region (such as the gastrointestinal tract, to the low drug concentration region (such as blood). This is a passive process and no energy is required, and the rate of drug diffusion is directly proportional to the concentration gradient [32]. Other factors influencing passive transport include the physicochemical properties of the drug, such as its lipid solubility,

molecular size, degree of ionization, on and the absorptive surface area available to the drug [30].

- (b)

Active transport requires energy to facilitate the transport of drug molecules against a concentration gradient, which usually occurs at specific sites in the small intestine. The majority of drugs that are absorbed via active transport share a similar structure with endogenous substances such as ions, vitamins, sugars, and amino acids [30,33]. A schematic of active and passive transport is given in Figure 11.

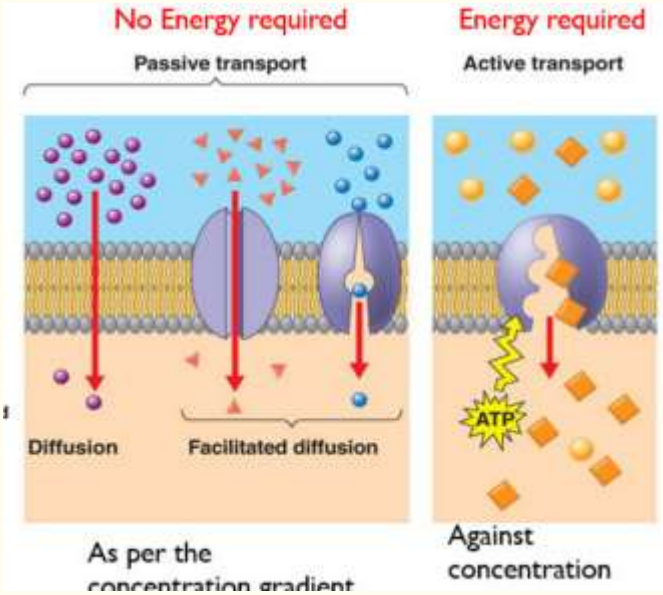


Figure 11

Schematic of transport of drug through the plasma membrane by passive transport and active transport (reproduced from [34] with permission from the OpenStax, (part of Rice University, which is a 501(c)(3) nonprofit) and [35] licensed under Creative Commons Attribution (CC BY 4.0) international license).

3.2. Distribution

Distribution is a reversible transfer of a drug between the blood and the extravascular fluids and tissues of the body (for example fat, muscle, and brain tissue). Drug distribution governs the amount of drug reaching target sites as compared to the rest of the body, and thus plays an important role in drug efficacy and toxicity. Various factors affecting drug distribution include blood flow, lipophilicity and molecular size of the drug, and binding affinity of the drug with plasma proteins [36,37]. For example, a drug with a high protein-binding affinity (e.g., warfarin), possesses a very little amount of free drug in the target

site to exert a desired therapeutic response. Warfarin drug, due to strong protein binding efficacy, can replace any other drug bound to plasma proteins and allow it to be free to show the therapeutic response [30]. Additionally, there are anatomical barriers found in certain organs like the blood-brain barrier preventing certain drugs from going into brain tissue (Figure 12). Drugs with high lipophilicity, smaller size, and low molecular weight can cross the blood-brain babarriers29].

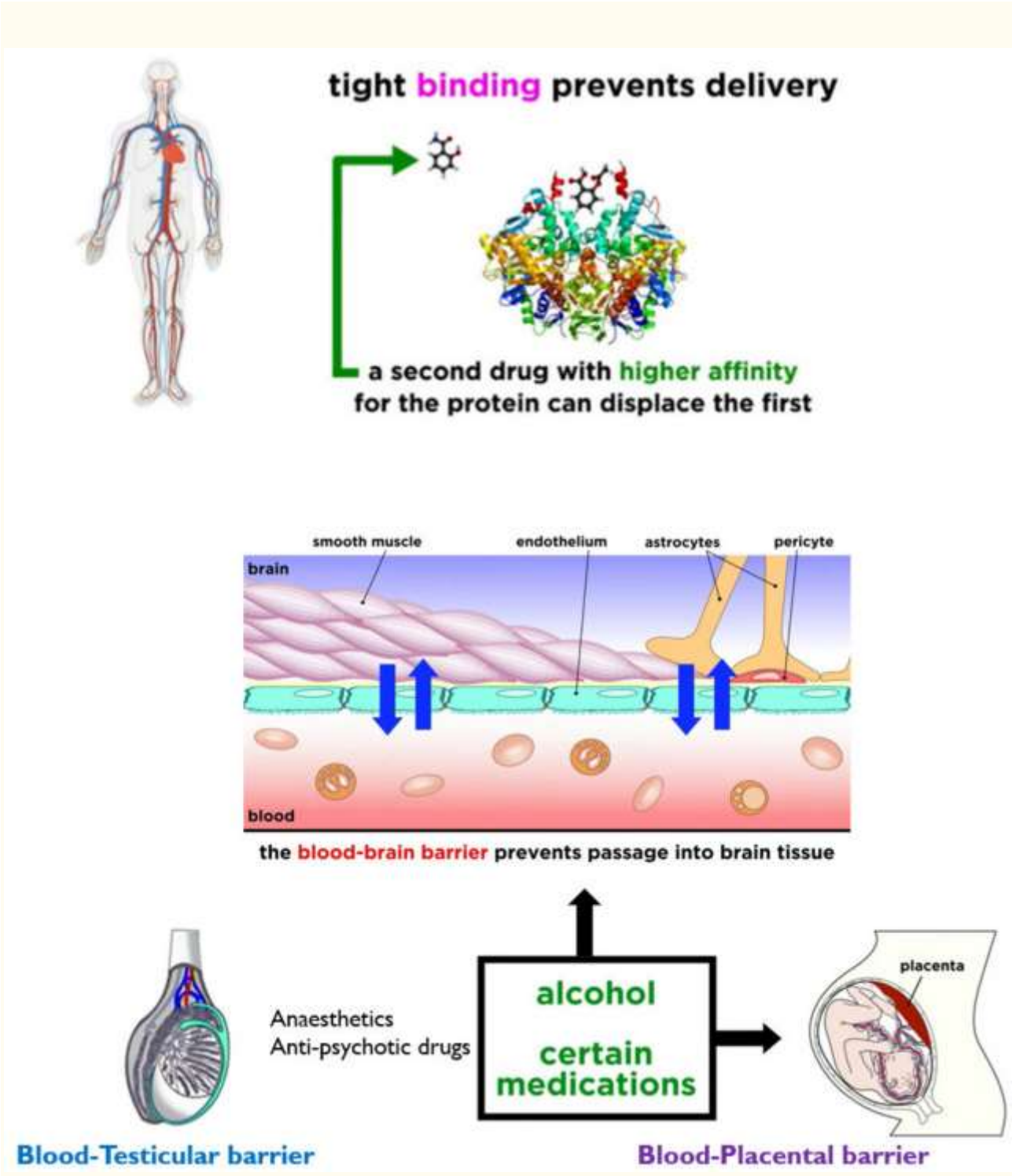


Figure 12

Schematic of barriers to drug distributions (**a**) Plasma protein binding, (**b**) Anatomical barriers.

3.3. Metabolism

The metabolism of drugs (in the gut wall and liver) into inactive or less active components before being absorbed into the systemic circulation. The concentration of a drug, especially after oral administration, is significantly reduced before reaching the bloodstream [37,38]. It is the fraction of drug that is lost during absorption, and cytochrome P450 (CYP450) enzymes of the liver are accountable for the metabolism or biotransformation of about 70–80% of the drugs in clinical use [30]. The drug metabolism is schematically explained in Figure 13.

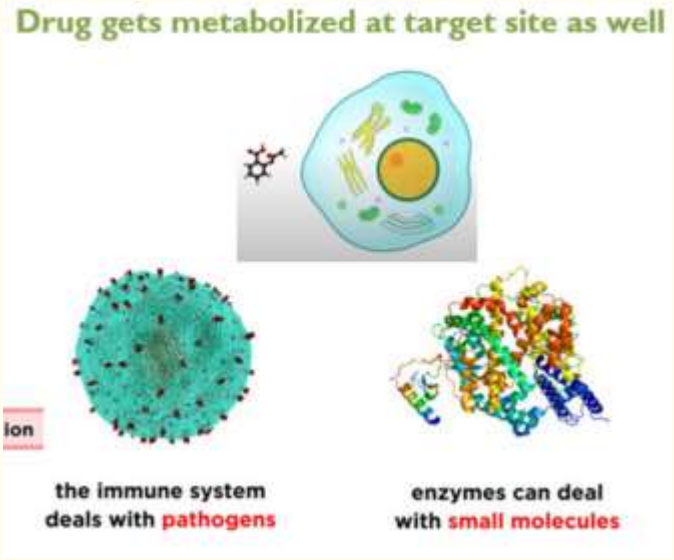


Figure 13

Schematic of drug metabolism in the liver as well as the cells.

