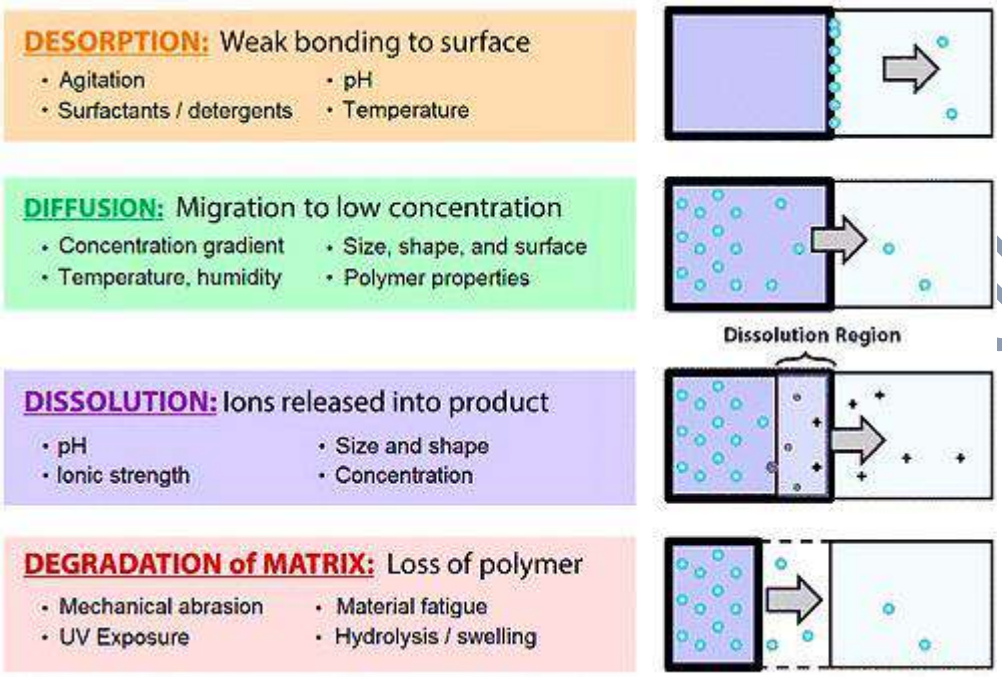
Drug Delivery Materials

Definition of Drug Delivery:

Drug delivery is the technique or procedure to administer pharmaceutical compounds to accomplish the therapeutic impact in humans or animals. Drug delivery is a broad field of research on the development of novel materials or carrier systems for effective therapeutic delivery of drugs. Such systems playing an important role in treating multiple ailments.

- The drug delivery may be:
  1. Steady
  2. Controlled
  3. Targeted
- Drug delivery systems are ideally devised to disseminate a drug when and where it is needed and at minimum dose levels. Polymeric drugs and delivery systems provide that possibility through several different approaches, such as:
  1. Polymeric drugs,
  2. Polymeric drug conjugates,
  3. Drug carriers,
  4. Polymeric prodrug systems,
  5. Bioerodible matrices,
  6. Diffusion through membranes or from monolithic devices,
  7. Osmotic pumps.



Drug delivery systems (DDSs)

It is new strategies and an idea on controlling the pharmacokinetics, pharmacodynamics, nonspecific toxicity, immunogenicity, bio-recognition, and efficacy of drugs were generated. In another word, DDSs are like a bridge between a patient and a drug. Basically, the DDSs can be divided into two main types:

(1) Conventional DDSs and

(2) Novel DDSs that are sometimes called controlled DDSs:

(a) Targeted Drug delivery system.

(b) Controlled Drug delivery system.

(c) Modulated Drug delivery system.

Conventional DDSs

1- Conventional DDSs are classical methods for delivery of a drug into the body. Generally, these systems are used more often when the goal is quickly absorption of a drug; therefore, a quick release of the drug is required.
2- The conventional drug delivery forms include simple oral, topical, inhaled, or injections methods.
3- These methods cannot keep the drug concentration at a fixed and constant level for a given period of time (Temporal Delivery).

Note: Oral drug delivery is the preferred route for medication administration due to its lower cost and higher patient convenience than other methods such as injection and implantation.

Figure (1): Solid unit dosage forms: (a) Tablets (b) Effervescent tablets (c) Chewable tablets (d) Pills (e) Hard-gelatin capsules (f) Soft-gelatin capsules (g) Lozenges (h). Granules

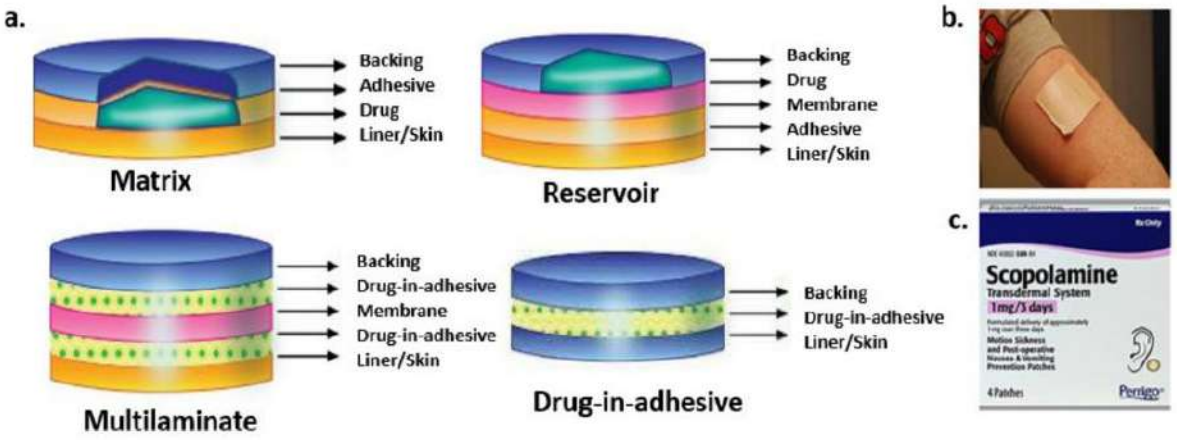


Figure (2): (a) Types of transdermal patches (b) Transdermal patch applied on skin (c) First commercially available Scopolamine transdermal patch.

Novel (Controlled-release) DDSs

1- Novel drug delivery system (NDDS) also called controlled-release drug delivery system is a combination of advanced techniques and new dosage forms to introduce better drug potency, control drug release, provide greater safety, and target a drug specifically to a desired tissue.

2- In other words, controlled release must have two properties such as predictability and reproducibility in the release kinetics.

3- NDDSs lead to efficient use of expensive drugs and excipients, and reduce in production cost.

4- NDDSs are divided into four categories including:

(1) Rate-preprogrammed,

(2) Activation-modulated,

(3) Feedback-regulated, and

(4) Site-targeting DDSs

Drug Release Profiles

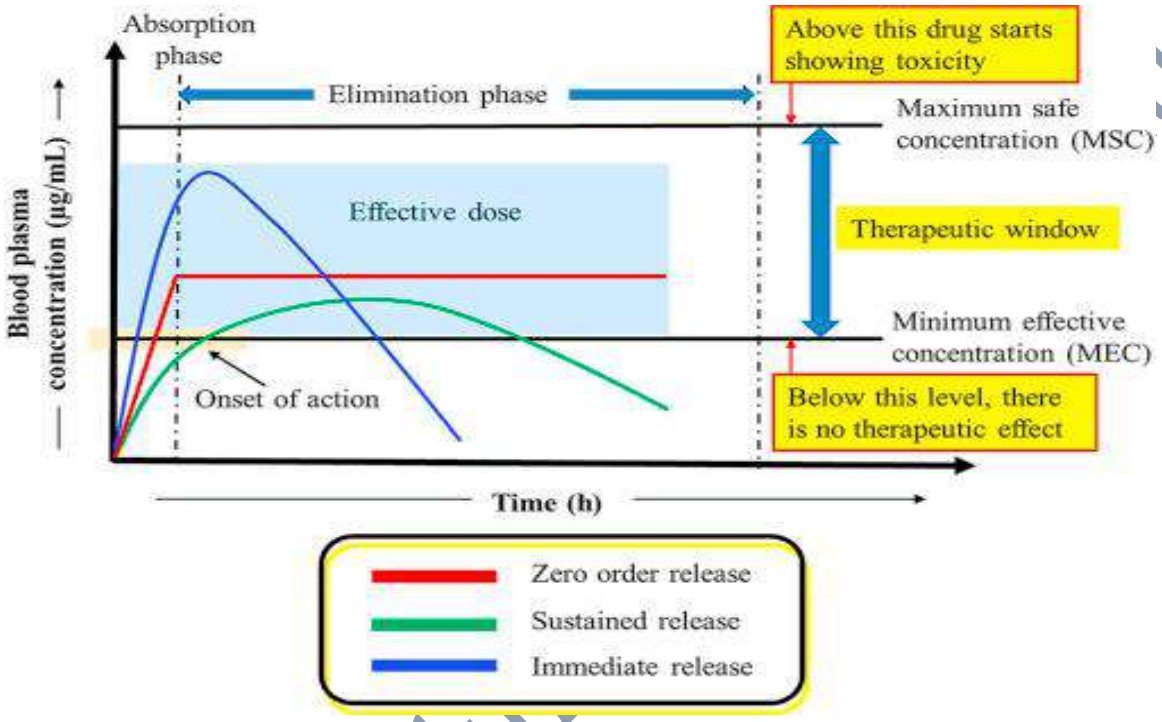


Figure (3): Common drug release profiles.

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

Drug Release Profiles

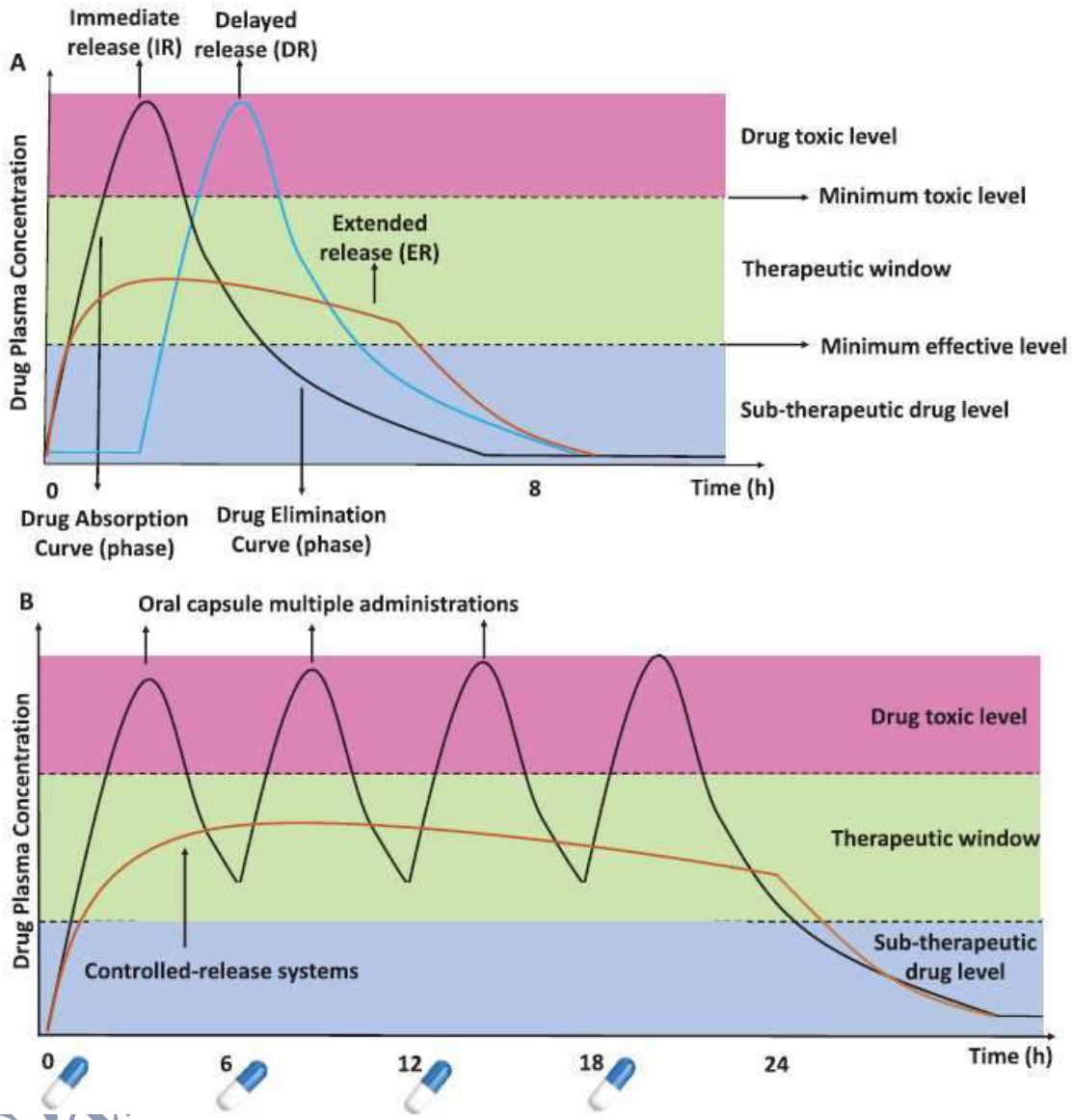


Figure (4): Schematic illustration of the drug plasma concentration from advanced drug delivery systems (DDSs) and conventional formulations. (A) This graph demonstrates the lower treatment efficacy and the higher toxicity risk of the immediate-release (IR) and delayed-release (DR) systems versus the higher effectiveness of the extended-release (ER) formulations. (B) Drug plasma concentration in IR systems that require multiple administrations to stay in the therapeutic window.

