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IBUPROFEN-LOADED CORE-SHELL NANOPARTICLES FOR OSTEOARTHRITIS: A REVIEW

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ABSTRACT

Core-shell nanoparticles present a revolutionary approach in local nanomedicine, featuring highly adjustable physicochemical structures. The advanced bimodal nanoparticles contain a specifically designed hydrophobic core for the encapsulation and molecular stabilization of the therapeutics, which is then covered by a customized biodegradable polymer shell responsible for the precise and controlled release kinetics. This review paper explores the synthesis methods, advanced characterization techniques, and stimuli-responsive mechanisms of coreshell nanoparticles, highlighting the unique ability of these nanoparticles to penetrate extracellular matrix selectively. We further explore the application of these advanced nanoparticles in the treatment of osteoarthritis, which is a degenerative chronic disease affecting the whole joint. Traditionally, osteoarthritis has been treated using oral ibuprofen, a non-steroidal anti-inflammatory drug that is limited by its extremely short plasma half-life and toxicity to gastrointestinal and renal system. Using ibuprofen-loaded core-shell nanoparticles to deliver the drug directly into the synovial cavity would maintain the optimal concentration of the drug and eliminate its side-effects.

KEYWORDS: Osteoarthritis; Core-shell Nanoparticles; Ibuprofen; Localized Drug Delivery; Articular Cartilage Targeting; Sustained Release Kinetics.

INTRODUCTION

Osteoarthritis (OA) is one of the most common, long-term, painful diseases that affect the entire joint. It represents a substantial socioeconomic and medical burden globally.[1] Pathogenesis of this disease involves the gradual destruction of articular cartilage, local inflammation of the synovial membrane, and subsequent changes in subchondral bone.[1] In order to deal with pain and inflammatory symptoms caused by this disease, nonsteroidal anti-inflammatory drugs (NSAID), including ibuprofen, are administered systemically and intra-articularly.[2] Nevertheless, intravenous and intramuscular administration of ibuprofen is extremely difficult due to the rapid pharmacokinetics and very short biological half-life of this drug.[1] Thus, to achieve a therapeutically significant concentration of ibuprofen in poorly vascularized joint cavity, high doses and frequently administration of this drug are required.[3] resulting in the increased toxicity of the treatment regimen for the gastrointestinal, renal, and cardiovascular systems.

In order to solve these problems, nanoscale drug delivery systems (DDS) such as core-shell nanoparticles are highly promising for targeted therapy.[4] Core-shell nanoparticles represent complex, multi-layer structures consisting of distinct core and outer covering shell, which can be constructed using biocompatible and biodegradable materials like poly (lactic-co-glycolic acid) (PLGA) and meso-silica layers.[4,5] In this two-phase system, the hydrophobic core of the particle serves as the drug carrier of ibuprofen, whereas the outer shell controls the release rate of the drug and prevents its degradation.[4]

Thanks to the recent development of bio-responsive nanotechnology, the core-shell nanoparticles have become increasingly better at engaging with the microenvironment in the joint that is affected by disease.[1] The incorporation of the polymeric shell with an ability to respond to certain internal triggers like the acidic environment of the inflamed joint allows the delivery of ibuprofen with sustained control directly to the area where cartilage damage occurs.[2] Thus, ibuprofen remains confined to the target tissue, completely avoiding any unwanted exposure of healthy tissues, which means there is no risk of adverse effects and a possibility to block the inflammatory cascade leading to OA.[3] This review provides a detailed analysis of ibuprofen-loaded core-shell nanoparticles synthesis, structure, and potential therapeutic applications.

Disease profile: Osteoarthritis (OA) is a progressive and chronic whole-joint disease that is marked by degradation of articular cartilage, subchondral bone remodeling and synovial inflammation. Initially regarded only as "wear and tear" condition, OA is nowadays considered as a complex disease, caused by biomechanical, metabolic factors and cellular senescence.[9]

Pathophysiology of osteoarthritis

The disease represents a joint homeostasis imbalance and dominance of catabolic processes over anabolic ones. Major structural abnormalities include:

