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Controlled drug delivery systems

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ABSTRACT
Drug delivery systems (DDS) have evolved significantly, offering advanced alternatives to conventional formulations. Among various administration routes, the oral route remains the most preferred due to its convenience and ease of industrial production. A critical aspect of modern DDS is the differentiation between controlled and sustained release mechanisms—each aiming to optimize therapeutic efficacy by modifying pharmacokinetic and pharmacodynamic profiles. Controlled release involves pre-designed drug release using polymers, whereas sustained release extends the drug's action over time, typically following first-order kinetics.
DDS technologies have expanded to include nano-based delivery systems, molecularly imprinted polymers, and 3D printing, enhancing precision targeting, controlled drug localization, and overcoming biological barriers such as the blood–brain barrier. These systems also reduce toxicity, improve drug bioavailability, and minimize degradation. Solid dosage forms—tablets, capsules, lozenges, and granules—continue to dominate due to stability and patient compliance, while semi-solid and bulk powders serve specialized therapeutic roles. Sublingual and buccal formulations further offer rapid systemic absorption by bypassing gastrointestinal and hepatic metabolism.
Nanotechnology plays a pivotal role in DDS development. Liposomes, polymer micelles, and solid lipid nanoparticles significantly enhance drug solubility, stability, and tumor targeting while minimizing side effects. These advancements demonstrate the integration of multidisciplinary approaches to tailor drug delivery to specific physiological environments, supporting personalized medicine and improving therapeutic outcomes.

I. INTRODUCTION

Introduction Drugs can be administered through multiple routes, but the oral route remains the most convenient and widely used due to its ease of administration and scalability in manufacturing. Traditional dosage forms, however, often suffer from fluctuations in drug levels, leading to suboptimal therapeutic outcomes.
Controlled Drug Delivery Systems (CDDS) address these limitations by using polymers or carriers that regulate the drug release rate and location. Unlike sustained release systems that mimic zero-order kinetics, CDDS aims to achieve precise, consistent release patterns. This approach enhances pharmacokinetic and pharmacodynamic profiles, improving drug efficacy and safety.
Modern DDS technologies include nanoparticles, molecularly imprinted polymers (MIPs), and 3D printing. These innovations enable site-specific targeting, improved drug absorption, reduced toxicity, and enhanced therapeutic index. Additionally, CDDS supports drug delivery through complex barriers like the blood-brain barrier, while minimizing side effects and maintaining optimal drug concentration.
By leveraging multidisciplinary approaches, DDS platforms continue to evolve with a focus on targeted delivery, controlled release, and reduced adverse effects — meeting critical needs in personalized medicine and modern therapeutics.

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Drug Molecular	Challenges	Solution
Prota(Proteolysis)	High molecular weight, poor bioavailability,poor stability	Antibody drug conjugates (ADC) Three-dimensional printing (3DP) Transdermal prepation Implanted catheter
Peptides and Proteins	Immunogenicity, Short half-life	Polymeric nanoparticles (PNPs) Peptide drug conjugate(PDC) Implanted cathed catheter
Anti-Body	Toxicity, Immunogenicity	Cell drug delivery systems Antibody drug conjugates(ADC) Implanted Catheter
Nuleic acid	Extrahepatic delivery,Immugenicity ,Enzyme Degradation	Liposomal drug delivery systems Viral drug delivery systems Bioparticle drug delivery systems Coupling targeted drug delivery systems
Cell	Unstable drug characteristics, Poor tissue permeability	Liposomal drug delivery systems Polymeric nanoparticles (PNPs)

