Spanish Journal of Innovation and INTEGRITY
ISSN: 2792-8268
Volume: 39, Feb-2025
http://sjii.indexedresearch.org

Review of the Controlled Drug Delivery Method, Dosage Form Categorization, and Therapeutic Impact on the Human Body

Darwn H. Kak Bchkol
School of Natural and Applied Science-Department of Chemistry-Fırat university-Turkey

Osama. S. Mohammed
Collage of Science_Department of Chemistry-Charmo university-Kurdistan Region, Iraq

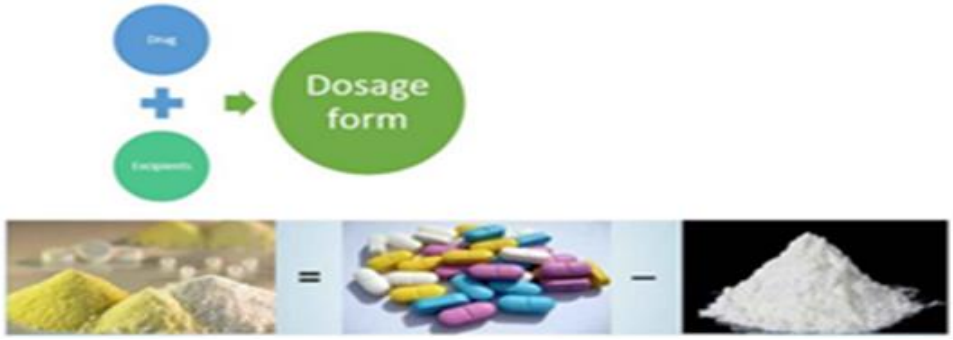
Abstract: *To provide the intended therapeutic effect, the drug delivery system makes it possible for the active pharmaceutical component to be released. Traditional drug delivery methods (tablets, capsules, syrups, ointments, etc.) cannot provide continuous release due to their low bioavailability and variations in plasma drug levels. The entire therapy procedure may be ineffective in the absence of an effective delivery system. To get the highest level of safety and efficacy, the medication must also be administered at a carefully regulated pace and at the intended location. The development of controlled drug delivery systems aims to address the issues with traditional medication delivery. Over the past 20 years, controlled drug delivery systems have advanced significantly, moving from macro- and nano-scale to intelligent targeted delivery. With a focus on the medication's pharmacokinetics, the first section of this paper offers a fundamental grasp of drug delivery methods. The limitations of traditional medication delivery methods are also covered. Furthermore, the design considerations, classifications, and drawings of controlled drug delivery systems are covered in detail. The use of stimuli-responsive and intelligent biomaterials for targeted and intelligent drug delivery, as well as nano-drug delivery, is also covered with recent important discoveries.*

Keywords: *Pharmacokinetics, nanodrug delivery, smart and stimuli-responsive delivery, controlled release dosage forms, and intelligent biomaterials.*

1. INTRODUCTION

Drug is a substance (recognized in official pharmacopoeia) 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 as represented in Figure 1.1. APIs are the actual chemical components used to treat diseases [2].

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



API **Dosage form** **Excipient**

Figure 1.1. Dosage form composition.

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 the 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, 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: coloring 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 improve 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 colorants 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., glipalamide, 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].

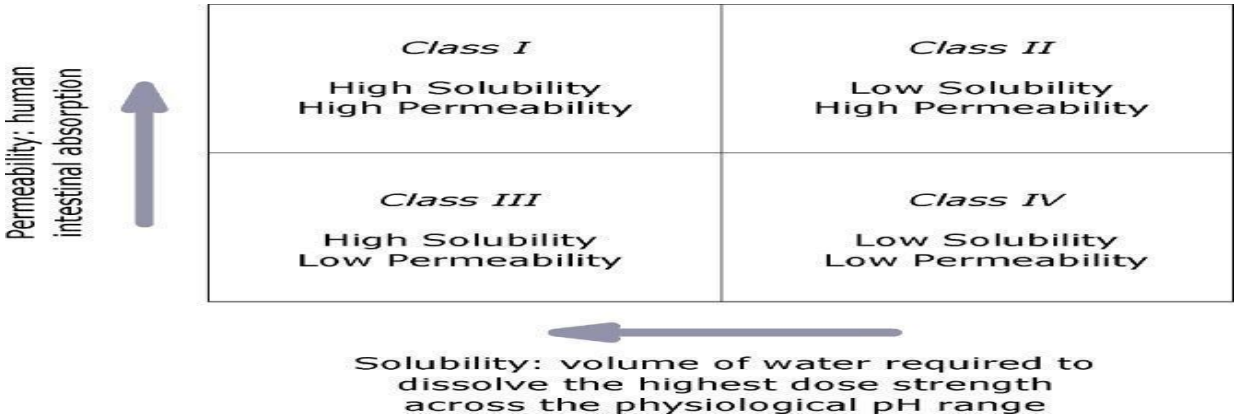


Figure 1.2. BCS Classification of drugs.

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, syrups and injections. Various routes of drug administration are tabulated in Table 1.1 and Figure 3.1. 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 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 1.1. Routes of drug administration.

Oral	Swallowed by Mouth as a Tablet, Capsule, Lozenge, or Liquid.
Buccal	Held inside the cheek Sub-lingual.
Enteral	Delivered directly into the stomach or intestine Inhalable.
Buccal	Held inside the cheek Sub-lingual.
Enteral	Delivered directly into the stomach or intestine Inhalable.
Nasal	Given into the nose by spray or pump Ophthalmic.
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 over time Intramuscular.

Intravenous	Injected into a vein or an IV line.
Subcutaneous	Injected just under the skin.
Transdermal	Given through a patch placed on the skin.
Infused	Injected into a vein with an IV line and slowly dripped in over time Intramuscular.

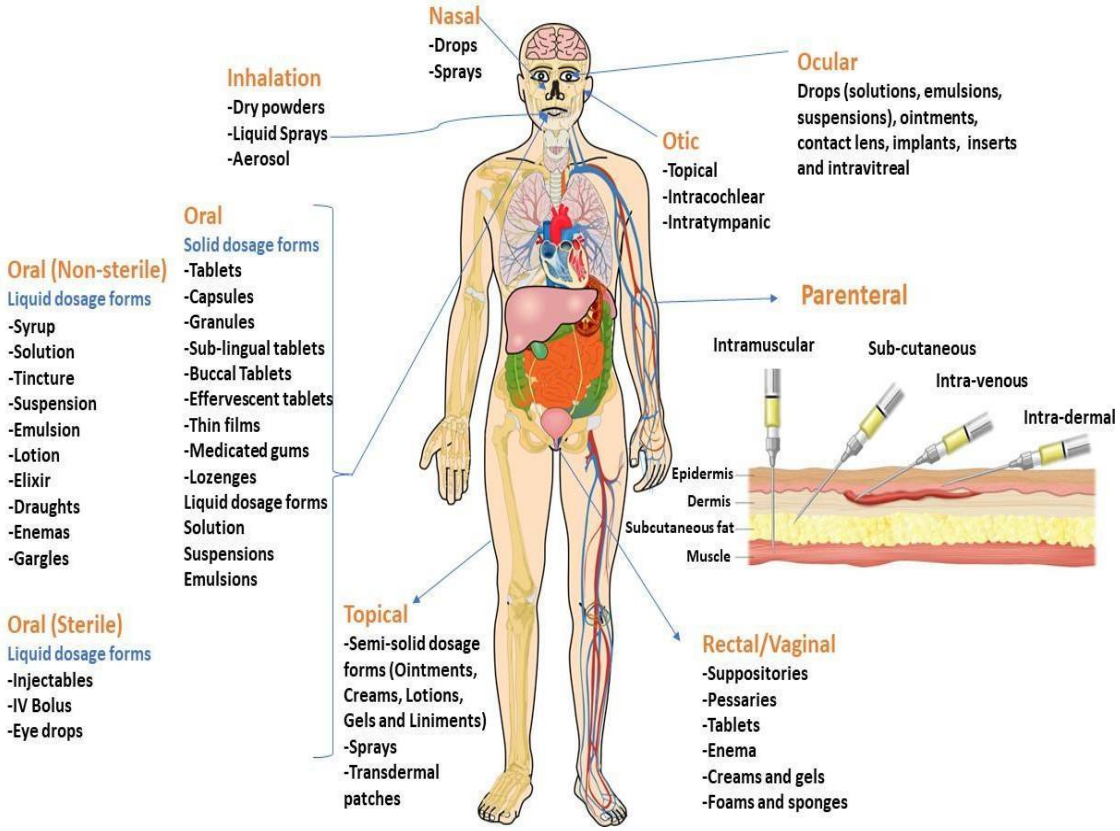


Figure 1.3. Various routes of drug administration.

