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NANO-PHOTOCRYSTAL DRUG DELIVERY OF NATURAL PRODUCT

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ABSTRACT
Nanotechnology-based drug delivery systems address key limitations of traditional drug administration by enhancing drug solubility, stability, bioavailability, and enabling targeted delivery. Nanoparticles improve therapeutic outcomes while reducing systemic toxicity, making them especially valuable in treating cancer and chronic diseases. A key challenge remains the effective delivery of poorly water-soluble drugs, which these systems aim to overcome through innovative formulations and carrier designs. For example, the development of albumin-bound paclitaxel nanoparticles significantly improved the safety profile and therapeutic performance of paclitaxel by enhancing solubility and reducing toxicity. Similarly, nanoparticle encapsulation of natural compounds such as ginkgo biloba extract has demonstrated improved stability, prolonged drug release, and enhanced tissue distribution. Despite these advancements, several challenges remain, including nanoparticle toxicity, physicochemical instability, large-scale manufacturing difficulties, immunogenicity, and complex regulatory requirements, which limit their widespread clinical application. The future of nanoparticle-based dds is highly promising, with potential applications in antitumor therapy, gene therapy, radiotherapy, vaccine delivery, protein delivery, and the treatment of chronic illness. Emerging technologies such as multifunctional nanoparticles, theragnostic systems, and near-infrared-ii responsive nanocarriers offer opportunities for simultaneous diagnosis, targeted therapy, and real-time monitoring of treatment outcomes. Furthermore, advances in photodynamic and photothermal therapies have expanded the role of nanoparticles in cancer treatment. Continued research focusing on biocompatibility, biodegradability, eco-friendly synthesis, and scalable manufacturing processes will be necessary for successful clinical translation and global accessibility. All things considered, drug delivery systems based on nanoparticles offer a revolutionary platform for the creation of safer, more efficient, and individualized treatment approaches.

KEYWORDS: Nanotechnology, drug delivery systems, nanoparticles, targeted drug delivery, cancer therapy, personalized medicine.

INTRODUCTION

Natural products have played an essential role throughout human evolution and have been widely used in various fields, ranging from ancient applications such as paper-making to modern to uses in perfumes, spices, and the prevention and treatment of numerous diseases.[1] With advancements in separation techniques and pharmacological evaluation methods, an increasing number of biologically active compounds have been identified from natural sources. Despite their significant therapeutic potential, the clinical effectiveness of many natural products has remained limited. Most pharmaceutical industries are hesitant to invest in their development because of challenges such as poor water solubility, limited biological distribution, rapid metabolic clearance, and low bioavailability. In addition, compound with high molecular weight and low lipophilicity often show poor permeability across biological membranes, resulting in inefficient drug transport and short half-lives[1] to overcome these limitations, novel drug delivery system has been developed. Among these, liposomes have emerged as promising drug carriers because of their low toxicity, high biocompatibility, and low immunogenicity. Liposomes are capable of encapsulating both hydrophilic and lipophilic drugs, thereby improving drug stability, absorption, and therapeutic efficiency.[2] Currently, the development of advanced drug delivery strategies to maximize the therapeutic efficacy of natural product is major focus of scientific research. These innovations are expected to lead to the development of safer and more effective drugs with reduced side effects in the future.[1]

Selection of natural products

❖ Alkaloids

Alkaloids are nitrogen-containing organic compound derived mainly from amino acids and isolated from plants. They isolated from plants. They are classified into groups such as is quinoline, quinoline, indole, and pyridine alkaloids. Alkaloids exhibit several pharmacological activities including anticancer, antiviral, antibacterial and anti-inflammatory effects. Drugs such as paclitaxel, calprotectin, and berberine are widely used clinically.[3]

However, many alkaloids show poor pharmacokinetic properties, low solubility, instability in biological media, and aggregation, which limit cellular uptake and therapeutic efficacy. Nano-drug delivery system help overcome these problems by improving stability, permeability, and retention of alkaloid drugs. Functionalized protein and polymer-based nanoparticles are commonly used to encapsulate hydrophobic alkaloids and enhance controlled drug release.[4]

❖ Flavonoids

Flavonoids possess a c6-c3-c6 backbone structure and are known for antioxidant anticancer, anti-inflammatory, cardioprotective, and neuroprotective activities. They have potential roles in preventing cardiovascular diseases, Alzheimer's diseases, and breast cancer. Despite their therapeutic benefits, flavonoids suffer from poor solubility, low gastrointestinal absorption, rapid metabolism, and instability. Nano-carrier systems have been developed to improve their pharmacokinetics and bioavailability. Gambogic acid, a flavonoid-based anticancer drug, shows strong activity against colon, pancreatic, and breast cancers but has poor solubility and dose-dependent toxicity. To improve its delivery, hyaluronic acid-coated chitosan nanoparticles were developed for tumour-specific intracellular delivery, enhancing bioavailability and therapeutic efficacy.[5]

