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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 6: Drug Loading and Controlled Release Mechanisms

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Abstract

Nanoparticle-based drug delivery systems have been shown to be a promising method to improve the effectiveness and safety of anticancer drugs. The traditional chemotherapy drugs used to treat cancer are toxic and non-selective, and typically have a high systemic toxicity and multidrug resistance, low bioavailability, and strong side effects caused by the poor therapeutic efficacy. The unique characteristics of site specific delivery, prolonged circulation and controlled release of chemotherapeutic agents in drug loaded controlled release carriers allows for an advanced platform for targeted cancer therapy with nanoparticles.

There are several nanocarriers, such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, metallic nanoparticles, and Mesoporous silica nanoparticles that showed great potential for improving the encapsulation efficiency of drugs and the controlled release properties. The chapter highlights the basic principles of drug loading technologies such as adsorption, entrapment and covalent conjugation methods for the formulation of nanoparticles. Additionally, the factors that influence the ability to load these drugs including particle size, surface charge, drug-polymer interactions and the physicochemical properties of the therapeutic agent are discussed.

Besides, various types of controlled release systems such as diffusion controlled, pH controlled, enzyme controlled, thermally controlled, magnetically controlled and stimuli-controlled release systems are well discussed. Also, the use of nanotechnology to control the release of drugs in the initial stages and to enhance the therapeutic drug level in the tumor site, due to the EPR effect, is also discussed.

A special focus on clinical translational and regulatory aspects of the recent advances of smart nanocarriers and multifunctional nanoparticles for personalized cancer therapy is provided. The use of controlled drug delivery systems in the treatment of breast, lung, colorectal and glioblastoma cancer is also discussed. In conclusion, nanoparticle loading and controlled delivering drug systems are a novel approach in contemporary oncology with great promise of improved efficacy, decreased toxicity and increased adherence.

Keywords: Nanoparticles; Drug loading; Controlled release; Cancer therapy; Nanocarriers and targeted drug delivery.





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1. Introduction

Today, cancer remains one of the most serious health challenges, and is characterized as an abnormal proliferation of cells, invasion of cells from their original site to new locations, and metastasis. Although the diagnosis and therapy of cancer has improved greatly, nanosize drug delivery systems are still being developed to better deliver anticancer drugs to cancer tissue. Conventional chemotherapy is frequently blamed for the poor aqueous solubility of therapeutic agents, rapid drug elimination, lack of specificity of biodistribution, systemic toxicity, and poor concentration at the tumor site and multidrug resistance. These restrictions may lead to a decrease in therapeutic effectiveness and to unintended high amounts of cytotoxic agents to healthy tissues. This has created an interest in research and development of advanced drug delivery systems which can improve the localization of the drug, control the release and minimize the systemic toxicity of the drug [1].

Nanotechnology is a new strategy with a great potential to solve many problems associated with the conventional cancer chemotherapy. A nanoparticle-based drug delivery system can include a therapeutic molecule or molecules inside or attached to a nanoparticle carrier that can be targeted to a specific biological site for delivery. Nanocarriers have several properties: They have a large surface area, whose physicochemical properties can be tuned by their sizes and are more soluble in the blood stream than other drugs; they provide protection to the encapsulated molecule from premature degradation; they can be used to target the tumour passively or actively; they have a longer circulation time in the blood. Many different nanocarriers have been investigated for delivery of anticancer agents including polymeric nanoparticles, lipid nanoparticles and liposomes, niosomes, dendrimers, nanogels, metallic nanoparticles and hybrid nanoparticles.

For such systems, parameters of the formulation directly affecting therapeutic activity of the nanocarrier, such as drug loading, is an important parameter. Drug Loading: Introduction of active pharmaceutical ingredient in or on a nanoparticle system. Depending on the nature of drug and carrier, the approach for loading could be: encapsulation, physical entrapment, adsorption, ionically interacting, hydrophobic interaction, hydrogen bonding, covalent conjugation, etc. An adequate payload of drug and maintenance of structural integrity, stability and desired biological properties of the carrier should be achievable for an appropriate designed nanoparticle [2].

Drug-loading capacity and entrapment (or encapsulation) efficiency are usually used to evaluate drug incorporation efficiency. The percentage of the total amount of the drug added to the formulation that is contained within the nanoparticles is referred to as the entrapment efficiency and the percentage of the drug per unit weight of the carrier or final formulation is called the drug loading capacity. These parameters are particularly important for the development of nanoparticles as they affect the dosage delivered, the formulation size, the stability of the drug and the release rate. An increase in the level of drug loading will mean a





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decrease in the amount of carrier needed to deliver a therapeutic dose of drug, but also if the amount is too high, there will be a risk of drug crystallization, aggregation, leakage, instability or undesirable changes in the particle characteristics of the carrier [3].

The drug loading process depends on several parameters such as: Physicochemical characteristics of the drug, polymer or lipid composition, drug to carrier ratio, drug preparation method, solvent system, pH, temperature, molecular interaction between the drug and the carrier, surface characteristics of the nanoparticles. The lipophilic anticancer drugs may be high affinity to the lipophilic or polymeric portion of the carrier, and the loading of a hydrophilic drug may be different. Additionally, the functional groups on and/or in nanoparticles can interact with drugs that are charged. Hence, it is crucial to recognize the interactions between the drug and the carrier to be able to incorporate the drug reproducibly and efficiently. In cancer therapy, the requirement for drug loading is particularly crucial because many effective anticancer drugs are poorly soluble, unstable in water or have short biological half-life or a dose limiting toxicity. A system of nanoparticles may be used to protect this type of drugs, their apparent solubility and stability can be improved. The drug may also be protected from being exposed to biological components before it reaches the target site and encapsulation may also help the drug to reach the tumor tissue. Thus, drug loading is not only a means by which a drug is loaded into a carrier, but an integral part of the overall design strategy to improve the therapeutic activity [4].

The release mechanism of the anticancer drug from the nanoparticles may be diffusion, dissolution, swelling, erosion, degradation, desorption, disruption of the membrane, chemical reactions or enzymatic reactions. Drug release from many systems is by more than one mechanism. The main mechanism is determined by the composition and shape of the nanoparticle, the physical and chemical characteristics of the drug, interaction between the drug and the nanoparticle and the biological environment.

One of the most common diffusion controlled release is seen in the drug delivery system as a nanotechnology. The movement of the drug from the nanoparticle matrix or internal compartment to the surrounding medium is caused by the concentration gradient in this process. The particle size, porosity of matrix, polymer density, drug solubility, and molecular size & drug-carrier interaction affect the rate of diffusion. High pore volume of the nanoparticles can result in a relatively high drug diffusion rate, but a high affinity of the drug to the carrier would result in a low drug release rate. The other important mechanism is polymer degradation or erosion controlled release. Biodegradable polymers can be broken down by hydrolysis or enzymes in the body. The drug is released in the polymeric matrix as it slowly dissolves. Aliphatic polyesters are extensively researched for controlled drug delivery because of the ability to modify polymer degradation by changing polymer composition, molecular weight, and/or formulation parameters.





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The hydrophilic polymeric nanocarriers have the ability of swelling and releasing a cargo. The polymer absorbs water and expands when in contact with water. This allows polymer chains to become more mobile, and can form channels through which the drug can migrate. The swelling rate and extent will vary with the hydrophilicity of the polymer, the extent of cross-linking, environmental pH, ionic strength and temperature. Another promising strategy is enzyme responsive drug delivery, which involves the use of nanoparticles that are sensitive to enzymes that are secreted in tumour tissue or in specific organelles. Similarly redox responsive systems may take advantage of the difference in reducing conditions at extra- and intracellular. These methods could be useful in improving the spatial and temporal release of drug and may be useful to reduce premature drug release before nanocarrier reaches its target location [5].

The release behavior of a nanoparticle formulation is usually investigated in vitro under optimum experimental conditions. The release of the drug is plotted as a percentage of the total amount of drug, of the total cumulative drug released, against time to give a release profile. An insight into the kinetics and mechanism of release is then achieved through mathematical modelling. The most popular models are zero-order model, first-order model, Higuchi model and Korsmeyer–Peppas model. The zero order kinetic phenomena take place when the rate of drug release is almost constant with time and the first order kinetic phenomenon occurs when the rate of drug release is proportional to the quantity of drug remaining in the delivery system. The Higuchi model is often linked to diffusion-controlled release systems, and the Korsmeyer–Peppas model can be used to gain some knowledge of the mechanism of drug transport, through the use of the release exponent.