- ***Advantageous of novel drug delivery systems over conventional formulation:***

1. Increased bioavailability.
2. Protection of drug from physical, enzymatic and chemical degradation.
3. Targeted drug delivery to desired tissues.
4. Improved drug stability.
5. Controlled and defined drug release.
6. Minimized side effects.
7. Enhanced drug efficacy.
8. Better patient compliance.

Drug release kinetics

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

2- ***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.*

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

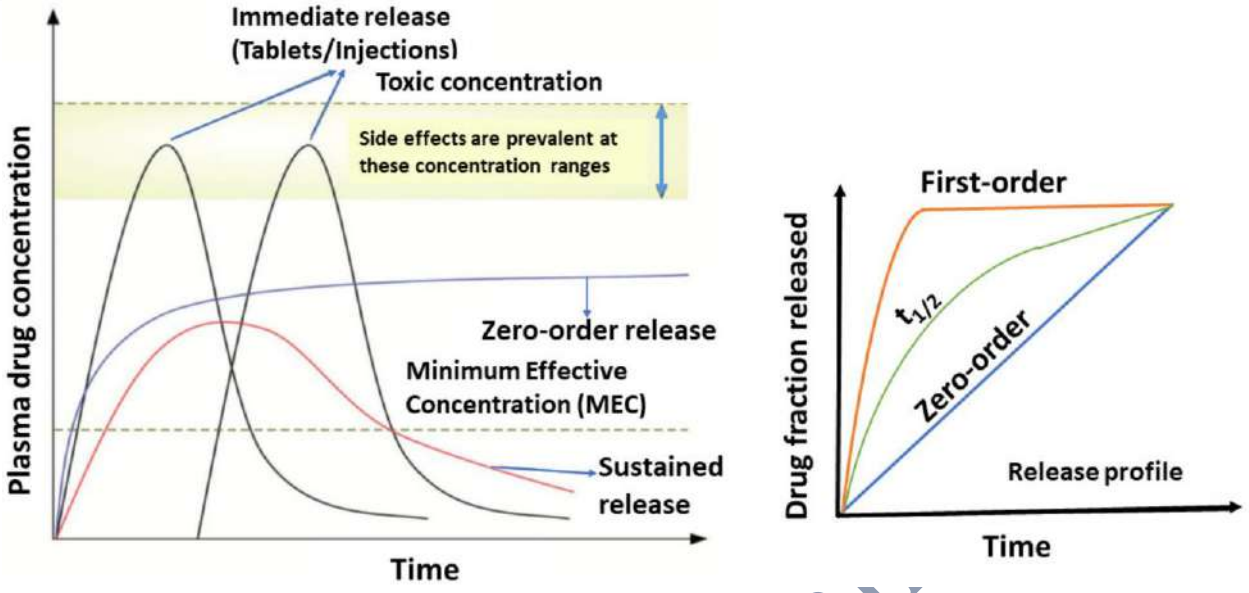
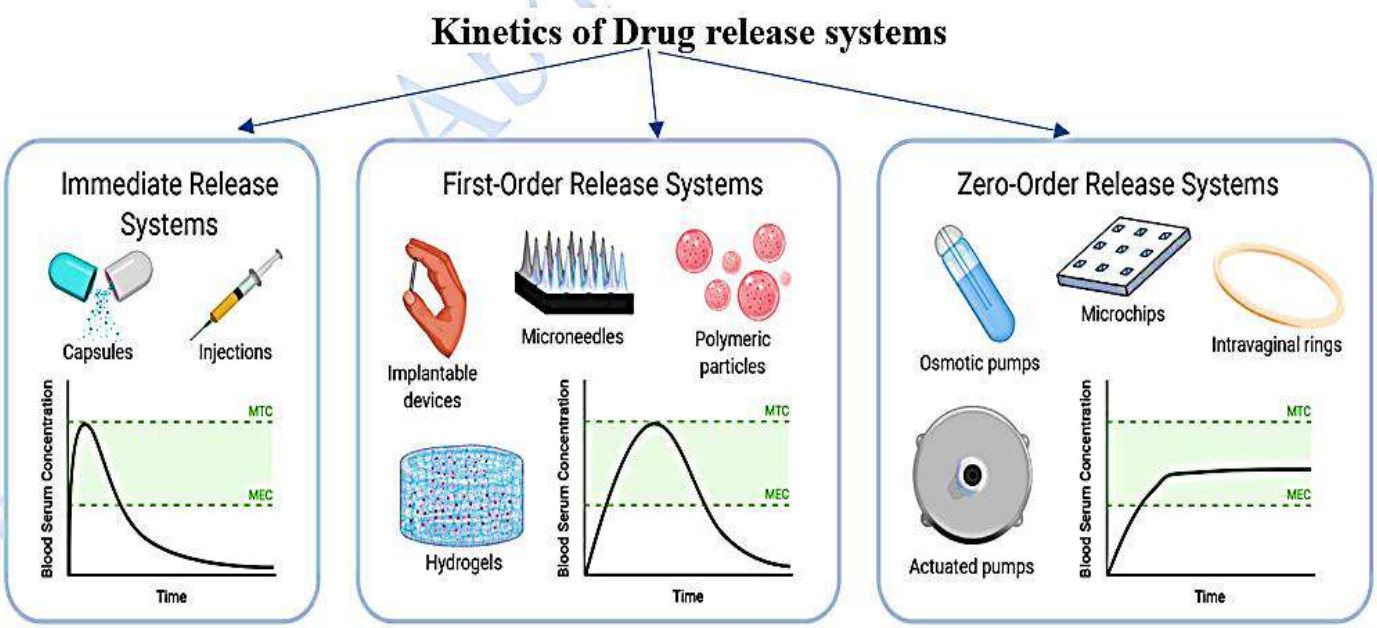
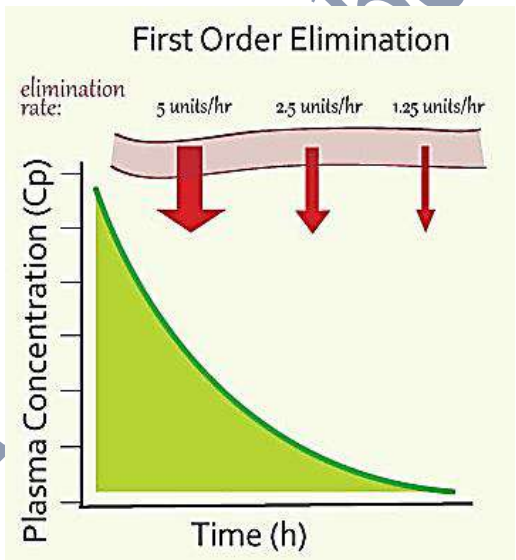
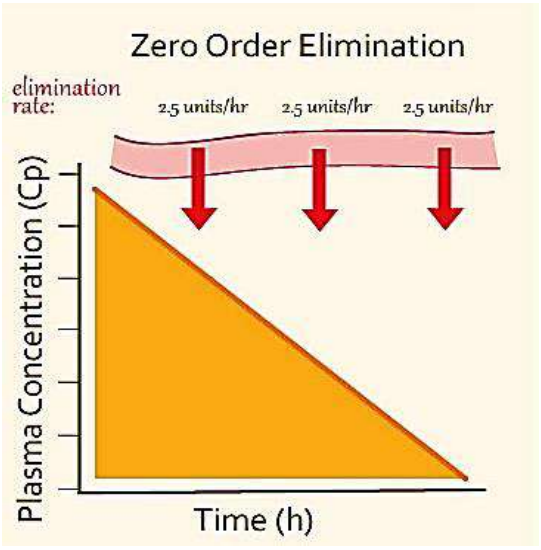


Figure (5): Drug plasma levels and release profiles.



First Order Kinetics	Zero order Kinetics
1- First order kinetics refers to chemical reactions whose rate of reaction depends on the molar concentration of one reactant.	1- Zero order kinetics refer to chemical reactions whose rate of reaction does not depend on the reactant concentration.
2- Graph of reactant vs. Time is a curved graph.	2- Graph of reactant concentration vs. time is a linear graph.
3- Reactions depend on the reactant concentration.	3- Reactions do not depend on the reactant concentration.
4- Rate law includes the rate constant multiplied by the reactant concentration.	4- Rate law includes the rate constant.
5- 	5- 

Drug Delivery System Approaches:

1. ***Polymeric Drugs:***

Polymeric drugs are macromolecules that elicit biological activity. Many synthetic polymers are biologically inert. However, some exhibit toxicity, while others exhibit a wide range of therapeutic activities. There are three kinds of polymer drugs: polycations, polyanions, and polynucleotides.

2. ***Polymeric Drug Conjugates or Drug Carriers:***

Many potentially effective drugs cannot be used because of host elimination or rapid metabolization. In some instances, this can be amended by using drug-polymer conjugates. The drug is covalently bonded to an appropriate polymer carrier. These large molecules diffuse more slowly and are adsorbed at distinct pharmacological interfaces. Consequently, polymer-drug conjugates can prolong therapy at sustained dosages. Polymeric drug carriers have desirable properties such as:

1. Sustained therapy,
2. Slow release,
3. Prolonged activity, and
4. Drug latentation.

These conjugate systems can consist of the following isolated or combined design elements of:

1. Molecular weight,
2. polydispersity,
3. biodegradation,
4. swelling, crosslinking,
5. chemical functionality,

6. composition, and
7. release kinetics.

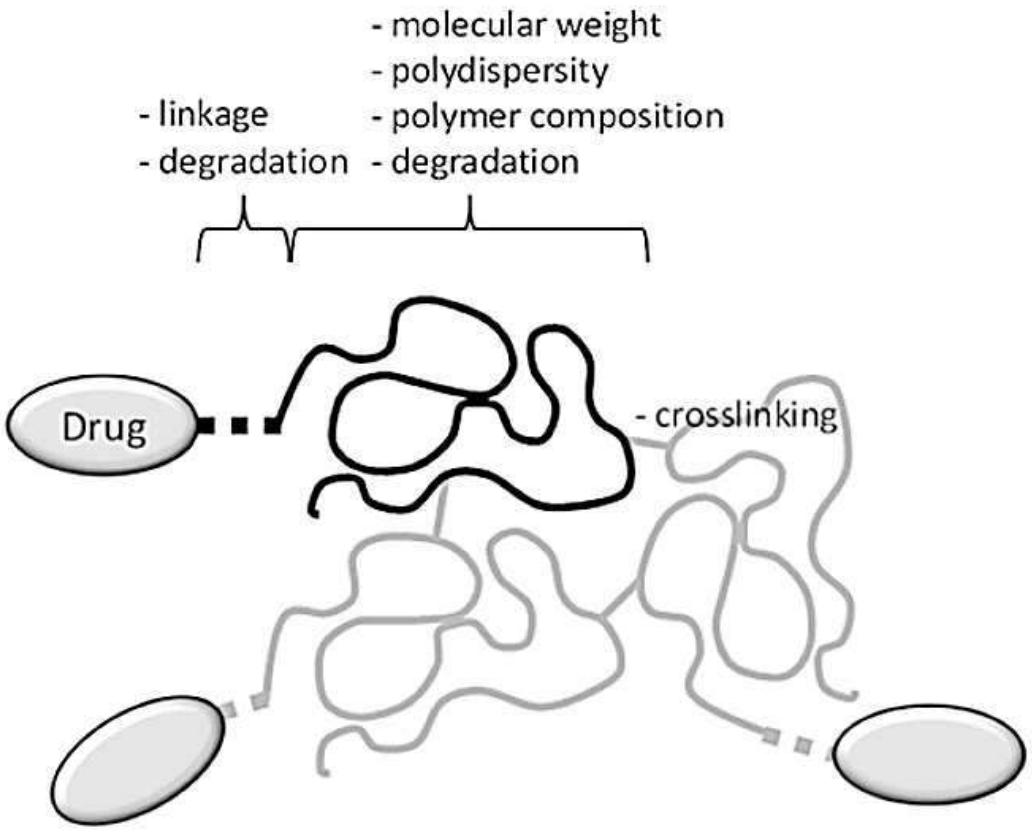


Figure (6): Diagram of the components of drug–polymer conjugate systems.

3. ***Targeted Polymeric Drugs***: Polymer drug targeting to a specific biological site is an enormous advantage in drug delivery because only those sites involved are affected by the drug. This precludes the transport throughout the body, which can elicit serious side effects. Ideally, a targetable drug carrier is captured by the target cell to achieve optimum drug delivery while minimizing the exposure to the host.
4. ***Polymeric Prodrugs***: The term "prodrug" can be defined as a chemically modified inert form of active drugs, which upon administration into body activate by

enzymatic or chemical reaction and release an active drug, which is responsible for of therapeutic activity.

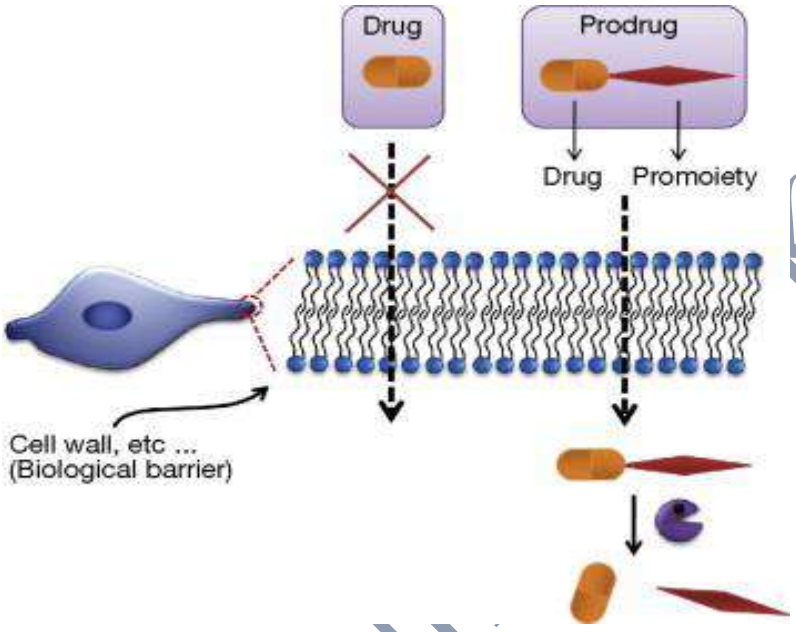


Figure (7): prodrug is a conjugate of a known drug and a promoiety.