- Cartilage degradation: Loss of proteoglycans and collagen with consequent cartilage fibrillation, fissuring and complete cartilage loss.[11]
- Bone remodeling: Development of marginal osteophytes and subchondral bone sclerosis accompanied by changes in subchondral bone reactivity and development of subchondral bone disease.[12]
- Synovial inflammation: Mild to moderate synovitis causing pain and further disease progression.[9]
- Muscle atrophy: Weakness and atrophy of extensor muscle group around the knee is common.[12]
- Soft tissue abnormalities: Ligament laxity/contraction and capsular contracture.[12]

Clinical features: Pain is characteristic mechanical pain – exacerbation with activity and relief with rest.[11]

- Stiffness: The so-called "gel phenomenon" is associated with stiffness after period of inactivity, usually lasting less than 30 minutes in the morning.[12]
- Physical findings: Joint crepitus, bony enlargement (e.g., Heberden's nodes in fingers), joint restriction.[11]

Risk factors:

- Age and gender: The prevalence becomes much more prevalent after the age 50; women have increased risk of OA in comparison with men.[10]
- Obesity: Increased lifetime risk of symptomatic knee OA due to mechanical loading and systemic inflammatory adipokines reaches 60.5%.[11]
- Metabolic disorders: The development of diseases such as diabetes and thyroid dysfunction can increase inflammatory processes and promote rapid degradation.[11]
- Trauma: Previous joint injuries (post-traumatic OA) greatly accelerate the onset of disease.[9]

Current Treatment strategies

Non-pharmacologic treatments: The non-pharmacologic treatments are universally recommended as basic treatment for all patients.[12] including.

Education and self-management: Understanding of pathophysiology and need for lifestyle change is a cornerstone of treatment.[12]

Exercise therapy: Aerobic, resistance and neuromuscular exercise therapy are the first line strategies for improvement of pain and function.[12]

Manual and physical therapy: Short-term pain relief and facilitation of joint range of motion provided by therapies such as manual therapy (tuina), acupuncture and thermotherapy.[12]

Pharmacologic treatments[11,31]

NSAIDs: Oral non-steroidal anti-inflammatory drugs (NSAIDs) such as acetaminophen (paracetamol), ibuprofen, diclofenac and COX-2 inhibitors (celecoxib). Topical diclofenac is recommended as the first-line pharmacological treatment because of comparable analgesic effect with substantially reduced risks of side effects, including systemic gastrointestinal and cardiovascular side effects.

Intra-articular therapies: The direct joint injections are targeted to localize pain and inflammation. Effective short-term treatment for flare-ups or joint effusion is represented by corticosteroids. Hyaluronic acid promotes joint lubrication. Regenerative biologics such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are studied for regenerative purposes via growth factor mediated inflammation modulation.

DRUG PROFILE

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of variety of conditions including inflammatory disorders, rheumatoid disorders, mild to moderate pain, fever, dysmenorrhea, and osteoarthritis.[6]

MECHANISM OF ACTION[6]

The ibuprofen acts by selective inhibition of cyclooxygenase (COX). Which is an enzyme responsible for prostaglandin (mediators of pain and fever) and thromboxane (stimulators of blood clotting) synthesis by arachidonic acid pathway.[31]

The arachidonic acid pathway

The ibuprofen inhibits both COX-1 and COX-2 isoforms. COX-1 is found in most tissues constantly, responsible for gastric mucosa protection and platelet aggregation. COX-2 is produced under inflammation and mediates pro-inflammatory prostaglandins synthesis. Inhibition of these enzymes prevents the transformation of arachidonic acid to prostaglandins (PGE2 and others) and thromboxanes.

Clinical effects

Analgesia: Reduced level of prostaglandins prevents sensitization of nociceptors.

Antipyretic: Central effect that leads to decrease of body temperature set-point via hypothalamus by inhibiting PGE2.

Anti-inflammatory: COX-2 inhibition results in decreased vasodilation and edema formation at sites of injury.

PHARMACOKINETICS (ADME)[6,8]

The ibuprofen demonstrates the typical pharmacokinetics characterized by rapid absorption and short half-life.

Absorption: It is extremely absorbed by oral and the peak serum concentration can be obtained within 1-2 hours after extravascular administered. In the case of oral administration, the absorption of ibuprofen in adults is very fast in the upper GI tract.[31]

Bioavailability: High, approximately 80–100% after oral administration. Tmax: Reaches 1-2 hours after oral ingestion of standard tablets.

Food effect: Slightly delays Tmax but does not affect absorption (AUC). Distribution:

Protein binding: High, ~99% to albumin. More than 99% is bound to plasma proteins and site.