Table 1. The challenges and solutions to drug molecular delivery

Figure 1. Main types of drug delivery systems

1.1 Classification of Solid Dosage Forms

Solid dosage forms are further classified into two main categories based on the type of dose, i.e., unit dose and bulk dose. (a) Unit dose: Each dose is fixed and formulated as a separate dosage form and the patient needs to take a single unit of a specific dose at a time. Examples of unit dosage forms include tablets, capsules, pills, lozenges, chewable tablets, effervescent tablets and dry powder inhalation in metered-dose containers. (b) Bulk dose: As the name itself says, it is a bulk solid powder where the individual dose is not formulated (Figure 3) [4,5]. Dose dumping is a major problem with bulk powders. However, bulk powders are generally used as dressing powder for surgical and injury wounds. Examples of bulk dosage forms include insufflation powder, dressing powder, etc. [4]

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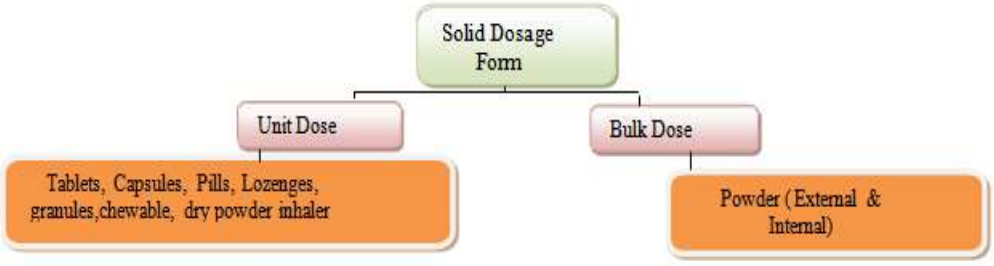

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1.2 Semisolid Dosage Forms

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

1.3 Liquid Dosage Forms

Liquid dosage forms are pourable pharmaceutical formulations comprising of API and excipients either dissolved or dispersed in a suitable solvent/s. These are intended to offer a fast therapeutic response in people with trouble swallowing solid dosage forms. Liquid dosage forms are available as ready-to-use liquids or dry powders for reconstitution. These can be administered by oral (syrups, suspensions, etc.) and/or parenteral (injectable, ophthalmic, nasal, otic and topical) routes. Oral liquids are generally nonsterile, while the parenteral liquid dosage forms are offered as sterile and non-sterile formulations (Figure 7). Liquid dosage forms are classified based on the number of phases present into two types: Monophasic (solutions) and biphasic (suspensions and emulsions) [17].

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Figure 7. Sterile and non-sterile liquid dosage forms.

a) Oral solutions are monophasic clear liquids for oral use comprising of one or more active ingredients dissolved in a suitable solvent system .
b) Oral emulsions are biphasic liquids for oral use where the drug is present in oil-inwater emulsion either in single or dual phases .
c) Oral suspensions are biphasic liquid dosage forms for oral use comprising of one or more APIs suspended in a suitable solvent.

Carrier-Based Drug Delivery Systems

Nano-Based Drug Delivery Systems (NDDSs) "Nanotechnology" initially proposed in 1959 [23], is currently experiencing rapid scientific and industrial growth, and its integration with biotechnology, information technology and cognitive science has propelled life sciences into a new era. Nanotechnology possesses unique physical, chemical, and biological properties, and the resulting nano formulations are anticipated to find extensive applications in the biomedical field. The application of nanotechnology in constructing drug delivery systems can effectively enhance drug solubility, stability, and tumor targeting, and mitigate toxic side effects [24]. A diverse array of materials is employed in the construction of NDDSs, encompassing liposomes, nanodrugs, polymer micelles, hydrogels, and inorganic nanodrug delivery systems [24,25].

1.3 Liposomes

Liposomes, characterized by their ordered bilayers of lipids forming enclosed vesicles, possess a hydrophobic shell and a hydrophilic core, with a particle size ranging from 20 to 1000 nm. Owing to their distinctive composition and structure, liposomes exhibit excellent biocompatibility and can be metabolized normally. Consequently, they can enhance drug solubility and mitigate drug toxicity. Liposomes are capable of encapsulating both hydrophilic and hydrophobic drugs, thereby protecting them from degradation and preventing drug accumulation in other tissues and organs . The development of liposome drug delivery systems grounded in nanotechnology has taken nearly half a century to be integrated into clinical practice; this advancement has catalyzed a quantum leap in the development of anti-tumor, anti-bacterial
infection drugs and vaccines. For instance, in the case of the anticancer agent resveratrol, the utilization of solid lipid nanoparticles for its delivery led to a significantly increased brain concentration of resveratrol in Wistar rats compared to free resveratrol, indicating high penetration into brain tumors and minimal systemic toxicity [33].