3.4. Excretion

The removal of unchanged drugs or their metabolites from the body is called drug excretion [39]. There are many different routes of excretion, including urine, bile, sweat, saliva, tears, milk, and stool [30]. An illustration of various modes of drug excretion is presented in Figure 14.

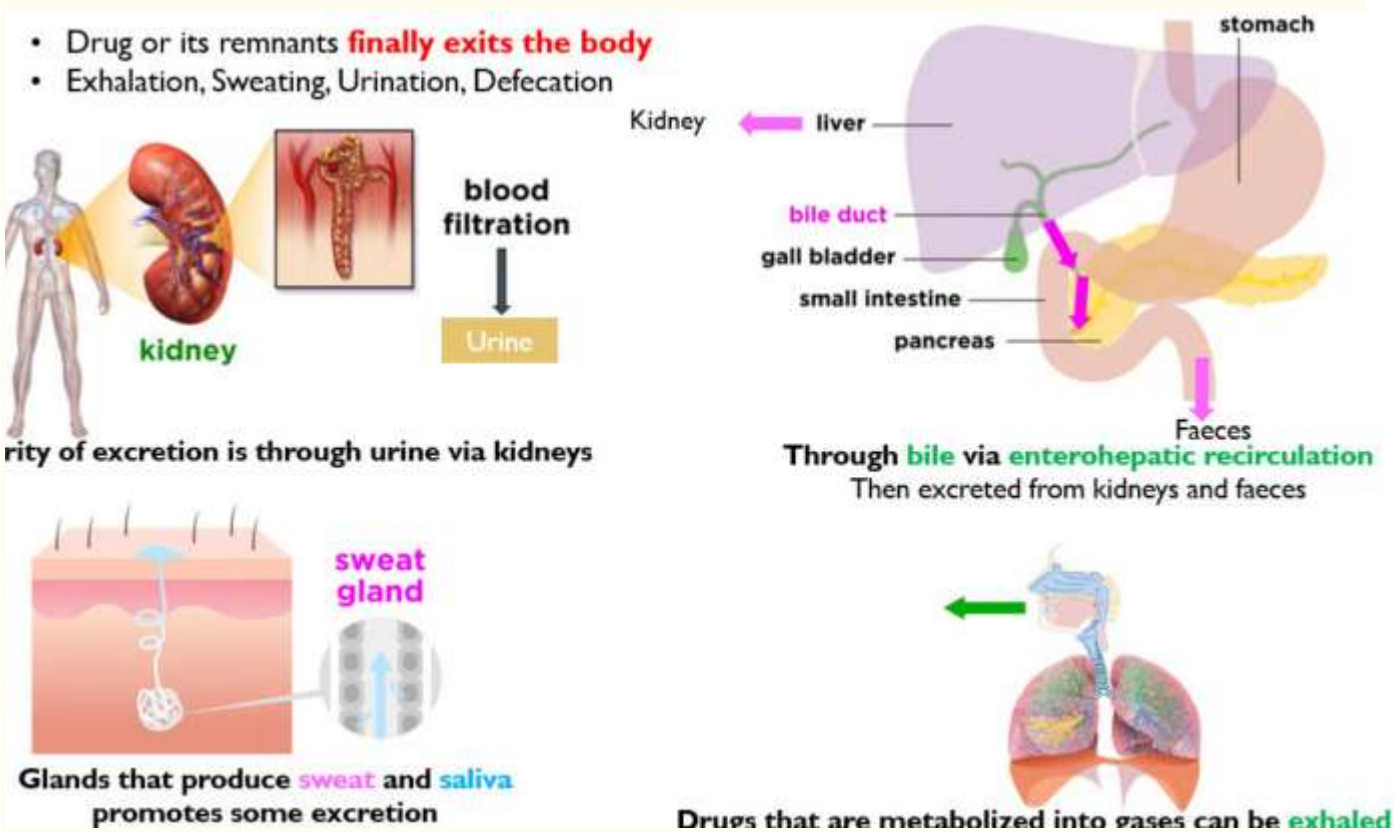


Figure 14

Schematic illustration of drug excretion from the body by kidneys, liver, skin, n and airways.

3.5. Bioavailability

This is the fraction or percentage of administered drug absorbed into the systemic circulation. Drugs with high hepatic metabolism and faster excretion have low bioavailability. The sub-therapeutic dose is present at the target site and results in low efficacy. Hence, for low bioavailable drugs, a high dosage is needed. Drugs that are absorbed via the Gastro-Intestinal Tract (GIT) are circulated to the liver first via the hepatic portal vein. The liver then acts as a filter (CYP enzymes metabolize). Only part of the drug is reached systemically. The greater the first-pass effect, the lesser the bioavailability. The IV route offers 100% bioavailability [40,41]. A schematic of factors accountable for the reduction in bioavailability is represented in Figure 15.

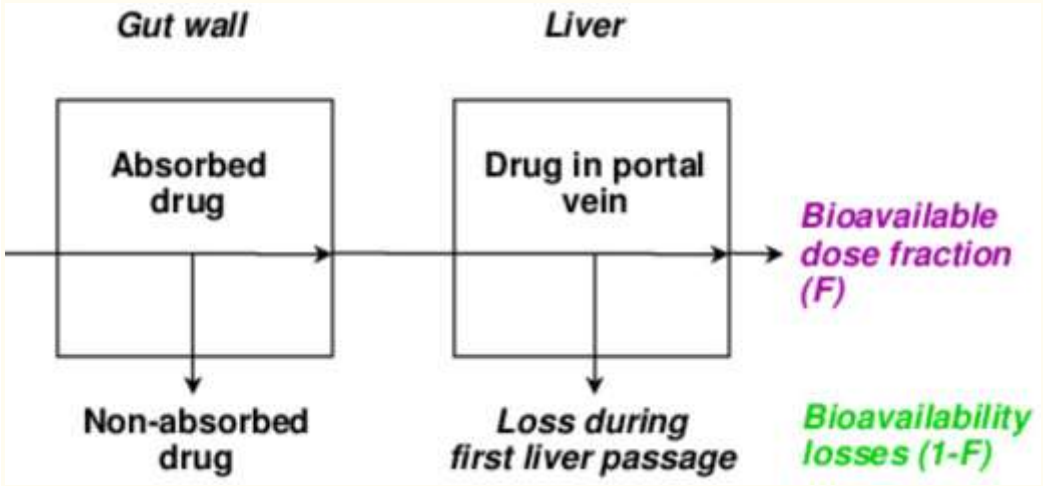


Figure 15

Schematic of factors accountable for the reduction in bioavailability.

3.6. Biological Half-Life ($t_{1/2}$)

Elimination half-life or Biological half-life ($t_{1/2}$) is the time at which the mass of an unchanged drug becomes half (50%) of the initial concentration. Simply, $t_{1/2}$ refers to how long it takes for half of the administered dose to be metabolized and eliminated from the bloodstream [42]. The half-life of a drug can be determined using the following equations:

$\mathbf{t_{1/2} = (0.7 \times V_d)/Cl}$, where V_d is the volume of distribution and Cl is clearance.

$\mathbf{t_{1/2} = 0.693/K_t}$, where K_t is the Elimination rate constant.

Drugs with a short biological half-life need frequent dosing to achieve a therapeutic response for a longer duration. The goal is to maintain the therapeutic blood level over extended periods, for which the drug must enter the systemic circulation approximately at the same rate at which it is eliminated. Elimination of a drug varies due to factors like age, weight, other medications are taken, other medical conditions present, kidney function, liver function, etc. Therefore, the half-life is used as a guide or an estimate of how long it may take for the drug to be removed from the body [41].

Go to:

4. Drug Release Kinetics Basic Concepts

The drug release profile is generally expressed as a plot of plasma-drug concentration versus time. In the plot shown in Figure 16, two important concentration levels are shown: The minimum effective concentration, below which the drug is ineffective, and the toxic concentration, above which undesirable side effects occur. Maintenance of drug concentration at any instance between minimum effective concentration to minimum toxic concentration is critical for safety and therapeutic effectiveness [42]. Drug release kinetics is said to be zero-order kinetics when a constant amount of drug is eliminated per unit time but the rate is independent of the concentration of the drug. Zero-order DDS has the potential to overcome the issues faced by immediate-release and first-order systems by releasing the drug at a constant rate, thereby maintaining drug concentrations within the therapeutic window for an extended period [43,44].