II of purified albumin. Binding appears to be saturable and becomes non-linear at concentrations exceeding 20 mcg/ml.[31]

Volume distribution (Vd): Low (~0.1 L/kg); mostly restricted to plasma, although enters synovial fluid, thus making it useful for joint pain.

Metabolism

Site: Ibuprofen is metabolized Mostly in the liver. The major metabolites are hydroxylated and carboxylated derivatives.

Pathways: Oxidation is contributed by the cytochrome P450 enzymes (CYP2C9 and CYP2C8) to inactive metabolites:

- (+)2-hydroxy ibuprofen
- (+)3-carboxy ibuprofen

In addition to oxidation, it is subject to glucuronidation.

Excretion Route: Route: Primarily renal (~95%), mostly metabolized or conjugated, less than 10% in unchanged form. It gets entirely excreted within 24 hours of the last dose, and almost all of the drug is metabolized and represents ~99% of the amount of the drug excreted. Excretion by the biliary route of the unchanged drug and its phase II active metabolites represents 1% of the amount of the drug administered.[31]

Half-life (t1/2): Half-life of ibuprofen is short; it is ~1.8-2 hours. Impaired hepatic function may lead to prolonged half-life, ~3.1-3.4 hours.[31]

Clearance: It depends on various factors such as route of administration, enantiomer and dosage types. It varies between 3-13 L/hr.

PHARMACODYNAMICS[6,7]

Analgesic & antipyretic (low dosage): Low dosages ranging from 200-400 mg result in the inhibition of prostaglandins synthesis (PGE2) within the central nervous system and peripheral inhibition, resulting in analgesia and antipyretic effects.

The prostanoids are primary mediators of pyresis in hypothalamus preoptic area. In dental procedures, it is used due to the local inhibitory action on prostanoids and anti edematous action and increased levels of plasma beta-endorphins.[31]

Anti-inflammatory (high dosage): The high level of anti-inflammatory action is obtained by using higher dosages ranging from 1200-3200 mg per day through the mechanism of COX-2 inhibition. prevent leukocyte migration and lysosomal enzyme release.

Antiplatelet effect: Ibuprofen exhibits a mild, temporary effect on platelet aggregation via its action against platelet COX-1 that results in decreased synthesis of thromboxane A2.

On the other hand, in the research work conducted on ibuprofen, it has been shown to reduce neurodegeneration in small doses of the drug. Another use of ibuprofen in Parkinson's disease is the importance of inflammation and oxidative stress in the pathology. The research shows 50% reduction in breast cancer.[31]

Use of ibuprofen in osteoarthritis

Ibuprofen is widely used as the first-line therapy for inflammatory pain relief and improvement of physical function in knee or hip OA.[17] Evidence from the IPSO study suggests that ibuprofen has superior analgesic properties in comparison with other common analgesics. Single doses of 400 mg and daily regimen of 1200 mg are significantly better analgesics in comparison with paracetamol (single dose of 1000 mg or 3000 mg/day) in 14-day period.[14] It results in considerable improvements of joint stiffness, physical function and functional

disability as measured by the Western Ontario and McMaster Universities Osteoarthritis Index.[14] In one study, daily dose of 1200 mg ibuprofen had similar effectiveness in reducing OA pain and improving physical function as 1500 mg/day of Curcuma domestica extracts.[16] Conventional ibuprofen has short half-life (~2 hours), which requires 3–4 doses a day. Sustained-release (SR) preparation allows taking of one daily dose (1600 mg), effectively treating both daytime and nighttime pain with high patient compliance (98.6%).[15] Analgesic effect can be seen in 1 week; while full anti-inflammatory effect takes up to 3 weeks of continuous treatment.[17] Specialists recommend to use the smallest possible dose for the shortest period of time to minimize risks.[17]

Safety and side effects

Ibuprofen usage in OA requires careful control, especially in case of comorbidities and in older adults, as ibuprofen poses an increased risk of gastro-intestinal (GI) complications, which manifest as nausea, dyspepsia, abdominal pain and gastritis.[15] Although having smaller risk of gastroduodenal bleeding in comparison with some other NSAIDs (e.g., piroxicam), ibuprofen still is more gastrotoxic than paracetamol or Curcuma extracts.[14] As in other NSAIDs, there are cardiovascular risks including increased risk of major vascular events.

