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Multiparticulate Drug Delivery System

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ABSTRACT

Multiparticulate drug delivery systems like pellets, granules, micro particles, minitablets etc., prove to be promising and highly flexible systems with ease of formulating with different drug release kinetics. These multiparticulate dosage forms are essential where drug-excipients or drug-drug physicochemical interactions are possible in a single-unit formulation. In present times, pelletization technologies are gaining much attention as they represent an efficient pathway for manufacture of oral drug delivery systems. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing semi-spherical units. Pellets, being multiparticulate systems, are widely used due to the technological as well as therapeutic advantages over single-unit dosage forms. The present review focus on advantages, disadvantages, formation of pellet growth, different pelletization techniques, characterization, marketed pellets products and also outlines recent developments in the pharmaceutical approaches that have been used to prepare pelletized dosage forms with different techniques like Hot Melt Extrusion-Spheronization, Freeze and Cryopelletization, Microtableting technology.

Introduction

Drug delivery systems play a vital role in optimizing the administration of therapeutic agents within the body. They are engineered to enhance drug efficacy, minimize adverse effects, and ensure a controlled release for sustained therapeutic benefits. Advanced systems enable targeted delivery to specific tissues or organs, reducing harm to healthy cells and improving treatment outcomes. These innovations also prioritize patient convenience through methods like sustained-release formulations and transdermal patches. Moreover, specialized systems are designed to address chronic conditions like diabetes or cancer, tailoring drug delivery to individual needs. Such advancements have revolutionized healthcare, bridging science with enhanced patient care.

Multiparticulate drug delivery systems (MDDS) are advanced pharmaceutical formulations composed of numerous small, discrete units—such as pellets, beads, microspheres, or granules—each containing an active drug. This approach enables controlled, sustained, or targeted drug release, offering advantages over conventional single-unit systems by improving drug distribution, bioavailability, and reducing the risk of dose dumping. The development of MDDS began in the late 20th century, driven by the need for more predictable and flexible oral drug delivery. Over time, advancements in pharmaceutical technology have established MDDS as a key innovation, enhancing therapeutic efficacy and patient compliance.

Drug delivery systems are crucial in advancing therapeutic efficacy by optimizing how medications are absorbed, distributed, and released within the body. These systems enable precise targeting of drugs to specific tissues or cells, enhancing the drug's effectiveness while minimizing off-target effects and adverse reactions. Innovations such as controlled and sustained release formulations ensure that therapeutic concentrations are maintained for extended periods, reducing dosing frequency and improving patient compliance³⁵. By overcoming challenges like poor solubility and rapid metabolism, advanced drug delivery systems significantly improve bioavailability, resulting in more consistent and effective treatment outcomes.

Multiparticulate drug delivery systems offer significant advantages over conventional single-unit dosage forms. By comprising numerous small, discrete units, these systems provide more uniform drug distribution and predictable absorption, reducing variability in therapeutic response. They minimize the risk of dose dumping and local irritation, enhance bioavailability, and allow for controlled or customized drug release profiles. Additionally, multiparticulate systems improve patient compliance, especially in pediatric and geriatric populations, due to easier swallowing and flexible dosing. Their ability to reduce systemic toxicity and provide consistent pharmacokinetics makes them a superior choice for optimizing therapeutic outcomes compared to traditional drug delivery methods.

Types of Multiparticulate Drug Delivery System

Microspheres are small, spherical particles typically ranging from 1 to 1000 micrometers in diameter, composed of natural or synthetic polymers, proteins, or other materials. They serve as multiparticulate drug delivery systems designed to provide controlled, sustained, or targeted release of therapeutic agents, thereby improving drug bioavailability, stability, and minimizing side effects.

Types of Microspheres:

Microspheres can be classified based on their structure and function:

- **Microcapsules:** These have a core containing the drug, surrounded by a distinct capsule wall, allowing for encapsulation and controlled release.
- **Micromatrices:** Here, the drug is uniformly dispersed throughout the polymer matrix of the microsphere, enabling gradual diffusion and release.
- **Bioadhesive Microspheres:** Designed to adhere to mucosal surfaces, enhancing localized drug delivery and retention.
- **Magnetic Microspheres:** Contain magnetic materials, allowing targeted delivery to specific sites using an external magnetic field.
- **Floating Microspheres:** Engineered to remain buoyant in the gastrointestinal tract for prolonged drug release.
- **Radioactive Microspheres:** Used for targeted radiotherapy in cancer treatment.
- **Polymeric/Biodegradable Microspheres:** Made from biodegradable polymers for sustained drug release and reduced toxicity.