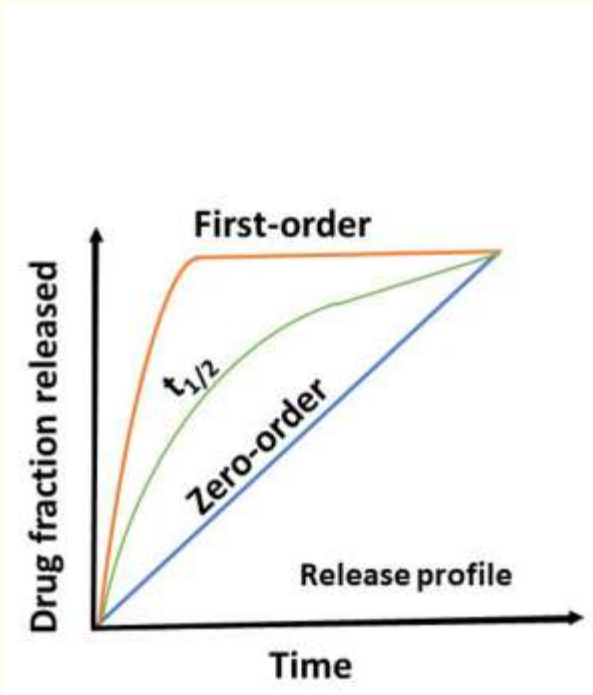


Figure 16

Drug plasma levels and release profiles.

Minimum effective concentration (MEC): The lowest level of concentration of a drug in the body that shows desired therapeutic effect [45].

Zero-order release: Zero-order kinetics is described when a constant amount of drug is eliminated per unit of time but the rate is independent of the concentration of the drug [45].

First-order release: The drug release rate is directly proportional to the concentration gradient and is a function of the amount of drug remaining in the dosage form [45].

Sustained-release: This is designed to achieve slow release of a drug over an extended period after administration of a single dose [45].

9.3.10. Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical large molecules consisting of a hexagonal arrangement of graphene sheets (hybridized carbon atoms), which may be formed by rolling and capped with spherical fullerene. CNTs shows unique electrical property due to the delocalized π-electrons on the *z*-axis. CNTs are classified into three types based on the wall number: Single-walled CNTs, double-walled CNTs, and multi-walled CNTs. single wall CNTs (SWCNTs) are a cylinder made of a single graphene sheet, while multiwalled CNTs (MWCNTs) are multilayers of rolled graphene sheets [102]. Carbon nanotubes have recently gained importance due to their high surface area which can conjugate with drugs (both molecules and cells), showing higher efficiency and specificity [103]. Until now, carbon nanotubes have been designed for delivering anti-cancer drugs [104]. However, research is being conducted to design carbon nanotubes for other drugs and also to reduce toxicity. From a broader perspective, Carbon nanotubes can be designed to carry proteins, peptides, nucleic acid,s, and drugs to deliver thetoin different cells and tissues. Functionalized carbon nanotubes are less immunogenic and impart minimal toxicity [105,106].

9.3.11. Nanoemulsions

Nanoemulsions are a heterogeneous system of oil into water (two immiscible liquids) which are stabilized by surfactants or emulsifiers. They are used to carry drugs that are hydrophobic and administered via various routes of administration. They have better stability to flocculation, creaming, and sedimentation as compared to conventional emulsions. The larger surface area and other characteristics allow nanoemulsion to deliver a drug efficiently to a specific target site [107].

9.3.12. Hydrogels

Hydrogels are made from water-soluble/insoluble polymers with cross-linked networking. In hydrogels, the drug is dispersed in a glassy polymer which upon contact with water, swells and releases the drug. The release is water penetration and swelling controlled [108]. Hydrogels swell beyond a certain boundary, several folds greater than their actual volume which facilitates polymer chain relaxation and drug diffusion [109]. Hydrogels can offer Spatio-

temporal control over the release of various therapeutic agents, including macromolecular drugs, small-molecule drugs, and cells. Owing to their tunable physicochemical properties, controllable degradability,y and protecting capability of labile drugs from degradation, hydrogels serve as a carrier to control drug release. The hydrogels when exposed to water open the cross-linked network to open the spaces in between the polymers. The diffusion of the drug depends on the size of the pores and porosity. The drug diffuses freely from a highly porous hydrogel, whereas network erosion is needed for the release of drugs from less porous hydrogels. The temperature, pH, and ionic strength are useful in exploiting the swelling of the hydrogel [110,111].

Supramolecular hydrogels are three-dimensional cross-linked networks with inter and intra-molecular bonding which offer high water retention capacity, drug loading efficiency, and biocompatibility as compared to conventional hydrogels. These hydrogels are mainly useful in self-healing and injectable applications [112]. Bacterial nanocellulose is one such example of supramolecular hydrogel which has been extensively studied in drug delivery in recent times. Interpenetrating network (IPN) hydrogels consist of two or more polymeric networks which are at least partially interlocked on a polymer scale [113,114]. Nanocarriers in controlled drug delivery are schematically shown in Figure 32. The advantages and disadvantages of various nanocarriers in drug delivery are tabulated in Table 9 and Table 10.

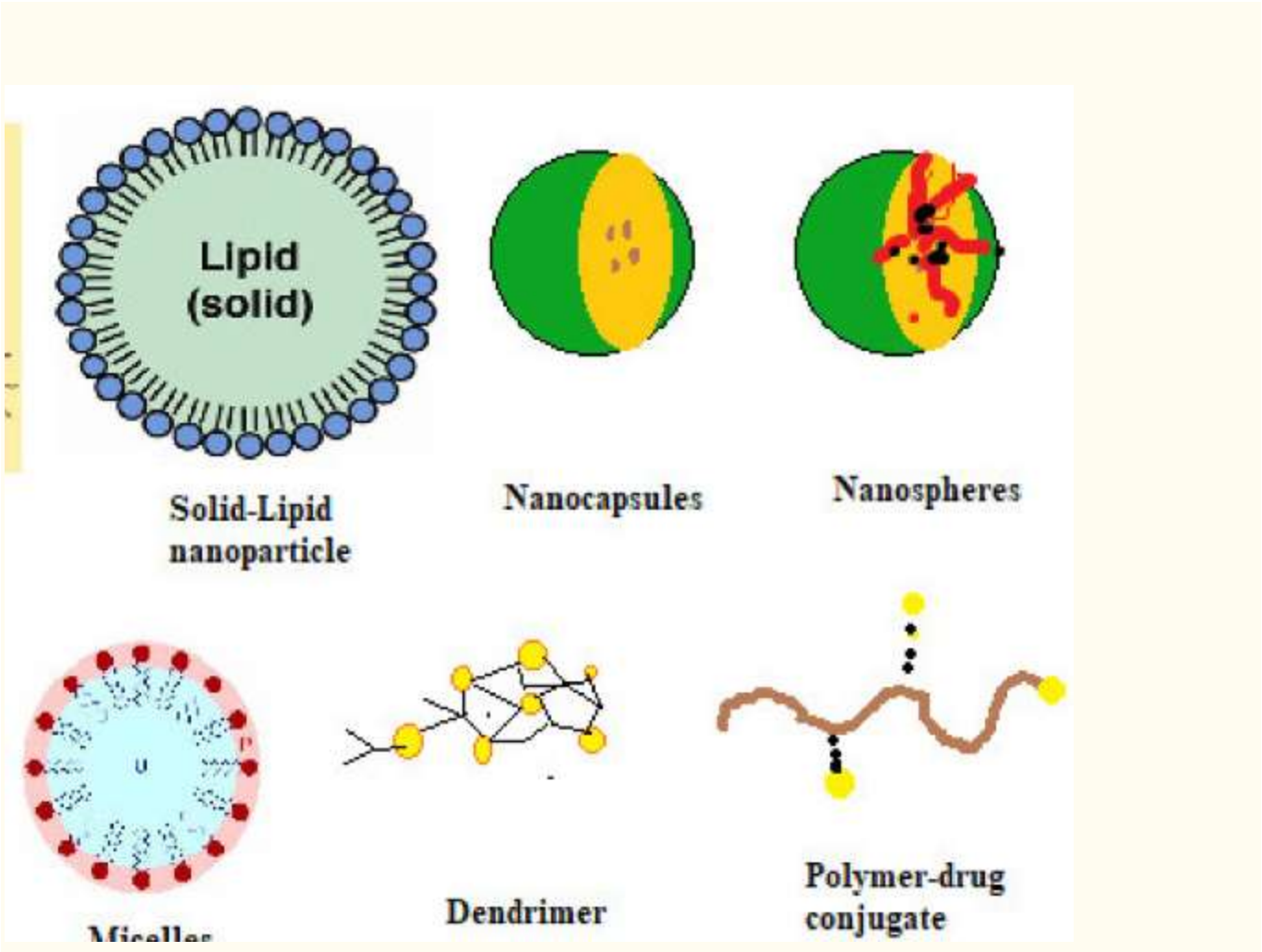


Figure 32

Some common examples of nanocarriers in controlled drug delivery.

