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Solid Lipid Nanoparticles as Next-Generation Carriers for Targeted Prostate Cancer Therapy: A Comprehensive Review

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Abstract

Solid lipid nanoparticles (SLNs) represent a rapidly advancing nanotechnology platform for the delivery of abiraterone acetate, with promising applications in drug delivery, clinical therapeutics, and biomedical research. This review provides a comprehensive overview of SLNs, including their objectives, production techniques, advantages, limitations, and potential strategies to overcome these challenges. Additionally, the review summarizes commonly employed SLN preparation methods, characterization approaches, and routes of administration. The in vivo behavior of SLN carriers, including their biodistribution and fate within biological systems, is also discussed.

Keywords

Solid Lipid Nanoparticles (SLNs), Targeted Drug Delivery, Prostate Cancer Therapy, Nanomedicine, Lipid-Based Drug Delivery Systems

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INTRODUCTION

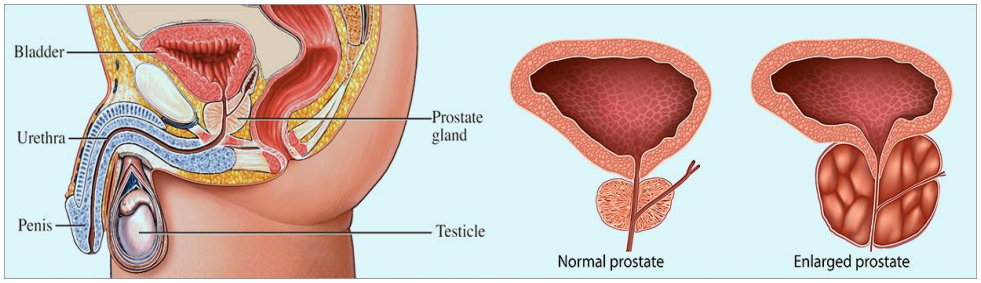
The prostate gland is a chestnut-shaped male reproductive organ situated directly below the urinary bladder. Its primary function is to secrete fluid that contributes to the semen during ejaculation. The gland encircles the urethra, the duct responsible for the passage of both urine and semen. Anatomically, the prostate is broad and rounded superiorly and tapers to a blunt apex inferiorly. It measures approximately 4 cm (1.6 inches) at its widest region.

Two ejaculatory ducts, which transport sperm and seminal vesicle secretions, merge within the central portion of the prostate and join the urethra. From this junction, the urethra continues through the lower segment of the prostate and exits near the apex.

Histologically, the prostate is composed of numerous tubulars or sac-like glands that open into the urethra and ejaculatory ducts. These glands are lined with a moist, folded mucous membrane that expands during fluid storage. Beneath the epithelial lining lies connective tissue containing a dense network of elastic fibers and blood vessels. Surrounding the glandular structures is interstitial tissue composed of collagen fibers, elastic fibers, and smooth muscle, which provide structural support and firmness. The entire gland is enclosed within a capsule made of dense interstitial connective tissue.

In humans, the prostate contributes approximately 15–30% of the total seminal volume. Prostatic fluid is

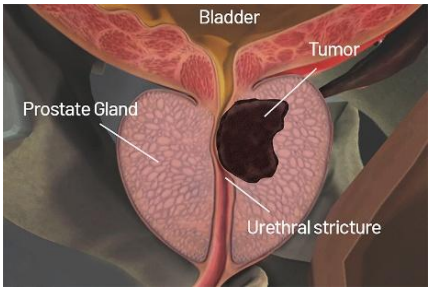
clear, slightly acidic, and rich in several components including proteolytic enzymes, fibrolysin (which breaks down blood and tissue fibres), citric acid, acid phosphatase, and ions such as sodium, zinc, calcium, and potassium. These constituents play essential roles in sperm motility, semen liquefaction, and overall reproductive function.



Prostate Gland

Prostate cancer

Prostate cancer develops when prostate epithelial cells lose normal regulatory control. Under typical conditions, these cells undergo controlled proliferation, differentiation, and apoptosis. When these mechanisms become dysregulated, aberrant cells evade apoptosis and continue uncontrolled replication, leading to the formation of a neoplastic lesion. These lesions may be benign (non-malignant) or malignant, with the latter exhibiting oncogenic potential.



Prostate Cancer

The majority of prostate malignancies are indolent, progressing slowly and remaining clinically silent for many years. However, a subset of tumors demonstrates high-risk, aggressive behavior, characterized by rapid proliferation, higher Gleason grading, and a propensity for metastatic dissemination to distant sites, including bone, lymphatic tissue, and pulmonary structures.