❖ Polyphenols

Polyphenols are natural compounds containing multiple hydroxyl groups with strong antioxidant and anti-inflammatory properties. They show anticancer, hepatoprotective, and anti-obesity activities. However, polyphenols are unstable under light, heat, and alkaline conditions and usually have poor solubility and low bioavailability. Non-drug delivery system has been developed to improve the stability and absorption of polyphenols such as resveratrol and curcumin. Resveratrol, found in grapes and peanuts, protects blood vessels and DNA from oxidative damage. Transferrin-modified peg liposomes have been used for targeted res delivery in glioblastoma therapy, resulting in enhanced stability, controlled release, and improved cancer cell targeting.[6]

❖ Terpenoids

Terpenoids are compounds composed of c5h8 units and possess antitumor, anti-inflammatory, antimicrobial, antiviral, and cardiovascular protective activities. Triptolide, derived from *tripterygium wilfordii* is a diterpenoid with anticancer, analgesic, and immunomodulatory properties. Although tp has significant therapeutic potential, its clinical use is limited by toxicity and poor delivery characteristics. To address these issues, glycosylated chitosan-triptolide nanoparticles were developed for targeted hepatocellular carcinoma treatment. These nanoparticles showed sustained drug release, enhanced tumour accumulation, and reduced systemic toxicity compared with free tp administration.[7]

Category	Representative compound	Type of nanocrystalline formulation	Preparation related technologies	Main pharmacological result
Alkaloids	Camptothecin	Hyaluronic acid coated camptothecin nanocrystals	Solvent-antisolvent precipitation	High drug loading efficiency, improved aqueous dispersion extend cycling and enhanced stability.
	Coumarin 6	Coumarin 6 nanocrystals	Solvent-antisolvent precipitation	Improved oral bioavaibility by enhancing the drug ability of insoluble drugs and increasing the solubility of poorly water-soluble drugs
Flavonoids	Quercetin	Quercetin Nanocrystals in nano suspension	Microfluidic technology	Significant improvement in dissolution properties and oral bioavaibility
	Puerarin	Oral delivery of puerarin nano crystals	High pressure homogenization	Improve drug dissolution in gastrointestinal tract and enhance bioavailability
Polyphenol	Resveratrol	Resveratrol nanocrystal based dissolving microneedles	Wet media milling	Improved therapeutic outcomes in rheumatoid arthritis by improving the shortcomings of long-term oral drug delivery
	Genistein	Transferrin-modified genistein nanocrystals	Wet media milling	5.8-fold increase solubility and significant enhancement of dissolution kinetics.
Terpenoids	Oridonin	Oridonin nanocrystals	Solvent-antisolvent precipitation	Increased dissolution rate and transmembrane volume
	Parthenolide	Parthenolide nanocrystals	Nano edge technology	Improved poor water solubility of ptl

Synthesis methods

Nanocrystal preparation technology converts poorly soluble drugs into nanosized crystals to improve drug delivery. These methods are classified into three main categories: top-down, bottom -up, and combination approaches.[8]

1. Top- down approach

The top-down method reduces the size of active pharmaceutical ingredients to the nanoscale using mechanical forces. The two major techniques are wet media milling (wmm)and high-pressure homogenization. In wmm drug particles are dispersed in a liquid medium with grinding beads. Mechanical actions such as collision, rotation, and shear break coarse particles into nanocrystals. Important factors influencing particle size include milling time, rotation speed, bead volume, and drug loading. Studies using dual asymmetric centrifugal (dac) mixers showed higher milling efficiency than conventional wet milling while maintaining drug crystallinity. In hph, a drug suspension is forced through a narrow gap under high pressure. Cavitation, impact, and shear forces reduce particle size to the nanoscale. Hph includes micro fluidization and piston-gap homogenization techniques. Although hph may produce slightly larger particles than wet milling, it generates fewer impurities and offers better product purity.[9]

2. Bottom-up methods

Bottom-up methods produce nanocrystals through precipitation from a supersaturated drug solution. Supersaturation can be achieved by solvent evaporation, cooling, or adding a counter-solvent. Common techniques include solvent–anti-solvent precipitation, supercritical fluid methods, solvent evaporation, and freeze-drying. Among these, solvent–anti-solvent precipitation is the simplest and most economical. A counter-solvent that does not dissolve the drug is mixed

with the drug solution, creating supersaturation and causing nucleation and nanocrystal formation. External factors such as ultrasound, microfluidics, evaporation, and high gravity can further reduce particle size. However, this method faces challenges such as controlling nucleation, selecting suitable stabilizers, and managing solvent residues, limiting industrial application.