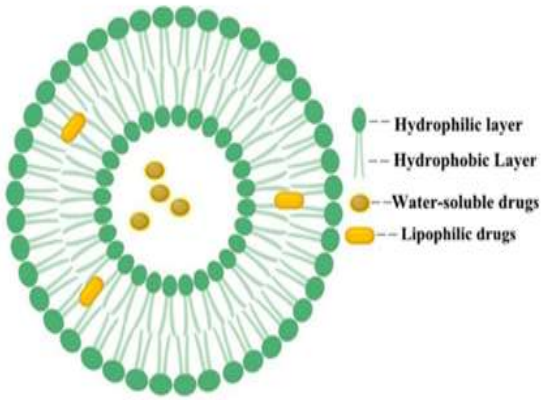

Figure 8. The hydrophilic and hydrophobic structure of liposome drug delivery system.

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In tumor therapy, liposome-encapsulated radiosensitizers can augment X-ray radiation to tumor sites. Zhao et al. Lipid nanoparticles (LNPs) represent a pivotal technology within liposome delivery systems and have emerged as a substantial advancement in the field of oligonucleotidebased therapeutic agents. LNPs are a specialized subset of liposomes devoid of hydrophilic cavities, composed of cationic phospholipids and negatively charged nucleic acid components that are electrostatically complexed, forming multilayer cores interspersed between lipid layers. Oligonucleotides.

Dendrimers, macromolecules with a dendritic structure formed by repetitive and linear linkage of oligomers via branching units, have shown promise in this regard. Hydroxy polyamidoamine (PAMAM) dendrimers can traverse the BBB and blood-cerebrospinal fluid barriers, effectively delivering small molecule drugs to targeted sites, particularly in injured brain tissue [68]. PAMAM dendrimers with a size of 6.7 nm exhibit longer blood circulation times and greater accumulation in the brain compared to those with a size of 4.3 nm [69]. Furthermore, PAMAM dendrimers with cationic surface properties have been shown to cross the BBB and localize in neurons and glial cells following carotid artery administration.

Polymers (MIP), also termed "synthetic antibodies", are produced through molecular imprinting technology (MIT). The fundamental concept of MIP involves the formation of a template molecule-functional monomer complex through covalent or non-covalent interactions, followed by polymerization in the presence of a cross- linking agent, and ultimately the removal of the template molecule to create a binding site or cavity that matches the template in terms of size, shape, and chemical affinity

Tocosome

Tocosome, a sophisticated colloidal and vesicular bioactive carrier system, predominantly comprises alpha- tocopherol phosphate (TP), a derivative of vitamin E.

Vitamin E naturally exists in eight distinct forms, with alpha-tocopherol being the most prevalent, abundant, and biologically active.

TP stands out for its narrow particle size distribution, commendable encapsulation efficiency, minimal immunogenicity, exceptional biocompatibility, and augmented dissolution and penetration capabilities, all of which contribute to its prolonged stability [54].

The multifaceted attributes of Tocophersolan render it an adaptable constituent in the engineering of drug delivery systems. Tocosomes, akin to liposomes, are composed of amphiphilic molecules that form bilayer colloidal structures, displaying analogous behaviors in drug delivery mechanisms and release patterns, despite their unique chemical compositions [55].

Alongside TP, Tocopherol formulations incorporate various phospholipid and cholesterol combinations, which have been effectively utilized in the encapsulation and controlled release of the anticancer agent 5-fluorouracil [54].