Applications:

Microspheres are widely used in:

- **Controlled and Sustained Drug Release:** Ensuring prolonged therapeutic effect and reducing dosing frequency.

- **Targeted Drug Delivery:** Directing drugs to specific organs or tissues, such as in cancer therapy, to maximize efficacy and minimize systemic side effects.
- **Vaccine Delivery:** Providing slow and sustained antigen release for improved immune response.
- **Gene and Monoclonal Antibody Delivery:** Facilitating the transport and release of genetic material or antibodies for advanced therapies.
- **Pediatric and Geriatric Formulations:** Improving compliance through easier administration and tailored release profiles.
- **Other Medical Fields:** Including oncology, radiology, gynecology, cardiology, pulmonology, and diabetes management.

Microspheres thus represent a versatile and effective platform for modern drug delivery, offering multiple advantages over conventional dosage forms in terms of efficacy, safety, and patient compliance.

Pellets are small, free-flowing, spherical particles produced by agglomerating fine powders or granules of drugs and excipients, typically ranging from 0.5 to 2 mm in diameter. Their significance in drug delivery lies in their ability to provide uniform drug distribution, reproducible pharmacokinetics, and flexible dosing options. Pellets facilitate controlled or sustained drug release, minimize the risk of dose dumping, and reduce gastrointestinal irritation. Their multiparticulate nature ensures consistent gastrointestinal transit and absorption, making them especially beneficial for pediatric and geriatric patients. Pelletization technologies have become essential in modern pharmaceutical formulations for their technological and therapeutic advantages over single-unit systems

Beads play a pivotal role in controlled drug release by acting as multiparticulate carriers that encapsulate active pharmaceutical ingredients within a polymer matrix or as coated reservoirs. These systems, such as hydrogel or floating beads, can be engineered to modulate drug release rates through mechanisms like swelling, diffusion, and erosion, enabling sustained or time-dependent delivery. Floating beads, for example, remain buoyant in gastric fluids, prolonging gastric residence time and ensuring gradual drug release, which enhances bioavailability and maintains steady therapeutic level. The ability to tailor release profiles and minimize side effects makes beads highly valuable for advanced oral drug delivery applications.

Nanoparticles :

Innovations in Nanoparticle Drug Deliver

Recent years have witnessed remarkable advancements in the use of nanoparticles for drug delivery. Nanoparticles—engineered at the scale of 1 to 100 nanometers—enable precise targeting of drugs to specific cells or tissues, improving therapeutic efficacy and minimizing systemic side effects. Innovations include the development of core-shell nanoparticles, which encapsulate drugs within a protective shell, shielding them from degradation and allowing for controlled, targeted release. These systems can be tailored using polymers, lipids, or inorganic materials to optimize drug loading, compatibility, and release profiles, advancing both personalized and precision medicine.

Smart nanocarriers represent another major innovation, responding to stimuli such as pH, temperature, or enzymes. For example, pH-sensitive nanoparticles release their payload only in acidic tumor environments, ensuring localized treatment and reducing harm to healthy tissues. Additionally, theranostic nanoparticles combine diagnostic and therapeutic functions, improving cancer treatment precision by enabling real-time monitoring and targeted therapy.

Formulation Techniques :

1. Spray Drying

Spray drying converts liquid feeds (solutions, suspensions, or emulsions) into dry powders through atomization and rapid drying in a hot gas chamber. This method produces spherical particles with controlled size, morphology, and stability, making it ideal for heat-sensitive drugs and amorphous solid dispersions to enhance solubility. It is widely used for creating inhalable powders and improving bioavailability of poorly soluble drugs.

2. Extrusion-Spheronization

This technique involves four steps:

- **Wet granulation:** Mixing drug and excipients with a binder.
 - **Extrusion:** Forcing the wet mass through a die to form cylindrical strands.
 - **Spheronization:** Rolling extrudates on a rotating friction plate to shape them into uniform pellets.
 - **Drying:** Removing moisture to stabilize the pellets.
- Extrusion-spheronization yields dense, spherical pellets with consistent size, suitable for controlled-release formulations.