Supercritical fluid methods overcome many of these limitations. Scfs act as solvents or anti-solvents under high pressure and rapidly vaporize after depressurization, leaving minimal solvent residue and producing highly pure nanocrystals. Techniques such as ress, resolve, and sas are suitable for heat-sensitive drugs.[10] Freeze-drying and spray drying remove solvents physically, leading to crystallization through supersaturation. Proper selection of solvent, stabilizers, and drying protectants is essential to prevent agglomeration, solvent residue, or crystal transformation.

3. Combination of bottom -up and top -down approaches

Combined techniques first produce coarse crystals using bottom-up methods and then reduce and standardize particle size using top-down processes. This approach produces nanocrystals with smaller and more uniform particle sizes. Baxter's nano edge technology, introduced in 2003, was the first combined nanocrystal technology. It uses precipitation followed by hph to improve particle uniformity and stability. Similar systems include h69, where precipitation occurs inside the homogenizer, and other combinations such as freeze-drying + hph, spray drying + hph, and media milling + hph. Other representative technologies include plh and art crystals. These synergistic systems can produce very small nanocrystals. For example, clonidine nanocrystals prepared using antisolvent precipitation, rotary evaporation, and hph achieved particle sizes of 140–180 nm with good stability and drug loading. Despite their advantages, combined methods are less common in industrial production because they increase processing time, energy consumption, equipment wear, and overall manufacturing costs.[8]

Mechanism of action

Nanoparticle-based drug delivery systems (dds) are intended to carry medications specifically to target sites without altering the therapeutic activity of the drug.[11] Drugs are attached to nanoparticles through encapsulation, non-covalent interactions, or covalent conjugation with polymers. The size and molecular weight of the polymer-drug conjugate influence drug solubility, permeability, and hydrophobicity. Drug loading capacity depends on matrix density and can be improved by reducing drug solubility and increasing ionic interactions between the polymer matrix and the drug. Drug-polymer linkers are usually ph.-sensitive or enzyme-sensitive, enabling controlled drug release.[12] To avoid rapid removal by immune cells, np surfaces are coated with biodegradable and hydrophilic polymers such as poly-glycolic acid, poly-lactic acid, and polyethylene glycol (peg). Pegylation improves circulation time, reduces toxicity, and prevents serum protein adsorption. Ligands such as antibodies, peptides, carbohydrates, proteins and nucleic acids are also attached to np surfaces for targeted drug delivery.[13] Nanoparticles can enter the body through oral, intravenous, transdermal, inhalation, or arterial routes. After administration, drug-np conjugates circulate through the bloodstream and deliver drugs to specific tissue or cells. Unlike conventional dds, nanoparticle-based dds reduce side effects and increase therapeutic efficacy by precisely targeting diseased cells.

Types of targeting

1. Passive targeting

Passive targeting takes place due to the enhanced permeability and retention phenomenon. Tumour blood vessels contain large pores that allow nanoparticles to gather more easily in tumour tissues than in normal tissues. Drug release occurs gradually through diffusion from the nanoparticle matrix.[14]

2. Active targeting

Active targeting uses ligands, antibodies, or aptamers attached to np surfaces that specifically bind to receptors highly expressed on target cells. Nanoparticles enter cells through receptor-mediated endocytosis, forming endosomes and lysosomes where the drug is released in response to acidic ph or enzymatic degradation.[15]

Controlled drug release

Controlled release of drugs from nanoparticles can occur through:

1. Biodegradation of polymeric materials
2. Modification of pore size in the polymer matrix
3. Alteration of nanoparticle size and surface area

Smaller nanoparticles have larger surface areas, leading to faster drug dissolution and release. Drug release mechanisms mainly include diffusion, swelling, erosion, and polymer degradation. Nano-fluidic systems can further regulate constant and site-specific drug release.[12]

Physicochemical characterisation

Nanoparticles are characterized mainly by their size, shape, surface charge, hydrophobicity, drug release, and drug entrapment efficiency. Analysis frequently uses sophisticated methods including dynamic light scattering (dls), atomic force microscopy, transmission electron microscopy (tem), and scanning electron microscopy (sem).[16]