Overcoming the regulatory barrier of the blood–brain barrier (BBB) to deliver drugs to the brain remain a significant research challenge.

Manipulating the degradation/bond scission of polymers can also modulate the in vivo release kinetics and facilitate the clearance of delivery carriers in vivo. Surface PEGylation of nanomedicines significantly extends their circulation time in the bloodstream and enhances their permeability and retention (EPR) effect. Therefore a Near Infrared (NIR) light-triggered dePEGylation/ligand-presenting strategy has been developed, relying on the thermal decomposition of azo bonds. This approach involves the self-assembly of Dox/Pz-IR nanoparticles from long PEG chain polymers (Pz-IR) connected by thermo-labile azo molecules, cRGD conjugated IR783 (rP-IR) with short PEG chains and doxorubicin. Overcoming the regulatory barrier of the blood–brain barrier (BBB) to deliver drugs to the brain remain a significant research challenge.

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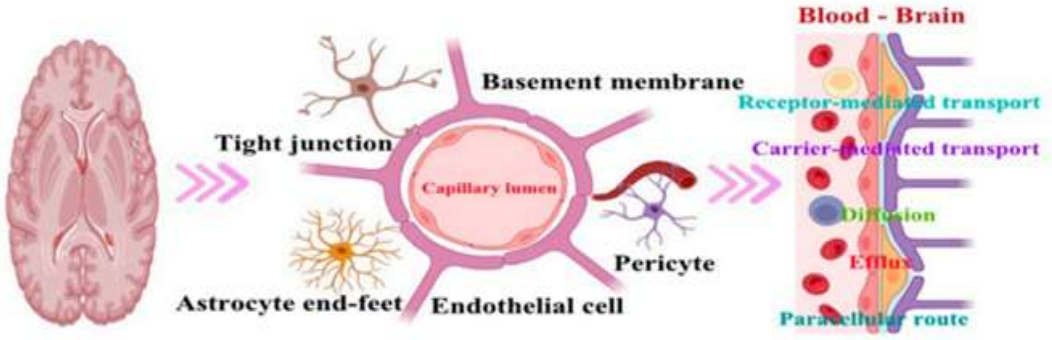

Figure 9. Nano medicine crossing BBB and delivering therapeutic molecules to target sites in

II. GENERAL ADVANTAGES OF CONTROLLED DRUG DELIVERY SYSTEM

The release of the active ingredient (drug) may be constant over a long period; it may be cyclic. The environment or other external events may trigger it. Controlled release drug delivery systems provide one or more of the following advantages

- Maintenance of drug level within the desired range
- Delivery of „difficult" drugs: the slow release of water-soluble drugs, and/orfast release of poorly soluble drugs
- Reduces dosing frequency
- Eliminates over or underdosing
- Prevention or reduction of side effects

2.1 Disadvantages of the controlled drug delivery systems Various disadvantages of the controlled drug delivery systems are mentioned below:

- Unpredictable and often provide poor in-vitro - invivo correlations
- May cause dose dumping, if the release design is failed
- Provides less scope for dosage adjustment
- Effective drug release period is influenced and limited by the gastric residence time Clinical
- The possibility of dose dumping in the case of a poor formulation strategy
- Increased potential for first-pass metabolism

2.2 Selection of Drug Candidates

All the drugs cannot be formulated as their controlled release dosage forms. A drug must have the following characteristics for the formulation of controlled release dosage forms.

- Very short elimination half-life
- Very long elimination half-life
- ✓ Narrow therapeutic index
- ✓ Rate of absorption
- ✓ Mechanism of absorption
- ✓ First pass effect Factor Influencing the Design and Performance of Controlled Drug Delivery System

1. Biopharmaceutic characteristics of the drug

- The molecular weight of the drug
- The aqueous solubility of the drug
- Apparent partition coefficient
- Drug pKa and ionization physiological pH
- Drug stability
- Mechanism and site of absorption
- Route of administration.