Model for polymer drug carrier:

Figure (8) shows A model for pharmacologically active polymer drug carriers. In this schematic representation, four different groups are attached to a biostable or biodegradable polymer backbone. One group is the pharmacon or drug, the second is a spacing group, the third is a transport system, and the fourth is a group to solubilize the entire biopolymer system.

- The pharmacon or drug is the entity that elicits the physiological response. It can be attached permanently by a stable bond between the drug and the

polymer, or it can be temporarily attached and removed by hydrolysis or by enzymatic processes.

- The transport system for these soluble polymer drug carriers can be made specific for certain tissue cells with homing or targeting moieties such as:
  1. PH-sensitive groups.
  2. Receptor-active components, such as antibody-anti-gent recognition.

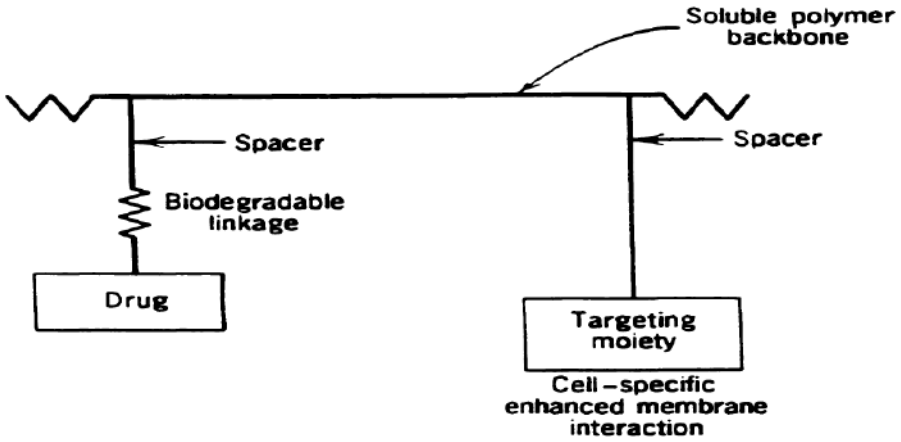


Figure (8): Model for polymer drug carrier.

Table (1): Biomaterials used as carriers for drug delivery.

Biomaterials	Examples
Natural – biodegradable	Hyaluronic acid Collagen Elastin Polysaccharides
Synthetic – biodegradable	Polyesters Polyanhydrides Polyortho esters PLGA
Synthetic – non-biodegradable	Silicone Poly(ethylene–co-vinyl acetate) (PEVA) Polyacrylate

5. *Bio erodible matrices:*

"Bioerodible" as using biological processes to mechanically erode a polymer. Water can erode a polymer via mechanical means (e.g. friction) and/or solubilise the polymer. In this sense, "bioresorbable" is a synonym of bioerodible; the implication is that the polymer is resorbed, or adsorbed, into the surrounding tissue. Thus, the chemistry of the polymer is not fundamentally changed; rather, the physical state has changed from a solid structure to a solubilized polymer.

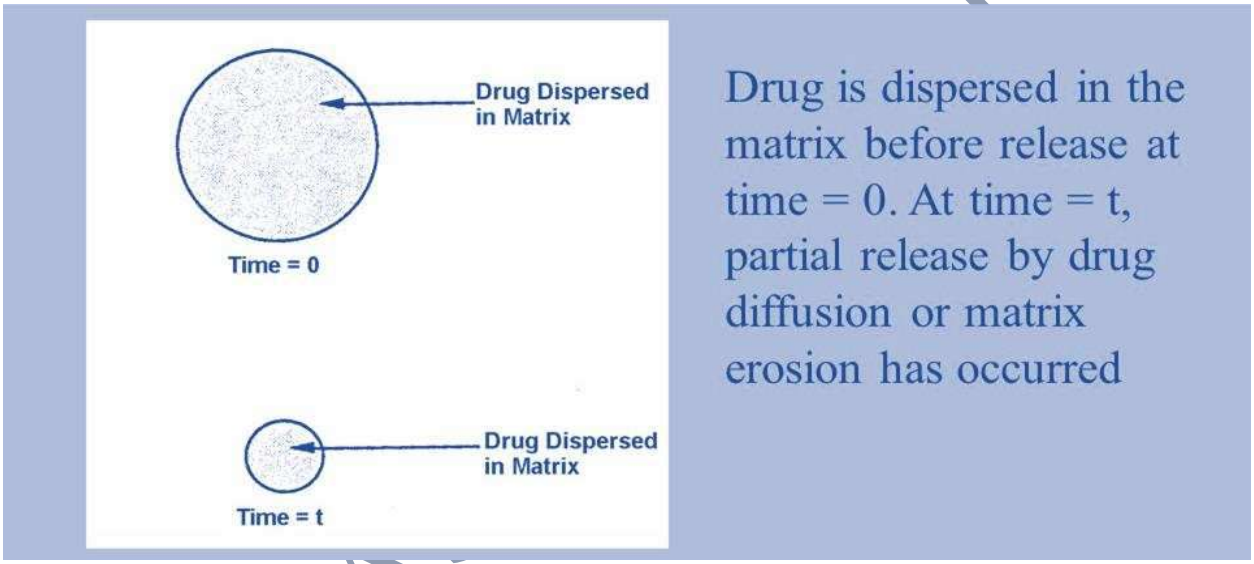


Figure (9): Bio erodible matrix system.

6. *Diffusion from monolithic devices:*

Monolithic devices typically exhibit an initial burst of release from the surface, and the release rate decreases with the passing time. This phenomenon is a consequence of the distance of the drug from the surface. A monolithic system prepared with an erodible polymer can release the active agent by erosion, diffusion, or both, depending on the relative velocity of two phenomena.

The release steps of the active agent from monolithic systems can be different (Figure 10).

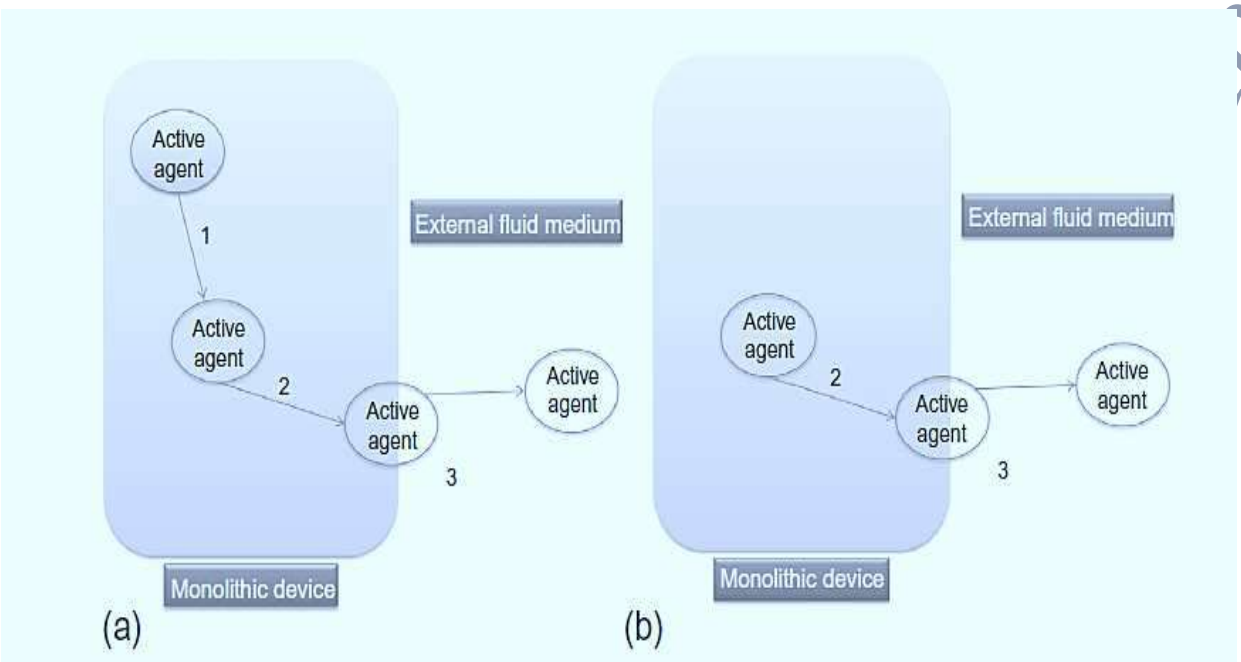


Figure (10): Schematic representation of steps of release from a monolithic system of an active agent dissolved (a) or not (b): ***(1) dissolution in the matrix; (2) diffusion through the matrix to the surface; (3) transport from the system surface.***

7. Osmosis:

Osmosis may be defined as the action in which the solvent is transferred through a semipermeable membrane to dilute a solution containing solute and solvent. When two solutions of different concentrations are separated by a semipermeable membrane that is permeable to the smaller solvent molecules but not to the large solute molecules, then the solvent will tend to flow through the

semipermeable membrane from the less concentrated to the more concentrated solution. It is an effort to equalize concentrations of the impermeable solutes on both sides of the membrane (Figure 11).

The rate of osmotic flow across a unit area of the membrane is determined by:

1. The concentration and nature of osmolytes on both sides of the membrane
2. Temperature
3. The hydraulic permeability of the membrane, which can be determined by measuring water flow when hydrostatic pressure is applied across the membrane

These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt e.g. NaCl) within a semi permeable membrane made from biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is they created, under which the drug solutes are continuously pumped out of tablet through small delivery orifice in tablet coating over a prolonged period of time through the delivery orifice. This type of drug system dispenses drug solutes continuously at a zero-order rate. Release of drug is independent on the environment of the system.

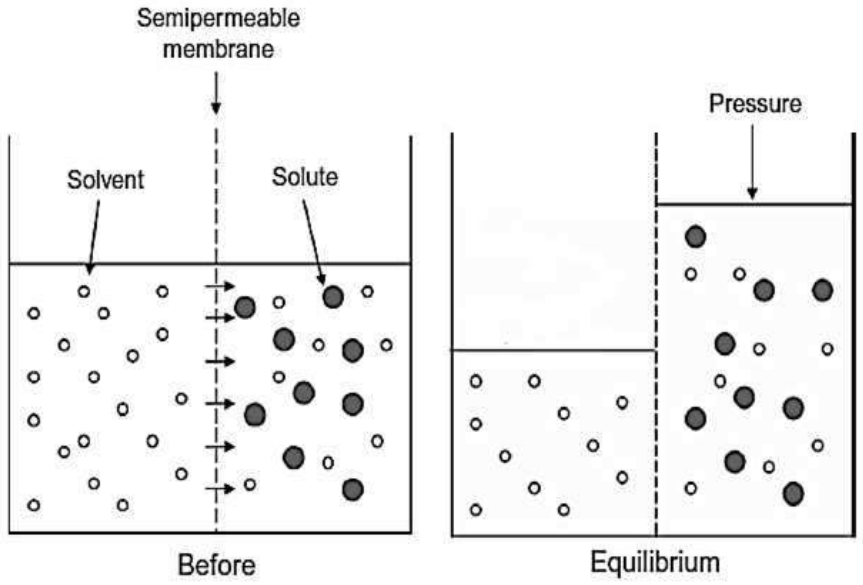


Figure (11): Diagram of principle of osmosis.

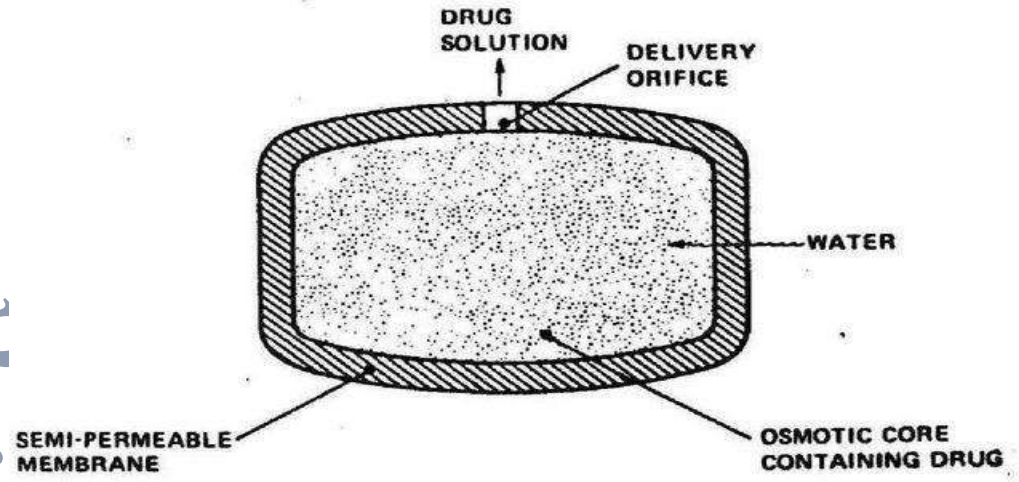
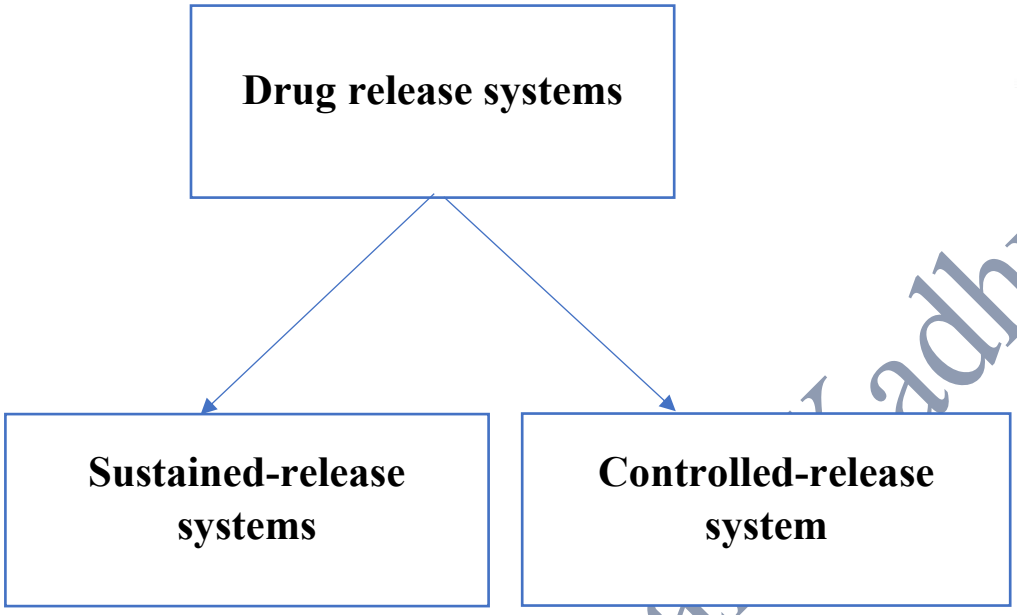


Figure (12): Osmotically controlled release system.