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 2.1.

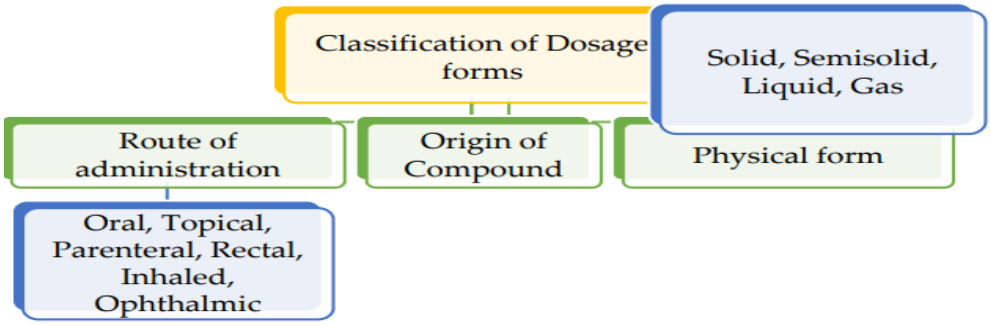


Figure 2.1. Classification of conventional dosage forms.

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) Bulk dose: As the name itself says, it is a bulk solid powder where the individual dose is not formulated Figure 2.2. [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].

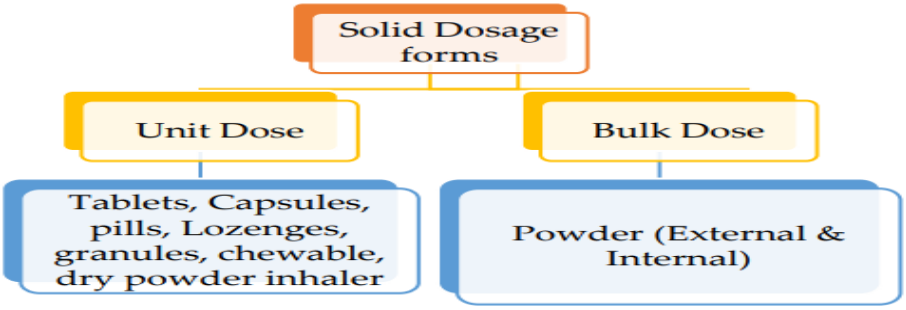


Figure 2.2. Classification of solid dosage forms.

2.2.1. 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 tabletting, 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, sweeteners and flavouring 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, an aesthetics 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].

Figure 2.3. Solid unit dosage forms: (a) Tablets, (b) Effervescent tablets, (c) Chewable tablets, (d) Pills, (e) Hard-gelatine capsules, (f) Soft-gelatine capsules, (g) Lozenges. (h). Granules.

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, coloring 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 or cosmetic applications. Semisolid dosage forms include ointments, creams, gel/jelly, lotions, pastes, suppositories and transdermal patches Figure 2.4. and Table 2.1 [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 2.1. 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 basically an ointment where The liquid phase is trapped	The liquid phase is trapped a high percentage of insoluble within a three-dimensional solids are added polymeric matrix
Translucent to opaque Greasy	Opaque Less greasy	Opaque Less greasy	Transparent Non-greasy

Figure 2.4. Semisolid dosage forms.

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 spread ability is less. Hence, ointments may be used as emollients or to apply suspended or soluble drugs to the smaller portions of skifor 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, in cosmetics, for lubricating purposes and 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 basically 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].

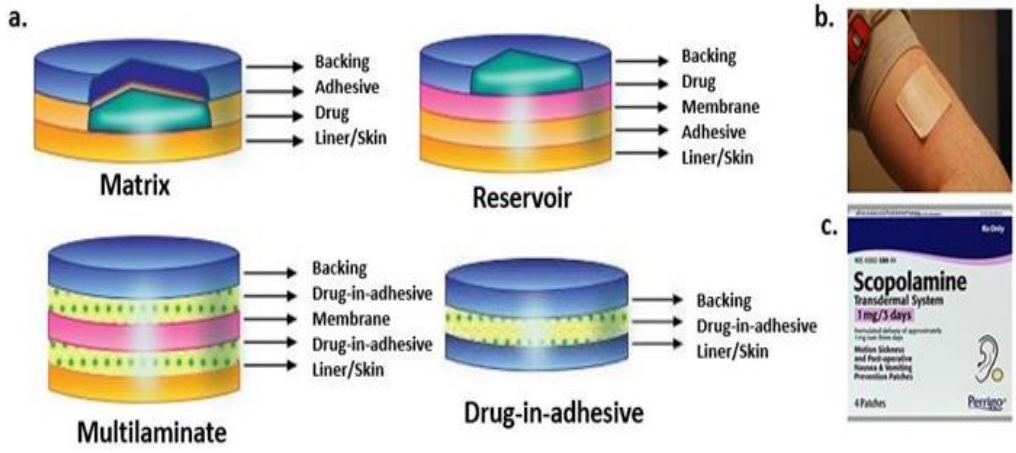


Figure 2.5. (**a**) Types of transdermal patches, (**b**) Transdermal patch applied on skin, (**c**) First commerciallyavailable Scopolamine transdermal patch (reproduced from [21] with permission from Perrigo, licensed under Creative Commons Attribution (CC BY 4.0) license).

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 exert 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 of API and excipients either dissolved or dispersed in a suitable solvent/s. These are intended to offer a fast therapeutic response in 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 and 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 2 .6. 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. Flavoured 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 flavours. 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 agitate it by 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].

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.