Noteworthy is the fact that ibuprofen inhibits the cardioprotective effects of aspirin by inhibition of platelet function.[17] Ibuprofen increases the risk of hypertension in some patients with arthritic disorders. There are also the risks associated with kidneys, especially in older people and in presence of chronic kidney diseases since ibuprofen can cause sodium retention, worsening of GFR and causing acute kidney injury.[17]

Core-shell nanoparticle

The core-shell nanocomposites are specifically those functional materials which consist of more than two materials. It comprises an inner core and an outer shell. This forms a single particle which performs better than individual material.[18]

Classification of core-shell nanostructures

Core-shell nanoparticles can be classified based on their architecture, materials used and pore size. Architectural classification includes not only simple spherical cores, but also more complicated core architectures such as reverse core-shell, multi-core-shell (several cores within single shell), yolk-shell (movable core within hollow shell, aka rattle-type structure) and complex multi-shell structures with single core with successive shells such as bimetallic multishell or multilayer semiconductor structures like quantum dot quantum wells.[18,20]

Compositional classification involves inorganic-inorganic (e.g. metal-metal, metal-metaloxide, ore, semiconductor-semiconductor), inorganic-organic (inorganic cores such as gold, iron oxide etc. coated with polymers, surfactants and ligands for improving biocompatibility, stability, dispersibility; in addition cores may be magnetic or non-magnetic) and organicinorganic (polymer cores coated with silica or metals) and organic-organic (organic cores or polymers, covered with other organic layer, highly popular in drug delivery with controlled release).[19,20,21]

Pore size depends on shell diameter and can be divided into three categories: microporous (<2 nm), mesoporous (2-50 nm) and macroporous (>50 nm) that affect molecular diffusion and interactions.[18]

METHODS OF SYNTHESIS

There are two general groups of methods that can be used for synthesis of nanoparticles: physical and chemical-based.

Various methods can be applied: top-down, bottom-up and hybrid.

Physical Synthesis Methods (Top-Down Approach)

Physical methods involve mechanical or high-energy process of fragmentation of bulk materials or deposition of atoms in nanostructures. The most common physical methods include:

Ball milling: High-energy mechanical grinding of bulk materials in planetary or shaker ball mill.[2] Mechanical processes such as machining, grinding, polishing and milling are used for reducing of bulk materials to nanoparticles.[22]

Sputtering: Vacuum-deposition when the target is bombarded by high-energy ions that eject atoms forming nanoparticle or thin film.[5,18]

Laser ablation/erosion: High-energy laser radiation of solid target in liquid medium causes ablation and formation of nanoparticles.[5,22]

Nanolithography: Various methods such as UV, electron-beam, ion-beam, scanning probe and near field optical lithography used for precise dimensioned nanostructure formation.[22]

Electro-spraying: High-voltage spraying of liquid drops for formation of nanoparticles.[2]

Electron beam evaporation: Electron beam induces vaporization of material for deposition.[2]

Additional physical methods: arc discharge, hydrogen plasma-metal reaction (HPMR), laser chemical vapor pyrolysis (LaCVP) and others.[5,19]

Chemical Synthesis Methods (Bottom-Up Approach)

Chemical methods are widespread and give the opportunity to modify the structural and optical properties

of nanoparticles by varying temperature, reactants concentration and reaction time.

Sol-Gel method: Popular wet-chemical method for synthesis of metal oxide nanoparticles that involves the hydrolysis, polycondensation, aging, drying and calcination of metal precursors in sol-gel medium resulting in nanostructure formation; the transformation from solution (sol) to gel takes place.[5,10,22]

Hydrothermal procedure: Has low reaction temperatures and easy controllable particle size; environmentally-friendly, cost-efficient and gives the possibility of tuning of morphology by changing the precursor concentration and reaction time. Hydrothermal decomposition, degradation, reaction and treatment methods can be used.[20] The reactions take place in aqueous medium at high temperature and pressure, and in particular hydrothermal carbonization, when biomasses such as glucose create carbon shell around the core due to dehydration and polymerization.[21]

Co-precipitation method: Popular method when soluble precursors are precipitated to form nanoparticles; includes the nucleation, growth and agglomeration steps.[20] Vapor synthesis of transfer involves reaction of zinc and oxygen vapors that result in nanostructure formation, with strict controlling of zinc vapor to oxygen pressure ratio to obtain desired geometry and size of the nanostructure.[2]

Chemical Vapor Deposition (CVD): Involves the chemical interactions of gases or vapors with core that results in formation of target shell layers at temperatures below the melting point of substrate material.[18]

Biogenic/Green Synthesis: Biological entities (algae, yeast, fungi, bacteria) are used for chemical reduction and stabilization of nanoparticles.[18]

Additional chemical methods: microemulsion and polyol methods.