A close relationship exists between drug loading and drug release behaviour. The high loading capacity of a nanoparticle does not guarantee optimal therapeutic activity, if the drug is released too quickly or too slowly from the nanoparticle. However, a formulation with a very slow drug release cannot assure adequate therapeutic concentrations at the target site. Hence, it is necessary to have a balance between drug incorporation and release properties when developing a formulation with nanoparticles. These parameters need to be optimized to achieve the desired therapeutic window.

Important, controlled release cannot be considered separately as a property of a formulation, but must be taken into consideration together with targeted delivery. The ideal outcome of cancer therapeutics using nanoparticles is to deliver the correct amount of treatment to the correct tissue at the correct speed [6]. From this perspective, it is necessary to take into consideration the techniques used for loading the drugs, type of carrier, targeting strategies, release kinetic and biological activities of the nanoparticles. The optimization of a nanoparticle system generally involves a series of Preformulation investigations, formulation development, optimization, physicochemical characterization, loading of the drug into the nanoparticles, in vitro release studies, kinetic modelling, stability studies and biological evaluation. The formulation is first designed considering the physicochemical properties of the selected





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anticancer agent. Different carrier materials and preparation methods then were investigated to obtain the optimal particle formulation that incorporates the drug and has the proper particle properties. Optimized formulation is then tested for release rate and therapeutic activity.

2. Drug Loading in Nanoparticles

One of the basic steps in the formulation of Nanoparticle mediated Drug Delivery Systems is drug loading. It carries the ability to carry therapeutic agents into a nanoparticle and to target the agent to its therapeutic site. The efficient loading of drugs into the carriers is particularly important in cancer therapy because many of the anticancer drugs are poorly water soluble, unstable and have dose-dependency toxicity and short biological half-lives. Such drugs can be encapsulated by the nanoparticles, and can be protected, transported, targeted and controlled to release properly in a proper microenvironment.

Drug loading may be accomplished in the matrix of the nanoparticle, in a vesicular compartment, on the surface of the particle or chemically attached to the particle. The primary factor to consider for determining the loading method that will be used will be the physicochemical property of the drug, and the composition of the nanocarrier [7]. An ideal nanoparticle system for drug delivery should be able to achieve sufficient loading of the drugs with no changes in particle size, stability, morphology, surface characteristics, etc., and/or release properties.

Table 1 the following table contains the structure and location of the drug molecules [8].

Nanoparticle/System	Possible Drug Location	Typical Loading Principle
Polymeric nanoparticles	Polymer matrix	Entrapment or incorporation
Lipid nanoparticles	Lipid matrix	Partitioning/solubilisation
Liposomes	Aqueous core or lipid bilayer	Encapsulation
Niosomes	Aqueous core or surfactant bilayer	Encapsulation/partitioning
Nanogels	Swollen polymeric network	Physical entrapment or interaction
Dendrimers	Internal cavities or surface groups	Encapsulation or surface association
Metallic nanoparticles	Surface	Adsorption or chemical attachment
Hybrid nanoparticles	Multiple structural regions	Combination of loading mechanisms





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2.1 Concept of Drug Loading

Drug loading can be defined as the integration of a therapeutic agent into a nontherapeutic carrier. The carrier acts as a vehicle which can carry the drug and carry it through the bio-environment. Drug molecules can be found in various regions of the nanoparticle, depending on its structure. In the case of polymeric nanoparticles, the drug can be dispersed in the polymeric matrix. It can be used as a component of the lipid phase in lipid based nanoparticles. For vesicular systems, hydrophilic drugs can be found in the aqueous compartment and lipophilic drugs can associate with the lipid compartment [9].

Drug placement is crucial as it can affect the retention/elimination of the drug from the nanoparticle. A drug, which is in close proximity to the surface, might be released sooner, while a drug that is well embedded in a polymeric or lipidic matrix may be released for a longer period.

Table 2 Fundamentals of Drug loading in Nanoparticle based drug delivery [10].

Sr. no.	Aspect	Description
1.	Definition	Incorporation of a therapeutic drug into, within, or onto a nanoparticle carrier
2.	Primary purpose	To carry and deliver the drug to the desired biological site
3.	Drug location	Internal matrix, lipid phase, aqueous core, polymeric network, or nanoparticle surface
4.	Major interactions	Hydrophobic, electrostatic, hydrogen bonding, van der Waals, and covalent interactions
5.	Important parameters	Drug loading capacity and entrapment efficiency
6.	Major influencing factors	Drug properties, carrier composition, drug-to-carrier ratio, particle size, pH, temperature, and preparation method
7.	Common loading approaches	Passive loading, active loading, encapsulation, entrapment, adsorption, and chemical conjugation
8.	Effect on release	Influences drug retention, diffusion, burst release, and controlled-release behavior
9.	Importance in cancer therapy	Facilitates incorporation and delivery of anticancer drugs and may improve their stability and therapeutic performance
10.	Desired outcome	Adequate drug loading with good nanoparticle stability and an appropriate drug-release profile





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2.3 Drug–Carrier Interaction

The interaction between the drug and the nanocarrier plays a key role in the drug loading. The interactions that occur between these two influence the affinity of the drug for the NP and ultimately affect drug retention/release.

Hydrophobic interactions play an important role in the incorporation of poorly water soluble drugs into hydrophobic carrier domains. Interactions between oppositely charged drug and carrier molecules are electrostatic interactions. Other stabilizing forces that can affect drug association are hydrogen bonding and van der Waals interactions. In some more sophisticated delivery systems, the drug can be chemically attached to the carrier molecule via a proper chemical linker.

These interactions need to be managed and controlled. Premature drug release can occur with very weak interactions, while too strong interactions can hinder efficient release of the drug at the target site.

2.4 Drug Loading and Entrapment Efficiency

Evaluation of the performance of the drug loading and entrapment efficiency of the nanoparticle based drug delivery systems is important. They control the amount of therapeutic drug loaded into nanocarrier and the efficiency of the process of formulation. These parameters are of special significance in cancer therapy where many of the anticancer drugs are poorly soluble in water, unstable or have dose related toxicity. Drug protection and targeted delivery may be enhanced by efficient incorporation into nanoparticles, and controlled release at the desired site can be achieved [11].

2.4.1 Drug Loading

The percentage of drug attached to a given amount of drug-loaded nanoparticles is called the drug loading. It's usually given as a percentage. More drug loading means that the dosage for a therapeutic effect can be administered with less carrier material.

The drug can be within the matrix of the nanoparticle, lipid bilayer, aqueous core, polymeric network or on the surface of the particle. The loading capacity will depend on the physicochemical properties of the drug and the properties of the Nanocarrier chosen.

The capacity to load the drug can be determined as:

$$\text{Drug Loading (\%)} = \frac{\text{Amount of drug incorporated in nanoparticles}}{\text{Total weight of drug loaded nanoparticles}} \times 100$$

If 10 mg of drug is incorporated successfully into 100 mg of drug loaded nanoparticles, the drug loading capacity in the nanoparticles is 10%.

2.4.2 Entrapment Efficiency

Entrapment efficiency (EE%) or also known as encapsulation efficiency refers to the percentage of the initial amount of the drug used in the formulation that is encapsulated in the nanoparticle system [12].

It can be calculated using:





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The entrapment efficiency (%) = Total amount of drug added / amount of drug entrapped in nanoparticles $\times 100$

For instance, during preparation of the nanoparticles, 100mg of drug is used, and 85mg is successfully entrapped, the entrapment efficiency is 85%.

From the obtained results, it is concluded that the difference between the drug loading and the entrapment efficiency of each particle size is negligible.

These parameters are correlated but each offers a different piece of information:

Parameter	Meaning	Indicates
Drug Loading (DL%)	Amount of drug present in the final nanoparticle formulation	Capacity of the carrier to accommodate drug
Entrapment Efficiency (EE%)	Percentage of initially added drug incorporated into nanoparticles	Efficiency of the formulation process

If there is a large amount of carrier material being used, a formulation can be very efficient at entrapping the drug but have a relatively low drug loading. Hence, optimization of the two parameters is required during the optimization of nanoparticles [13].