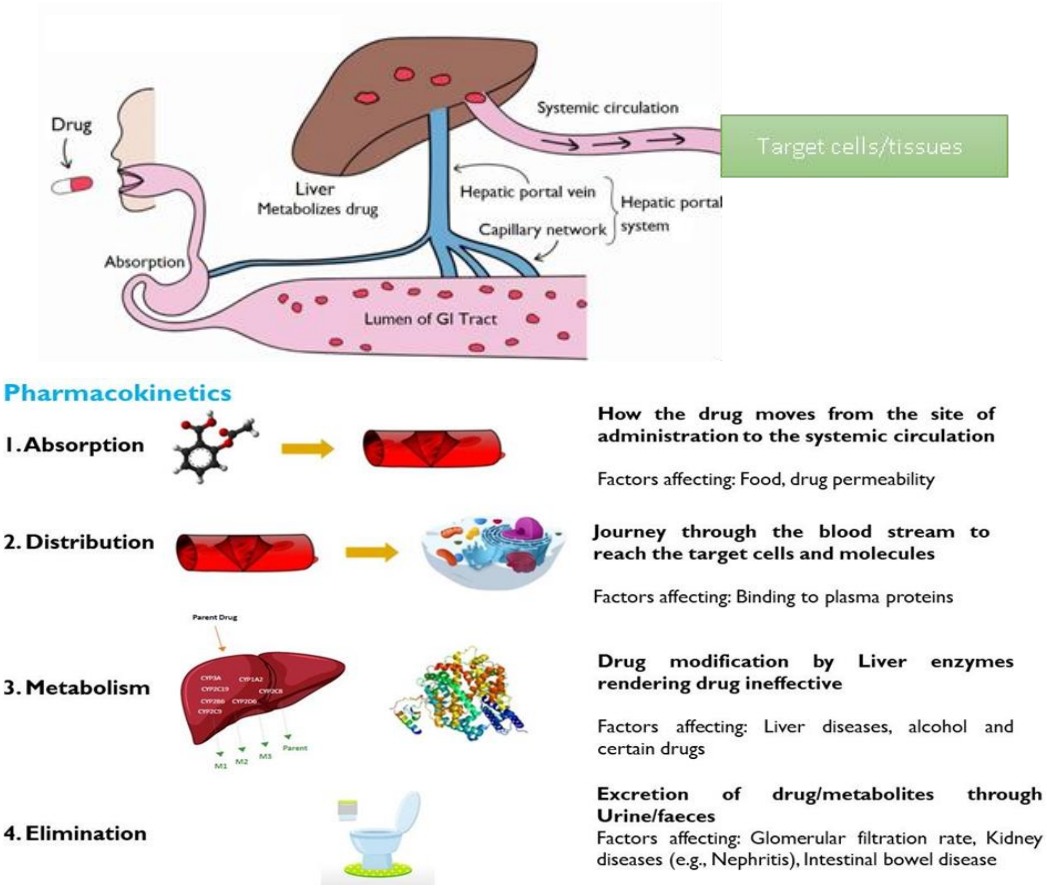


Figure 3.1`. Pharmacokinetic phases of a drug: 1. Absorption, 2. Distribution, 3. Metabolism, 4. Excretion.

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 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 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 3.2.

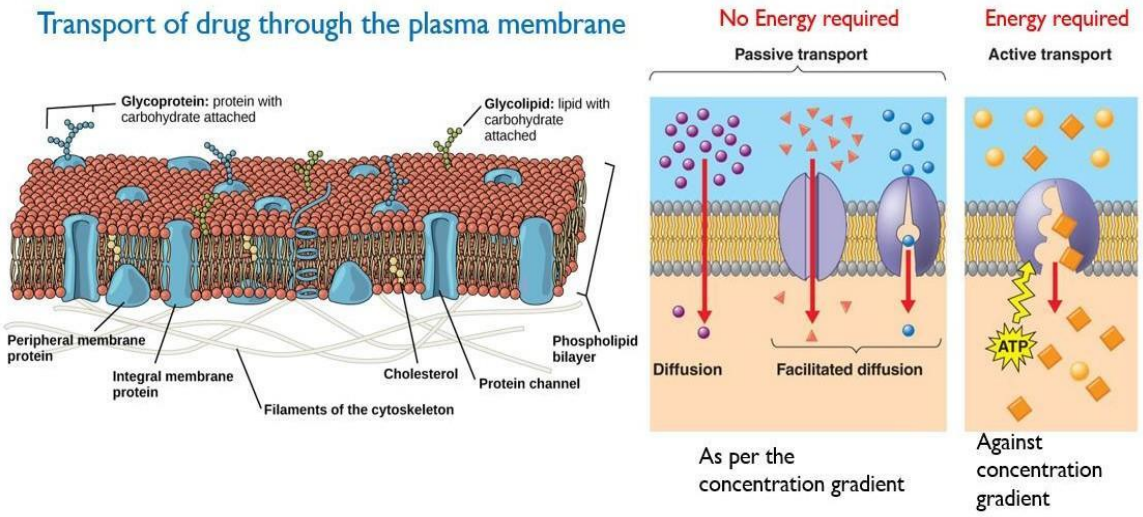


Figure 3.2. . Schematic of transport of drug through the plasma membrane by passive transport and active transport (reproduced from [34] with permission from the OpenStax, (part of Rice University, which is a 501(c)(3) nonprofit) and licensed under Creative Commons Attribution (CC BY 4.0) international license).

3.2. Distribution

Distribution is a reversible transfer of a drug between the blood and the extra vascular 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 3.3. Drugs with high lipophilicity, smaller size, and low molecular weight can cross the blood–brain barrier [29].

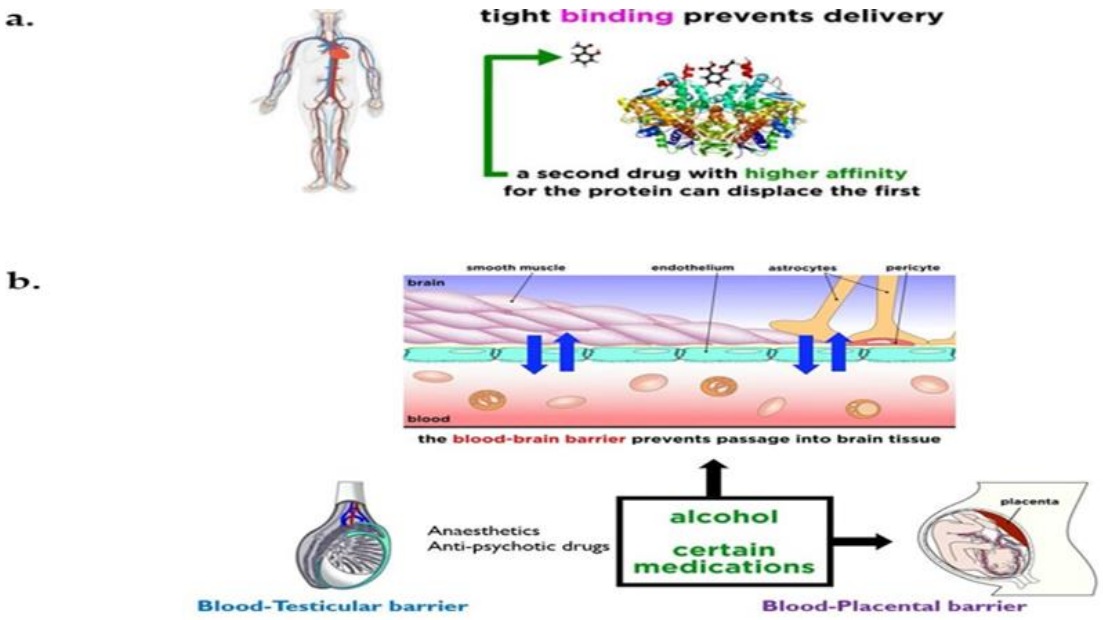


Figure 3.3. Schematic of barriers to drug distributions (**a**) Plasma protein binding, (**b**) Anatomical barriers

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 3.4.