ABIRATERONE ACETATE

Biraterone is a potent, selective, and irreversible inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17), a key enzyme involved in androgen biosynthesis and expressed in testicular, adrenal, and prostatic tumour tissues. By inhibiting CYP17, abiraterone effectively suppresses androgen production from all known sources.

Abiraterone received regulatory approval from the FDA, EMA, and other global agencies in April, July, and September 2011, respectively. It is indicated for the treatment of metastatic castration-resistant prostate cancer (mCRPC) as well as metastatic hormone-sensitive high-risk prostate cancer (mHSPC).

Due to the parent compound's poor oral bioavailability and susceptibility to esterase-mediated hydrolysis, abiraterone acetate was developed as an orally administered prodrug. This formulation confers enhanced chemical stability and significantly improved gastrointestinal absorption, enabling effective systemic delivery of abiraterone.

MECHANISM OF ACTION

- 17α-hydroxylase/C17,20-lyase (CYP17) is a critical enzymatic regulator of androgen biosynthesis. It is predominantly expressed in testicular and adrenal tissue, as well as in prostatic tumour cells. CYP17 catalyses the 17α-hydroxylation of pregnenolone and progesterone, followed by C20,21-lyase activity that converts these intermediates into dehydroepiandrosterone (DHEA) and androstenedione, both of which serve as key precursors in the synthesis of testosterone.
- Dysregulated androgen production and aberrant activation of the androgen receptor (AR) pathway are central to the pathogenesis and progression of several forms of prostate cancer.

- Androgen-dependent prostate tumors respond to therapies that suppress circulating androgens. Standard androgen deprivation strategies—such as gonadotropin-releasing hormone (GnRH) agonists or surgical orchiectomy—effectively reduce testicular androgen synthesis but do not suppress androgen production from adrenal sources or from intratumoral steroidogenesis.
- Abiraterone functions by selectively inhibiting CYP17, thereby blocking androgen biosynthesis across all sources (testicular, adrenal, and intratumoral). CYP17 inhibition also leads to upregulation of mineralocorticoid synthesis, which can result in mineralocorticoid-related adverse effects.

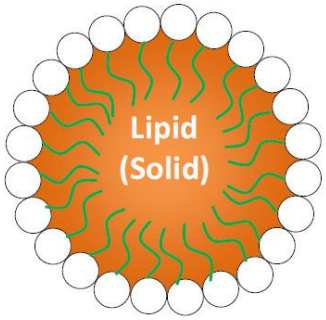
Solid lipid nanoparticles (SLNs) for Prostate cancer

Solid lipid nanoparticles (SLNs) have emerged as an advanced drug-delivery system designed to enhance the performance of poorly water-soluble pharmaceutical and cosmetic active compounds. Nanoparticles are colloidal carriers typically ranging from 10 to 1,000 nm and may be composed of synthetic or natural biodegradable lipids selected to optimize drug delivery while minimizing toxicity.

SLNs have gained attention as a versatile alternative to liposomal systems due to their unique physicochemical characteristics, including small particle size, large surface area, high drug-loading capacity, and favorable interfacial properties. These attributes make SLNs particularly attractive for improving the stability, bioavailability, and controlled release of incorporated therapeutic agents.

SLNs are defined as aqueous colloidal dispersions in which the particle matrix consists of solid biodegradable lipids. They combine the advantages of other colloidal drug-delivery carriers while avoiding several of their limitations. Benefits include enhanced physical stability, protection of labile drugs from degradation, controlled and sustained drug release, and excellent biocompatibility and tolerability. SLN formulations have been extensively developed and evaluated for multiple administration routes, including parenteral, oral, dermal, ocular, pulmonary, and rectal delivery. Serving as a novel colloidal carrier system, SLNs provide a promising alternative to traditional polymer-based nanoparticles. They are structurally analogous to oil-in-water emulsions used in parenteral nutrition, but with the liquid lipid phase replaced by a solid lipid core, resulting in improved stability and drug-delivery performance.

They have many focal points, for example, great biocompatibility, low danger and lipophilic medications are better conveyed by Solid lipid nanoparticles and the framework is physically stable.



Advantages of SLN

- Small estimate and generally contract measure dissemination which gives natural chances to site particular medication conveyance by SLNs.
- Conventional emulsion producing techniques pertinent
- Can be stop dried to shape powdered detailing
- Controlled arrival of dynamic medication over a long stretch can be achieved.
- Excellent biocompatibility
- Improve stability of pharmaceuticals
- Excellent reproducibility with a savvy high-weight homogenization technique as the readiness methodology.
- High and enhanced drug content.
- The achievability of consolidating both hydrophilic and hydrophobic medications
- The transporter lipids are biodegradable and consequently protected. Avoidance of natural solvents. Enhanced bioavailability of inadequately water dissolvable atoms.
- Avoidance of natural solvents underway strategies.