3. Drug-Loading Strategies

The loading of the drug into a nanocarrier is an important process in the formulation of a drug delivery system where the nanoparticles are loaded with therapeutically active agents, and the therapeutic agent is released at the target site. There are several factors in determining the appropriate loading, such as the physicochemical properties of the drug, composition and architecture of the nanocarrier, drug-carrier interactions, loading efficiency, stability and release profile. Generally, nanocarrier loading can occur in a passive way, active loading, remote loading, encapsulation, surface adsorption, and for some systems, chemical conjugation. The various methods have different pros and cons and should be used depending on the type of therapeutic molecule and not indiscriminately.

In order to achieve the most effective nanoparticle mediated cancer therapy, the loading strategy should be designed to allow for high drug incorporation, low loss of the drug, formulation stability, reproducible drug content, and an appropriate drug release profile. Importantly, however, high loading efficiency does not always represent a better formulation; subsequent drug release and interactions between drug and carrier will also depend upon the capacity of the formulation to localize the drug in the carrier.





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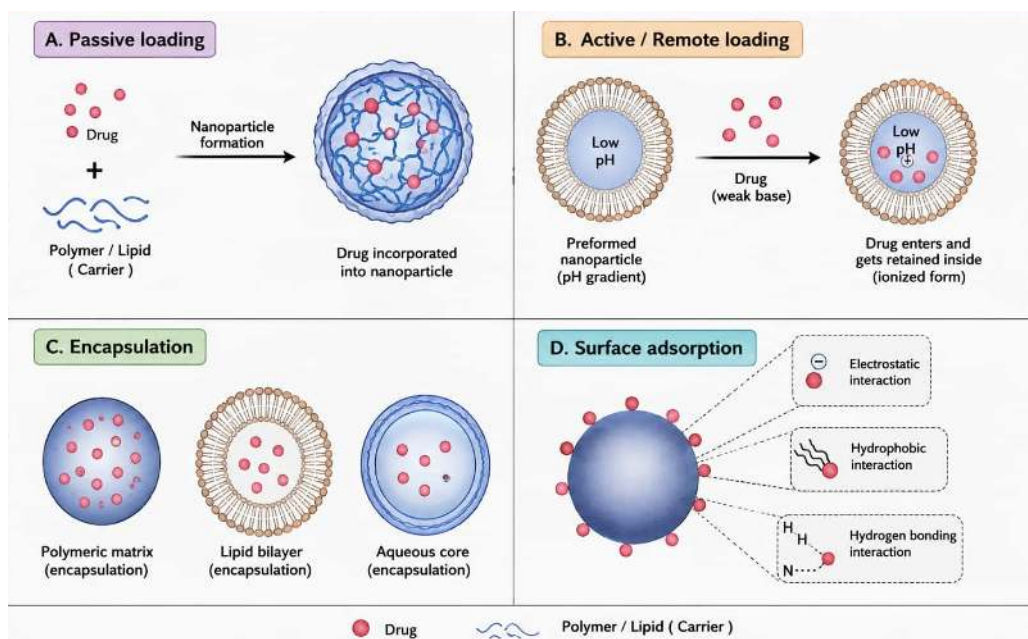


Fig.1 Schematic representation of passive drug loading in nanoparticles [14]

3.1 Passive Loading

Passive loading is the process of embedding the drug in the nanoparticles during their formation or preparation. During the preparation of the carrier structure, the drug is in the formulation medium and becomes trapped in the structure (lipid phase, aqueous phase or other structural region) of the nanocarrier. The final drug loading is thus highly formulation dependent and also strongly depends on the affinity of the drug for the carrier. Passive loading is broadly applicable as no additional driving force is needed for drug incorporation.

Polymeric nanoparticles may embed the drug physically in the polymeric matrix when they are synthesized. In lipid based systems, lipophilic drugs can partition into the lipid phase, while hydrophilic molecules can be inclined to partition into an aqueous compartment. Thus, the efficiency of passive loading is dependent on the solubility, lipophilicity, polymer/lipid composition, ratio of drug to carrier, particle size and preparation method, choice of solvent and process conditions.

3.2 Passive Loading Limitations

The drawback is that the drug may not be carried in an efficient manner when it is of poor affinity to the carrier. In some lipidic or polymeric systems the low encapsulation of some hydrophilic small molecules may be due to their tendency to stay predominantly in the external aqueous phase. Passive loading can thus lead to potential loss of drug and relatively low loading of some drug–carrier combinations.

Another constraint is the presence of a small proportion of the drug attached to the surface of the nanoparticle and not embedded in the carrier material. This surface associated drug may be responsible for the first release peak [15].





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3.3 Relevance to Cancer Drug Delivery

Passive loading is still of value for anticancer drugs that have proper affinity with the nanoparticle matrix selected. The method can be especially beneficial if the drug is very soluble in the formulation process and is compatible with the polymeric or lipidic carrier. Optimization of formulation is however, crucial to ensure an optimum balance of drug loading, particle stability and controlled drug release.

3.4 Active Loading

Active loading, or remote loading, is the process of loading the drugs into a preformed Nanocarrier in a physicochemical driving force. The drug does not have to be present at the formation of the nanoparticle as it is during passive loading. However, a gradient or other driving force facilitates the motion of the drug into the carrier.

The pH-gradient mediated loading of weakly acidic or basic drugs into liposomes is one of the well established examples. In this method, a pH difference is created across the lipid bilayer. The drug first enters the membrane in a suitable state, and then turns into an ion or becomes trapped in another form in the internal compartment, leading to an increase of the drug in the internal compartment. The use of remote loading has proven to be successful for some drugs, including doxorubicin.

For appropriate drugs, active loading may yield significant drug incorporation over passive loading. A review on the remote loading of liposomes has been reported, indicating that a very high drug loading efficiency can be achieved by active loading and that only certain drugs can be loaded by conventional remote-loading method.

3.5 Major Mechanisms of Active Loading

1. pH-gradient loading:

The movement and retention of drug molecules that contain ionizable groups is driven by trans membrane pH gradient [16].

2. Ion-gradient loading:

Concentrations of ions may vary across a carrier membrane, creating a gradient that can help to accumulate a particular drug.

3. Chemical-gradient loading:

Any chemical difference between the inside and outside of the container can favour the partitioning of the drug into the carrier.

4. Electrical or membrane potential based loading:

The incorporation of charged molecules in appropriate nanocarriers might be assisted by an electrochemical gradient.

3.6 Advantages of Active Loading

- Potentially high drug-loading efficiency.
- Improved incorporation of drugs.
- Reduced loss of drug into the external formulation medium.





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- Can enhance the retention of drugs in appropriate carriers.

Very useful for some ionized drugs used in cancer treatment

3.7 The limitations of active loading

Active loading doesn't work for everyone. The drug needs to have suitable physicochemical properties to react with the applied driving force. Furthermore, the method can involve extra processing operations and optimization of internal and external environment of the nanocarrier. The significance of formulation composition is illustrated by the investigation of the formulation of doxorubicin-loaded liposomes in which the composition of lipids, cholesterol content, pH, and the magnitude of the pH gradient were found to affect the drug loading and release behavior.

The active loading principles have also been recently investigated for pH-gradient in niosomes, suggesting that these principles are not exclusive to liposomes, and may be extended to other vesicular systems.

3.8 Active Loading in Cancer Therapy

The active loading is especially important when dealing with anticancer drugs since it can lead to high drug loading along with high levels of drug retention in the carrier. This can help to slow down the circulation and controlled drug release if the carrier is designed properly. An example of active loading combined with nanocarrier design to modulate drug distribution and release is the doxorubicin loaded liposomal systems [17].

3.9 Encapsulation

Encapsulation is the process of entrapment of a drug inside the internal structure of a nanoparticle or vesicular carrier. The drug may be physically included in a polymeric matrix, lipid membrane, aqueous compartment or other type of carrier. Encapsulation is one of the most popular methods for the protection of therapeutic agents and control of their release.

Encapsulation can be achieved by matrix loading, cavity loading or vesicular incorporation, depending on the characteristics of the drug. The various loading concepts are classified as molecular-level loading, surface loading, matrix loading and cavity loading as a reflection of the structural organization of the carrier that allows the incorporation of the drug in the structure.

3.9.1 Matrix Encapsulation

In matrix systems, the drug molecules are homogeneously dispersed in the carrier material. An example is polymeric nanoparticles. Release of the drugs can then follow by diffusion, swelling of the polymer, erosion or degradation.

The sealing of a cavity or compartment. Sealing of a compartment or cavity.