- ***Sustained-release systems*** are traditionally a mix of agents that affect the net rate of dissolution of the drug molecule.
- ***Controlled-release systems*** are comprised of a drug molecule (i.e., active agent) and a bioinert or biocompatible polymer.

Mechanisms for Obtaining Sustained Drug Release :

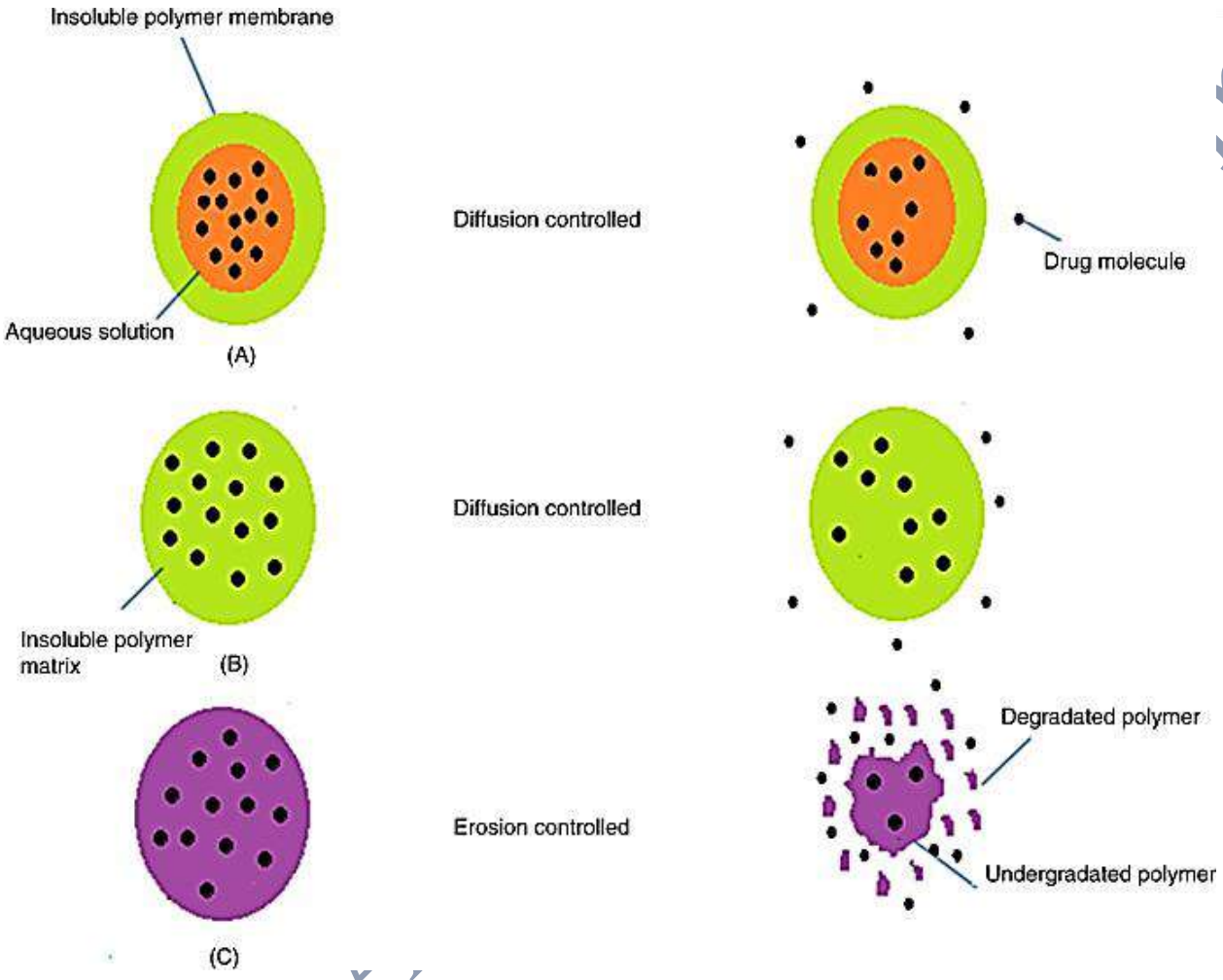


Figure (13): Diagram of three main mechanisms for obtaining sustained drug release. (A–B) **Diffusion** via matrix or shell of insoluble polymer, and (C) **Erosion** of a polymer matrix.

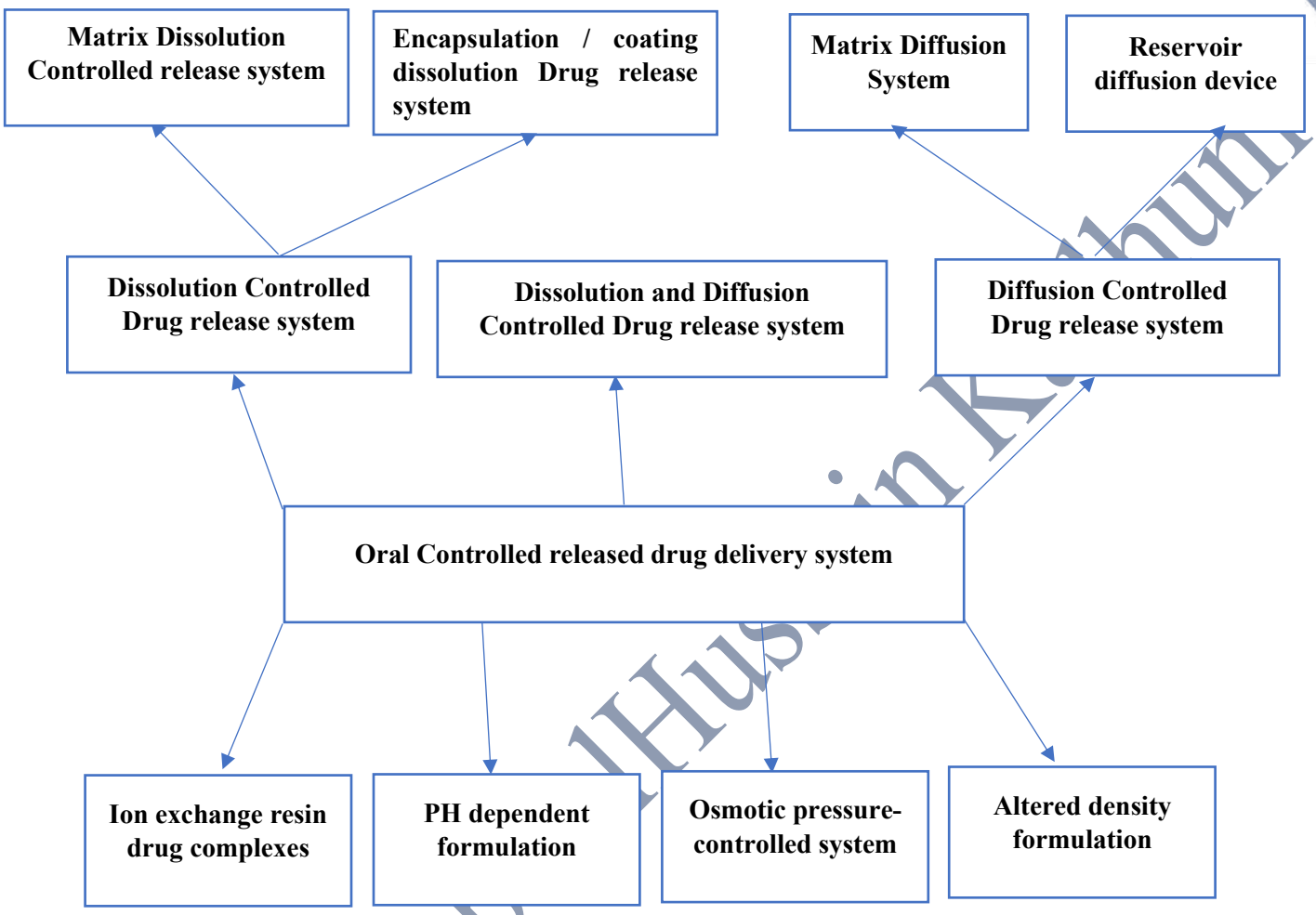


Figure (14): Approaches of oral controlled release drug delivery system.

Question: *What is the desired location in the human physiology to which this treatment is going to be applied?*

Controlled systems can be applied to a person through oral, ocular, parenteral, and sublingual sites.

Diffusion:

Diffusion is defined as the process of mass transfer of individual molecules of a substance from one part of a system to another, carried by random molecular motions, and is associated to forces such as concentration gradient. In diffusion, the mass transfer is a kinetic process that occurs in systems that are not in equilibrium.

Considering the scheme of **Figure 15**, it is possible to say that the mass transfer from point 1 to point 2 is governed by the concentration gradient and the distance. The amount of mass (*M*) flowing through a unitary transversal surface (*S*), in a time *t*, is defined as flux:

$$J = \frac{dM}{S \cdot dt}$$

This is Fick's first law, where the molecule flux is proportional to the gradient of concentration:

$$J = -D \cdot \frac{dC}{dx}$$

$$\frac{\partial C}{\partial t} = -D \cdot \frac{\partial^2 C}{\partial x^2}$$

Where J is the rate of transfer per unit area of the section, C is the concentration of the diffusing substance, x is the distance between the two points, and D is called the diffusion coefficient.

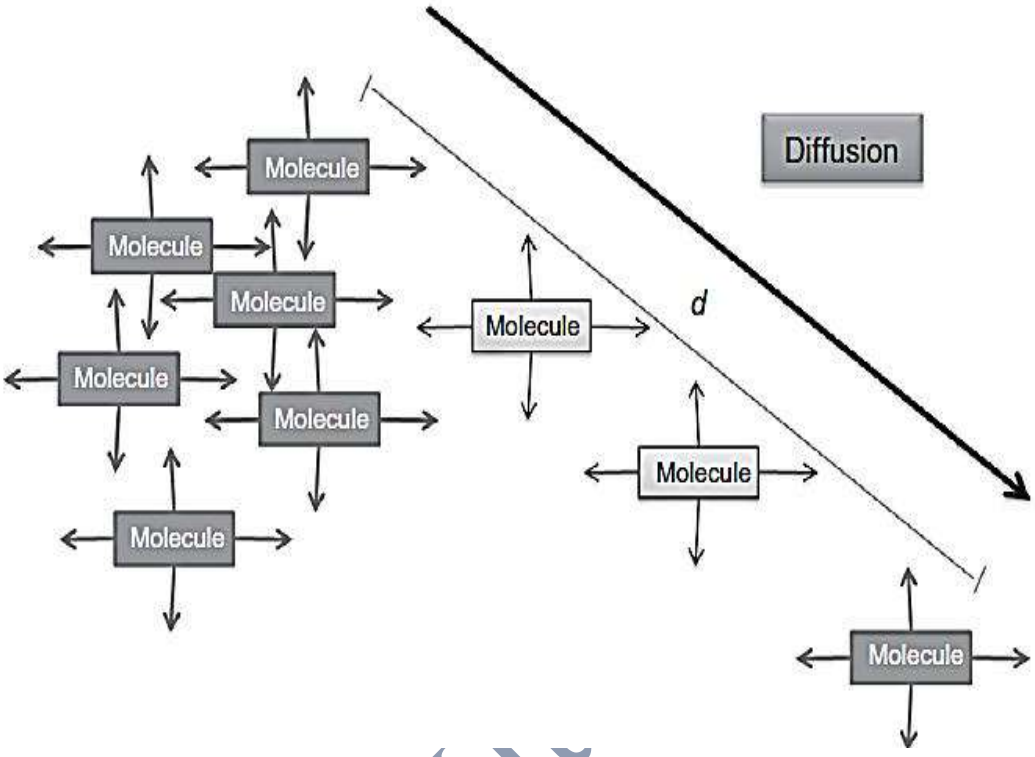


Figure (15): Diffusion process of molecules through a solvent: (d) represents the distance of molecule movement.

Matrix based Diffusion system	Reservoir diffusion systems
1-The drug is combined with a polymer to form a composite matrix where water permeation leads to either swelling or osmotically controlled systems.	1-In reservoir systems, the drug solution is encapsulated within a polymer droplet, creating a permeable barrier between the drug solution environment and the surrounding environment.
2- Since the matrix is composed of both polymer and drug molecules, the swelling effect is seen as a uniform volume expansion of the bulk polymeric material, causing the opening of pores throughout the matrix structure	2- Since the reservoir is composed of a permeable polymer barrier coating, the swelling effect is seen as a nonuniform volume expansion, where the barrier coating allows for water permeability and swells, while the internal components can diffuse out of the system.
3-No danger of dose dumping in case of rupture.	3- Rupture can result in dangerous dose dumping, where; Dose dumping can occur due to pinhole defects and cracks in the membrane.
4- Suitable for both non-degradable and degradable system.	4- Degradable reservoir systems may be difficult to design.
5-Achievment of zero-order is difficult.	5- Achievement of zero order release is easy.