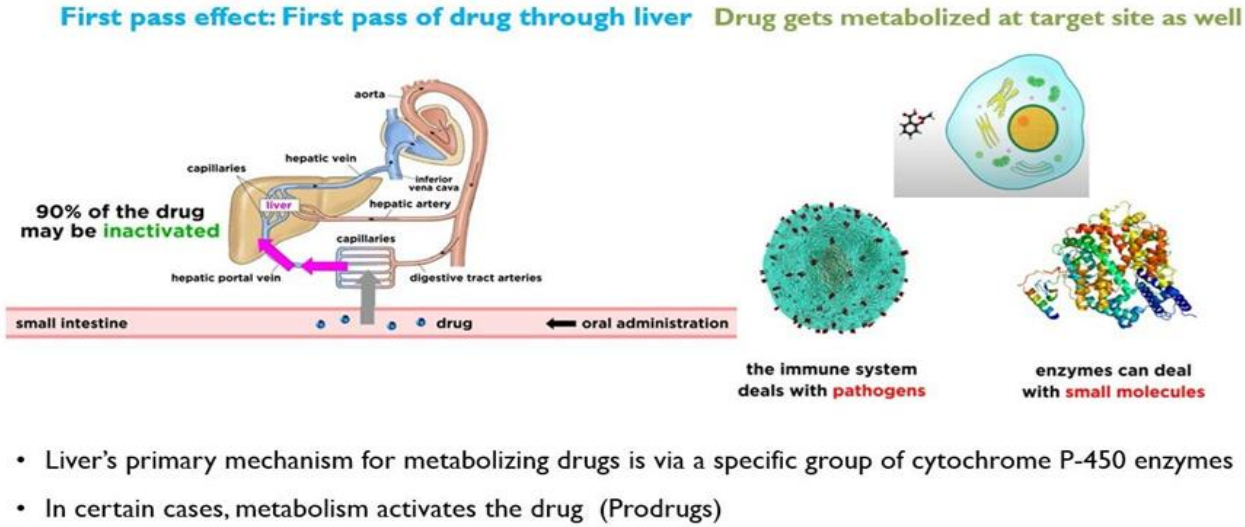


Figure 3.4.. Schematic of drug metabolism in the liver as well as the cells.

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 3.5.

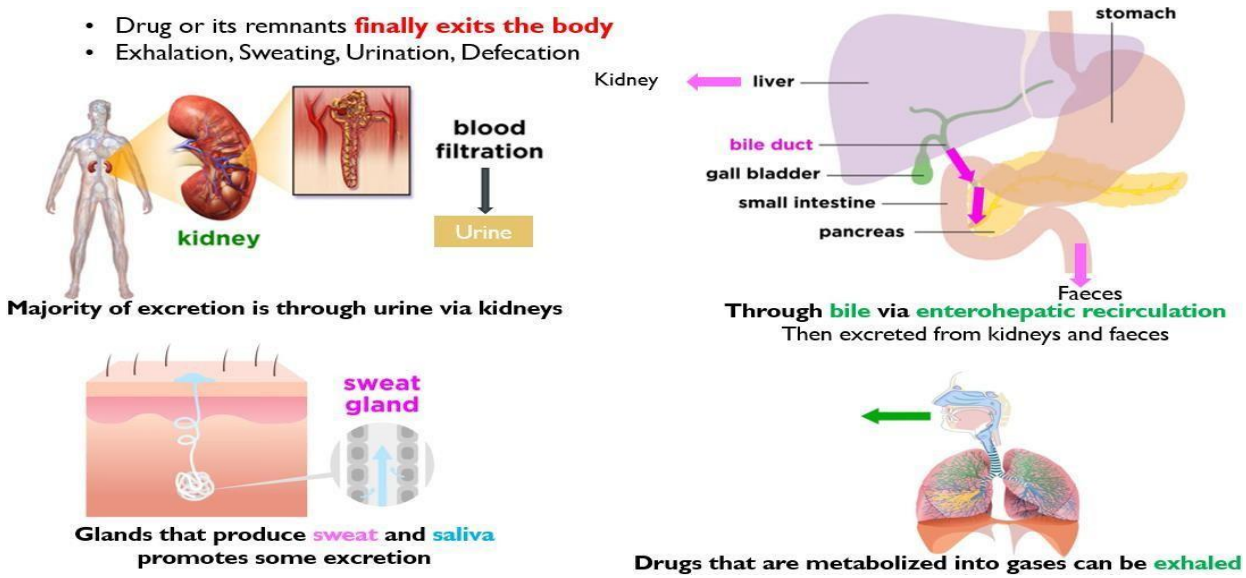


Figure 3.5. Schematic illustration of drug excretion from the body by kidneys, liver, skin and airways

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, 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 3.6.

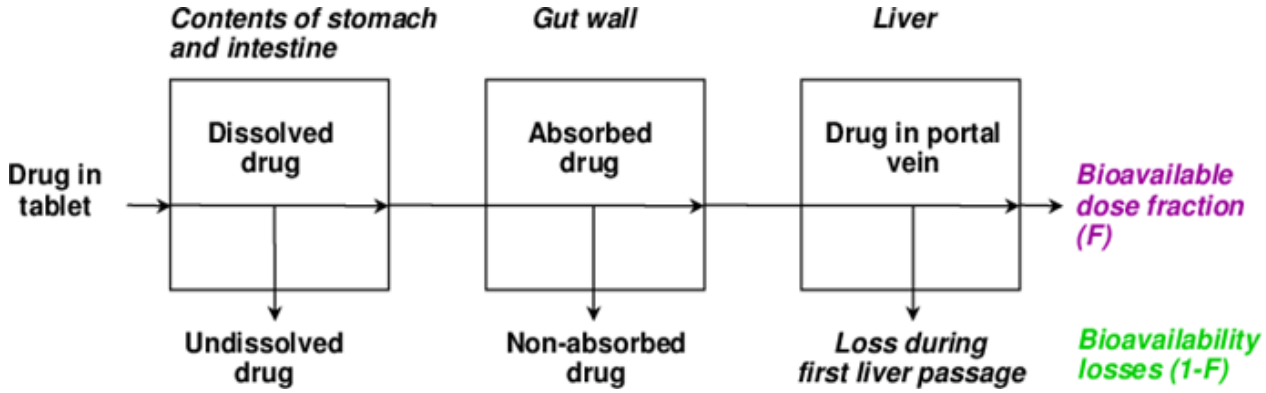


Figure 3.6. Schematic of factors accountable for the reduction in bioavailability.

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:

$t^{1/2}$ = (0.7 × Vd)/Cl, where Vd is volume of distribution and Cl is clearance.

$t^{1/2}$ = 0.693/Kt, where Kt 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 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].

4. RESULTS AND SISSCUSSIONS

4.1. Conventional vs. Controlled Drug Delivery Systems

Conventional DDS (tablets, capsules, syrups, etc.) get eliminated from the body very quickly and the dose is not well maintained within the therapeutic window. After taking a single conventional dose, the drug metabolizes very quickly and the drug level increases, immediately followed by an exponential decrease. The time frame may not be long enough to produce a significant therapeutic effect and result in a sub-therapeutic response. Figure 18 illustrates the plasma drug fluctuations in conventional DDS. Hence, to maintain the plasma drug concentration above the minimum effective concentration (MEC) and below the toxic concentration, multiple approaches have been sought. Administering multiple doses at regular intervals of time might seem to be an alternative to a single dose, but the former results in fluctuations in plasma drug levels and often reaches below effective levels and above toxic levels. Taking several doses within a day result in poor patient compliance. Another approach is by administering a single dose greater than the required dose, which leads to adverse effects other than the effects intended by the drug Figure 4.1. Hence, controlled release DDS are required to maintain the plasma drug levels at a constant rate within the therapeutic window and offer the desired therapeutic effect for a longer duration of time. [43]. A schematic of the disadvantages of conventional DDS is given in Figure 4.2. The advantages and disadvantages of conventional and controlled DDS are presented in Tables 4.1 and Table 4.2.