Applications

Biomedical applications: The core-shell nanoparticles are widely used in biomedicine due to improved biocompatibility, functionalization, drug delivery and diagnostic. Targeted drug and gene delivery: Core-shell nanoparticles are used as carriers of therapeutics for tumor or cancer treatment allowing active/passive targeting with drug release at specific locations, in particular tumors. 3-D dendrimers and lipid-based nanoparticles are well-suited for encapsulation of drug molecules within the internal cavity. The magnetic core (e.g. iron oxide) allows magnetically controlled site-specific delivery.[20]

Bio-imaging and biosensing: These nanoparticles act as contrast agents for bio-imaging (MRI) and as platforms for biosensing including detection of damaged DNA, RNA, glucose, cancer cells and cell labeling and separation in research.[20]

Photothermal therapy: Specialized core-shell nanoparticles allow photothermal tumor therapy; Ag/Au core-shell systems have high photothermal conversion efficiency and allow destruction of cancer cells under laser irradiation.[19]

Environmental Remediation and Sensing: Core-shell nanoparticles provide the novel approach to monitoring and remediation of environmental pollution.

Water treatment: Core-shell nanoparticles allow degradation of harmful dyes (e.g. methylene blue) under solar irradiation with efficiency exceeding 90%.[19]

Contaminant removal: Magnetic shell-crosslinked nanoparticles were used for removal of hydrophobic oil contamination from water at the ratio of 10 mg oil/1 mg of particles.[21]

Gas purification: The microporous core-shell nanoparticles are used in gas purification by selective interaction of gas molecules.[18]

Environmental remediation: Coatings such as Fe2O3 on MgO or CaO nanoparticles increase adsorption of toxic gases (SO2 and H2S).[20]

Catalysis and chemical monitoring: The unique core-shell structures allow increased catalytic activity by such structures as sharp nanocube edges or high-aspect-ratio nanowires.[19]

Electrochemical reduction: Ag/Au bimetallic nanowires are catalysts for electrochemical reduction of CO2 to CO with 100% Faradaic efficiency.[19]

Improved catalysis: Bimetallic core-shell nanoparticles (e.g. Au/Pd, Co/Pt) usually exhibit better catalytic activity in comparison with single metal counterparts due to synergetic effects, and are used in direct methanol fuel cells and degradation of pollutants (ammonia).[20]

Sustainable pigments: Core-shell technology improves color stability of pigments in harsh environments and makes them suitable for coloring of asphalt and concrete in architectural design.[22]

Electronics and energy applications: Core-shell nanoparticles contribute to the advancement of electronics and energy storage devices.

Bioelectrodes: The 3-D Ag/Au core-shell nanowire foams are used in microbial fuel cells, providing the porosity, conductivity and chemical stability that enhances microbial electroactivity.[19]

Energy storage: Carbon-coated Li2S core-shell spheres are used for creation of highperformance lithium-sulfur batteries.[18]

Optoelectronics: High-aspect-ratio nanowires improve electron transport and directional current conduction, being beneficial for advance electronic and optical devices; the Au nanoparticles provide various platforms for optical applications.

The magnetic core-shell nanocrystals allow high-density information storage. In particular, special architectures such as movable Sn cores within carbon hollow shells, were shown to be promising as anodes in secondary lithium batteries.[21]

Characterization

1. **Microscopy:** it provides direct visualization of particle size and structure

Scanning electron microscopy (SEM): SEM is a widely used technique for the analysis of particle size and shape, providing surface images. It is usually used together with EnergyDispersive X-ray Spectroscopy (EDX) for shell surface analysis.[18,20]

Field Emission SEM (FSEM): High-resolution FSEM helps to determine whether the shell surface is smooth or rough.[18,20]

Transmission Electron Microscope (TEM): TEM is very important for the confirmation of core/shell surface formation by the contrast difference. This microscopy enables the direct visualization of the core and shell, thus allowing for the simultaneous measurement of the core size and shell thickness.[18,20]