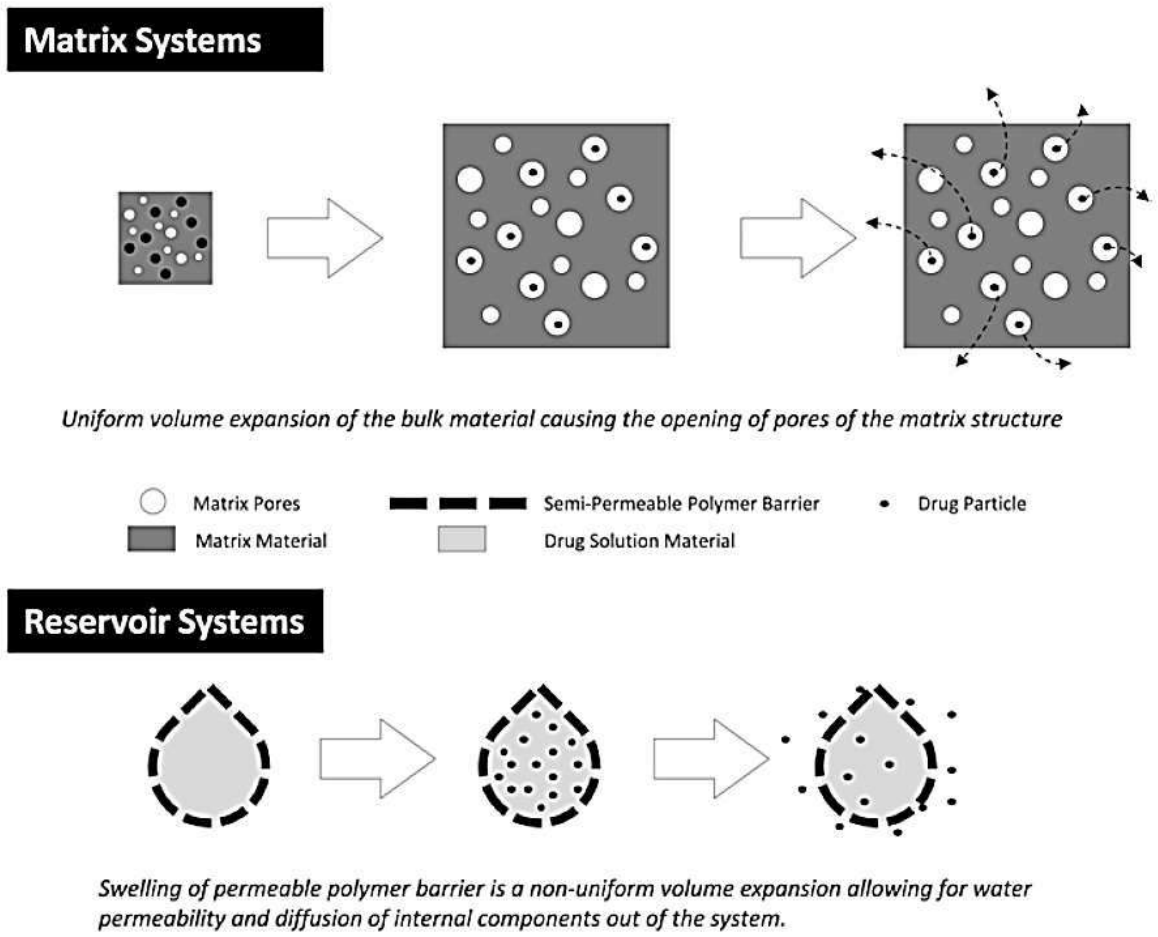


Figure (16): Diagram of basic controlled-release systems for drug delivery.

Diffusion controlled system

***Question*:** *What factors can we manipulate in order to allow for control over the swelling or permeability of the barriers utilized in matrix or reservoir systems?*

Ans: In matrix systems, the crosslinking of either a covalent or secondary bonding between, or within, polymer chains is used to stabilize the physical integrity while the system passively takes up water. In reservoir systems, crosslinking is also typically utilized with similar bonding as in matrix systems; however, the volumetric limitations of the swelling behavior are distinctly different) **Figure (16).**

❖ **The Release Steps of Active Agents from A Reservoir System:**

1. Diffusion along the reservoir;
2. Dissolution or partitioning between the carrier fluid and the membrane;
3. Diffusion through the membrane;
4. Partitioning between the membrane and the external fluid medium;
5. Transport from the system surface. The concentrations of active agent through the sites are (C_d) reservoir; (C_1) inner membrane; (C_2) outer membrane; (C_r) external medium (Figure 17).

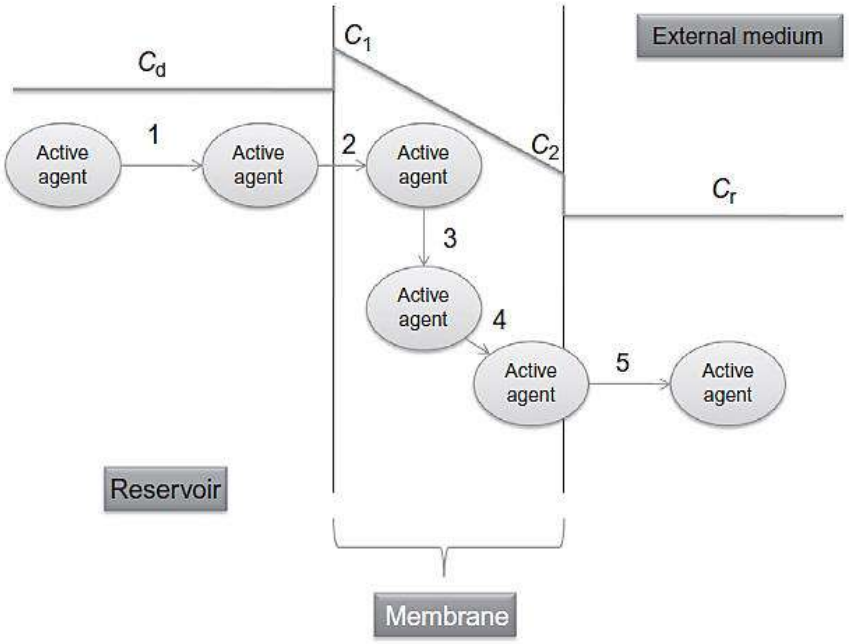


Figure (17): Schematic representation of steps of active agent release from a reservoir system.

Swelling:

Many materials display the characteristic of swelling when in contact with water. This is due to their hydrophilic behavior and the interaction between water and their molecules. Polymers are the main materials employed for preparation of

controlled drug release systems, and their polymer chains can organize in a three-dimensional fashion. When a polymer network is surrounded by water, the network expands and chemical or physical bonds are formed **Figure (18)**. Compared to osmosis, the swelling process is very similar. Water enters the polymer relatively rapidly, while dissolution of the polymer into water, if it occurs, is comparatively slow because of the need for polymer chains to disentangle. This expansion of volume and the consequent emergence of greater spaces between the polymeric chains can be used to control the release of active agents from polymeric systems (matrix or reservoir).

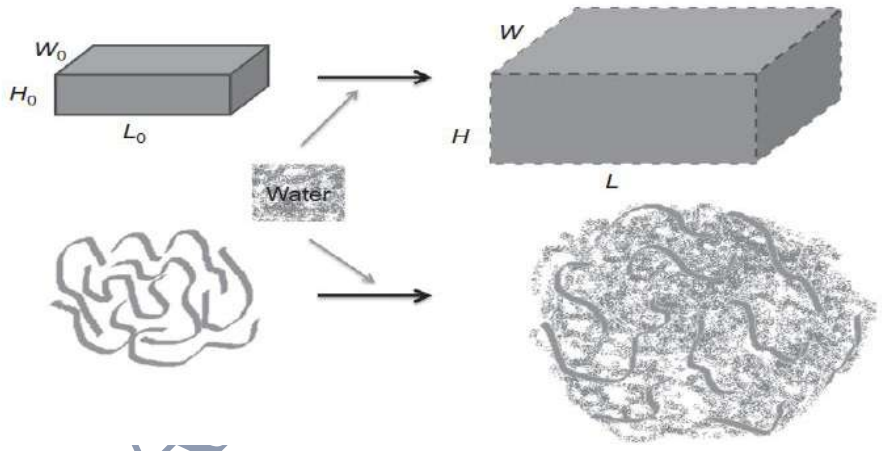


Figure (17): Schematic diagram of swelling process: (W_0) initial width; (H_0) initial height; (L_0) initial length; (W) final width; (H) final height; (L) final length.

However, sometimes the swelling of material is ***limited*** and the matrix does not disappear (Figure 18 b). This phenomenon can occur when:

1- The water and the polymer are insufficiently compatible,
2- If polymer chain length is sufficiently large, or
3- If cross-links are introduced to form a polymer network.

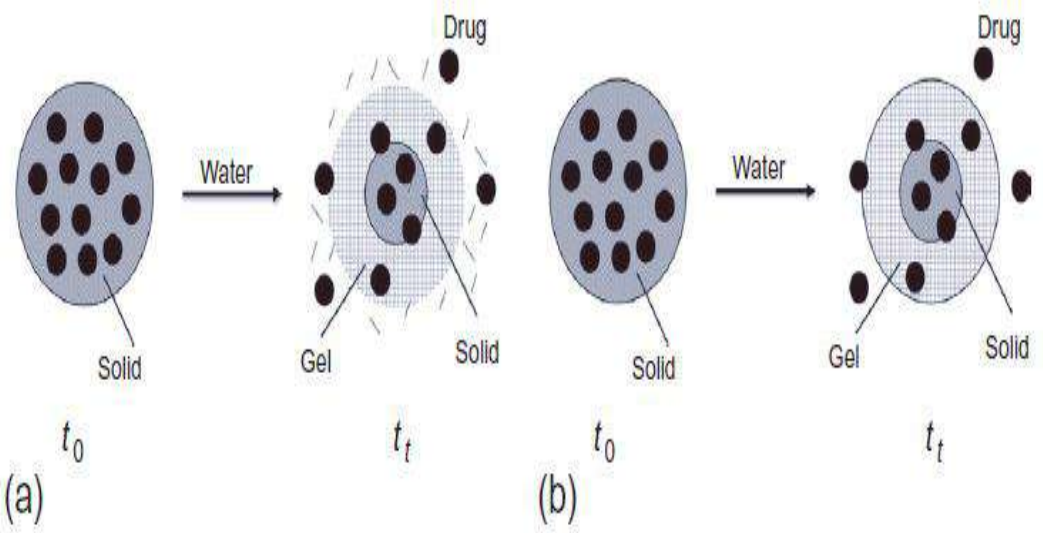


Figure (18): Swelling process during the time period of $t_0 - t_t$: (a) unlimited and (b) limited.

Swelling controlled release systems

Swelling controlled release systems are typically glassy polymers at room and body temperatures. It is possible to divide the swelling agents into chemical and physical. In the first group are the polymers that possess all chains cross-linked to each other by covalent bonds. During the synthesis of chemical polymeric material, a cross-linker is used to link the polymeric chains. When the precursor hydrophilic polymer is treated physically, a physical polymeric material is originated. Polymers should therefore contain functional groups capable of reacting with ions, or other functional groups like aldehydes.

When in contact with water, the glassy polymer at the surface of the system relaxes to a configuration that is more compatible with water, and swells. This opens the way for water to intrude even further, and a moving front is often observed, separating a swollen outer layer from a dry inner core. **Cross-link content**, **ionic content** and **hydrophilic content** are the three major elements of swelling process control.

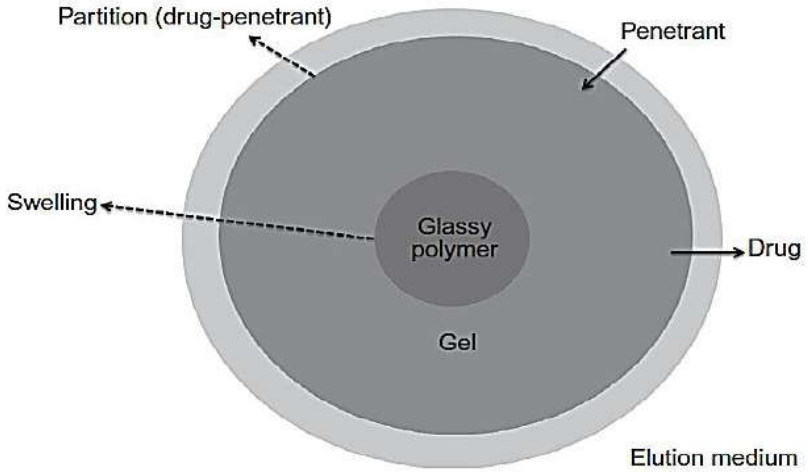


Figure (19): Schematic representation of phenomena that occur in swelling-controlled release systems.

Q/ How can be modulated the swelling process and the control release rate?

Ans: The active agent, additives, proper selection of polymer, temperature and pH can modulate the swelling and the control of release rate

Degradation-Controlled Systems

The primary modes of erosion-based drug delivery are through the release of the drug, typically from a bulk phase, which consists of a drug composite. Therefore, the rate-limiting step of degradation-controlled release systems is dissolution.

Table (2): Common erosion effects encountered by biomedical materials.