3. Microencapsulation

Microencapsulation entraps drugs within a polymeric matrix or coat using techniques like:

- **Coacervation:** Phase separation of polymers around drug particles.
- **Spray congealing:** Solidifying atomized droplets via cooling.
- **Solvent evaporation:** Removing solvents from emulsions to form solid microcapsules. This method enables targeted drug delivery, protects sensitive APIs, and allows pulsatile or sustained release.

Key Applications

- **Spray drying:** Amorphous solid dispersions, pulmonary delivery
- **Extrusion-spheronization:** Oral controlled-release pellets.
- **Microencapsulation:** Protecting biologics, taste masking, and targeted therapies

Role of Excipients in Multiparticulate Formulations

Excipients are essential components in multiparticulate drug delivery systems, serving functions far beyond inert fillers. They play a critical role in enhancing the solubility and bioavailability of active pharmaceutical ingredients (APIs), particularly for drugs with poor water solubility. Excipients help stabilize the API, maintain dose uniformity, and support controlled or sustained drug release by modulating the physicochemical properties of the formulation. They also improve the manufacturability of multiparticulate systems by acting as binders, lubricants, and disintegrants, ensuring the formation of uniform pellets, beads, or microspheres. Additionally, excipients can protect the drug from degradation, extend shelf life, and optimize patient compliance by improving taste, appearance, and ease of administration. The careful selection and combination of excipients are crucial for achieving the desired therapeutic outcomes, product stability, and safety in multiparticulate formulations.

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Coating Techniques for Controlled and Sustained Release

1. Film Coating

Mechanism: Applies a thin polymer layer (e.g., hydroxypropyl methylcellulose, ethylcellulose) to tablets or pellets to modulate drug release via diffusion, erosion, or osmosis.

Applications:

- **Sustained release:** Hydrophobic polymers (e.g., ethylcellulose) slow drug diffusion.
 - **Delayed release:** pH-sensitive polymers (e.g., Eudragit®) dissolve in specific gastrointestinal regions.
- Advantages:** Precise control over release kinetics, compatibility with heat-sensitive drugs, and scalability^[5]^[7].

2. Enteric Coating

Mechanism: Uses pH-dependent polymers (e.g., Eudragit L/S) to prevent gastric dissolution, releasing drugs in the intestine.

Applications:

- Protecting acid-labile drugs (e.g., proton pump inhibitors).
- Minimizing gastric irritation (e.g., NSAIDs like diclofenac)[⁴][⁷].

3. Compression Coating

Mechanism: Dry-coating method where excipients are compressed around a core tablet, eliminating solvents.

Applications:

- Encapsulating incompatible drugs.
- Developing delayed or extended-release formulations for moisture/heat-sensitive APIs[⁴].

4. Aqueous Film Coating

Mechanism: Replaces organic solvents with water-based polymer solutions (e.g., HPMC, PVA) for safer processing.

Applications:

- Taste masking and moisture protection.
- Modified-release formulations (e.g., extended-release metformin)[²][⁵].

5. Specialized Techniques

- **Electrostatic Dry Coating:** Uses charged particles for uniform coating without solvents, ideal for sensitive drugs[⁶].
- **Magnetically Aided Impaction Coating:** Enhances coating adhesion for controlled-release pellets[⁶].

Mechanism of Action

Drug release dynamics in multiparticulate systems can be tailored as controlled, sustained, or pulsatile to meet specific therapeutic needs. Controlled release systems are designed to deliver drugs at a predetermined rate, maintaining consistent plasma concentrations and minimizing fluctuations, which enhances efficacy and reduces side effects. Sustained release formulations prolong drug action by gradually releasing the active ingredient over an extended period, reducing dosing frequency and improving patient compliance. Pulsatile release systems, in contrast, deliver drugs in rapid bursts following a defined lag time, often synchronized with circadian rhythms or specific disease states, ensuring drug availability at the optimal time for therapeutic effect.

Drug release from multiparticulate systems is influenced by several key factors, including the type of carrier material used, the amount and distribution of drug within the particles, and the nature of the release-controlling polymers or coatings. Mechanistically, drug release can occur through diffusion, where water penetrates and dissolves the drug, which then diffuses out; erosion, where the coating or matrix gradually breaks down; and osmosis, where water influx generates pressure that pushes the drug out. Additional factors such as particle size, surface area, and environmental pH also play crucial roles in modulating the rate and extent of drug release.