Disadvantages of SLN

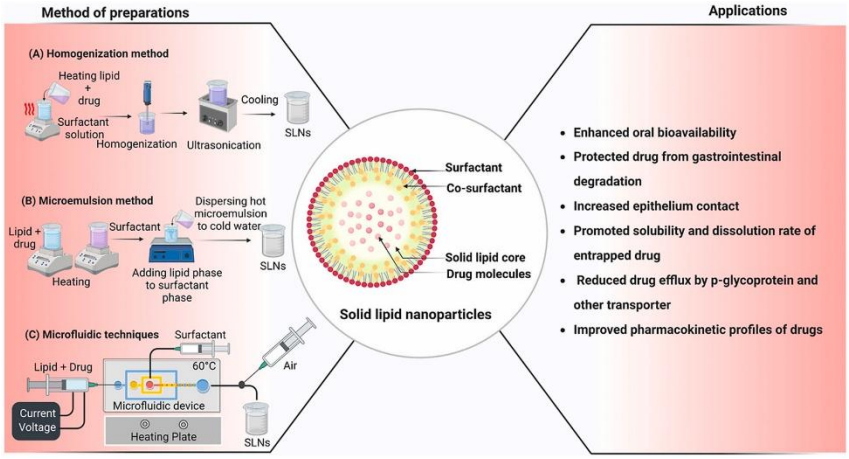
- Poor sedate stacking limit.
- Drug ejection after polymeric move amid capacity.
- Unpredictable gelation propensity.

- The low ability to stack hydrophilic medications because of apportioning impacts amid the generation procedure.

Methods of Preparation of Solid Lipid Nanoparticles

Strategy for readiness of SLN incorporates high shear homogenization, ultrasonication, microemulsion based SLN planning, supercritical liquid innovation, splash drying, dissolvable emulsification/vanishing, dissolvable infusion method and dissolvable emulsification-dissemination

1. High weight homogenization
   - Hot homogenization.
   - Cold homogenization.
2. Ultrasonication/fast Homogenization
   - Test Ultrasonication
   - Shower Ultrasonication Solvent evaporation method
3. Solvent emulsification-diffusion method
4. Supercritical fluid method
5. Microemulsion based method
6. Spray drying method.
7. Double emulsion method.
8. Precipitation technique
9. Film-ultrasound dispersion.



HOT HOMOGENIZATION

Melting of the lipid & dissolving/dispersing of the drug in the lipid

⬇

Dispersing of the drug loaded lipid in a hot aqueous surfactant mixture.

⬇

Premix using a stirrer to form a coarse pre-emulsion

⬇

High pressure homogenization at a temperature above the lipid M.P.

⬇

Hot O/W nano emulsion

⬇

Solid Lipid Nanoparticle

Ultrasonication:

Adv:

1) Equipment used is very common
2) No temperature induced drug degradation

Disadv.:
1) Potential metal contamination
2) Broader particle size distribution

COLD HOMOGENIZATION

Melting of lipid & dissolving/dispersing of the drug in the lipid

↓

Solidification of the drug loaded lipid in liquid nitrogen or dry ice

↓

Grinding in a powder mill

↓

Dispersing the powder in a aqueous surfactant dispersion medium

↓

High pressure homogenization at room temperature or below.

↓

Solid Lipid Nanoparticles

Solvent emulsification:
Lipophilic material is dissolved in a water immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase.
Upon evaporation of solvent, a nanoparticle dispersion is formed by ppt of lipid in aq. Medium.
Adv.: Avoidance of any thermal stress
Dis adv.: use of organic solvents.
Using Microemulsion:
Preparation by stirring optically transparent mixture at 65-70° c composed of a low melting fatty acid, emulsifier, emulsifier & water.
This hot microemulsion dispersed in cold water (2-3°c) & stirring.
By using Supercritical fluid
Can be prepared by Rapid Expansion of Supercritical Carbon dioxide solution methods (RESS)
Adv.:
1) Solvent less processing.
By Spray drying method
Alternative to lyophilization
Dis adv.:
1) particle aggregation due to high temp., shear forces & partial melting of particles.
2) Recommended use of lipid with M.P. >70° c for spray drying.