Erosion effects	
Adhesion	Physical interaction with another surface via friction causing displacement
Abrasion	Loss of material due to hard materials (i.e., particles) that are pressed against the surface
Fatigue	Surface is weakened by cyclical application of load
Fretting	Surface is weakened by cyclical rubbing
Cavitation	Physical interaction with another physical state
Corrosion	Wear created by chemical reactions with surface functionalities

The changes to the bulk phase can be segregated into two distinct categories: bulk erosion and surface erosion. In the case of ***bulk erosion***, the material degrades or deforms uniformly throughout the bulk of the material. As the deformation proceeds, the volume of the material remains constant while the mass of the material reduces, resulting in a decrease in the density of the degrading material.

In the case of ***surface erosion***, the material degrades from the outer surface inward uniformly only at the interface between the bulk of the material and the

surrounding environment. As the deformation proceeds, the volume of the material decreases linearly with mass, which results in the density of the material remaining constant **(Figure 20).**

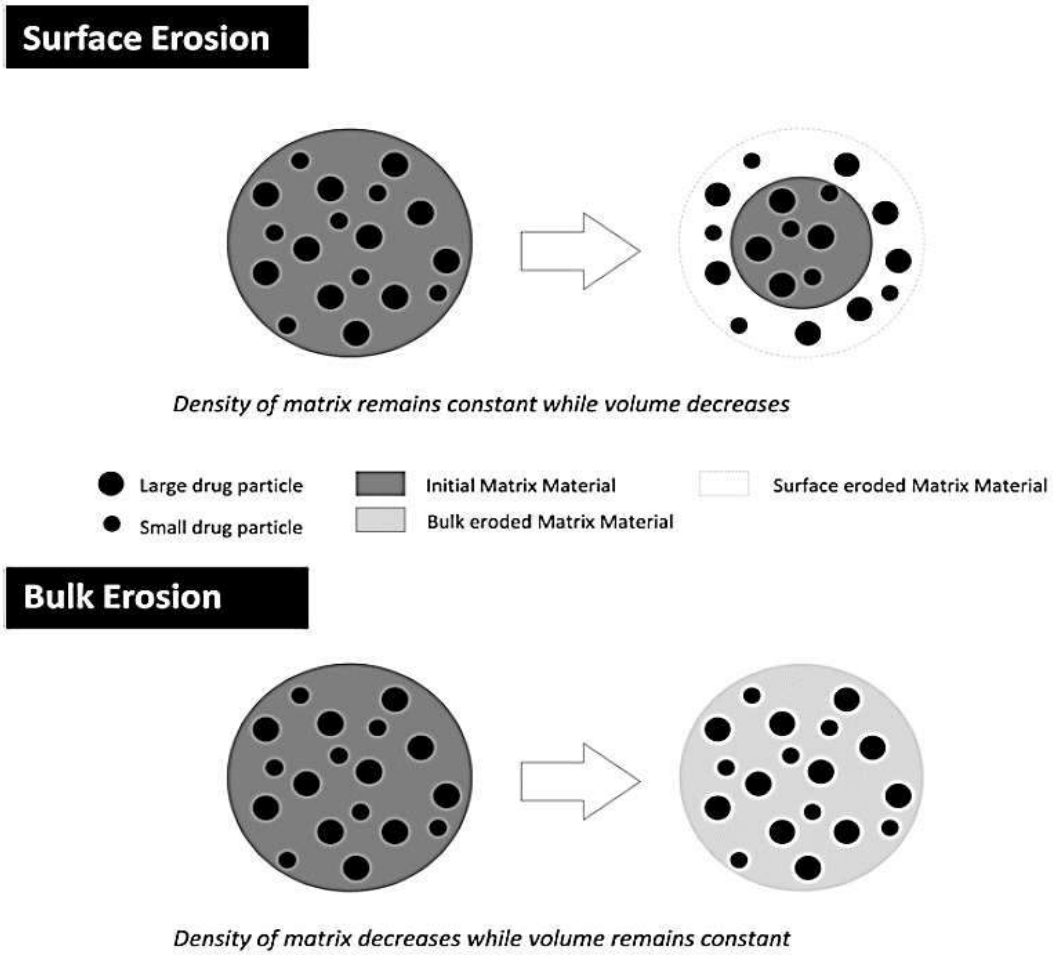


Figure (20): Diagram of erosion mechanisms found in matrix systems.

Q/ How could swelling and dissolving impact a material's properties?

Ans. Materials that retain volume but reduce density become porous and brittle over time, with weaker mechanical integrity. This effect can occur with swelling or dissolution, covalent bond rupture, and secondary bond dissociation within the system.

Environment response systems as DDSs

Chemical Stimuli-Responsive Biomaterials

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.

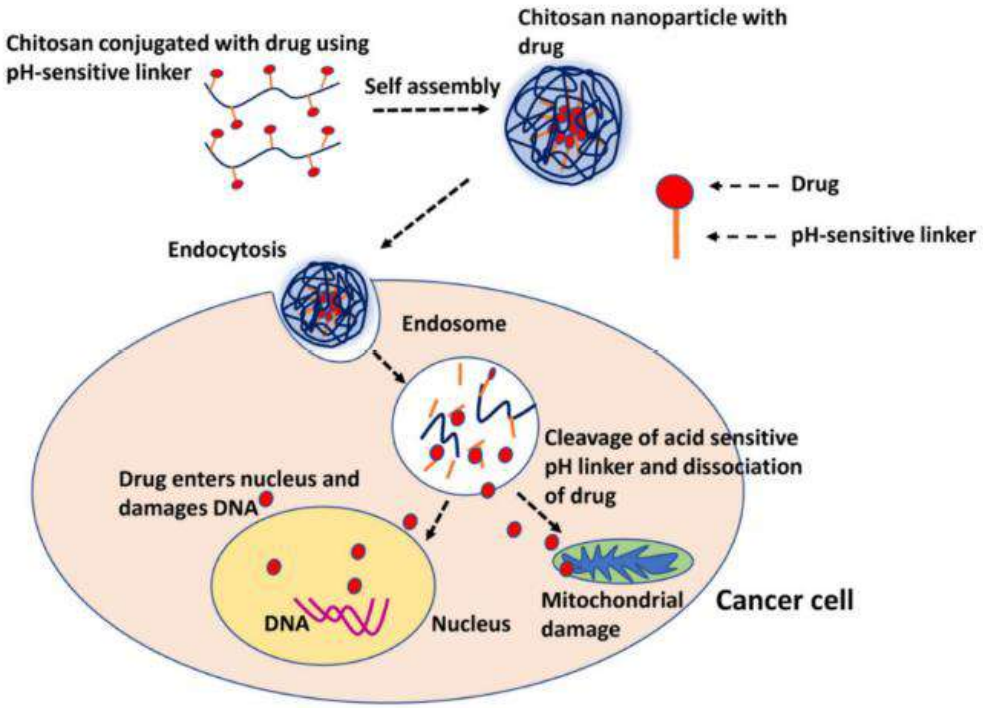


Figure (21): pH-responsive drug release of Tamoxifen from chitosan nanoparticles.

Environment response systems as DDSs

Chemical Stimuli-Responsive Biomaterials

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.

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.

Environment response systems as DDSs

Physical Stimuli-Responsive Biomaterials

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. In a recent study, green laser light was used as a stimulus to heat up and shrink the nanogel for drug release (**Figure 22**). 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.

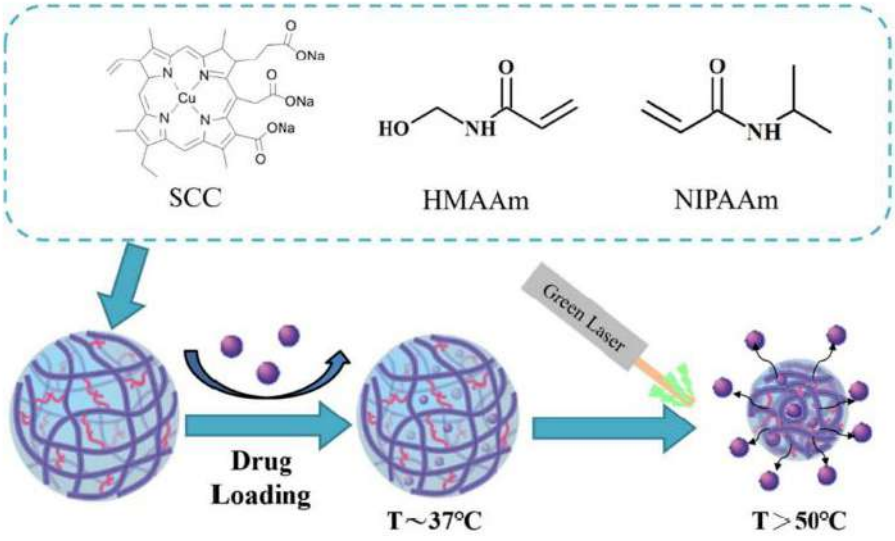


Figure (22): Green laser light induced nanogels.

Environment response systems as DDSs

Physical Stimuli-Responsive Biomaterials

2- Thermo-Responsive

Temperature is the stimulus for drug release. Thermo-responsive polymers possess lower critical solution temperature (LCST). Below LCST, polymers are soluble, 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 PNIPAM) can exhibit such characteristics. One of the significant advantages of thermosensitive polymers is that they can avoid any organic solvent which is toxic in nature. They also possess the ability to deliver both hydrophilic and lipophilic drugs and at specific sites. They can also deliver the drug at sustained dosage with minimized side effects. Examples could be poly(N-isopropyl acrylamide PNIPAM) and poly(methyl vinyl ether).

Environment response systems as DDSs

Physical Stimuli-Responsive Biomaterials

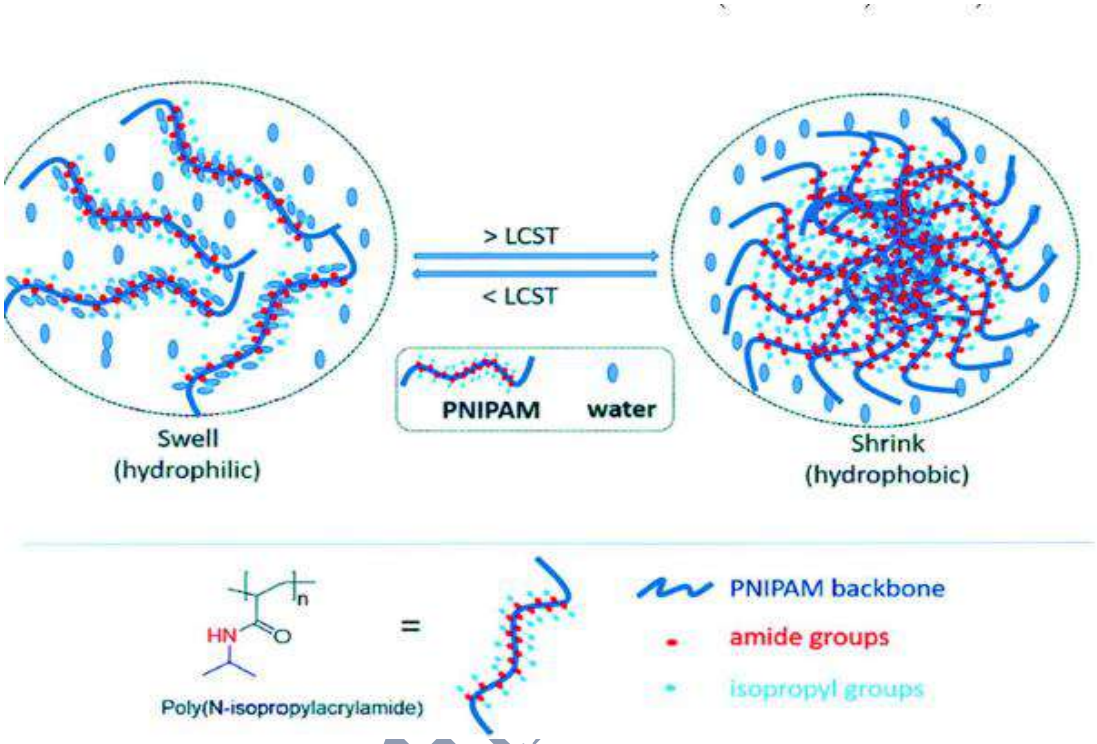


Figure (23): Thermo-responsive drug release by PNIPAM hydrogel.

3- Electric responsive polymers

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

4- Magnetic Responsive

Magnetic responsive nanoparticles, when applied with high-frequency magnetic field, generate heat. Magnetic nanoparticles are often encapsulated in

colloidal carriers including cyclodextrins, liposomes, micelles 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.

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 and cavitation. 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. An illustration of this is given in **Figure 24**.