Applications

Oral drug delivery systems are the most preferred method for administering medications due to their convenience, non-invasiveness, and high patient compliance. These systems encompass a wide range of pharmaceutical forms, including tablets, capsules, and liquids, designed for absorption through the gastrointestinal tract. Oral delivery allows for flexible dosing and cost-effective manufacturing, making it suitable for both acute and chronic therapies. Despite challenges such as first-pass metabolism and variable bioavailability, advancements like nanoparticles, liposomes, and controlled-release formulations have significantly improved drug absorption and therapeutic outcomes, ensuring oral drug delivery remains central to modern pharmaceutical practice.

Targeted therapies utilize advanced drug delivery systems to direct therapeutic agents specifically to diseased organs or tissues, significantly improving treatment efficacy while minimizing harm to healthy cells. By employing nanocarriers, ligand-receptor interactions, and stimuli-responsive mechanisms, these systems ensure that drugs accumulate at the intended site, such as tumors or inflamed tissues, and release their payload in a controlled manner. This approach is particularly transformative in cancer, neurological disorders, and infectious diseases, as it enhances drug concentration at the target, reduces systemic side effects, and enables personalized treatment strategies tailored to individual patient profiles, ultimately optimizing therapeutic outcomes.

Pediatric and geriatric formulations are specifically designed to enhance medication compliance in these sensitive populations. For children, age-appropriate dosage forms such as flavored liquids, dissolvable tablets, and sprinkles address challenges like difficulty swallowing and taste aversion, making medicines more acceptable and easier to administer. Similarly, geriatric formulations often feature modified-release profiles, easy-to-handle packaging, and palatable forms to accommodate swallowing difficulties, polypharmacy, and sensory impairments. Both pediatric and geriatric products require precise dosing flexibility, safety, and stability, ensuring effective therapy while minimizing medication errors and adverse effects. These tailored approaches significantly improve adherence and therapeutic outcomes.

Advanced drug delivery technologies have transformed the pharmaceutical landscape by enabling more precise, efficient, and patient-centered therapies. Innovations such as nanotechnology allow for targeted delivery and stimuli-responsive release, ensuring drugs act specifically at diseased sites while minimizing side effects. Smart inhalers and implantable devices provide real-time monitoring and consistent dosing.

for chronic conditions, improving adherence and outcomes 3D printing enables the creation of personalized drug formulations and complex delivery structures tailored to individual patient needs These advanced systems enhance therapeutic efficacy, reduce frequency, and support the development of personalized medicine, marking a significant leap forward in clinical care

Advantages and Limitations

Advanced drug delivery systems offer significant benefits, including precise dosing, improved bioavailability, and minimized side effects. By enabling targeted delivery, these systems ensure that drugs reach specific tissues or cells, enhancing therapeutic efficacy while reducing exposure to healthy areas and thus lowering the risk of adverse reactions. Controlled and sustained release formulations maintain consistent drug levels in the body, further improving bioavailability and reducing dosing frequency. The combination of accurate dosing and site-specific action not only optimizes treatment outcomes but also enhances patient compliance and safety, marking a substantial advancement over traditional drug delivery methods

Multiparticulate drug delivery systems face significant challenges, including complex manufacturing processes that demand precise control over particle size, uniformity, and coating integrity, often requiring advanced equipment and expertise. Cost concerns arise from high raw material expenses, energy-intensive production methods, and stringent quality control measures, which can limit accessibility. Stability issues, such as drug degradation, moisture sensitivity, and unpredictable release profiles under varying physiological conditions, further complicate formulation development. These hurdles necessitate ongoing innovation in scalable production techniques and excipient optimization to ensure consistent performance, regulatory compliance, and cost-effectiveness, while maintaining therapeutic reliability and patient safety.

Recent advantage

The integration of nanotechnology into multiparticulate drug delivery systems has enabled the creation of highly functional, customizable platforms for advanced therapeutics. By incorporating nanoparticles with tailored chemical and physical properties, these systems can achieve enhanced drug loading, targeted delivery, and controlled release profiles. Modular and integrated synthesis approaches allow for the precise assembly of nanoparticles within multiparticulate matrices, optimizing their performance for specific applications. Additionally, combining nanoparticles with different functionalities—such as

magnetic, optical, or catalytic properties—enables the development of multifunctional materials that can address complex therapeutic needs and improve overall treatment efficacy