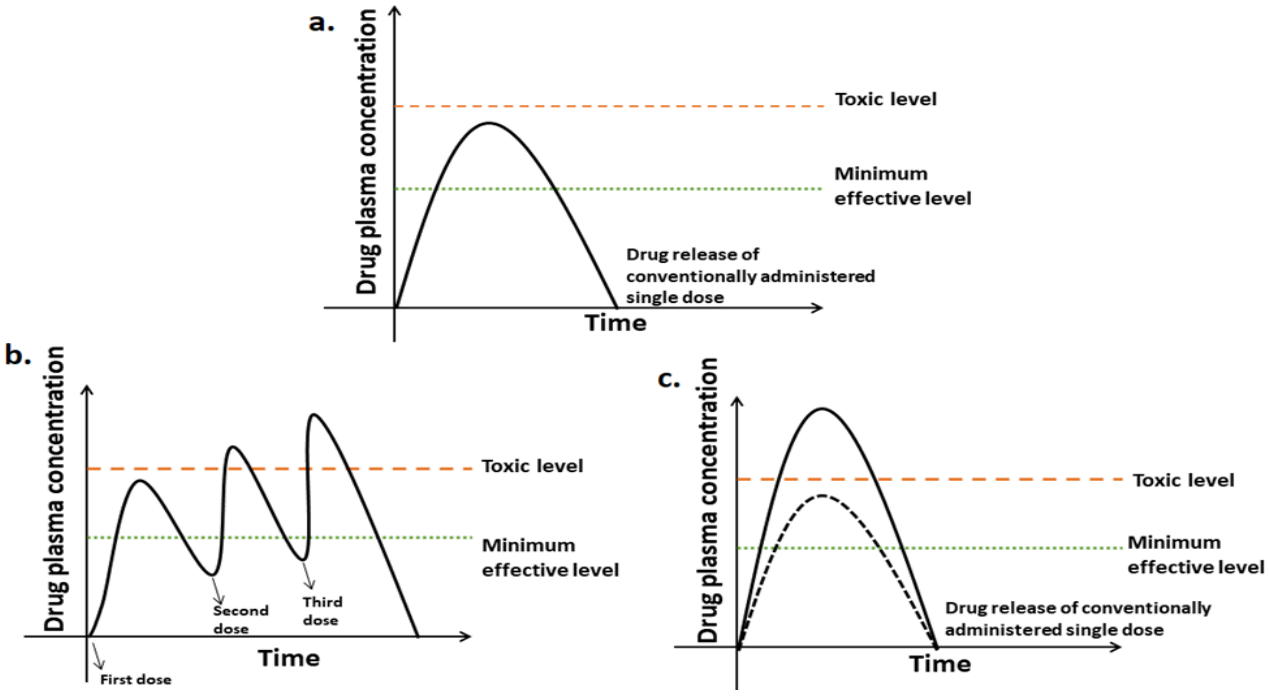


Figure 4.1. Plasma drug levels with time after administering (**a**) Single conventional dose, (**b**) Multiple doses, (**c**) Increased single dose.

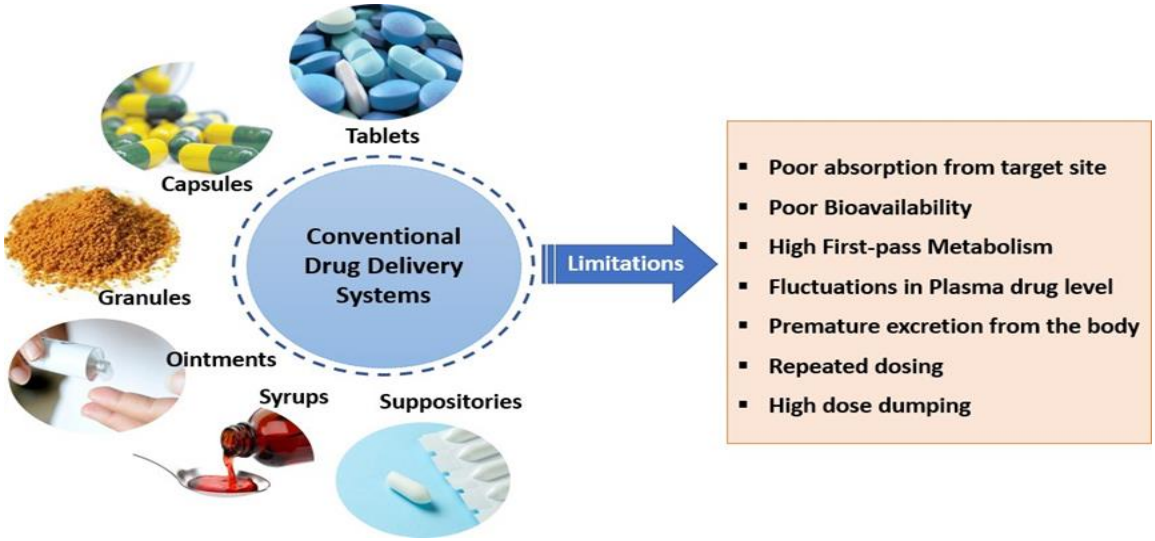


Figure 4.2. Limitations of Conventional drug delivery systems

Table 4.1. Advantages and disadvantages of conventional delivery systems.

Advantages of conventional DDS	Disadvantages of conventional DDS
Low cost	Poor patient compliance
Convenience in administration	Poor absorption from site of administration
Higher shelf-life	Premature metabolism of the drug
Non-invasive and better IVIVC	No target specificity
Flexibility for physician to dose adjustment	Repeated dosing
Accurate and measured unit dosage form	Premature excretion from the body Higher shelf-life
Accommodate patient variation	Poor bioavailability Flexibility for physician to dose adjustment

Table 4.2. Advantages and disadvantages of controlled drug delivery systems.

Advantages of controlled DDS	Disadvantages of controlled DDS
Protection from metabolism by enzymes/chemicals	Uptake by RES reduces efficacy
Controlled or defined drug release	Possible toxicity of materials used
Low dosing frequency	Limited standards
Target specificity	Dose dumping
Better patient compliance	Higher manufacturing cost
Long residence of drug	Invasive procedure to implant or remove the system Protection from metabolism by enzymes/chemicals
Improved bioavailability	Poorer IVIVC

4.2. Controlled Drug Delivery Systems

This is the drug delivery system in which a constant level of a drug is maintained in blood and tissue for an extended period. Pharmacokinetics (PK) curves of plasma concentration of a drug versus time for two types of delivery systems, conventional and controlled, are represented in Figure 4.3. In a conventional delivery system, there is typical bolus PK for multiple dosing with oral tablets or injections, where the drug level fluctuates above and below the minimum effective concentration. The controlled

delivery system, on the other hand, shows zero-order PK with just a single dose of controlled drug delivery from a specific formulation or device. The drug levels are maintained constantly within the therapeutic window [47].

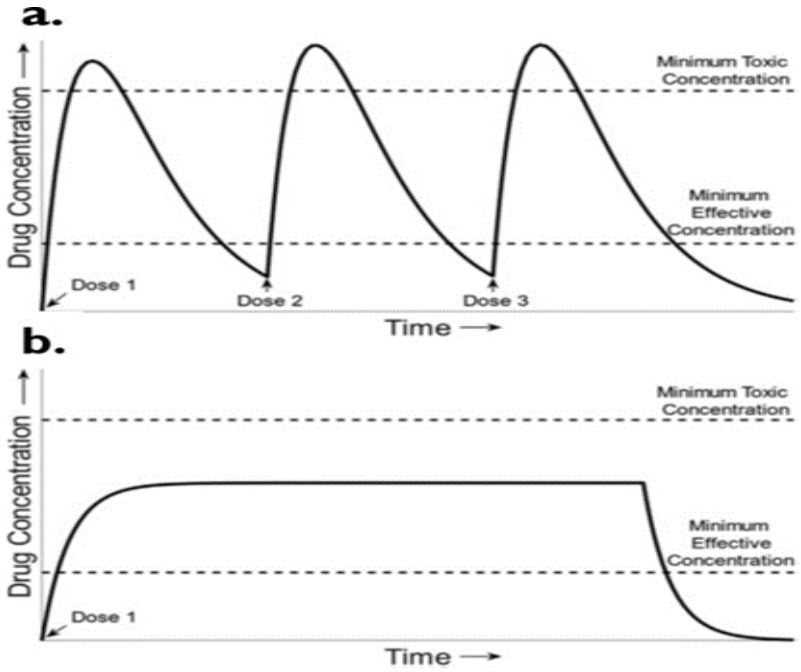


Figure 4.3. A typical bolus of (a) Conventional DDS; (b) Controlled DDS.