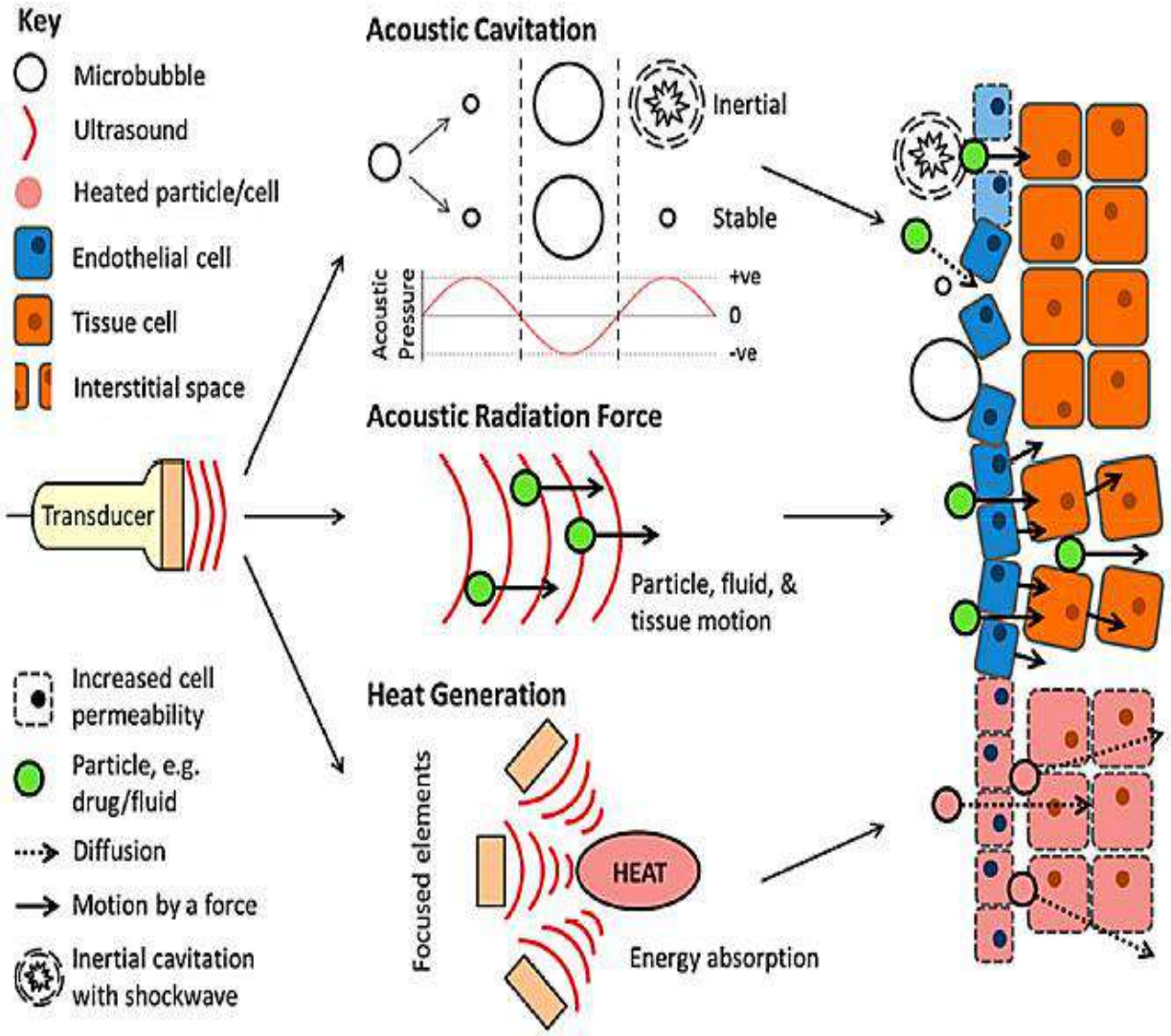


Figure (24): Ultrasound triggered release from microbubbles by mechanical effects by acoustic cavitation and thermal effects by acoustic radiation.

Drug delivery Carriers

1- Lipids:

Lipids are characterized by hydrophobic and hydrophilic parts, and this has an important bearing on their function. Lipids are naturally occurring molecules that perform important functions in organisms:

(a) They provide energy storage;

(b) They form the structural element of the cell membranes;

(c) They have important signaling functions.

2- Polymeric micelles:

Polymeric micelles (PMs) typically possess a core/shell structure with sizes of 20–200 nm. PMs are formed via the self-assembly of amphiphilic copolymers, driven by the hydrophobic interactions of the hydrophobic blocks of amphiphilic copolymers, generating a hydrophobic core surrounded by a hydrophilic shell.

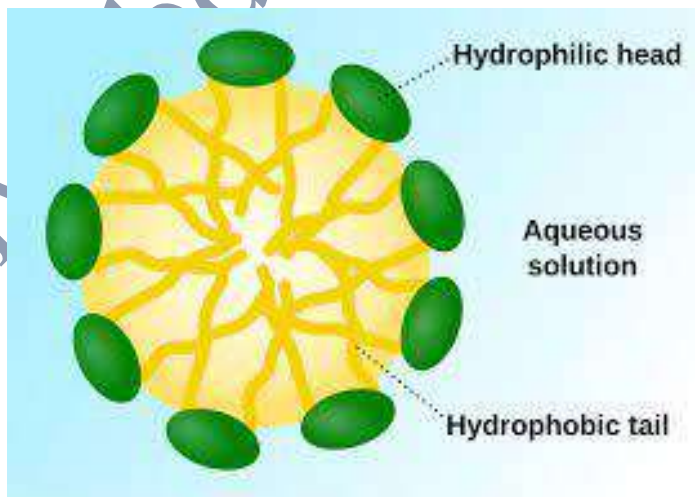


Figure (25): Micelle.

3- Liposomes:

Liposomes are spherical particles composed of phospholipid bilayers. They can be smaller than 100 nm in diameter, or tens of μm across. Liposomes have been successfully translated into clinical use due to their biocompatibility, and can be used to encapsulate hydrophilic drugs within the inner water phase and hydrophobic drugs within the lipid membranes. Liposomes have been used for the encapsulation and release of various payloads, including chemotherapeutics

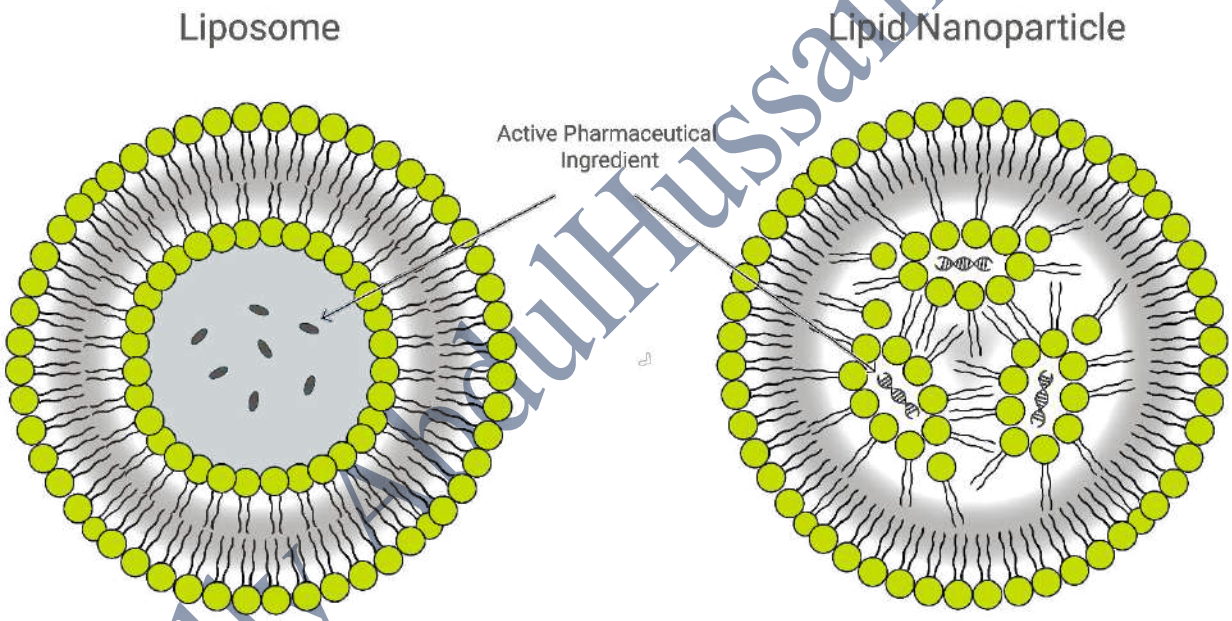


Figure (26): Liposomes and lipid nanoparticle.

Note: *Liposomes and block copolymer micelles are widely used in drug delivery, where the hydrophobic region (micelle core or liposome bilayer) or the aqueous center (liposome) can carry a hydrophobic drug or hydrophilic drug, respectively.*

4- Liquid Crystals:

Liquid crystals exist as an intermediate form between solid and liquid crystalline matter. Based on their class of order and orientation ion they can be structurally classified into nematic, sematic, cholesteric and columnar. All the materials that demonstrate liquid crystal behaviour are either lyotropic or thermotropic. Lyotropic crystals are formed because of the interactions between anisotropic aggregates of amphiphilic molecules and the phase transition is a function of temperature and concentration whereas, thermotropic crystals are formed due to interactions between partially rigid anisotropic molecules in which the phase transition occurs due to change in temperature.

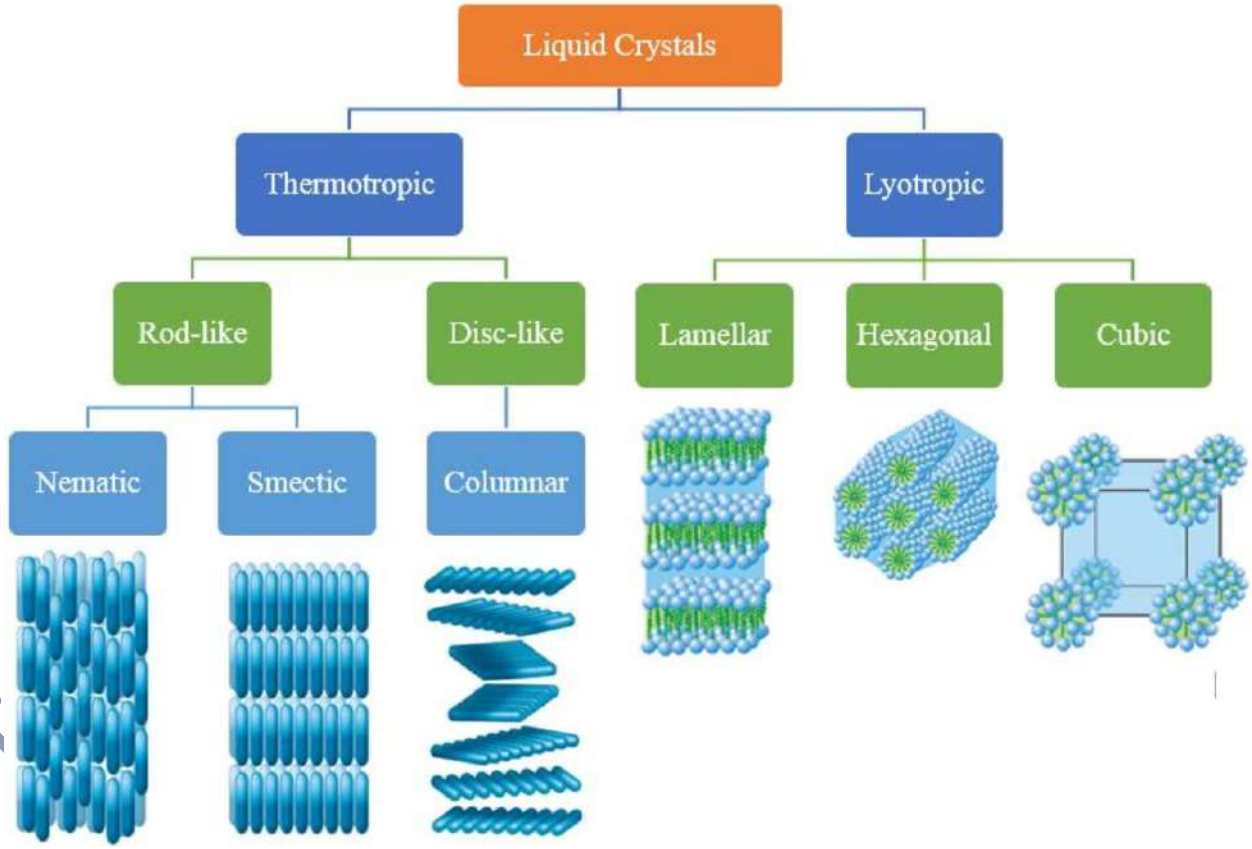


Figure (27): A flow chart of the two distinct types of Liquid Crystals with their sub divisions and phases.

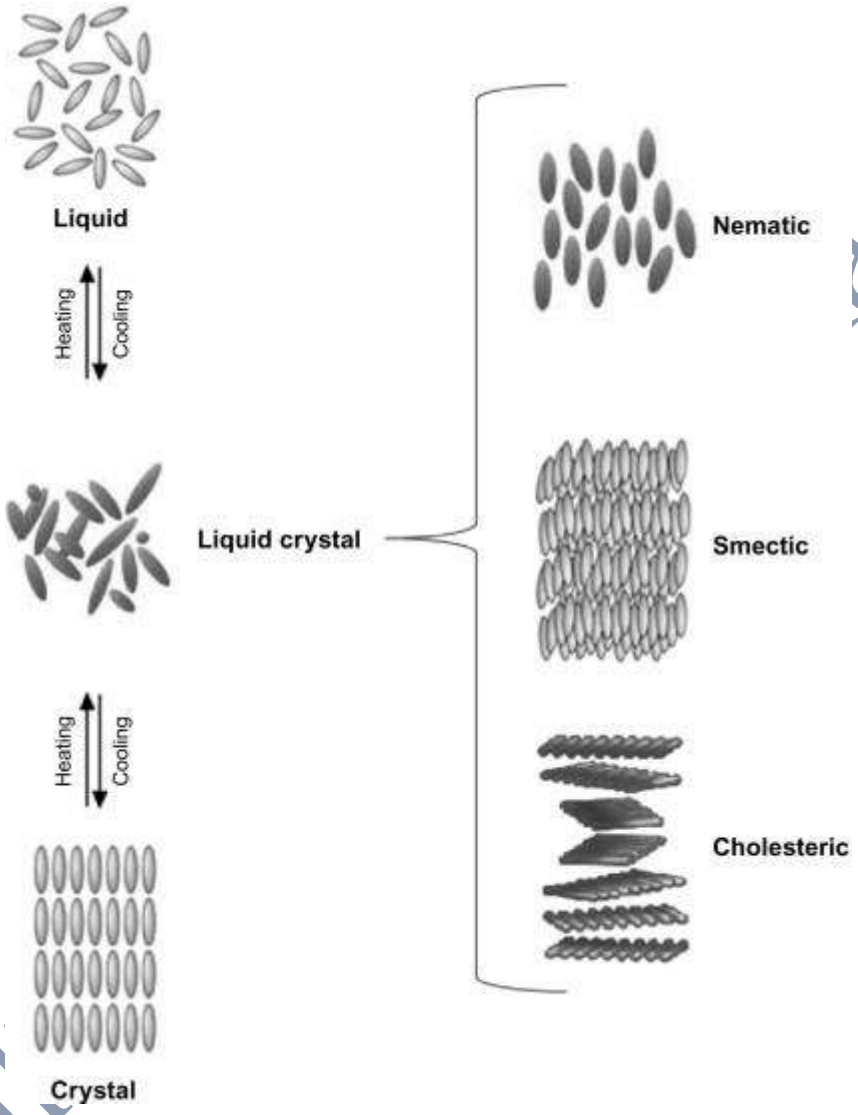


Figure (28): Lyotropic Liquid Crystal.