The development of innovative drug delivery mechanisms has transformed modern therapeutics by enabling precise, targeted, and patient-friendly treatments. Advances such as nanoparticles, liposomes, and polymeric micelles allow for enhanced solubility, protection from degradation, and site-specific drug release, significantly improving therapeutic efficacy and minimizing side effects. Other breakthroughs include transdermal patches and microneedle technologies, which offer non-invasive, controlled drug administration and improved patient compliance. Stimuli-responsive systems, implantable devices, and smart technologies further enable personalized dosing and real-time monitoring, ensuring optimal drug concentrations and better treatment outcomes. Collectively, these innovations are reshaping healthcare delivery and patient experiences

Success stories in research and clinical applications of advanced drug delivery systems, particularly those utilizing nanotechnology, are reshaping modern medicine. Notable achievements include the development of nanoparticles capable of transporting peptides across the blood-brain barrier, enabling new treatments for neurological conditions. For example, the enkephalin pain medicine candidate NES100, delivered via peptide nanoparticles, has shown promise in addressing the opioid crisis and has won multiple innovation awards. Clinically, nanotechnology-based formulations like PEGylated liposomal doxorubicin (Doxil) and albumin-bound paclitaxel (Abraxane) have improved cancer therapy by increasing efficacy and reducing side effects. These advances highlight the transformative impact of nanomedicine

Challenges and Opportunities

Manufacturing scale-up in drug delivery systems faces significant hurdles, including translating laboratory processes to large-scale production, where minor variations in temperature, mixing, or raw materials can lead to inconsistencies and quality issues. Ensuring reproducibility and optimizing processes are essential, as differences in equipment and process dynamics often impact product yield and performance. Regulatory challenges further complicate scale-up, as manufacturers must demonstrate equivalence between lab-scale and commercial operations and comply with stringent Good Manufacturing Practices (GMP) to secure approval from agencies like the FDA and EMA. Effective collaboration, early scalability planning, and robust supply chain management are critical to overcoming these obstacles.

Innovative drug delivery systems significantly enhance patient compliance by simplifying medication regimens, reducing dosing frequency, and offering patient-friendly administration routes such as oral controlled-release tablets, transdermal patches, and implantable devices. These advances address common barriers to adherence, including complex schedules and side effects, making it easier for patients to follow prescribed therapies and achieve better health outcomes. The integration of smart technologies, such as wearable sensors and real-time monitoring devices, further supports adherence by enabling personalized dosing and remote communication with healthcare providers. However, for widespread market feasibility, these systems must also overcome regulatory, scalability, and cost-effectiveness challenges.

Future research in drug delivery is focused on developing highly targeted, intelligent, and patient-centric systems that maximize therapeutic efficacy while minimizing side effects. Innovations include the use of nanomaterials and multifunctional carriers for precise targeting, stimuli-responsive release, and enhanced permeability, particularly in challenging areas like cancer and neurological disorders. Advances in smart polymers, hydrogels, and biodegradable nanoparticles are enabling self-regulating, long-term depot formulations and gene delivery platforms. Integration of digital health tools, automation, and personalized medicine approaches will further refine dosing and monitoring. Overcoming biological barriers, improving selectivity, and ensuring scalability remain key priorities for future breakthroughs.

Conclusion

Multiparticulate drug delivery systems are significant advancements in pharmaceutical science, offering formulations composed of numerous small particles that enable precise control over drug release profiles and reduce the risk of dose dumping. By distributing the drug across multiple discrete units—such as microspheres, pellets, or granules—these systems enhance drug absorption, provide sustained or controlled release, and minimize local irritation within the gastrointestinal tract. Their flexibility allows

for tailored therapies, improved bioavailability, and better patient compliance, especially in populations with swallowing difficulties. Overall, multiparticulate systems represent a cornerstone in modern drug delivery, supporting safer, more effective, and patient-friendly treatments

Multiparticulate drug delivery systems have played a transformative role in revolutionizing pharmaceutical practice by offering more effective, precise, and patient-friendly treatment options. By breaking down medications into numerous tiny particles, these systems enable gradual and steady drug release, improving therapeutic outcomes, extending shelf life, and reducing adverse effects. Their flexibility supports combination therapies and tailored dosing, enhancing treatment for diverse patient populations, including those with swallowing difficulties. As a cornerstone of modern pharmaceutical development, multiparticulate systems have set new standards for controlled, targeted, and reliable drug delivery, paving the way for ongoing innovation and improved patient care in the industry

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