Controlled DDS maintain drug plasma levels constantly by releasing the definite dose of the drug at each time point for a pre-determined duration. This helps in reducing the dose and dosing frequency and improves patient compliance. Lesser drug exposure to the biological environment reduces drug toxicity and adverse effects. The overall efficacy of the dosage form is augmented [43]. The medical rationale behind controlled DDS is schematically represented in Figure 4.4..

Figure 4.4. Medical Rationale behind controlled release drug delivery systems (CRDDS).

4.3. Design Considerations of Controlled Release Drug Delivery Systems

In designing a controlled release drug delivery system, various factors and parameters need to be considered; Figure 22 briefly illustrated the design considerations. The parameters are broadly classified as formulation related and drug related. Under formulation-related parameters, the biomaterial properties, route of administration, pharmacokinetics and stability enhancement are the major factors. In addition, the drug- related parameters include drug binding efficiency with plasma proteins and the ability of the drug to cross biological barriers and regulatory aspects are also the foremost criteria in designing the dosage form [43].

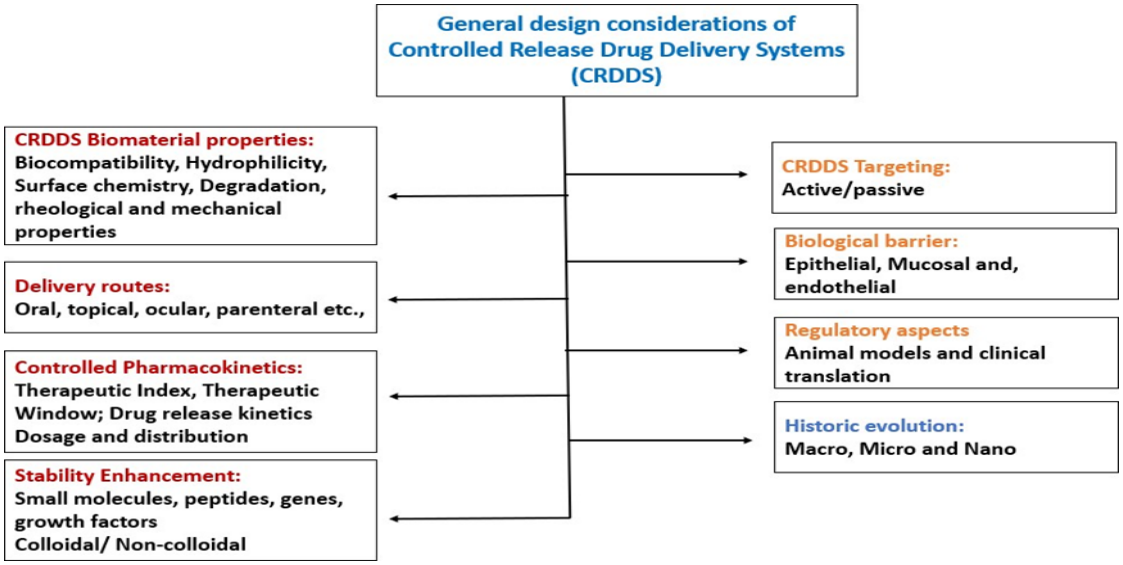


Figure 4.5. General design considerations of controlled release drug delivery systems (CRDDSs).

Biomaterial properties such as biocompatibility, surface chemistry, hydrophilicity, degradation, mechanical and rheological properties need to be studied. In addition, the behaviour of the biomaterials at various pH and temperatures also needs to be assessed. The routes of drug administration are critical for choosing the suitable biomaterial and designing the dosage form. For instance, rectal administration needs the melting point of the biomaterial to be at or above 37 °C or it is soluble at that pH so that the drug gets released. For certain drugs which are not stable in harsh conditions, including peptides, proteins, genes (DNA), growth factors and colloidal/non-colloidal particles, the stability enhancement should be done while designing the controlled release carrier. This can be achieved by incorporating the particular drugs in specialized carrier systems [48].

Targeting the drug to the site wherever the intended pharmacological activity is needed is of utmost importance to prevent the unwanted drug effects on other organs. This could be achieved by antibody tagging, attaching ligands and localized delivery. The biological barriers are a hindrance to targeting drug delivery to certain areas including the brain, bone and testicles. Drugs formulated with permeation enhancers and nanocarriers are the alternatives that can cross the barriers and deliver the drug to the target site [49]. Suitable animal models need to be established for each kind of delivery system to get the best in vitro in vivo co-relationship (IVIVC). This helps to bridge the gap between in vivo animal studies and the clinical study results [50].

4.4. Evolution of the Controlled Release Dosage Forms

First-generation: The first generation of controlled release dosage form drugs was from 1950–1980. This generation of dosage forms mainly employs four types of mechanisms for drug release, which accelerates the oral and transdermal formulations. The four types of mechanisms are dissolution, osmosis, diffusion, and ion exchange. Diffusion and dissolution-controlled systems are the most

commonly used mechanisms of drug delivery. The success of the first generation of drugs is mainly the development of the oral and transdermal routes. With these drugs, the correlation between in-vitro and in-vivo formulation was well understood and there were no biological barriers detected for this generation [63].

Second-generation: These are less successful; unlike the first generation they have formulations for prolonged release using biodegradable polymers for delivering proteins and peptides. During this period, pulmonary delivery systems were developed for delivering insulin. Due to its lesser bioavailability, it is delivered many times higher per dose than is required for the parenteral injection which results in adverse effects. In the last decade of the second generation, nanoparticles that target the gene and the tumour were studied [47]

Third generation: The new technologies for drug delivery are delivery of poorly water-soluble drugs, long-term and non-invasive technology for delivering protein/nucleic acid/peptide, drug delivery to the targeted site using nanoparticles and the drug delivered through self-regulation [63,64]. **20**

4.5. Concept of Biomaterials in Controlled Drug Delivery

Biomaterials in the drug delivery system help to modulate the pharmacokinetics of the drug. A biomaterial is a substance that has been engineered to interact with biological systems for a medical purpose, either a therapeutic or a diagnostic one. The choice of polymers or biomaterials plays an important role in designing a DDS with defined physicochemical properties and drug release profiles. The different types of biomaterials like polymers, polysaccharides, proteins, lipids and peptides are used in DDS in scales of varying lengths from nano-sized to macro-sized in different routes of applications. Biomaterials should be selected according to the type of formulation, site and route of drug delivery. It should be biocompatible, biodegradable, non-toxic, preferably hydrophilic and mucoadhesive along with optimum mechanical strength. Both non- degradable and biodegradable biomaterials are used in controlled drug delivery. Biodegradable polymers are preferred, as the degradation removes the DDS from the body and helps prevent the accumulation of toxic remnants. In the case of a non- biodegradable biomaterial-based system, if any complication occurs, chelator and reducing agents can be introduced to disintegrate [48].