Characterization of Solid Lipid Nanoparticles (SLNs)
Characterization of solid lipid nanoparticles (SLNs) presents a significant challenge due to their nanoscale dimensions and the complex nature of the delivery system. Comprehensive evaluation requires assessment of several critical quality attributes, including particle size and size distribution, surface charge (zeta potential), degree of crystallinity, lipid polymorphism, presence of additional colloidal structures (e.g., micelles, liposomes, supercooled melts, drug nanocrystals), drug incorporation efficiency, in vitro drug-release profile, and surface morphology.
Particle Size and Zeta Potential
Particle size is a key determinant of SLN performance, influencing drug-loading capacity, release kinetics, biodistribution, and physical stability. Multiple analytical techniques can be employed to determine particle size, including:

- Photon correlation spectroscopy (PCS)
- Transmission electron microscopy (TEM)
- Scanning electron microscopy (SEM)
- SEM coupled with energy-dispersive X-ray spectroscopy (EDX)
- Atomic force microscopy (AFM)
- Laser diffraction analysis
- Scanning probe microscopy techniques

Among these, PCS and electron microscopy (SEM and TEM) are the most widely utilized. SEM and TEM provide detailed insights into particle shape, size, and morphological characteristics, as well as particle distribution within the formulation.

AFM represents an advanced imaging technique that enables visualization of particles in their unaltered, native state, allowing assessment of surface topography with spatial resolution up to 0.01 µm.

Laser diffraction can also be applied for particle-size determination in the submicron range, with calculations based on the refractive index of the dispersing medium (water: 1.33) and the lipid matrix.

ROUTES OF ADMINISTRATION

Solid lipid nanoparticles (SLNs) can be administered through multiple routes depending on the therapeutic objective, formulation characteristics, and target tissue distribution.

1. Oral Administration

SLNs may be administered orally either as aqueous dispersions or after conversion into conventional solid dosage forms such as tablets, pellets, capsules, or sachet-filled powders. During tablet manufacture, SLN dispersions can be incorporated directly as a granulation fluid. Orally administered SLN formulations include liquid dispersions and SLN-loaded solid dosage forms. Within the gastric environment, particle aggregation may occur due to low pH and high ionic strength, which can influence stability and drug-release performance. Additionally, the presence of food is expected to have a significant impact on SLN absorption and therapeutic efficacy.

2. Parenteral Administration

SLNs can be administered parenterally, predominantly via the intravenous route. Studies have demonstrated that intravenously delivered SLNs achieve enhanced drug concentrations in organs such as the lung, spleen, and brain, while conventional formulations tend to show greater distribution in the liver and kidneys.

SLNs have also shown superior systemic exposure compared with corresponding commercial drug preparations following intravenous injection.

For parenteral use, SLN dispersions must be sterile. Due to their particle size, sterile filtration is often not feasible, making aseptic manufacturing or terminal sterilization essential.

3. Transdermal Administration

SLNs with low lipid content (≤5%) typically exhibit the smallest particle sizes, which is advantageous for dermal delivery. However, low lipid concentration and low viscosity of aqueous dispersions can limit direct application to the skin. Therefore, SLN dispersions are often incorporated into ointments, creams, or gels to produce formulations suitable for transdermal administration.

4. Pulmonary Administration

Pulmonary delivery represents a promising application for SLNs. Direct administration of SLN powders is impractical because particles of this size tend to be exhaled. A more efficient approach is aerosolization of aqueous SLN dispersions, provided that the nanoparticles remain stable and do not aggregate during nebulization. Upon deposition in the bronchial passages and alveoli, SLNs enable controlled drug release from their lipid matrix, supporting their utility for targeted pulmonary therapy.

5. Rectal Administration

Rectal administration is widely used in pediatric populations due to ease of application. When rapid pharmacological action is required, the rectal route may be advantageous and is often considered alongside parenteral administration. SLN-based rectal formulations may enhance mucosal absorption and improve onset of action.

CONCLUSION:

The global burden of disease continues to increase, highlighting the limitations of conventional drug-delivery systems, which often fail to achieve optimal therapeutic outcomes due to challenges such as **poor** oral bioavailability, low dissolution rates, and insufficient site-specific targeting. These constraints underscore the need for innovative strategies capable of overcoming the inherent drawbacks of traditional formulations.

Advances in nanotechnology-based drug-delivery platforms offer significant potential to address these challenges. Nanocarrier systems, including solid lipid nanoparticles and other emerging modalities, provide opportunities for enhanced drug solubilization, improved pharmacokinetic profiles, targeted delivery, and integrated theranostic applications. These developments represent a promising direction for the optimization of therapeutic interventions and the advancement of precision medicine.

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