Scanning transmission electron microscopy (STEM): When combined with energy-dispersive X-ray Spectroscopy (EDS or EDX), it makes possible to distinguish between core/shell structure and an alloy. Line spectra help to see if certain elements are localized in the centre (core) or perimeter (shell).[18,20]

Atomic force microscopy (AFM): Unlike electron microscopy, AFM can study particles under ambient or liquid conditions, providing 3D surface topography and height information.[20]

High-Angle Annular Dark-Field Scanning TEM (HAADF-STEM): It is very popular for bimetallic research, for example, Ag/Au nanocubes.[19]

2. Spectroscopic study

Spectroscopy analyses optical and chemical changes occurring in the coating process

UV-visible and Photoluminescence (PL): This is one of the widely used techniques for the analysis of nanoparticles absorbing energy in the UV-Visible spectrum.[20] This method compares the spectra of the core, shell, and the composite.[20] For CSNPs, the individual spectra of the core, shell, and core-shell material are compared, thereby indirectly confirming the coating process.[18] PL spectroscopy is used to characterise the constituents of the pure shell and indirectly confirm the shell coating on the core surface.[19]

X-ray photoelectron spectroscopy (XPS): This technique is employed to study the surface such as the composition of elements, their chemical state, empirical formulae, and depth profiling.[18,20] Shell signals start appearing as core signals disappear because of the thick coating.[18,20]

Fourier Transform Infrared spectroscopy (FTIR): This technique is used to analyse chemical bond formation during the coating process, such as O-Si-O bond on silica-coated iron oxide core.[20]

3. Scattering and Structural Analysis

This method will give us the statistical information about the entire sample.

Dynamic light scattering (DLS): Also called photon correlation spectroscopy, determines the hydrodynamic diameter of suspended or dissolved particles. The size measurement before and after coating will enable one to determine the thickness of the shell that has been coated on the surface.[18,20]

Powder X-ray Diffraction (XRD): It helps in identifying the crystal structure and grain sizes. A uniformly coated shell layer causes the diffraction peak intensity of the core materials to decrease or totally disappear if the shell thickness is enough.[20]

Small Angle X-Ray Scattering/Wide Angle X-Ray Scattering (SAXS/WAXS): They play the same role as XRD. Their advantage is that the sample can be in solid, liquid or even mixture form.[18]

Zeta potential: The measurement of the surface charge gives an indirect indication of successful surface modification of the core.[19,20]

4. Additional techniques

Thermal Gravimetric Analysis (TGA): TGA and DTA are useful in studying the thermal stability of the core-shell materials. They play a significant role when a sacrificial core is used in synthesis since they help in eliminating the organic core through calcination to obtain a hollow shell. This method is mainly employed in the study of thermal stability of the core-shell materials.[19,20]

Drug loading (DL) and encapsulation efficiency (EE)

Efficiency of Entrapment (EE), commonly known as the encapsulation efficiency, is an important criterion, which represents the ratio of the amount of the drug entrapped relative to the initial amount of drug as a percentage. EE plays an important role in the formulation of ibuprofen delivery vehicles. It is calculated using an indirect method.[26]

$$EE\ \% = \frac{Weigh\ t\ of\ initial\ drug - Weigh\ t\ of\ free\ drug}{Weigh\ t\ of\ initial\ drug} \times 100$$

Drug Loading (% DL) or drug loading capacity refers to the amount of drug contained within a delivery system expressed as the ratio between the weight of the drug and the total weight of the delivery vehicle. In ibuprofen loaded nanoparticles, high drug loading is necessary to ensure that therapeutic levels are attained by using as little carrier as possible. It is calculated using an indirect method.[26]

$$DL\ \% = \frac{Weigh\ t\ of\ initial\ drug - Weigh\ t\ of\ free\ drug}{Weigh\ t\ of\ carrier\ and\ Drug} \times 100$$

Mechanism of drug release

According to the sources, drug release mechanisms depend on the chemical structure of nanocarrier, the nature of the drug, and such environmental factors as pH and ionic strength.

1. Release Controlled by Diffusion

The most common release mechanism considered is diffusion, studied mainly by kinetic models.