2. Pharmacokinetic characteristics of the drug

- Absorption rate
- Elimination half-life
- Rate of metabolism
- Dosage form index

3. Pharmacodynamic characteristic of the drug

- Therapeutic range
- Therapeutic index
- Plasma-concentration-response relationship

The fabrication of the formulation depends on the physicochemical properties of the drug and onthe pharmacokinetic behavior of the drug. In conventional dosage form, the rate-limiting step in drug"s bioavailability is usually absorption through the biomembrane; where as in

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4. Pharmacodynamic characteristic of the drug

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The fabrication of the formulation depends on the physicochemical properties of the drug and onthe pharmacokinetic behavior of the drug. In conventional dosage form, the rate-limiting step in drug‟s bioavailability is usually absorption through the biomembrane; where as in controlled drug delivery system the rate-limiting step is the release of drug from the dosage form.[77]

III. THE CURRENT STATUS OF DRUG DELIVERY TECHNOLOGY

For more than the last 10 years the most popular topic in the drug delivery field has been nanoparticles. This is a result of intensive support from the governmental funding agencies on nanotechnologies since the year 2000 [34]. Significant advances have been made in manipulating properties of nanoparticles that can be administered directly to the blood in a hope to deliver most of the drug to the target site. After all, the success of tumor treatment and gene therapy, among others, depends entirely on the ability of drug delivery systems to reach their intended targets. As listed in Table 1, the majority of the nanotechnology-based research has been focused on targeted drug delivery, such as anticancer drug delivery to tumors and siRNA delivery to target cells, using nanoparticles. Although all nanoparticle drug delivery systems showed improved efficacy over the control in shrinking the tumor size in small animal models, none of the nanoparticle formulations.

As shown in Fig. 3, the ultimate goal of the drug delivery research is to produce clinically useful formulations that can help patients in treating various diseases. Thus, the lack of successful translation to clinical applications by nanoparticle formulations requires careful review of the limitations associated with the current nanoparticle systems. In the drug delivery field, Jörg Kreuter may have been the first to use the term “nanoparticle” in 1976 [79]. In the JCR, Robert Gurny published the first research article using nanoparticulate systems for ocular drug delivery in 1986 [80]. Apparently, the term “nanoparticle” was not new in 2000 when the current nanotechnology revolution began, including the nanoparticle-based drug delivery systems.

Nanoparticles with enormous surface area may be useful for certain applications, such as increasing the dissolution rate of poorly soluble drugs, but other than that, no substantial advantages have been observed. Thus, a question is raised as to whether nanoparticle-based drug delivery systems will achieve truly targeted drug delivery. Numerous nanoparticle systems have been shown to accumulate at the tumor site more than the control non-particulate formulations due to the so-called enhanced permeation and retention (EPR) effect

IV. CONCLUSION

Drug delivery systems (DDS) have revolutionized the way therapeutic agents are administered, enhancing efficacy, safety, and patient compliance. Among all administration routes, the oral route remains the most preferred due to its convenience, non-invasiveness, and industrial scalability. However, advances in drug formulation technologies have enabled more precise delivery through controlled and sustained release systems, each tailored to optimize pharmacokinetic and pharmacodynamic profiles.

The classification of solid and semisolid dosage forms—including tablets, capsules, lozenges, granules, powders, and topical formulations—demonstrates the breadth of delivery options available to suit varying clinical needs and patient populations. Furthermore, innovations in DDS have embraced multidisciplinary approaches, particularly the integration of nanotechnology. Nanocarriers such as liposomes, polymer micelles, and lipid nanoparticles offer targeted delivery, improved bioavailability, and reduced toxicity, even in challenging applications like brain tumor treatment.

Despite significant progress, challenges such as dose dumping, biological barriers, and regulatory complexities persist. Overcoming these bottlenecks requires continued research into intelligent, responsive, and biocompatible drug carriers. The future of DDS lies in personalized medicine, where drug delivery is precisely tailored to the patient's physiological and pathological conditions, maximizing therapeutic outcomes while minimizing side effects.

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