Table 9

Advantages and disadvantages of nanocarriers in drug delivery [115,116].

Advantages	Disadvantages
Specificity and targeted delivery of drugs can be achieved	Unintended penetration and translocation of nanocarriers to the blood-brain barrier, and lungs results in toxicity
Improved tumor penetration for anticancer drugs	Nanocarriers can change in shape and size resulting in varied physicochemical interactions and activity
Enhanced Permeability and Retention can permit the passive accumulation	Suboptimal delivery due to heterogeneities of nanocarriers in vascular permeability
Enhanced bioavailability and efficacy	Uptake by RES can reduce the efficacy
Controlled delivery of drugs with low dose	Limited availability of animal models

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Table 10

Advantages and disadvantages of various nanocarriers in drug delivery.

Nanocarrier	Advantages	Disadvantages	Refs.
Liposomes	Less cytotoxic Amphiphilic and Self-assembly capability Can load both hydrophilic and lipophilic drugs High payload Longer duration of action	Could crystallize during long term storage Poor control over the drug release rate Lack of means to prevail against biological barriers Sufficient loading of drugs for which pH and ion gradients do not apply Leakage and fusion of loaded drug Phospholipids may undergo oxidation and hydrolysis	[117,118]
Dendrimers	Uniformity in molecular weight, size, shape, and branch length A high degree of branching results in a high surface area Availability of internal cavities with Polyvalencyoffersr high loading and targetting High water solubility Biocompatibility and absence of immunogenicity	Complex synthesis process Possibility of incomplete reactions with terminal groups Steric hindrance to the core molecule and dendrons obstructs the formation of high generation dendrimer	[119,120]

Nanocarrier	Advantages	Disadvantages	Refs.
Exosomes	Cell targetting and gene delivery Ability to load both hydrophilic and lipophilic drugs Exosomes membranes possess many proteins thousand show very high organotropism Immunocompatible if derived from autologous	Rapid clearance from the blood Current methods available suffer low drug loading and retention Purification and large scale extraction are a hassle	[121,122]
Metal Nanoparticles	Tunable sizes and shapes (spherical, triangular, cubic, rods, starts, etc.) Possibilities of easy functionalization Size-dependent activity	RES uptake might result in low biocompatibility and cytotoxicity Instability of nanoparticles	[88,123]
Mesoporous silica nanoparticles	Ordered porous structure High surface area Tunable pore size and functionalization Poorly water-soluble drugs and gene delivery	More studies are needed on cytotoxicity The presence of high surface silanol groups interacts with the phospholipids of the red blood cell membranes leads to hemolysis	[124,125]
Carbon nanotubes	High surface area, enhanced conductivity, and strength Vast functionalization sites Optical properties For targeted delivery	High immunogenicity, carcinogenicity, and cytotoxicity Non-biodegradable Poor aqueous solubility and poor absorption	[103,126]
Nanocapsules/nanospheres	Efficient drug accumulation at the target site Controlled release of drugs over weeks	Non-degradable polymers accumulate in tissues In vivo metabolism and elimination, routes are not elucidated	[127,128]
Quantum dots	Semiconductor nanocrystals with broad excitation spectra, narrow emission spectra, tunable emission peaks Possess long fluorescence lifetimes and negligible photobleaching Ability to conjugate with proteins and multiple molecular targets simultaneously	Quantum dot degraresults result in the leaching of heavy metals such as Cadmium which generates reactive oxygen species (ROS) High cytotoxicity	[129,130,131]

Nanocarrier	Advantages	Disadvantages	Refs.
Nanofibers	High specific surface area Multiple drugs with high loading capacity Tunable physicochemical properties Good Spatio-temporal distribution of drugs Great choice of polymers that are biodegradable and biocompatible Designed for various routes of administration for both hydrophilic and hydrophobic drugs	Scalability is an issue Poor control over nanofiber dimensions Need to optimize the solvent system for each polymer in the electrospinning process	[96,132,133,134]

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10. Stimuli-Responsive Drug Delivery Systems Using Smart Biomaterials

Stimuli-responsive drug delivery systems have progressed with the development of biomaterials that are sensitive to external physical environments or stimuli. This is achieved by the incorporation of special functional groups which can influence the chemical, physical and biological properties. These incorporated properties can render the biomaterial responsive to external environmental stimuli [134]. Stimuli-responsive drug delivery systems appear to be a promising approach to controlling and targeting drug delivery. When they are administered, the drug release is activated and then modulated through some action or external input and facilitated by the energy supplied externally. The responsive delivery systems respond to external stimuli such as temperature [135], pH [136], solvent [137], ultrasound [138], electric field [139] and magnetic field [140]. The changes in network structure in response to the external environment are reversible [141].

10.1. Chemical Stimuli-Responsive Biomaterials

10.1.1. pH-Responsive

The pH-responsive biomaterials sense the change in pH and undergo Physico-chemical changes in polymeric chains which trigger the release of the drug. These are most commonly used for triggering the release of the drug among the other stimuli. The traditionally used pH-responsive carriers show their effects based on the pH of different organs such as the intestine and stomach [142]. pH-responsive polymers can be either polyacids (which sense and release at basic

pH) or polybases (which sense acidic pH and release the drug). Examples of pH-responsive polymers are given in Table 7. Eudragit S100 is a citrus-coated pectin nanoparticle that specifically targets the colon of the anticancer drug, 5-Fluorouracil [143]. The carriers that are so designed can differentiate the changes in the pH value at specific sites of the disease like the ischemic tumor sites and inflammatory tissues. They can also be used to differentiate the pH value in different organelles like lysosomes and endosomes. The normal tissues have an extracellular pH of 7.4. In solid tumors because of an increase in the rate of glycolysis, the pH decreases to 7.0. The low pH of the tutumorcts aisa stimulus for the controlled drug delivery systems [144,145]. The stimulus of the pH can be combined with other stimuli including redox and temperature to achieve precise release at the specific targets, e.g., poly(2-(diisopropylamine) ethyl methacrylate) (PDPAEMA) [144]. In a recent study, Tamoxifen was loaded onto chitosan-nanoparticles by forming complexes,d tamoxifen was released more rapidly at pH 4.0 and 6.0 as compared to pH 7.4, which is a desirable characteristic for tumortargetedrug delivery [146]. In another study, chitosan nanoparticles were conjugated with an anti-cancer drug using a pH-sensitive linker, which cleaves and releases the drug, after being endocytosed into the cancer cell where the pH is acidic (Figure 33) [147].