CONCLUSION AND RECOMMENDATION

Drugs and excipients are combined to create the dosage form. Excipients are used to improve stability, give a substance structure, and cover the flavor. The traditional dose forms—solid, semisolid, and liquid—are hampered by variations in plasma drug levels, necessitating high dosage and frequency of administration with low patient adherence. A drug's bioavailability is essential to getting the intended effect from any dose form. As an alternative to the traditional kind, controlled drug delivery systems have gained popularity because they increase bioavailability, prolong drug release, and keep drug plasma levels within the therapeutic window while causing the fewest possible adverse effects. Drugs may be delivered selectively and at a predictable pace using controlled drug delivery, which also improves drug solubility and stability. There are several forms of controlled drug delivery methods, including chemically regulated, dissolution, diffusion, and water penetration. Stimuli-responsive delivery systems are helpful for controlling and targeting the discharge of various diseases, such as infections and cancer. Furthermore, regulated targeted distribution can be achieved by developing nanocarriers using additive manufacturing techniques and intelligent biomaterials. Drug delivery in the future will be centered on patient-specific treatment through the use of 3D-printed, microfluidic, and CRISPR cas9-based delivery systems combined with quantum sensing.

REFERENCES

1. Langer, R. Drug delivery and targeting. Nature 1998, 392, 5–10.

2. Benoit, D.S.; Overby, C.T.; Sims, K.R., Jr.; Ackun-Farmmer, M.A. Drug delivery systems. In Biomaterials Science; Elsevier: Amsterdam, The Netherlands, 2020; pp. 1237–1266.
3. Langer, R. New methods of drug delivery. Science 1990, 249, 1527–1533.
4. Chaudhari, S.P.; Patil, P.S. Pharmaceutical excipients: A review. IJAPBC 2012, 1, 21–34.
5. Jain, K.K. An overview of drug delivery systems. Drug Deliv. Syst. 2020, 2059, 1–54.
6. Patel, H.; Shah, V.; Upadhyay, U. New pharmaceutical excipients in solid dosage forms-A review. Int. J. Pharm. Life Sci. 2011, 2, 1006–1019.
7. Kalasz, H.; Antal, I. Drug excipients. Curr. Med. Chem. 2006, 13, 2535–2563.
8. Ku, M.S. Use of the biopharmaceutical classification system in early drug development. AAPS J. 2008, 10, 208–212.
9. Verma, P.; Thakur, A.; Deshmukh, K.; Jha, A.; Verma, S. Research. Routes of drug administration. Int. J. Pharm. Stud. Res. 2010, 1, 54–59.
10. Augsburger, L.L.; Hoag, S.W. Pharmaceutical Dosage Forms-Tablets; CRC press: Boca Raton, FL, USA, Boca Raton, FL, USA, 2016.
11. Qiu, Y.; Chen, Y.; Zhang, G.G.; Yu, L.; Mantri, R.V. Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice; Academic press: Cambridge, MA, USA, 2016.
12. Mahato, R.I.; Narang, A.S. Pharmaceutical dosage forms and drug delivery: Revised and expanded; CRC press: Boca Raton, FL, USA, 2017.
13. Bora, A.; Deshmukh, S.; Swain, K. Recent advances in semisolid dosage form. Int. J. Pharm. Sci. Res. 2014, 5, 3596.
14. Niazi, S.K. Handbook of Pharmaceutical Manufacturing Formulations: Volume Four, Semisolid Products; CRC Press: Boca Raton, FL, USA, 2019.
15. Mahalingam, R.; Li, X.; Jasti, B.R. Semisolid dosages: Ointments, creams, and gels. Pharm. Manuf. Handb. 2008, 1, 267–312.
16. Allen, L.V., Jr. Basics of compounding: Tips and hints, Part 3: Compounding with ointments, creams, pastes, gels, and gel- creams. Int. J. Pharm. Compd. 2014, 18, 228–230.
17. Prausnitz, M.R.; Langer, R. Transdermal drug delivery. Nat. Biotechnol. 2008, 26, 1261–1268.
18. Prausnitz, M.R.; Mitragotri, S.; Langer, R. Current status and future potential of transdermal drug delivery. Nat. Rev. Drug Discov. 2004, 3, 115–124.
19. Al Hanbali, O.A.; Khan, H.M.S.; Sarfraz, M.; Arafat, M.; Ijaz, S.; Hameed, A. Transdermal patches: Design and current approaches to painless drug delivery. Acta Pharm. 2019, 69, 197–215.
20. Dhiman, S.; Singh, T.G.; Rehni, A.K. Transdermal patches: A recent approach to new drug delivery system. Int. J. Pharm. Pharm. Sci. 2011, 3, 26–34.
21. Perrigo.Transderm-Scop, Scopalamine Transdermal Patch. Available online: https://investor.perrigo.com/2019-10-03-Perrigo- Announces-the-Relaunch-of-the-AB-Rated-Generic-Version-of-Transderm-Scop-R-1-5-MG (accessed on 15 August, 2021).
22. Gad, S.C. Semisolid dosages: ointments, creams and gels. In Pharmaceutical Manufacturing Handbook: Production and Processes; John Wiley & Sons: Hoboken, NJ, USA, 2008; 5, 267-312.

23. Rubio-Bonilla, M.V.; Londono, R.; Rubio, A. Liquid dosage forms. In Pharmaceutical Manufacturing Handbook: Production and Processes; John Wiley & Sons: Hoboken, NJ, USA, 2008; 5, 313–344.
24. Kumar, R.S.; Yagnesh, T.N.S. Pharmaceutical suspensions: Patient compliance oral dosage forms. World J. Pharm. Pharm. Sci. 2016, 5, 1471–1537.
25. Kalantzi, L.; Reppas, C.; Dressman, J.; Amidon, G.; Junginger, H.; Midha, K.; Shah, V.; Stavchansky, S.; Barends, D.M. Biowaiver monographs for immediate release solid oral dosage forms: Acetaminophen (paracetamol). J. Pharm. Sci. 2006, 95, 4–14.
26. SEARS, W. Linctuses. Practitioner 1951, 166, 91–92.
27. Payne, K.; Roelofse, J.; Shipton, E. Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 years—A pilot study. Anesth. Prog. 2002, 49, 109.
28. Van Schoor, J. Using gargles and mouthwashes: Medicine cupboard. SA Pharm. Assist. 2011, 11, 26.
29. Shargel, L.; Andrew, B.; Wu-Pong, S. Applied Biopharmaceutics & Pharmacokinetics; Appleton & Lange Stamford: Stamford, UK, 1999; Volume 264.
30. Jambhekar, S.S.; Breen, P.J. Basic Pharmacokinetics; Pharmaceutical Press: London, UK, 2009; Volume 76.
31. Fleisher, D.; Li, C.; Zhou, Y.; Pao, L.-H.; Karim, A. Drug, meal and formulation interactions influencing drug absorption after oral administration. Clin. Pharmacokinet. 1999, 36, 233–254.
32. Obata, K.; Sugano, K.; Saitoh, R.; Higashida, A.; Nabuchi, Y.; Machida, M.; Aso, Y. Prediction of oral drug absorption in humans by theoretical passive absorption model. Int. J. Pharm. 2005, 293, 183–192.
33. Hubatsch, I.; Ragnarsson, E.G.; Artursson, P. Determination of drug permeability and prediction of drug absorption in Caco-2 monolayers. Nat. Protoc. 2007, 2, 2111–2119.
34. Openstax, R.U. 1.1 The Science of Biology. Available online: http://cnx.org/contents/GFy_h8cu@10.53:rZudN6XP@2/Introduction (accessed on 12 August, 2021).
35. Quizlet. 2.1.5 Biological Membranes. Available online: https://quizlet.com/gb/377924943/215-biological-membranes-diagram/ (accessed on 12 August, 2021).
36. Seydel, J.K.; Wiese, M. Drug-Membrane Interactions: Analysis, Drug Distribution, Modeling; John Wiley & Sons: Hoboken, NJ, USA, 2009; Volume 15.
37. Gillette, J.R. Factors affecting drug metabolism. Ann. N. Y. Acad. Sci. 1971, 179, 43–66.
38. Ekins, S.; Ring, B.J.; Grace, J.; McRobie-Belle, D.J.; Wrighton, S.A. Present and future in vitro approaches for drug metabolism.