A drug may be enclosed within an internal aqueous compartment or within another enclosed area in a vesicular system. The drugs which are hydrophilic can bind more readily to aqueous compartments and the lipophilic ones can bind to lipidic membranes.

3.9.2 Importance of Encapsulation





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Encapsulation can:

- Keep the drug from harming the environment.
- Improve the apparent handling of poorly soluble drugs.
- Minimize the loss of drugs in their early stages.
- Slow or slow and steady release.
- Provide an opportunity for site-specific delivery.
- Alter the action of therapeutic agents on their pharmacokinetics.

But in the case of hydrophilic small molecules, encapsulation can be difficult, as their high aqueous solubility can lead to partitioning into the external aqueous phase. Thus, certain strategies may be necessary to enhance the encapsulation efficiency.

3.10 Surface Adsorption

Surface adsorption refers to non-covalent binding of drug molecules to the surface of nanoparticles. Some of these interactions are electrostatic attraction, hydrogen bonding, hydrophobic interactions, van der Waals forces, etc.

Surface adsorption is especially important if the nanoparticle has a large surface area, and functional groups that are appropriate for interacting with the drug. A large accessible surface with surface chemistry that can be tuned, for instance, for drug adsorption and controlled release can be achieved with mesoporous inorganic nanoparticles [18].

Surface adsorption has the advantage of relative simplicity as its advantage. Drug molecules do not have to innerize into the internal matrix of the nanoparticle and surface chemistry can be tailored to improve association of the drug.

But surface associated drug may be more prone to early release than deeply encapsulated drug. Thus, the strength of adsorption and the physiochemical environment should be carefully controlled.

Table 3 there are three types of interactions that take place during surface adsorption [19]

Interaction	Principle	Effect on Drug Loading/Release
Electrostatic interaction	Attraction between oppositely charged groups	Can enhance drug association
Hydrogen bonding	Interaction between suitable donor and acceptor groups	May improve drug retention
Hydrophobic interaction	Association of hydrophobic regions	Useful for poorly water-soluble drugs
Van der Waals forces	Weak intermolecular attraction	Contributes to overall adsorption





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π - π interaction	Interaction between aromatic structures	Can support adsorption of aromatic drugs
Covalent attachment	Formation of a chemical bond	Usually provides stronger drug retention

Table 4 Comparison of Drug-Loading Strategies in Nanoparticle-Based Drug Delivery [20]

Strategy	Basic principle	Major advantage	Major limitation	Cancer-drug delivery relevance
Passive loading	Drug incorporated during nanoparticle formation	Simple and broadly applicable	Loading may be limited by drug-carrier affinity	Useful for drugs compatible with the carrier
Active loading	Drug incorporated into preformed carrier using a gradient/driving force	High loading and improved retention for suitable drugs	Applicable only to selected drug/carrier systems	Highly useful for selected ionizable anticancer drugs
Encapsulation	Drug enclosed within matrix, core, or compartment	Protection and controlled release	Encapsulation efficiency varies with drug properties	Suitable for sustained delivery of anticancer agents
Surface adsorption	Drug associated with nanoparticle surface	Simple and flexible	Potential for premature release	Useful when strong surface interactions can be achieved
Chemical conjugation	Drug chemically linked to carrier	Strong association and programmable release	Requires chemical modification	Useful for targeted and stimuli-responsive systems

Choosing an appropriate loading strategy is also an important issue a suitable loading strategy is also important. The choice of drug loading should be guided by a systematic evaluation of the drug, the carrier, the proposed route of administration, the therapeutic goal and the desired release profile. Drugs that are hydrophobic can be incorporated as part of the matrix or lipid phase, while hydrophilic drugs would need to be compartmental encapsulated or loaded in





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specific ways. Drugs that are ionizable may be especially appropriate for the remote loading approaches, if a suitable gradient can be developed. Surface adsorption can be beneficial if the surface area of the carrier is large and there are complementary functional groups available. The method of loading should also be considered when considering the final release profile. This approach with high loading can be too acute for long-term cancer treatment. On the other hand, high degree of drug-carrier association can result in slow and incomplete drug release [21].

4. Controlled Drug Release: (Principles)

Controlled drug release is the intentional manipulation of the rate, duration and extent of drug ionisation from the dosage form to achieve and maintain a desired drug concentration in the blood stream for an appropriate period of time. Nanoparticle drug delivery is based on the delivery of the therapeutic agent in the interior, association or attachment to the nanocarrier, with this in turn controlling the release of the therapeutic agent in the surrounding biological environment. The goal of controlled-release nanoparticles is to have a more consistent drug release and to have the drug available for longer periods of time as compared to conventional immediate-release tablets, where drug release can happen very quickly and lead to variations in drug concentrations [22].

The principle of controlled release relies on the controlled release of the drug molecules from the nanocarrier to the surrounding medium through processes like diffusion, dissolution, swelling, erosion, degradation, desorption, etc. and changes in nanocarrier structure upon stimulus. The release behavior depends on a number of interrelated factors such as the physicochemical properties of the drug, composition and architecture of the nanocarrier, particle size, surface characteristics, drug-loading level, matrix porosity and strength of interactions between the drug and the nanocarrier. The complex interactions of the drug molecule with the components of the nanoparticles can occur by hydrophobic, electrostatic, hydrogen bonding and van der Waals forces, π - π , covalent interactions, which may affect the degree of drug retention in the carrier.

The weakness of drug-carrier interactions can lead to fast drug release, while a strong interaction can lead to drug being retained for a longer time, though too strong can hinder the availability of the drug and lead to incomplete release. Controlled release can be achieved in polymeric nanoparticles if the surrounding medium interacts with the matrix and the drug dissolves into the medium, thereby diffusing through the matrix. The mobility of the drug molecule can be increased due to swelling of the matrix and it may lead to increase in the number of diffusion pathways, and erosion or degradation of this carrier may lead to gradual release of the incorporated drug.

Degradation-controlled release is especially important in systems of polymers that are biodegradable, which are changed by mechanisms such as hydrolysis or enzymatic action over





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time. Another phenomenon of importance is the burst release which is the initial large release of drug, usually associated with surface associated or weakly entrapped drug [23].

The sustained release property of the formulation may be affected by excessive burst release, therefore, optimizing loading level, carrier composition, particle size, surface properties and preparation conditions are necessary. Other more advanced nanoparticle systems could utilize stimuli-responsive systems where the release of the drug is activated or enhanced under specific physicochemical or biological conditions like: pH, temperature, enzymes, redox conditions, light, magnetic stimuli. The tumor microenvironment is different from normal physiological conditions, and these differences can be used to harness a system to control drug release, which is an important aspect of cancer nanomedicine. Controlled release and nanoparticle mediated delivery can thus offer both temporal control over the release of the drug and, along with appropriate targeting strategies, better spatial control over the drug exposure.

This is especially applicable to cancer therapy where exposure to potent anti-cancer agents may be uncontrolled and can lead to undesirable effects and systemic toxicity. However, controlled release should not be judged only on the basis of the extended drug release; a good formulation should ensure an appropriate balance between the release and retention of the drug, prevent the release of the drug from the particles before the time for release, reduce the burst release, ensure the stability of the nanoparticles and ensure a reproducible release profile under the intended conditions.

Drug-release studies are generally performed in vitro using a release medium appropriate to the nanoparticles and the released sample is collected at regular intervals for quantitative drug analysis to assess controlled-release behavior. The cumulative release data thus obtained can then be analyzed by mathematical modeling like the zero order, first order, Higuchi model, and Korsmeyer–Peppas model to provide information on the release kinetics and possible mechanism of the drug liberation from the formulation [24].