Higuchi's model: According to this model, in which drug release rate increases with the increase in the square root of time, diffusion-controlled release of ibuprofen is observed for amorphous calcium silicate hydrate (CSH)/polymer hybrid nanoparticles. Higuchi's model is also observed for BSA-based core-shell nanoparticles under ambient conditions, when polyelectrolyte layers act as a diffusion barrier that limits release of the drug by means of diffusion. The speed of release can vary greatly depending on acidic or basic environment, which impacts the stability of carrier or the charges of the molecules.[13,24]

Concentration-Controlled Release: For "naked" BSA nanoparticles (without polyelectrolyte shell), the best fit would be the first-order rate model, when the release rate of the drug depends on its concentration in the carrier.[13]

Sequential Release: In nanoporous silica-organosilica core-shell nanoparticles, drugs are released in sequential manner depending on their spatial location. Drugs (for example, ibuprofen) stored in the outer organosilica shell are rapidly released because of the short distance of diffusion path.

Hydrophilic drugs (procaine hydrochloride, for instance) stored in the inner core have to diffuse longer through the shell, which works as a diffusion barrier, resulting in delayed release.[25]

2. pH-responsive Mechanisms

The release rate can be significantly modified depending on the pH level of the medium, either due to the carrier stability or changes in the charge of the molecules.

Nanoparticle Disintegration: Ibuprofen-BSA-dextran nanoparticles remain stable in the acidic medium while dissociate in the neutral and alkaline medium (pH=7.0, pH=9.0 and pH=11.0), since in the latter case both the drug and the protein carrier are negatively charged, thus inducing electrostatic repulsion and reduction in hydrophobic interactions.[23]

Structural Breakage: The release of the anticancer drug doxertaxel in CSH/polymer hybrid nanoparticles is faster in the acidic medium compared to the neutral medium (pH=5.5 versus pH=7.4), owing to the fact that the acidic conditions promote the structural breakage of the calcium silicate carrier, which is not chemically stable in the acidic medium.[24]

3. Intermolecular Interactions and Ionic Strength

Effect of Ions on Disrupting the Interactions: Increase in the ionic strength of the release medium (e.g., employing phosphate buffer solution) is one way of increasing the release rate from albumin nanoparticles. Ions present in the buffer tend to break the electrostatic and hydrophobic interactions between the drug and protein core.[23]

Cross-linking of Albumin Nanoparticles: Upon cross-linking of albumin nanoparticles using glutaraldehyde, these nanoparticles do not dissociate at high pH. However, the particle size decreases due to gradual diffusion of drug molecules out of the chemical cross-linked core, which reduces the rate of diffusion.

Repulsion Between Like Charged Molecules: In some core-shell nanoparticle system, where the protein core and polyelectrolyte shell get the same charge at physiological pH (7.4), the repulsive force results in rapid dissolution of drug molecules along with shell molecules into the surrounding medium.[13]

4. Bioactive Structural Transformation

When certain inorganic carriers such as CSH hybrid nanoparticles release the drug, there is always an associated transformation in the structure of the material used. For example, the complete transformation to hydroxyapatite occurs when ibuprofen is released from the nanocarrier in the simulation of body fluid, and this takes about 300 hours.[24]

Ibuprofen-loaded core shell nanoparticles

Osteoarthritis (OA) management by oral delivery of NSAID drugs (e.g., Ibuprofen) poses a significant clinical dilemma. Even though it reduces inflammation

and pain symptoms for a certain period, high doses of ibuprofen needed to achieve sufficient concentrations at the target site (improperly vascularized joint cavities) cause adverse effects on patients' health, namely, gastrointestinal bleeding and renal impairment.

Thus, nanotechnology creates a possibility of ibuprofen-loaded core shell nanoparticles used for delivering active substances directly to the lesion joint site.

Delivery and control mechanism of the drug delivery process

Hydrophobic Core: The core layer is designed as a protected drug storage area aimed at loading hydrophobic drugs (like ibuprofen). Being encapsulated in this core, ibuprofen remains in an amorphous, molecular state to avoid early crystallization and degradation in the physiological environment.[30]

Protective Shell: The outer layer acts as a regulator of the rate of drug diffusion. Being created from biodegradable materials (chitosan or poly (lactic-co-glycolic acid), PLGA), the shell works as a physical barrier slowly degrading or dissolving to prevent sudden release of the drug; hence, it provides a smooth and controlled release for several days or even weeks.[27]