    J. Pharmacol. Toxicol. Methods 2000, 44, 313–324.
39. Taft, D.R. Drug excretion. In Pharmacology; Elsevier: Amsterdam, The Netherlands, 2009; pp. 175–199.
40. Reinberg, A.E. Concepts of circadian chronopharmacology. Ann. N. Y. Acad. Sci. 1991, 618, 102–115.

41. Prabu, S.L.; Suriyaprakash, T.; Ruckmani, K.; Thirumurugan, R. Biopharmaceutics and Pharmacokinetics. In Basic Pharmacokinetic Concepts and Some Clinical Applications; IntechOpen: London, UK, 2015.
42. Hallare J, G.V. Half Life; StatPearls Publishing LLC: Treasure Island, FL, USA, 2020.
43. Hardenia, A.; Maheshwari, N.; Hardenia, S.S.; Dwivedi, S.K.; Maheshwari, R.; Tekade, R.K. Scientific rationale for designing controlled drug delivery systems. In Basic Fundamentals of Drug Delivery; Elsevier: Amsterdam, The Netherlands, 2019; pp. 1– 28.
44. Paarakh, M.P.; Jose, P.A.; Setty, C.; Christoper, G.P. Release kinetics–concepts and applications. Int. J. Pharm. Res. Technol. 2018, 8, 12–20.
45. Habet, S. Narrow Therapeutic Index drugs: Clinical pharmacology perspective. J. Pharm. Pharmacol. 2021, 73, 1285–1291.
46. Lowe, E.S.; BALIS, F.M. Dose-effect and concentration-effect analysis. In Principles of Clinical Pharmacology; Elsevier: Amsterdam, The Netherlands, 2007; pp. 289–300.
47. Park, K. Controlled drug delivery systems: Past forward and future back. J. Control. Release 2014, 190, 3–8.
48. Fenton, O.S.; Olafson, K.N.; Pillai, P.S.; Mitchell, M.J.; Langer, R. Advances in biomaterials for drug delivery. Adv. Mater. 2018, 30, 1705328.
49. Singh, A.P.; Biswas, A.; Shukla, A.; Maiti, P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. Signal Transduct. Target. Ther. 2019, 4, 1–21.
50. Mitragotri, S.; Burke, P.A.; Langer, R. Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies. Nat. Rev. Drug Discov. 2014, 13, 655–672.
51. Gupta, B.P.; Thakur, N.; Jain, N.P.; Banweer, J.; Jain, S. Osmotically controlled drug delivery system with associated drugs. J. Pharm. Pharm. Sci. 2010, 13, 571–588.
52. Wang, Z.; Shmeis, R.A. Dissolution controlled drug delivery systems. Des. Control. Release Drug Deliv. Systems. 2006, 139-172.
53. Siepmann, J.; Siegel, R.A.; Siepmann, F. Diffusion controlled drug delivery systems. In Fundamentals and Applications of Controlled Release Drug Delivery; Springer: Berlin/Heidelberg, Germany, 2012; pp. 127–152.
54. Siepmann, J.; Siepmann, F. Modeling of diffusion controlled drug delivery. J. Control. Release 2012, 161, 351–362.
55. Srikonda, S.; Kotamraj, P.; Barclay, B. Osmotic controlled drug delivery systems. Des. Control. Release Drug Deliv. Syst. 2006,1, 203.
56. Patil, P.B., Uphade, K.B.; Saudagar, R.B. A review: Osmotic drug delivery system. Pharma Sci. Monit. 2018, 9, 2.
57. Kumar, P.; Mishra, B. An overview of recent patents on oral osmotic drug delivery systems. Recent Pat. Drug Deliv. Formul. 2007, 1, 236–255.
58. Pfizer Laboratories Div Pfizer Inc, Procardia XL. Osmotic Pump. Available online: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=8ebcb33c-f43b-4b36-9f94-9774b2a59e06 (accessed on 15 August, 2021).

59. Sudafed Osmotic Pump. Available online: https://www.sudafed.com/products/sudafed-sinus-congestion (accessed on 15 August, 2021).
60. Inc., B. Viadur (Leuprolide acetate implantable osmotic pump). Available online: http://usrf.org/breakingnews/viadur_implant.html (accessed on 15 August, 2021).
61. Siepmann, J.; Siepmann, F. Swelling controlled drug delivery systems. In Fundamentals and Applications of Controlled Release Drug Delivery; Springer: Berlin/Heidelberg, Germany, 2012; pp. 153–170.
62. Kopeček, J. Polymer–drug conjugates: Origins, progress to date and future directions. Adv. Drug Deliv. Rev. 2013, 65, 49–59.
63. Yun, Y.H.; Lee, B.K.; Park, K. Controlled drug delivery: Historical perspective for the next generation. J. Control. Release 2015, 219, 2–7.
64. Guo, M.X. Dissolution Testing: In Vitro Characterization of Oral Controlled Release Dosage Forms; Wiley: Hoboken, NJ, USA, 2010.
65. Adeosun, S.O.; Ilomuanya, M.O.; Gbenebor, O.P.; Dada, M.O.; Odili, C.C. Biomaterials for Drug Delivery: Sources, Classification, Synthesis, Processing, and Applications. In Advanced Functional Materials; IntechOpen: London, UK, 2020.
66. Neuse, E.W. Synthetic polymers as drug-delivery vehicles in medicine. Met. Based Drugs 2008, 2008, 469531, doi:10.1155/2008/469531.
67. Srivastava, A.; Yadav, T.; Sharma, S.; Nayak, A.; Kumari, A.A.; Mishra, N. Polymers in drug delivery. J. Biosci. Med. 2015, 4, 69– 84.
68. Dan Mogoşanu, G.; Mihai Grumezescu, A.; Everard Bejenaru, L.; Bejenaru, C. Chapter 8—Natural and synthetic polymers for drug delivery and targeting. In Nanobiomaterials in Drug Delivery; Grumezescu, A.M., Ed.; William Andrew Publishing: Amsterdam, The Netherlands, 2016; pp. 229–284.
69. Palani, P M R., and Palani, Z M R.(2024). Factors Affecting on the Behaviour of Asymmetric COST.Best Journal of Innovation in Science, Research, and Development.3(12).166-172.14.
70. Palani, P. M. R. , yagob KG and Ahmed Y A. (2024). Measuring the impact of the general budgeton the trade balance in Iraq for the period (2004-2022). Journal of Garmian University 11(1):152–168.15.
71. Palani, P. M. R. and Hussen, A J. (2024). Efficiency of Pareto Optimality for ConsumptionandProduction. International Journal for Novel Research in Economics , Finance and Managemen.Volume 2, Issue 6, Nov-Dec 2024, PP: 113-118.16.
72. Palani, P. M. R. (2025). The Relationship of International Loans to Credit Wall (Worthiness): AReview. Spanish Journal of Innovation and Integrity, 38, 1–7. Retrievedfromhttps://sjii.es/index.php/journal/article/view/168.
73. Palani, P. M. R. (2025). Residential Crisis in Iraq: The Current Trends and Future Prospectus: A Review. Spanish Journal of Innovation and Integrity, 38, 121–128. Retrievedfromhttps://sjii.es/index.php/journal/article/view/185