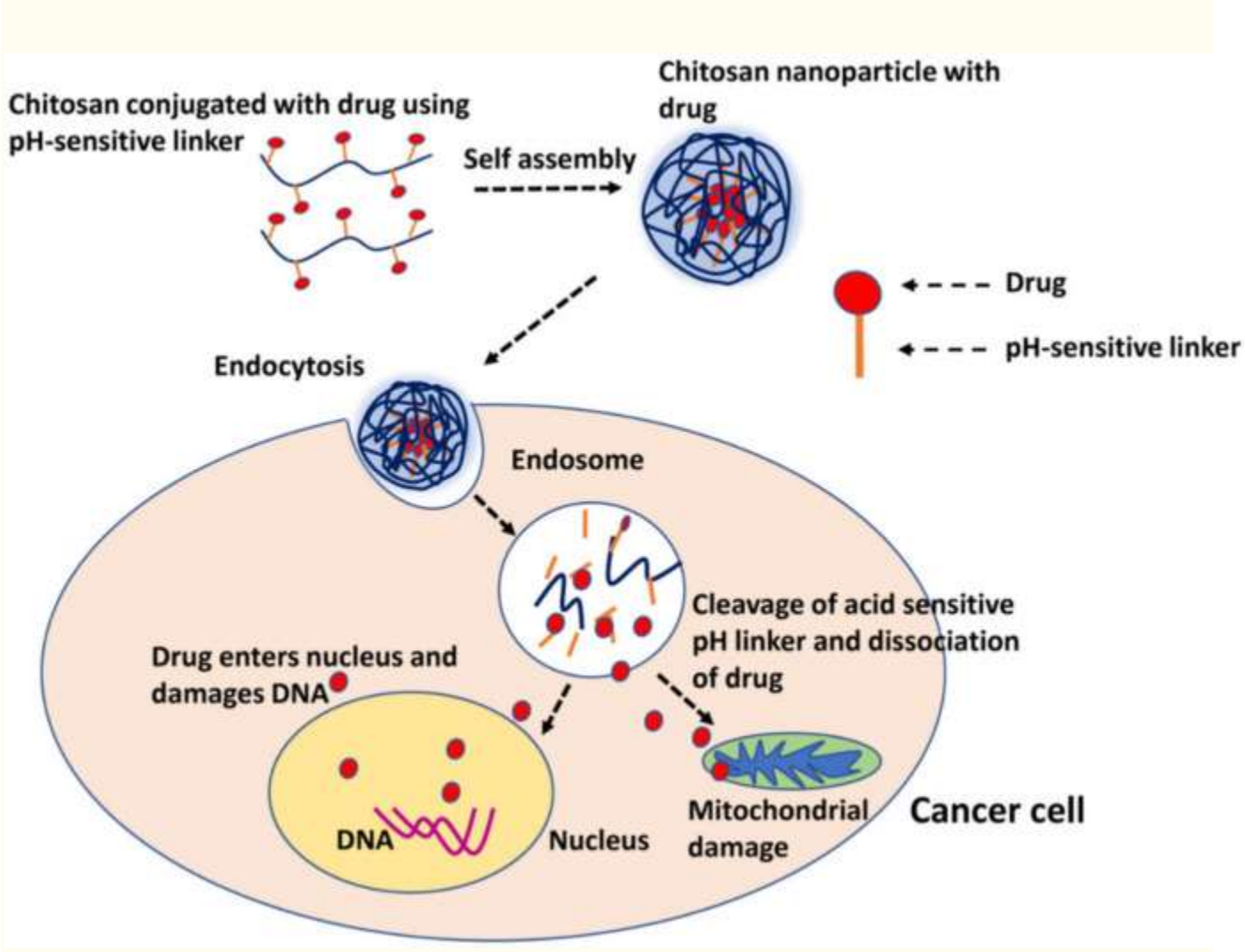

Figure 33

pH-responsive drug release of Tamoxifen from chitosan nanoparticles (adapted from [147] with copyright permission from *Marine Drugs*, MDPI licensed under Creative Commons Attribution (CC BY 4.0) license).

10.1.2. Redox Responsive

The change in redox potential triggers the drug release in redox-sensitive biomaterials. These are widely used in the treatment of diseases by use in intracellular drug delivery systems. The redox potential varies in the different tissues in the microenvironments that are useful in designing redox-sensitive drug delivery systems [148]. The designing of the nanoparticles that are glutathione (a redox system in cancer cells) responsive is used in the targeted drug delivery. The glutathione concentration in the normal extracellular matrix is found to be 2–20 μM, while its concentration in the cancer cells is 2–10 mM, which is ten times higher than the normal cells. Due to this difference in the levels of glutathione, it is used as a strategy in designing controlled drug delivery systems. Some diseased tissue uses the accumulated reactive oxygen which helps in targeting the tissues in the form of reactive oxygen species responsive drug delivery systems. The concentrations of reactive oxygen species are higher in the inflammatory tissues than in the normal tissues; exam for ple: ‘‘trimethyl-locked’’ benzoquinone (TMBQ) [149].

10.1.3. Enzyme Responsive

Here, enzymes are used as triggers in the drug delivery systems. They have unique properties like they are specific to the substrate and are highly selective in cases of mild conditions. As the enzymes are mostly related to the biological and metabolic processes, they can be used in achieving enzyme-mediated drug release at the site of inflammation. The main challenge while using the enzyme-responsive drug delivery systems is that the initial release of the systems has to be controlled precisely. They are named based on their interaction with effector molecules [150]. An example of enzyme-triggered release is illustrated in Figure 34. In this study, the anticancer drug doxorubicin was loaded into cathepsin B responsive liposomes made of PEG lipid GLFG-peptide linker. The liposomes are uptaken by endocytosis; in the presence of tumor-specific enzymes (cathepsin B, MMP2/9) and low pH of tumor cell, the lipids get hyhydrolyzednd and release the drug [151].

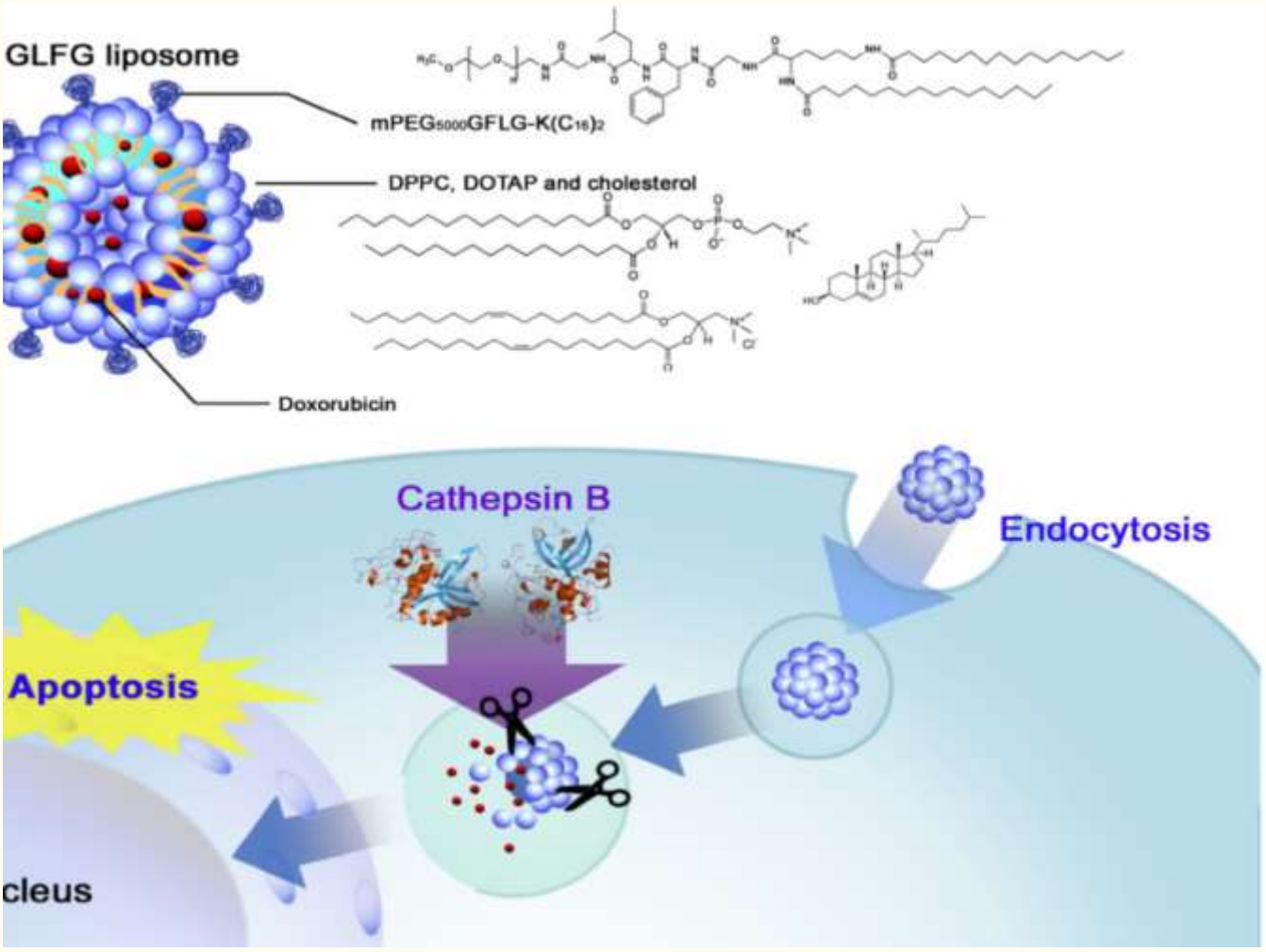

Figure 34

Enzyme-responsive drug release from doxorubicin-loaded PEG lipid-GLFG peptide liposome designed as a cathepsin B cleavable peptide linker to hydrolyze and release drugs specifically in tumor cells (reproduced from [151] with permission from *Polymers*, MDPI licensed under Creative Commons Attribution (CC BY 4.0) license).

10.2. Physical Stimuli-Responsive Biomaterials

10.2.1. Light Responsive

This helps in triggering the drug release by the external illumination of light. The photosensitive carriers can release the drug in an on-off system as the nanostructure opens by stimulation of the light. Due to the limitation in the penetration of the light into deep tissues, it restrains the application of the light in a non-invasive manner [152,153]. In a recent study, green laser light was used as a stimulus to heat up and shrink the nanogel for drug release (Figure 35). The elevated temperature and drug release exert an additive effect on cancer cell killing. Liposomes combined with nanoparticles made up of gold can be triggered by light stimulus [154,155].