Passive Targeting: It depends on the physicochemical characteristics of the carrier such as its size and charge to take advantage of the environment of the target tissue. For example, negatively charged ECM of articular cartilage provides an interesting option for targeting the tissue by utilizing positively charged (cationic) nanoparticles. Size-related penetration is crucial; particles smaller than 50-60 nm can easily penetrate the highly dense collagen fibrils of the cartilage matrix while larger particles can remain at the surface.[28,29]

Active Targeting: It involves decoration of the nanoparticle surface with affinity ligands, like antibodies or peptides, which recognize overexpressed receptors in a diseased state. The use of HA as a ligand targeting CD44 receptors overexpressed on the chondrocytes is a common approach. Another technique includes usage of collagen-binding peptides (such as WYRGRL)

in order to attach delivery vehicles to the degraded cartilage matrix, which significantly improves retention up to 72-fold.[28]

Mechanisms of Controlled Drug Release

Controlled release of drugs allows for the liberation of a drug at a specified rate which helps to avoid under- and over-dosage and decreases the frequency of administering it.

Diffusion-Controlled Drug Release: In the cubic nanoparticles case, the drug molecules are embedded into the matrix. It is released through diffusional passage of the drug molecules through the aqueous pores or polymeric matrix and follows the Higuchi's square-root equation.[30]

Degradation/Erosion: Polyesters (PLGA, PCL), which hydrolyze their ester bonds in aqueous conditions, slowly degrade and release drugs. The degradation can be adjusted; for instance, the increase in the percentage of hydrophobic lactide in PLGA leads to a slower drug release. Natural biopolymers are degraded enzymatically by lysozymes.[28,29]

Stimuli-responsive (smart) drug release: New generation nanocarriers can control drug release with the help of various stimuli.[29]

Internal Stimuli: The drug can be released depending on an acidic environment in inflamed joints or lysosomes (ammonium bicarbonate provides burst drug release at low pH) or redox state; intracellular glutathione cleaves disulfide bonds in the polymer backbone and releases nucleic acids/proteins.[28]

External Stimuli: Local heat production in response to physical stimuli (near-infrared (NIR) light, ultrasound, magnetic field) disrupts the nanoparticle shell and leads to drug release.[28]

Recent findings in research studies

Recent studies into polymeric and liposomal nanotechnology have proven to have some level of success in enhancing localized ibuprofen delivery:

Sustained Drug Elution Properties: Research into matrices based on nano-structured lipid and polymer matrices demonstrates high levels of entrapping efficiency for nano-encapsulated ibuprofen, generally ranging from 85% to 98%. Following administration, these matrices provide sustained release of the drug, where the diffusion of the drug continues beyond 24 hours, maintaining localized concentration.[26,30]

Prevention of Chondrocyte Toxicity: Administration of raw NSAIDs at high concentrations within a joint will result in localized cell toxicity. However, the problem can be solved through nanoparticle encapsulation; through leaching out the drug slowly, polymer-based nanoparticles increase cellular viability and limit the cytotoxicity of human articular chondrocytes, while successfully controlling inflammation.[29]

Bio-Responding Nano-Technology: Recent research is looking into "smart" bioresponsive technology. This is because the pathology of osteoarthritis includes change in the microenvironment, which is seen in the formation of local acidic pH due to inflammation, and this means that nanoparticle shells are increasingly designed to respond to this change in swelling ratio and degradation.[28]

Therapeutic Advantages

The shift from systemic administration of the tablets to targeting via core-shell nanoparticles brings many important benefits:

Core Advantages Over Conventional Therapy

Long-term Intramuscular and Joint Absorption: Free ibuprofen, directly introduced into joint cavity, is flushed out by the joint drainage system within hours. Particles avoid rapid elimination by lymph nodes and are retained in joint cavity providing prolonged treatment.[27,28]

Breaking the Cartilage Barrier: The articular cartilage contains highly dense, negatively charged extracellular matrix which repels any foreign molecule. Optimization of nanoparticles down to the nano-scale makes it possible for them to enter and pass through the dense tissue of cartilage and deliver drugs to chondrocytes.[28]

Reduced Dosage and Increased Safety: Thanks to core-shell design of nanoparticles, ibuprofen is administered constantly to the required site of inflammation, avoiding high oral dosages of medication. Plasma concentration of particles is almost undetectable, protecting the gastrointestinal tract and kidneys from classic NSAIDs toxic effects.[26,27]

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