Nanocarriers in Controlled Drug Delivery

1- Liposomes

These are the colloidal particles formed by combining the amphiphilic phospholipids that enclose an aqueous compartment surrounded by lipid bilayers. The size ranges from 25 nm to 200 nm. The formation of a closed bilayered structure is due to the hydrophobic effect that helps in organizing the amphiphilic molecules that decrease the interactions that are unfavourable between the hydrophobic chains and the surrounding aqueous environment. Liposomes are mainly used for tumor cell targeting due to enhanced permeability and retention (EPR).

2- Dendrimers

The term dendrimer means a tree and originates from a Greek word because it is similar to the branches of a tree. Dendrimers are symmetrical around a core and have a sphereshaped three-dimensional structure. They are synthesized from monomers that can be both natural or synthetic. Polyamidoamines (PAMAM) and polypropyleneimines (PPI) are the two types of dendrimers that are used for biomedical applications.

3- Exosomes

Exosomes are nano-sized cell-derived membrane-bound vesicles of 30–100 nm size that are involved in the intercellular transportation of exogenous and endogenous substances. Therapeutic agents, such as small proteins, mRNA or nucleic acid drugs, can be incorporated into exosomes and then delivered to specific types of cells or tissues for targeted drug delivery. Natural and engineered exosomes are being utilized for the delivery of peptides and genes. Exosomes membranes possess many proteins thus show very high organotropism.

4- Nanoparticles

These are originally solid colloidal particles of less than 100 nm comprising of macromolecules in which drugs can be entrapped or chemically bonded (covalent bond) to attain physical stability of the drug and to achieve controlled release property. Metallic, polymeric, inorganic-clay and solid-lipid nanoparticles are some of the examples. The nanoparticles are used in increasing the therapeutic effect of the drug and can be used in different routes for administration. Most importantly, the nanoparticle can deliver the drug to a difficult-to-reach site. It can execute the controlled release of the drug efficiently and can minimize the adverse effects.

5- Nanosphere or Nanocapsule

A nanosphere is a matrix type of DDS which is made of an oligomer or/and a polymer. A nanocapsule is a reservoir type of system consisting of an oily core that is surrounded by a shell polymer. Nanocapsules are used for lipophilic drugs and the size can vary from 5 nm to 1000 nm. Nanocapsules offer better protection and stability to the encapsulated drugs.

6- Solid-Lipid Nanoparticles

Solid-lipid nanoparticles (SLNs) have emerged as substitutes to conventional colloidal nanocarriers integrating the advantages of polymeric nanoparticles and liposomes while excluding the toxicity. SLNs are spherical nanoparticles of 50–1000 nm in size and made up of lipids that are solid at room temperature, emulsifiers and Active Pharmaceutical Ingredient (API). The SLN safety profile is based on biocompatible lipids that are highly tolerable to the lungs and body. SLNs have the potential to incorporate hydrophilic, lipophilic drugs in addition to proteins and nucleic acids which open new frontiers for drug and gene delivery. The phospholipid fatty

substances used for SLNs are smaller in size, flexible and biologically compatible, which allows them to pass through minute arterioles and fenestrations without clotting occurring.

7- Nanofibers

Nanofibers are solid fibers of a few nanometers to 1000 nm in diameter that have a higher surface to volume ratio which is well suited for using them as a carrier for drug delivery. The properties of nano-fibres, like diameter, morphology and porosity, can be modulated to obtain a wide range of drug release kinetics. High loading efficiency and spatial distribution of drugs can be achieved with nanofibrous delivery systems. Nanofibers can be synthesized by the electrospinning technique in which patterning could also be done to tune the drug release.

Nanofibrous drug delivery systems are characterized based on their mode of drug release, structure and composition. To obtain immediate drug release, the nanofibrous mesh is made of a suitable polymer with interconnected porous architecture, high specific surface area and high porosity. Drug release from the nanofibers can be modified as prolonged, stimulus responsive and dualmode/ biphasic. Mostly, swellable or biodegradable polymers are used to modify the drug release.

8- Polymersomes

Polymersomes are tiny synthetic vesicles that enclose liquid drugs. These are generally made of diblock copolymers as well as polymer–lipid composites that possess enhanced colloidal stability, encapsulation efficiency, membrane characteristics, etc. Polymersomes are more stable than liposomes and have been proved to have lesser toxicity in the body. They can encapsulate both hydrophobic and hydrophilic drugs.

9- Self-Assembled Polymeric Micelles

Self-assembled micelles are composed of amphiphilic polymers that spontaneously self-assemble to form micelles. The hydrophobic segment forms the core and the hydrophilic segment forms the shell. The size of micelles ranges from 10 nm to 100 nm.

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 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. 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. Carbon nanotubes can be designed to carry proteins, peptides, nucleic acids and drugs to deliver them in different cells and tissues. Functionalized carbon nanotubes are less immunogenic and impart minimal toxicity.

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. The larger surface area and other characteristics allow nanoemulsion to deliver a drug efficiently to a specific target site.

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. Owing to their tunable physicochemical properties, controllable degradability and protecting capability of labile drugs from degradation, hydrogels serve as a carrier to control drug release. 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.

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.

Interpenetrating network (IPN) hydrogels consist of two or more polymeric networks which are at least partially interlocked on a polymer scale.

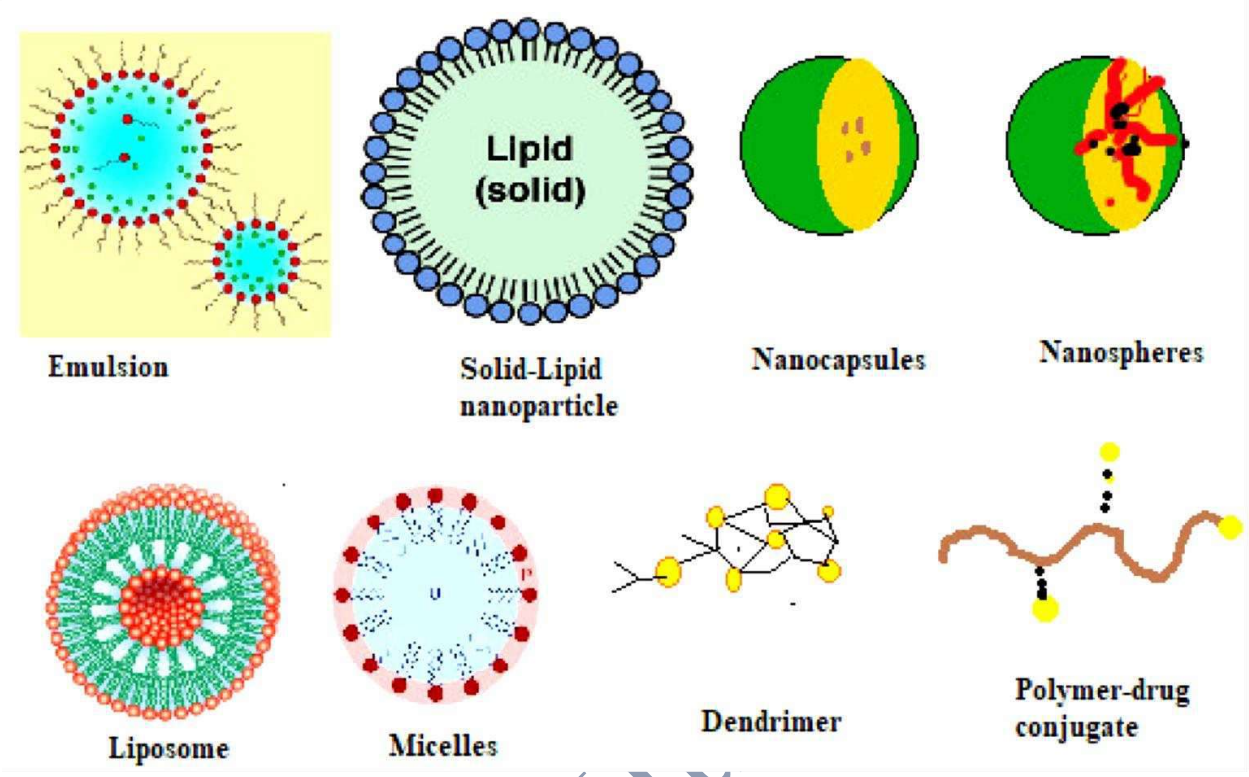


Figure (32): Some common examples of nanocarriers in controlled drug delivery.

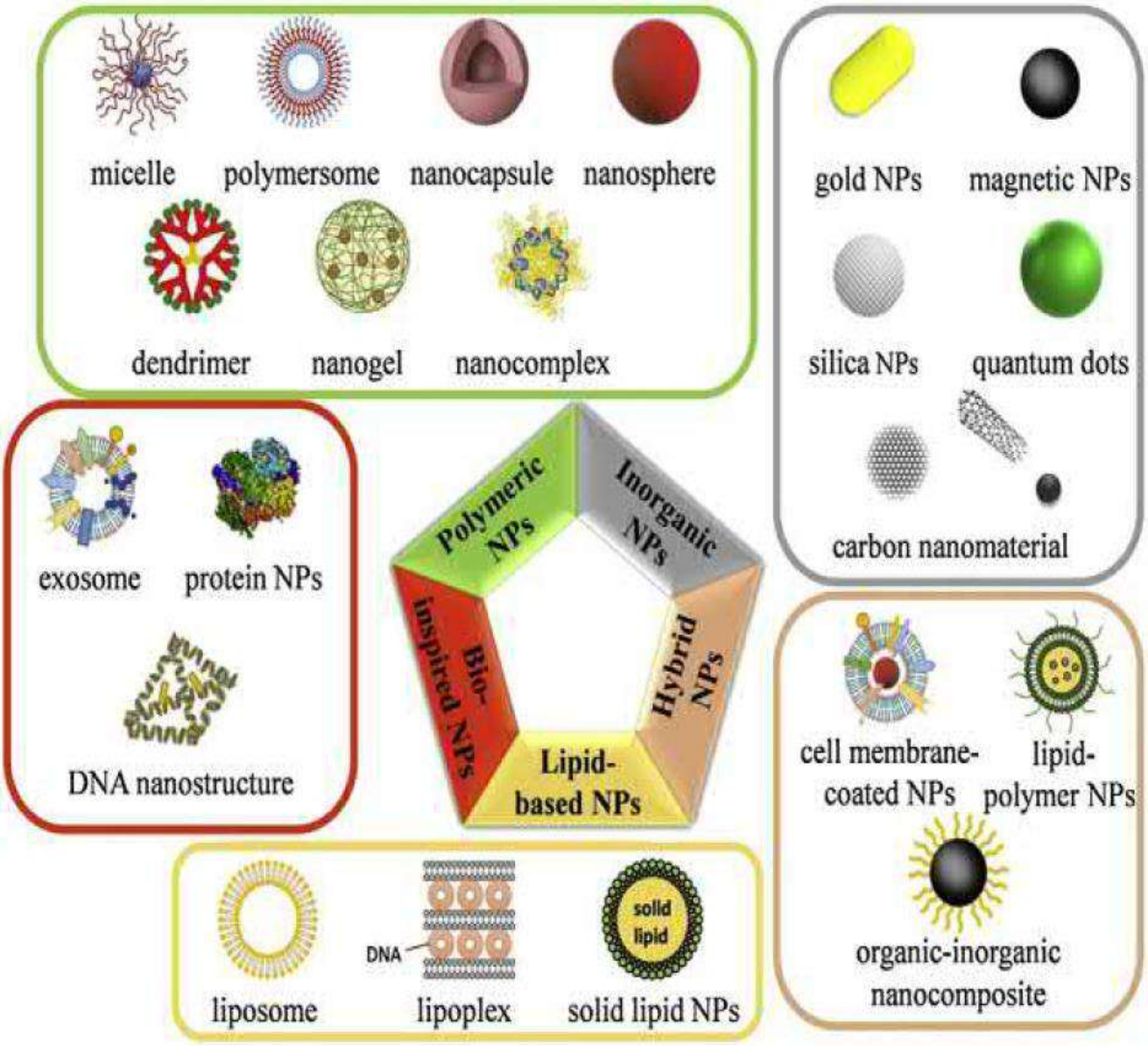


Figure (33): Categories of nanoparticles.

Advantages and Disadvantages of nanocarriers in Drug Delivery

- ***Advantages***

1- Specificity and targeted delivery of drugs can be achieved.

2- Improved tumour penetration for anticancer drugs.

3- Enhanced Permeability and Retention can permit the passive accumulation.

4- Enhanced bioavailability and efficacy.

5- Controlled delivery of drugs with low dose.

- **Disadvantageous:**

1- Unintended penetration and translocation of nanocarriers to the blood–brain barrier, lungs result in toxicity.

2- Nanocarriers can change in shape and size resulting in varied physicochemical interactions and activity.

3- Suboptimal delivery due to heterogeneities of nanocarriers in vascular permeability.

4- Uptake by Reticulo Endothelial system (RES) can reduce the efficacy.

5- Limited availability of animal models.