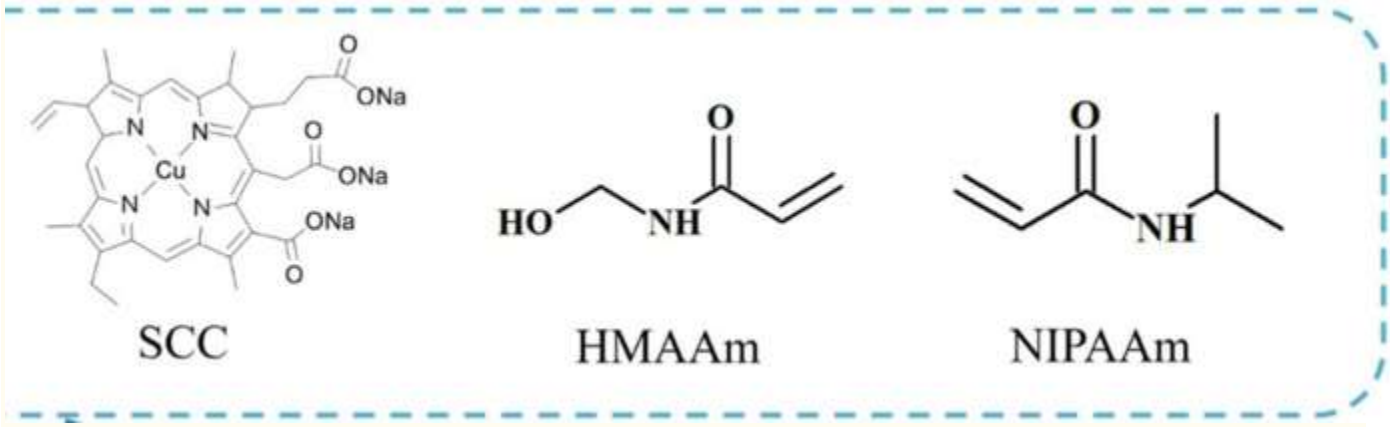

Figure 35

Green laser light induced nanogels (reproduced from [156] with permission from *Polymers*, MDPI licensed under Creative Commons Attribution (CC BY 4.0) license).

10.2.2. Thermo-Responsive

Temperature is the stimulus for drug release. Thermo-responsive polymers possess lower critical solution temperature (LCST). Below LCST, polymers are soluble and tend to be hydrated and swell, that is when drug loading is done. Above LCST, polymers tend to be in a shrunken dehydrated state and the drug gets released. A thermosensitive polymer known as poly(N-isopropyl acrylamide) can exhibit such characteristics [157]. These polymers are found to have hydrophobic groups (methyl or ethyl or propyl). The gelation of 5% polymer solution can become cloudy at 27 °C and on further increase in temperature (at about our body temperature), it forms a gel-like substance. In this physical form (gel-like form), this particular polymer poly(N-isopropyl acrylamide) expels out water from its gel substance [158]. It can revert to its solution state upon a decrease in temperature; see Figure 36. One of the significant advantages of thermosensitive polymers is that they can avoid any organic solvent which is ature. They also possess the ability to deliver both hydrophilic and lipophilic drugs and specific sites. They can also deliver the drug at sustaineddosagea ge with minimized side effects. Examples could be poly(N-isopropyl acrylamide) as discussed above and poly(methyl vinyl ether) [159].

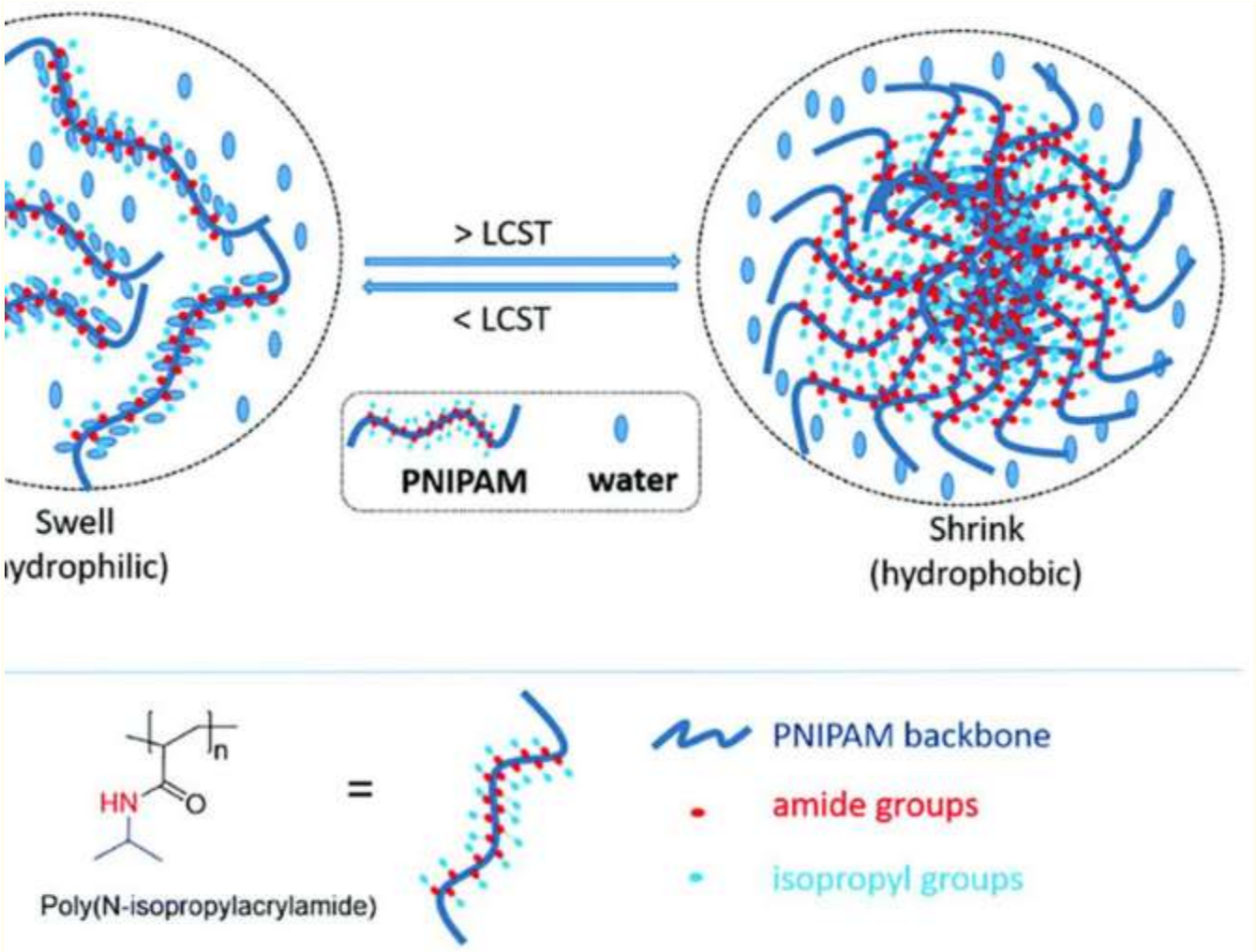

Figure 36

Thermo-responsive drug release by PNIPAM hydrogel (reproduced from [160] with permission from the Royal Society of Chemistry).

10.2.3. Electric Responsive

Electric responsive polymers such as polypyrrole [161], Polyaniline [162], poly-imines [163], and graphene [164] are used to fabricate drug delivery carriers. Electro-responsive graphene carriersfunctionalizedd with aldehydes (as model drug) through imine-based linkers through covalent bonding and its cleavage upon electrolysis releases the drug [165].

10.2.4. Magnetic Responsive

Magnetic responsive nanoparticles, when applied with the high-frequency magnetic field, generate heat. Magnetic nanoparticles are often encapsulated in colloidal carriers including β-cyclodextrins, liposomes, mice, lie,s, or solid nanoparticles which when exposed to the external magnetic field induce heat and trigger the drug release in cancer hyperthermia. In recent times, core-shell magnetic nanoparticles (i.e., Fe_3O_4 and $CoFe_2O_4$) coated with biocompatible polymeric shells (carbohydrate polymers, lignin, polyacids, dextran, etc.) have gained significant importance in cancer therapy [113].