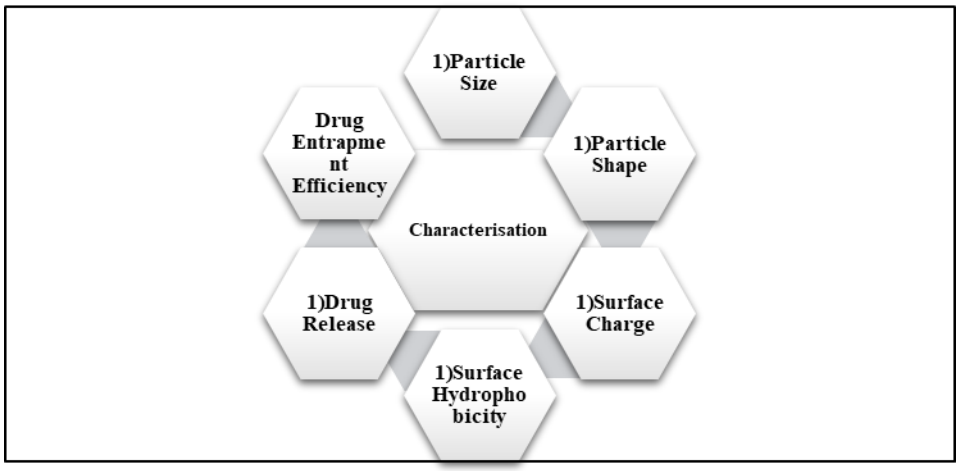

Fig. No. 1: physicochemical characterisation.

1) Particle size

Particle size, distribution, and morphology are important parameters in nanoparticle characterization because they influence drug release, degradation, and toxicity. Smaller particles provide a larger surface area, which can enhance drug release and polymer degradation. Techniques such as, tem, and sem are widely used to measure nanoparticle size and morphology.[20]

2) Particle shape

Sem is commonly used to study nanoparticle shape and surface morphology. Before analysis, nanosuspensions are usually lyophilized into solid particles and coated with platinum alloy using a sputter coater.[19]

3) Surface charge

Surface charge affects nanoparticles stability and interaction with biological systems. It is measured using zeta potential analysis, which provides information about colloidal stability. High positive or negative zeta potential values helps prevent particle aggregation and improve storage stability.[20]

4) Surface hydrophobicity

Methods including hydrophobic interaction chromatogra phy, biphasic partitioning, adsorption techniques, and co ntact angle measurements can be used to assess surface h ydrophobicity.

Chemical groups on the surfaces of nanoparticles can als o be identified using x-
ray photon correlation spectroscopy.[16]

5) Drug release

Drug release studies are important to understand how drugs are delivered from nanoparticles. Drug loading is generally expressed as the amount of drug bound per unit mass of polymer. Common in vitro drug release methods include:

1. Side-by-side diffusion cell
2. Dialysis bag diffusion techniques
3. Reverse dialysis sac techniques
4. Ultracentrifugation
5. Ultrafiltration technique.[17]

6) Drug entrapment efficiency

The amount of medication successfully integrated into nanoparticles is indicated by entrapment efficiency. Nanoparticles are separated by ultracentrifugation, and unentrapped drug is removed using phosphate buffer saline.

This parameter is important for evaluating nanoparticle formulation efficiency and drug-loading capacity.[18]

Challenges

One major challenge in nanotechnology-based dds is improving the safety and bioavailability of poorly soluble drugs. Paclitaxel (Taxol), a potent anticancer drug, originally required cremophor for solubility enhancement, but this formulation caused severe toxicity. To overcome this limitation, albumin-bound paclitaxel nanoparticles (Abraxane) were developed and approved by the. This nanoparticle formulation showed improved solubility, reduced toxicity, and better tissue distribution for the treatment of breast, lung, and pancreatic cancers.[21] Another challenge involves improving the bioavailability of natural compounds such as *ginkgo biloba* extract (gbe), which has low oral bioavailability and short half-life. Encapsulation of gbe into neosomal nanoparticles improved drug stability, prolonged release, and enhanced tissue distribution in organs such as the brain, heart, lungs, and kidneys.[22] Despite significant progress, challenges such as toxicity, stability, large-scale manufacturing, immune responses, and regulatory approval still limit the widespread clinical application of nanoparticle-based therapies.

Future perspective

Nanoparticle-based drug delivery systems (dds) have significant future potential in antitumor therapy, gene therapy, radiotherapy, vaccine delivery, protein delivery, and treatment of chronic disease such as hiv and cancer.[23] Multifunctional nanoparticles may simultaneously detect diseased cells, deliver multiple drugs, provide imaging, and monitor therapy with

minimal side effects. Recent advances in nanoparticle-based phototherapy, including photodynamic therapy (pdt) and photothermal therapy (ptt), have shown promise for cancer treatment. Researchers are focusing on molecular targets such as hypoxia-inducible factors and mitochondrial pathways to improve therapeutic efficacy under hypoxic tumor conditions.[24] Development of theragnostic nanoparticles that combine diagnosis and treatment may enable personalized and real-time monitoring of therapy. Near-infrared-ii (nir-ii) responsive nanoparticles are another emerging area because they allow deeper tissue penetration and improved targeting. Future progress in biocompatibility, biodegradability, eco-friendly synthesis, and cost-effective large-scale production will be essential for clinical translation and global accessibility of nanoparticle therapies.[25]

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