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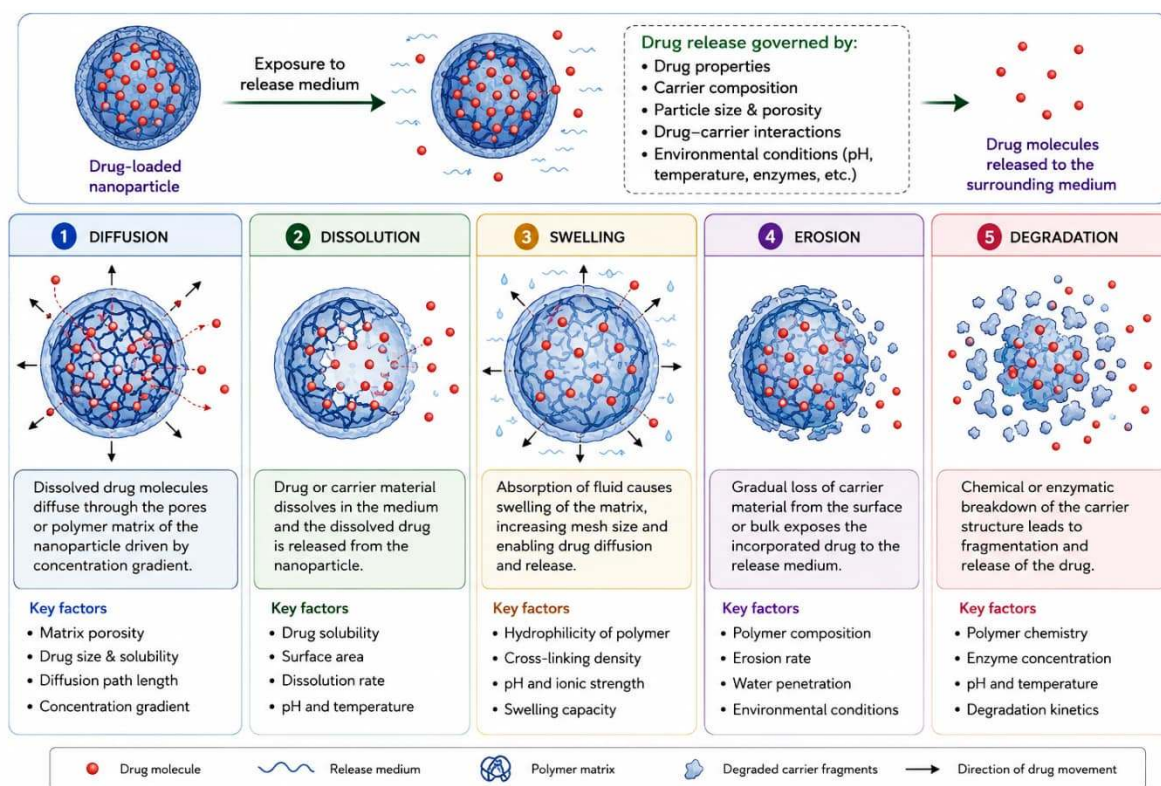


Fig.2 Schematic representation of the major mechanisms involved in controlled drug release from nanoparticles [25].

5. Mechanisms of Controlled Drug Release

The release of the controlled drugs from the nanoparticles depends on the interaction of incorporated drug, nanocarrier matrix and surrounding release environment. Once administered, the drug can be released by various mechanisms depending on the physico-chemical properties of the drug and the structure of the carrier. The main mechanisms are diffusion, dissolution, swelling, erosion and degradation. The mechanisms can work individually or in combination and the extent of each influence dictates the overall release profile. A knowledge of these mechanisms is key to the design of nanoparticle systems that can offer a predictable, sustained and therapeutic drug delivery [26].

5.1 Diffusion

Release of the drug from the nanoparticles is one of the most frequent mechanisms of diffusion. It is the diffusion of the drug molecules from a high concentration region inside of the nanoparticles towards a low concentration region in the release media. Physiological fluid can permeate the nanoparticle and release the drug. The dissolved molecules then diffuse through the polymeric matrix, lipid phase, membrane or pores in the Nanocarrier to the external environment. Drug molecular size, solubility, concentration gradient, matrix porosity, particle size, polymer composition, degree of hydration and interactions between drug and carrier affect





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the diffusion rate. The porosity or hydration of matrices tends to be greater for high porosity/hydrated matrices and less for dense matrices which tend to reduce the diffusion of molecules. Diffusion could also be affected by the site where the drug is associated with the NP; surface-associated drug is more readily available to the release medium than drug in the deep matrix of the NP. For many nanoparticle systems diffusion also happens in parallel to swelling, erosion or degradation, and it is difficult to separate out the full release profile into a single mechanism [27].

5.2 Dissolution

The dissolution-controlled release is the release of the drug or material associated with the drug in a way that changes the drug into a soluble form before it can enter the diffusion into the surrounding release media. Factors such as aqueous solubility of the drug, particle characteristics, surface area, pH, temperature, and composition of the release medium will affect the dissolution process. Nanosize formulation can alter the apparent dissolution behavior of poorly soluble drugs by increasing the surface area available for interaction with the medium, if the drug is incorporated into the nanoparticles. Dissolution may thus be a significant step prior to the diffusion of the drug from the carrier. In some systems, the dissolution of the carrier itself can be considered a process that takes place slowly over time, leading to a gradual release of the incorporated drug. The connection between dissolution and diffusion is especially significant because it is through dissolution that the mobile species of the drug are generated that then participate in diffusion. Thus, overall release rate will be dependent on whichever one of the processes is the predominant resistance to drug liberation [28].

5.3 Swelling

Swelling controlled drug release is a process in which the nanocarrier absorbs the fluid from surrounding environment and releases the fluid by swelling and/or structural relaxation. This effect is important in the case of hydrophilic polymeric systems and nanogels where the water penetration may have a significant effect on the internal structure of the carrier. The matrix may become more pliable as it becomes hydrated and swell, and the diffusion pathways available to the drug may increase. The incorporated drug is then able to penetrate the hydrated matrix and diffuse into the surrounding medium. Swelling depends on polymer composition and degree of cross-linking, Hydrophilicity, particle structure, pH, ionic strength and temperature. A highly cross-linked matrix may limit swelling and hence the diffusion of drugs while a more flexible hydrophilic matrix may have a greater capacity to swell and hence to release the drugs. Drugs may also be released with swelling, in addition to degradation or erosion, which creates a combined mechanism of drug release [29].

5.4 Erosion

Erosion controlled release is a gradual removal of the material that is making up the nanoparticle from the surface or bulk of the carrier causing exposure and release of the incorporated drug. Dissolution, hydrolysis, enzymatic activity and other processes can cause





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erosion of the carrier, which occurs gradually. In surface eroding systems, the material is being removed mostly from the outside of the carrier leading to relatively controlled release of incorporated drug. In a bulk eroding system, fluid flows through the matrix and degradation can happen within the matrix without significant loss of the carrier material. The ratio of surface to bulk erosion can be affected by carrier composition, molecular properties, water penetrability, environmental conditions, and degradation rates. When prolonged drug release is desired, erosion can prove to be very beneficial since the release of drug-containing regions can be continuous [30].

5.5 Degradation

The degradation controlled drug release refers to a process in which the constituent material of the nanoparticle or the nanoparticles themselves disintegrates into smaller particles or pieces, thereby releasing the drug. This degradation can be chemical hydrolysis, due to the activity of enzymes, to oxidation and reduction or other processes mediated by the environment, depending on the composition of the Nanocarrier. Biodegradable polymers are of special interest in this regard since the degradation process can be programmed to proceed gradually under physiological environments. This changes the carrier structure, making the drug molecule increasingly available to the surrounding medium, and then diffusing away from the nanoparticle [31]. The degradation rate is carefully controlled because too fast degradation will lead to too early release of the drug while too slow degradation will lead to the drug being in the system for too long to be therapeutic. Thus, degradation-controlled systems must be optimised with respect to the properties of the carrier, its molecular characteristics, the structure of the particles and their environment sensitivity [32].

Table 5 Major Mechanisms of Controlled Drug Release from Nanoparticles [33]

Sr no.	Mechanism	Basic principle	Major controlling factors	Typical consequence
1.	Diffusion	Movement of dissolved drug through the carrier	Concentration gradient, matrix porosity, drug size, carrier permeability	Gradual drug liberation
2.	Dissolution	Conversion of drug/carrier material into soluble form	Solubility, surface area, pH, temperature	Drug becomes available for diffusion
3.	Swelling	Fluid uptake causes expansion and relaxation of the matrix	Hydrophilicity, cross-linking, pH, ionic strength	Increased diffusion pathways





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4.	Erosion	Progressive removal of carrier material	Carrier composition, water penetration, erosion rate	Exposure and release of incorporated drug
5.	Degradation	Chemical or enzymatic breakdown of carrier	Polymer chemistry, enzymes, pH, temperature	Progressive drug liberation

Table 6 Comparative Characteristics of Controlled Drug-Release Mechanisms [34]

Sr no.	Mechanism	Drug movement	Role of carrier	Potential release behavior
1.	Diffusion	Through matrix or membrane	Acts as a diffusion barrier	Sustained release
2.	Dissolution	Following solubilization	Controls drug accessibility	Release dependent on solubility
3.	Swelling	Through hydrated matrix	Expands and modifies pathways	Hydration-dependent release
4.	Erosion	With progressive matrix removal	Gradually exposes drug	Erosion-dependent release
5.	Degradation	Following carrier breakdown	Structurally disintegrates	Degradation-dependent release

5.6 Combined Release Mechanisms

Drug release in practical nanoparticle systems is seldom of single mechanism. Swelling can occur concurrently with diffusion, and erosion and degradation can cause the diffusion pathway to continuously change. For instance, a biodegradable polymeric nanoparticle might first release surface-associated drug by diffusion, then gradually swell and hydrate its matrix and finally disintegrate the polymer. Likewise, a drug can dissolve inside the nanoparticle, then diffuse through the hydrated matrix and eventually be released when the carrier erodes. The relative importance of each mechanism will depend on the formulation composition, the properties of the drug, the particle architecture and the release environment. Therefore, it is important to take into account combined diffusion, dissolution, swelling, erosion and degradation phenomenon when interpreting the drug-release profiles of nanoparticles, instead of attributing the entire drug-release profile to a single phenomenon [35].