10.2.5. Ultrasound Responsive

Ultrasound waves (high frequency > 20 Hz) are used widely for diagnosis as they penetrate deeply into the tissues yet remain safer than X-rays. Ultrasound waves can give 3D images of different organs based on the varied echoes received from different tissues due to the differences in acoustic impedance. Acoustic energy attenuation by the tissues results in fluid streaming, tissue motion, and heating which can be used in thermal ablation, transdermal sonophoresis,s and cavitation [166]. A rapid fall in local pressure causes vaporization or evolution of dissolved gases as microbubbles. This helps to disintegrate gall and kidney stones. Ultrasound can be used in combination with pre-existing bubbles or other cavitation nuclei, at lower amplitudes, to harvest a series of mechanical effects that can be exploited for drug delivery [167]. An illustration of this is given in Figure 37.

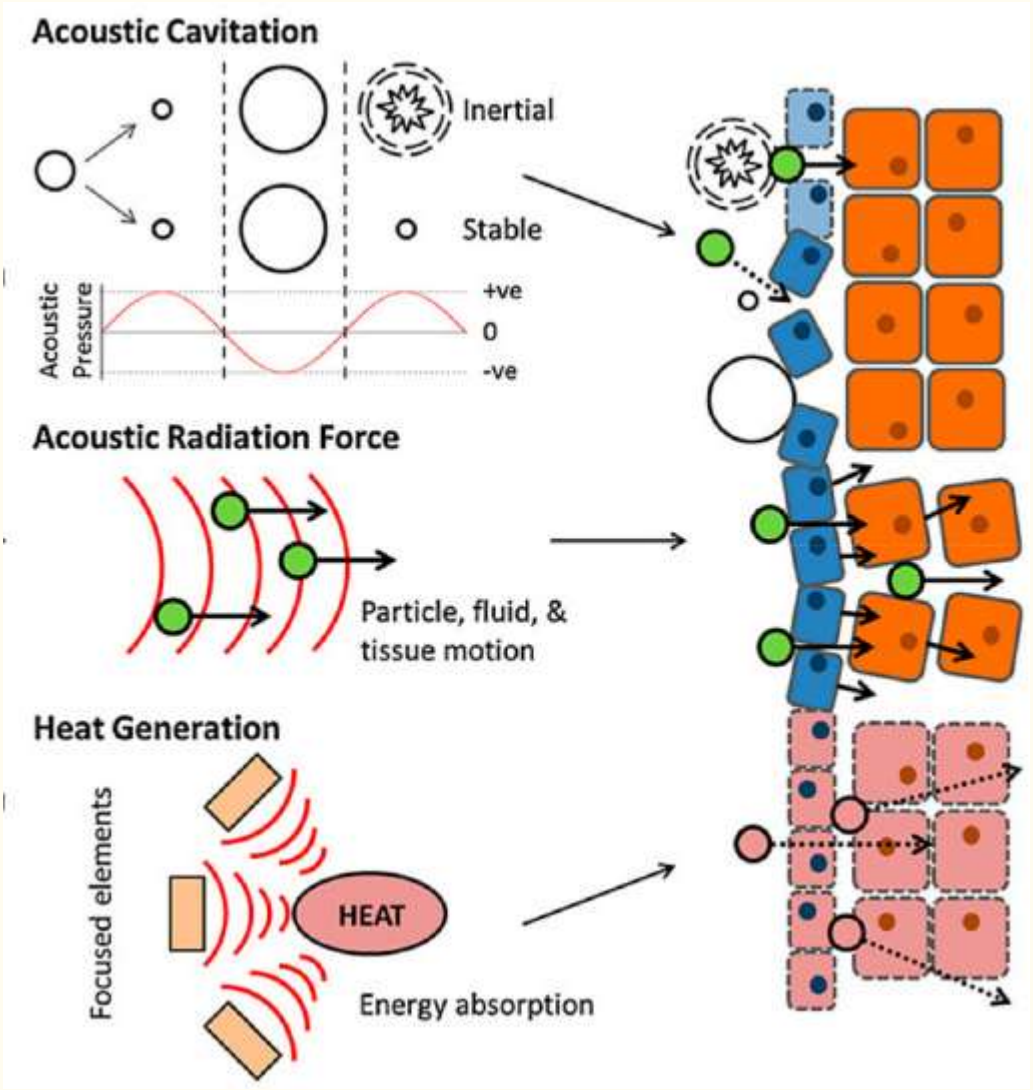

Figure 37

Ultrasound triggered release from microbubbles by mechanical effects by acoustic cavitation and thermal effects by acoustic radiation (reproduced from [167] with permission from *Fluids*, MDPI licensed under Creative Commons Attribution (CC BY 4.0) license).

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11. Challenges and Future Directions

There has been enormous advancement in controlled drug delivery systems in the past two decades. Nevertheless, there is still scope for advancement to combat the limitations and expand future possibilities.

11.1. Nanomedicine Challenges and Improvements

Nano-drug delivery systems have emerged as an excellent alternative to conventional delivery systems with several advantages including targeted drug delivery with enhanced efficacy. However, nanoparticulate systems need to be characterized concerning safety and toxicity. In several studies, nanoparticles resulted in uptake by the reticuloendothelial system and resulted in the inflammation of the liver, lung, and brain due to the oxidative stress induced by nanoparticles [168]. The ability of nanocarriers to cross the blood-brain barrier is beneficial in brain diseases; however, it causes neurotoxicity when the intended site of action is not the brain. In addition, nanoparticles provoke immunomodulatory effects in some cases. This immunomodulatory effect of nanoparticles can be harnessed to target inflammatory monocytes across the blood-brain barrier to prevent the progression of auto-immune disorders (e.g., autoimmune encephalomyelitis) [169]. Inorganic mesoporous nanoparticles have gained attention in controlled drug delivery as they comprise ordered mesopores (2–6 nm) and tunable size (50–200 nm) and shape and their easy surface modification make them ideal for improved targeting and endosomal release of the drugs. To avoid the premature release of drugs through the mesopores, they can be covered with stimuli-responsive polymers, which makes them capable of providingspatialotemporal control during the release of a specific drug into the cytosol of the target cell [170].

On the other hand, stimuli-responsive delivery systems seem to be a very interesting and useful approachtuningtune the drug release from outside and from within. However, there is a lot more research needed to improve the accuracy, precision, and repeatability of such dosage forms. Sensitivity to the specific stimuli must be higher because delivering a high amount of external stimuli (electric field, magnetic field, light, and heat) might cause damage to the healthy tissues. Until now, there are no discrete guidelines for nano-drug delivery and stimuli-responsive and functional biomaterials. There is an urgent need to develop and harmonize the regulatory guidelines on nano-drug delivery systems, stimuli-responsive deliverySystt, em,s and next-generation biomaterials for drug delivery. FDA should establish regulatory guidelines that specifically apply to nanomedicine products, particularly because the safety and toxicity of many nanomaterials have not been fully characterized. Hence, getting

regulatory approval for nanomedicine has been very difficult and pharmacoeconomic analysis has to be done before the development.

11.2. Microfluidics in Controlled Drug Delivery

Microfluidics systems for implantable and controlled delivery is an interesting field for future research. It is also known as lab-on-a-chip (LOC) technology which involves micro-devices that come with small chambers and channels [171]. These micro-devices control the behavior of the flow of fluids to deliver the drug to a specific site which is more efficient [67]. Recent studies have suggested the development of synthetic polypeptides by polymerizing α-amino acid N-carboxy anhydrides (NCAs), which can be organized into nanostructures and precisely deliver the drug at a particular site. Moreover, the release of the drug substances can be programmed by manipulating the physical and chemical properties of the polypeptide structure [68]. Antibodies discovery and cell delivery are other significant applications where microfluidics are being employed [172,173].

11.3. Molecularly Imprinted Polymers (MIPs)

Molecular imprinting polymers are cross-linked polymers that have binding sites that are specific to the target molecule. These are the cross-linked polymers that have binding sites specific to the target molecule. The molecularly imprinted polymers are developed from five components as the template, cross-linker, porogen, monomer, and initiator [174]. The template helps in determining the choice of a functional monomer. It acts as an artificial receptor of target molecules and functions as a biomimetic way of natural antibody-antigen systems. Their mechanism can be understood from lock and key where MIPs selectively bind the molecule with which they were templated during synthesis (Figure 38). MIPs are excellent and promising candidates in developing vaccines and biologic drug delivery as the drug-target specificity can be determined [175].