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6. Stimuli-Responsive Drug Release

An advanced technique of the Nanoparticle-mediated Drug Delivery System is Stimuli-responsive Drug Release which involves adjusting the release of a therapeutic material based on a particular internal or external stimulus. The difference between stimulated nanoparticles and conventional controlled-release systems, which typically rely on passive drug release through diffusion, swelling, erosion or degradation, is that the drug release mechanism is a physicochemical or structural change that occurs when the nanoparticles have a specific stimulus applied to them. This change might lead to the permeability of the carrier becoming higher, change the nanostructure, break chemical bonds, modify the interaction between drugs and carrier, or facilitate the diffusion of the drug, which in turn enhances the release of the drug. The main stimuli studied for the delivery of nanoparticles are pH, temperature, enzymes and redox conditions [36]. These stimuli are especially important for cancer therapy since the tumour microenvironment and the intracellular compartments might have a different physicochemical environment from normal tissues. Thus, nanoparticles can be designed to be particularly stable when in circulation and to be sensitive to the conditions that exist in the targeted location, resulting in better control of the timing and the amount of drug released.

6.1 pH-Responsive Drug Release

PH-responsive systems of drug release are so designed to react to the pH environment in the biological body. The principle is based on the incorporation of groups that are capable of being ionized or chemical linkages that are pH sensitive on the Nanocarrier. Variations in pH may affect the ionization, Hydrophilicity, swelling, solubility or structure of the carrier, which can affect the adsorption and release of the drug [37]. This is especially interesting to cancer nanomedicine where there are different pH conditions in different biological compartments. While there are more or less physiological conditions in the bloodstream in the systemic administration, acidic conditions can be found in some parts of the tumor and in some intracellular compartments like endosomes and lysosomes. Thus, a pH responsive nanoparticle may be developed to be relatively stable in physiological pH and change its structure in acidic conditions, allowing the drug to be released. The pH responsiveness may be incorporated by the inclusion of acid-labile linkages, protonatable functional groups, pH-sensitive polymers, etc. The degree and speed of response will be influenced by the pKa of the functional groups, the composition of the carrier, the architecture of the particles, interactions between drug and carrier and the magnitude of the pH change [38].

6.2 Temperature-Responsive Drug Release

Temperature responsive drug delivery systems take advantage of the physical or chemical changes of the nanocarrier in response to temperature changes. Thermoresponsive materials can transition between being soluble and insoluble, get hydrated, change the conformation of their polymers, change phase behavior, or change their organization in order with the approach to a specific temperature. These changes may alter the permeability of the carrier, and hence





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influence the release of the drug. Such temperature responsive nanoparticles may be configured to react to a temperature difference that occurs in the body or to a temperature applied from the outside. Localized hyperthermia can be used as an external stimulus to systems which are sensitive to temperature, and be used to enhance the release of drugs in the region of hyperthermia [39]. Thermoresponsive polymers are of special importance as these can be exploited in the design of nanoparticles that undergo a phase transition. The transition temperature, however, needs to be optimized carefully, so that the carrier is stable at normal temperatures and responds to the desired temperature stimulus. Thus the therapeutic potential of the temperature-sensitive systems is critically dependent on the characteristic transition properties, stability of nanoparticles, drug compatibility and extent of change in the structure at elevated temperatures [40].

6.3 Enzymes-Responsive Drug Release

The enzyme-responsive nanoparticles are engineered to take advantage of specific enzymes in biological tissues. Enzymes may react with the vulnerable chemical bonds, peptide sequences, polymeric components or surface structures embedded into the nanocarrier, resulting in structural modification and subsequent release of the drug. Such mechanism is especially captivating for cancer treatments, as some enzymes can be found in a different amount or have higher activity in the tumor tissues or organelles [41]. An enzyme-responsive carrier can then be stable until it reaches the desired environment containing the appropriate enzyme(s) and then release or unmask the drug molecule(s) by cleavage and/or degradation. The selectivity of this approach depends on the selectivity of the enzyme-responsible part. Such systems must be carefully designed taking into account the amount of enzymes available, enzyme accessibility, substrate specificity, stability of the carrier, and the rate of enzymatic cleavage. The enzyme-responsive release can then offer another level of biological control to the systems of nanoparticles and can be used in conjunction with other stimuli-responsive mechanisms to enhance the responsiveness of the nanoparticle systems.

6.4 Redox-Responsive Drug Release

Redox responsive drug release systems leverage the differences in oxidizing/reducing environment between the extracellular and intracellular space. The general definition of redox-sensitive nanoparticles is chemical linkages or components of the nanoparticles that are vulnerable to reductive cleavage or modification under specific redox conditions. Among the most studied intracellular reducing conditions, the high level of intracellular glutathione is an appropriate one, as it can interact with appropriate redox-sensitive bonds, causing structural changes in the nanocarrier [42]. Covalently linked molecules that contain disulfide bonds are often investigated as they may be reduced under the right intracellular conditions, thus releasing the attached drugs. Redox-responsive systems can thus have a relatively stable extracellular circulation but a more labile intracellular circulation. This mechanism is particularly applicable to the intracellular delivery of drugs, where a difference in redox





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potential may be used to control the release of the drug. These systems have different efficiencies depending on the concentration and type of redox-active species, the sensitivity of the chemical linkage, the accessibility of the responsive group, and the stability of the nanoparticle in extracellular environment.

Table 7 Significant stimuli responsive drug delivery systems [43].

Sr no.	Stimulus	Basic principle	Typical carrier response	Potential application
1.	pH	Response to changes in acidity/alkalinity	Ionization, swelling, bond cleavage, structural alteration	Tumor-associated and intracellular release
2.	Temperature	Response to temperature variation	Phase transition, polymer conformational change	Thermally triggered/localized release
3.	Enzyme	Response to specific enzymatic activity	Enzymatic cleavage or degradation	Biologically triggered release
4.	Redox	Response to reducing/oxidizing conditions	Cleavage or transformation of redox-sensitive groups	Intracellular drug release

7. Drug Release Kinetics and Mathematical Models

The drug-release kinetics is a quantitative method to describe the release of a therapeutic agent from a nanoparticles based delivery system over time. The release kinetic is important to evaluate since the percentage of drug released alone is not sufficient to explain the mechanism associated with the liberation of the drug [44]. Experimental release data is therefore used to define the relationship between the release and time with the help of mathematical models and to gain insight into the underlying release process. The zero-order, first-order, Higuchi, and Korsmeyer–Peppas models are among the most frequently-used models in this application of nanoparticles to drug delivery. These models vary according to their mathematical assumptions and offer various explanations of the release behavior. Importantly, kinetic models should not be used as a model with the highest correlation coefficient without taking into account the formulation characteristics and experimental conditions.

7.1 Zero-Order Kinetics

The zero-order model assumes that the release rate goes up and down in a theoretically constant manner with respect to time. This model assumes that the fraction of drug released is proportional to time, thus releasing the same quantity of drug per unit of time. This is desirable when a relatively constant level of drug is desired for an extended period.

The mathematical expression is:





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$$Q_t = Q_0 + K_0 t$$

If the initial amount of drug released is Q_0 :

$$Q_t = K_0 t$$

Where:

x_0 = initial amount of drug present in the sample

Q_0 = amount of drug released initially

The value of K_0 is zero-order release constant

t = release time

For a zero order behavior, a plot of cumulative amount released versus time will be used. A linear relationship means that there is compatibility between the two. The slope of the plot represents the release constant for the formulation and experimental conditions [45].

The zero-order behavior is especially suitable for controlled drug delivery since it offers a relatively constant drug delivery rate. The challenge is that in many nanoparticle systems, the concentration of the drug in the system, the diffusional pathway, the matrix structure, the swelling, the erosion and degradation can change during the release, which makes it difficult to achieve true zero-order release. Therefore, one has to interpret the model as a function of the real properties of the formulation.

7.2 First-Order Kinetics

The first order model is applied to drug release where the rate of release is proportional to the quantity of drug left in the delivery system. Thus, this rate of release will diminish with the amount of drug left in the nanoparticle. It is a typical model with concentration dependence release phenomenon.

The mathematical expression is equivalent to:

$$\frac{dQ}{dt} = -K_1 Q$$

Integrated form is usually written as:

$$\log Q_t = \log Q_0 - \frac{K_1 t}{2.303}$$

Equivalent mathematical forms may be given based on the convention used for defining the amount released versus the amount remaining.

Where:

Q_t = quantity of the drug still in or released from the formulation at time t ; the formulation is chosen by the selection of the equation.

Initial amount of drug (Q_0)

k_1 = 1st order release constant

t = time

The amount of drug remaining is usually plotted as the log of the value when applying conventional first-order analysis. When plotted on a graph, a linear relationship results in a 1st order reaction. First-order kinetic is observed in nanoparticle formulation where the release of the drug is highly dependent on the concentration of drug left in the carrier.





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The distinguishing feature of first order release is that the release rate starts off high when there is a lot of drug available and slowly decreases as the amount of drug is reduced. Thus, it is not a zero-order release like ideal zero order release [46].

7.3 Higuchi Model

One of the most common mathematical models used to describe diffusion controlled drug release from matrix-type delivery system is the Higuchi model. The model was initially developed to describe drug diffusion from planar and matrix systems and since then, widely used in pharmaceutical formulation research.

The simplified Higuchi equation is given as:

$$Q_t = K_H t$$

Where:

The amount of drug released per unit area after time t , Q_t

K_H = Higuchi dissolution/release constant

t = time

A plot of cumulative amount of drug released versus square root of time is used to assess the applicability of the Higuchi model. If it is linear, the model is assumed to be a good description of the release behavior.

If diffusion through a matrix is an important process for drug liberation, the Higuchi model is especially useful. However, assumption of the model needs to be taken into consideration for any application of the model. Real nanoparticle systems can swell, erode, degrade, change in porosity and/or interact with the drug, which may not be ideal Higuchi conditions. So, a good fit to the Higuchi equation must be considered in conjunction with the physicochemical properties of the formulation as well as with other kinetic models.

7.4 Korsmeyer–Peppas Model

The Korsmeyer–Peppas model is an empirical or semi-empirical model, which is widely used to describe the release behaviour of drugs when more than one mechanism is possible or the mechanism cannot be easily determined from simpler models [47].

The general formula is:

$$M_t \propto M_\infty = K K_P t^n$$

It's in the form of a logarithm, or log form:

$$\log(M_t \propto M_\infty) = \log K K_P + n \log t$$

Where:

M_t = amount of drug released by the time t

The amount of drug released at infinite time or the maximum amount of drug considered for the analysis is called M_∞ .

It is possible to calculate the kinetic constant $K_{\{K_P\}}$ that incorporates the structural and geometric characteristics.

The release-exponent or diffusional exponent is denoted by n .





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t = time

In the case of the appropriate systems, the release exponent n is of special importance, since it gives an indication of the dominant release mechanism. The value of n will depend on the geometry of the delivery system and there should not be universal numerical cutoffs unless there is a consideration of whether the system is spherical, cylindrical, or planar.

In the typical interpretation for formulation studies, the spherical nanoparticles are described as:

$n \approx 0.43$: Fickian diffusion

$n > 0.85$: turbulent flow transport

$n \approx 0.85$: Case-II transport

$n < 0.85$: Case-I transport

The ranges provided are not necessarily definitive – they are geometry and model dependent. The Korsmeyer–Peppas model is typically used for the first phase of release curve, which is usually limited to about 60% cumulative release, depending on the experimental design and literature convention. The main benefit of this model is that it can offer useful mechanistic information when there are multiple mechanisms involved in drug release, such as diffusion, swelling, polymer relaxation, etc.

Table 8 a comparison of Mathematical Models used for Drug-Release Kinetics [48]

Sr no.	Model	Basic equation	Plot used for analysis	Main interpretation
1.	Zero-order	$Q_t = Q_0 + K_0 t$	Cumulative drug released vs. time	Constant release rate
2.	First-order	$\log Q_t = \log Q_0 - 2.303 K_1 t^*$	Log amount remaining vs. time	Concentration-dependent release
3.	Higuchi	$Q_t = K H t$	Cumulative drug released vs. $\sqrt{\text{time}}$	Diffusion-controlled matrix release
4.	Korsmeyer–Peppas	$M_t/M_\infty = K K P t^n$	$\log(M_t/M_\infty)$ vs. $\log$ time	Mechanistic indication from release exponent

*The first-order equation should be written according to whether the analysis uses drug remaining or drug released; the convention should be stated clearly in the methodology.





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Table 9 Interpretation of Drug-Release Models [49]

Sr no.	Model	Characteristic release behavior	Important parameter	Application in nanoparticle systems
1.	Zero-order	Approximately constant amount released per unit time	K0	Assessment of sustained and relatively uniform release
2.	First-order	Release rate decreases with decreasing drug content	K1	Concentration-dependent drug release
3.	Higuchi	Drug release related to $\sqrt{\text{time}}$	KH	Evaluation of diffusion-dominated matrix release
4.	Korsmeyer–Peppas	Empirical description of release mechanism	n	Investigation of diffusion and anomalous transport

7.5 Selection and Interpretation of Kinetic Models

The students will identify and apply kinetic models. The students will be able to select and interpret kinetic models. The choice of mathematical model should be guided by the type of the nanoparticle, the experimental release profile, and the mechanics to be interpreted. Do not use a model based on "the best R² value". For instance, a high correlation with the Higuchi model could indicate that there is a considerable diffusion contribution, but this in itself is not an indication that diffusion is the sole mechanism at play. Likewise, the fit of a Korsmeyer–Peppas model should be analyzed along with the model parameter n, the geometry of the nanoparticles, and formulation properties [50]. The release behavior is better determined by comparing the release behavior of various models.

8. Comparative Drug loading and controlled release strategies

The optimization of drug loading and controlled release are closely interconnected and can be considered as an important part of the system of nanoparticle mediated drug delivery whose optimal performance depends on the optimization of both components. The amount of drug that can be incorporated and its position inside or on the nanoparticle is stipulated by the drug loading strategies, while controlled-release mechanisms dictate how, when and at what rate the incorporated drug becomes available. The patterns of drug incorporation and retention in the matrix may differ between passive loading, active loading, encapsulation, and surface adsorption; and the patterns of drug liberation will be different following diffusion, dissolution, swelling, erosion, degradation, and stimuli-responsive mechanisms [51].

If the drug incorporated in a nanoparticle is released too soon or too much, this is not an optimal therapeutic system, even if the capacity to load high levels of drug is achieved. Likewise, if the formulation has a too-low concentration of the drug, a very controlled release profile may be





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essentially unexploitable. Hence, it is crucial to have a compromise between the drug-loading capacity, entrapment efficiency, drug retention, release rate, release duration, and biological availability in an effective nanoparticle system. This balance is especially crucial in targeted cancer therapy where the nanocarrier needs to be stable during in vivo circulation, release the drug in a controlled manner, accumulate or be taken up at the therapeutic target, and then release the drug in a controlled manner.

Comparative evaluation of the various loading and release methods can, therefore, help to choose the right nanocarrier depending on the physicochemical characteristics of the therapeutic agent and the application. The ability to load drugs efficiently into the nanoparticles with a predictable controlled release ultimately gives rational basis to design a more therapeutic system with less undesirable exposure and a more precise control of the drug release from the nanoparticles [52].