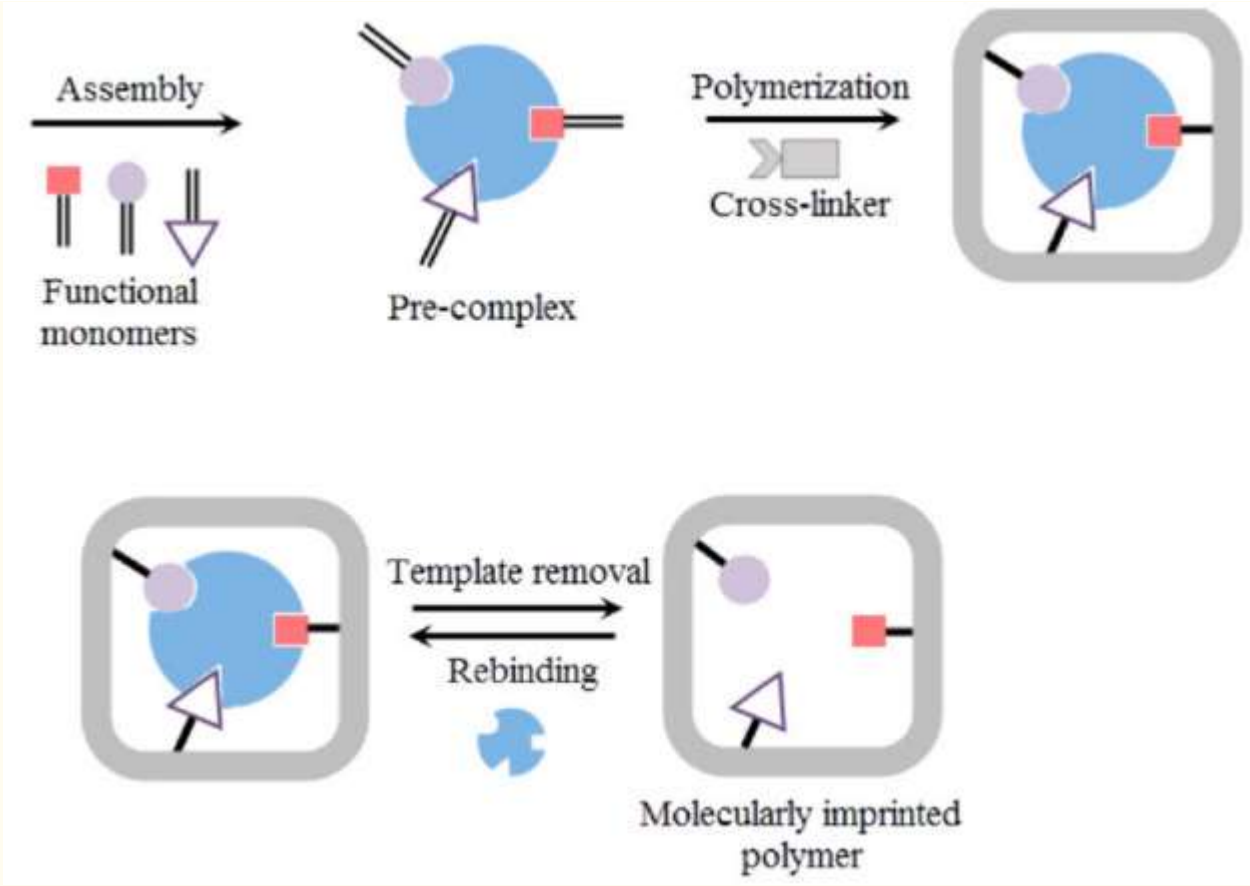

Figure 38

Molecular Imprinting polymers synthesis protocol (reproduced from [176] with permission from *Sensors*, MDPI licensed under Creative Commons Attribution (CC BY 4.0) license).

11.4. Intelligent Biomaterials

There is a huge scope for the development of intelligent biomaterials which can sense and auto adapt to the environment and control drug release, for instance, an intelligent hydrogel that can sense the blood sugar levels in the surrounding environment (either pH or temperature) to deliver the specific dose of insulin that is required to maintain the blood sugar levels. There is a need to develop smaller hydrogels but the current challenges that are present in developing smaller biosensor hydrogels are that they are more fragile and sufficient mechanical strength cannot be imparted to fulfill the purpose [68].

11.5. CRISPR CAS9 Based Systems

More recently, there has been an increase in attention towards drug release based on CRISPR or clustered regularly interspaced short palindromic repeats are a group of DNA sequences that are mainly found in prokaryotes as an adaptive immune system effector. It has brought revolutionary changes in the science of tissue-specific gene editing [176]. This newly developed delivery system based on CRISPR is composed of sgRNA or single guided RNA and a Cas9 endonuclease. This combination of sgRNA and Cas9 directs the protein (Cas9) to

a specific target site based on RNA and DNA. The specific target is recognized by crRNA or CRISPR RNA sequences. However, research is being conducted to minimize the off-target effects brought about by the combination of sgRNA and Cas9 protein. The whole mechanism is quite applicable while delivering any protein drug substance instead of Cas9 [70].

11.6. Quantum Sensing Drug Delivery

Another technology that has created a bridge between nanotechnology and drug assay is quantum dots or QDs. These are semiconductors of carbon-based nanoparticles of strong chemical inertness, higher specific surface areas, lower capacity to impart toxicity, and higher,r solubility [177]. QDs possess unique optical properties that display quantum confinement effect and emit fluorescence when excited with a light source which makes them a potential candidate for nano-probes and carriers for biomedical application. Most of the drug carriers which are made up of polymers have a limitation of real-time tracing of the drug, which can be achieved by using QDs due to their spectral characteristics. The Fluorescent emission of quantum dots is much better than organic dyes due to which QDs act as a tag for other drug carriers and the drug can easily be traced with the help of quantum dots [177]. Another study reported an RNA delivery approach by combining siRNA and QDs [71].

11.7. Three-Dimensional Printing in Drug Delivery

Three-dimensional-printed drug delivery systems have attracted attention in both tissue engineering and drug delivery due to the ability to specifically construct the systems with multiple materials and the unparalleled potential for printing complex physiological structures and organs. The latest innovations in 3D printing offer customized personalized medication for better therapeutic efficacy in customized medical devices, drug-eluting implants, and pointless (3D-printed tablets) with a tailored dose, shape, si, ze and release characteristics [178,179].

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12. Conclusions

The dosage form is a combination of drugs and excipients. Excipients are used to get a structure, enhance stability and mask the taste. Solid, semisolid, and liquid dosage forms are the conventional dosage forms that suffer from fluctuations in plasma drug levels which demands high dosing and dosing frequency with poor patient compliance. The bioavailability of a drug is crucial to achieving the desired action from any dosage form. Controlled drug delivery systems have

emerged as an alternative to the conventional sort, to improve the bioavailability, an example the drug, release and maintain drug plasma levels within the therapeutic window with minimal side effects. Controlled drug delivery increases the drug solubility and stability and offers the selective delivery of drugs with a predictable rate and mechanism to specific organ/tissue/cells. Dissolution, diffusion, water pe, penetration, and chemically controlled drug delivery systems are the types of controlled drug delivery systems. Stimuli-responsive delivery systems are useful in various disease conditions (cancer, infections, etc.) to target as well as control the release. Further, nanocarriers with intelligent biomaterials and additive manufacturing techniques can be developed to achieve controlled targeted delivery. The future of drug delivery is focused on patient-specific therapy using microfluidic-based, 3D-printed devices and CRISPR cas9-based delivery systems integrated with quantum sensing.

Go to:

Abbreviations

Abbreviation	Full form
API	Active Pharmaceutical Ingredient
FDA	Food and Drug Administration
BCS	Biopharmaceutics Classification System
BBB	Blood-Brain Barrier
IVIVC	In vitro In vivo Co-relationship
CYP450	Cytochrome P450

$t_{1/2}$	Biological half-life
TI	Therapeutic Index
TWO	Therapeutic Window
MEC	Minimum effective concentration
PK	Pharmacokinetics
ED_{50}	The effective dose in 50% of subjects
TD_{50}	The toxic dose in 50% of subjects
DDS	Drug delivery systems
CRDDS	Controlled release drug delivery systems
EPR	Enhanced permeability and retention
PLK 1	Serine/threonine-protein kinase
siRNA	Small interfering Ribose Nucleic acid

CNTs	Carbon nanotubes
SWCNTs	Single-walled carbon nanotubes
MWCNTs	Multiwalled carbon nanotubes
MMP	Matrix metallo proteinases
LCST	Lower critical solution temperature
MIP	Molecularly Imprinted Polymers
CRISPR Cas9	Clustered regularly interspaced short palindromic repeats
sgRNA	Single guide RNA
LOC	Lab-on-a-chip
QD	Quantum dots
RES	Reticulo Endothelial system

Go to:

Author Contributions

S.A.: Conceptualization, writing original draft preparation, review and editing; S.R.: review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable.

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Conflicts of Interest

The authors declare no conflict of interest.

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Footnotes

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