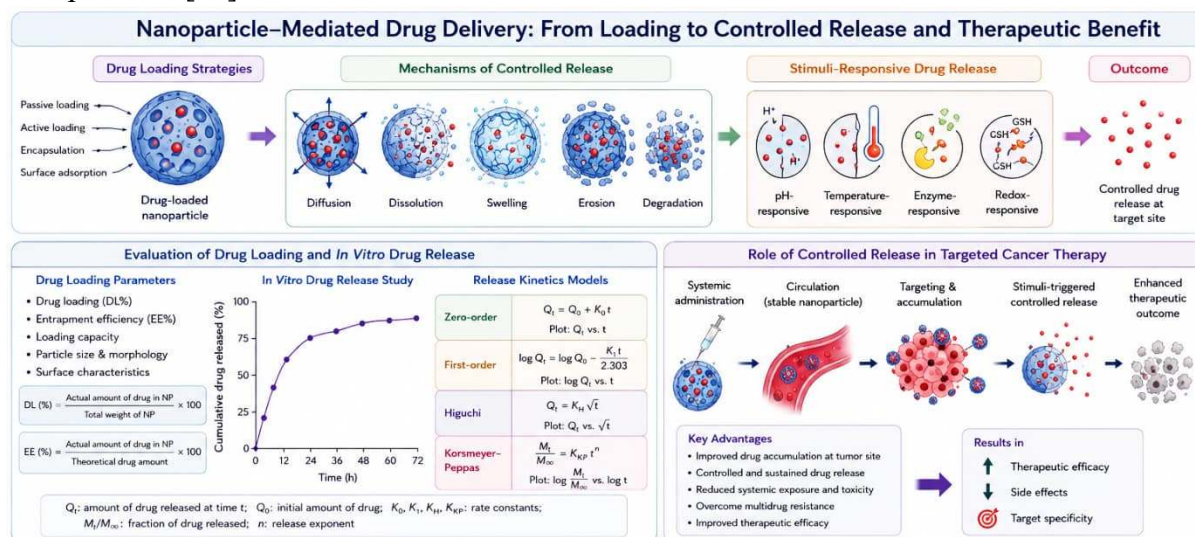


Fig. 3. Integrated overview of drug loading, controlled release, and targeted cancer therapy [53]

9. Recent Advances in Nanoparticle Based Controlled Drug Delivery

The controlled drug delivery based on nanoparticles has come a long way since the first use of such systems, and the systems now in development are able to control at least the loading, transport, release, and therapeutic activity of the drug. Moreover, recent strategies have shifted from the more traditional passive release systems to stimuli-responsive, multifunctional, targeted and combination nanocarriers that offer more control over the availability of the drug. The development of polymeric nanoparticles, lipid-based nanoparticles, nanogels, hybrid nanoparticles or other multifunctional platforms has made possible the incorporation of therapeutic agents with various physicochemical properties and has offered the chance to control the release properties by using diffusion, degradation, swelling, erosion and environmental responsiveness [54]. pH, temperature-, enzyme-, and redox-responsive systems have been of special interest since they are able to react to a specific physiological or





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pathological state and to release the drug at the desired location. Furthermore, surface engineering and ligand-mediated targeting have been combined with controlled-release systems to enhance targeting and interaction with cells.

More recent developments also highlight the co-delivery of several therapeutic agents, where nanoparticles are used to carry two or more therapeutic molecules, including anticancer drugs, nucleic acids or other therapeutic molecules, and thus target several biological pathways.

The integration of imaging or diagnostic elements has added to the ability to create multifunctional nanoplateforms with both therapeutic and diagnostic properties [55]. The formulation optimization, physicochemical characterization, release-kinetic modeling and engineering of nanocarriers have enhanced the understanding of the correlation between the structure of nanoparticles and the release-kinetic behavior of the drug. Despite these improvements, issues of reproducibility, stability over time, scaling up production, toxicity, biological variability, and clinical translation are highlighted. As a result, there is a growing interest in the development of easy-to-prepare, reproducible, biocompatible and clinically translatable nanoparticle systems that offer predictable loading and controlled release of a therapeutic agent, while preserving therapeutic performance [56].

Moreover, the recent research has also shown the importance of co-delivering and combination therapy through nanoparticle platforms. Treatment for cancer could require several different therapies, and nanoparticles could allow for the delivery of two or more therapies in one system. Co-loading the two drugs might enable sequential release or different release rates to be designed based on the therapeutic requirement. Another area of interest is the use of nanoparticles to carry multiple small molecule drugs and biological therapeutics, such as nucleic acid therapeutics. Physicochemical compatibility and loading efficiency of the individual therapeutic components, their stability, release properties and biological activity must be carefully considered for such systems. The emergence of co-delivery systems is therefore the shift from simple single drug carriers towards more complex drug delivery systems that are able to perform multiple therapeutic tasks.

Another significant development is hybrid nanoparticle systems, that is, systems that bring together the properties of various classes of materials in a single delivery system. For instance, the polymer–lipid hybrid nanoparticles can combine the structural features of polymeric systems with the interfacial and drug-solubilizing properties of lipid components. The combinations can offer possibilities of enhancing physical stability, drug incorporation, surface modification, and release control. Likewise, nanogels and other hydrated networks at the nanoscale can also contain drug molecules in an aqueous environment, while the matrix itself can react to changes in swelling, pH, temperature, etc., or to changes in the environment. The formulation potential for a drug with a range of different physicochemical properties is thus increased when developing hybrid systems [57].





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Controlled drug-delivery systems have also been developed through the advances that have occurred in surface engineering and functionalization of nanocarriers. The changes of the surface of the nanoparticles may affect the colloidal stability, protein interaction, cellular uptake, biodistribution, and targeting behavior. The surface characteristics, like charge, hydrophilicity, hydrophobicity, and ligand density can be optimized for the intended use. Surface modification may also minimize unwanted interactions with biological species, as well as enhance the stability of nanoparticles in physiological environments. But, over functionalization may change the size, drug loading, release profile and biological activity of the particles, so optimization of surface properties must be carried out in conjunction with other formulation parameters.

Although there has been significant progress, the use of nanoparticles to deliver a controlled dose of drugs to tissues into the real world has come with both a number of challenges. The following factors must be noted: batch-to-batch reproducibility, scale-up, long-term stability, sterilization, storage, complexity of manufacture, toxicity, degradation, biological variability, and regulatory requirements. A good formulation in the laboratory may not work in the complex biological environment. The behaviour of nanoparticles can be modified by changes in the adsorption of proteins, internalisation, tissue distribution, enzymatic degradation and clearance. The need for standardized characterization, reproducible manufacturing processes, proper in vitro–in vivo correlations, and systematic safety and therapeutic performance assessment should be more emphasized in future studies [58].

One key aspect of future development is towards a simpler but multipurpose nanocarriers. Highly complex systems can give sophisticated control of drug release, but the more complex it is, the more difficult it will be to manufacture and evaluate it for regulatory purposes. An ideal next generation nanoparticle, therefore, does not necessarily have to be the most structurally complex system, but one that would bring an acceptable balance between the capacity for loading, controlled release, targeting, stability, biocompatibility, manufacturability, and therapeutic activity. The rational choice of material and optimization of formulation parameters can thus be more critical than the mere complexity of the functionalization of the nanocarrier [59].

10. Conclusion

Controlled drug delivery using nanoparticles is a general method that can be used to control the delivery and release of therapeutic agents, and has great potential in targeted cancer therapy. The drug loading should be efficient, giving a sufficient therapeutic dose, and its release should be controlled, both in terms of rate and time. Drug release can be from diffusion, dissolution, swelling, erosion, degradation, or all of these processes; stimuli-responsive systems can also be used to control the release of the drug based upon a certain biological or external stimulus. The release kinetics can be analyzed using mathematical models like zero-order, first-order, Higuchi and Korsmeyer–Peppas models, which can be helpful to understand the possible





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contribution of different mechanisms. The potential of these systems has since been widened by the development of targeted, multifunctional, hybrid, co-delivery and stimuli-responsive nanoparticles.

But formulation issues, repeatability, stability, safety, scaling up, and clinical translation issues are significant. Hence, for the development of controlled drug delivery system using nanoparticles, it is essential to have an integrated knowledge of drug properties, architecture of nanocarrier, loading efficiency, release behavior, biological interactions and therapeutic requirements. Ongoing studies aimed at rational formulation design, standardized assessment of activity, biocompatible materials, and clinically relevant activity will pave the way for the development of clinically useful, reliable, and effective therapeutic applications of advanced nanoparticle systems.

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