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Current advance in liposomal drug delivery system as nano-carriers for the management of genital tuberculosis.

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ABSTRACT :

Genital tuberculosis (GTB), a significant cause of infertility in reproductive-aged individuals, is caused by Mycobacterium tuberculosis and often presents diagnostic and therapeutic challenges due to its silent progression and intracellular persistence. Conventional anti-TB therapy is limited by poor drug penetration into macrophages, long treatment duration, systemic toxicity, and rising antimicrobial resistance. Liposomal drug delivery systems have emerged as advanced nanocarriers capable of encapsulating both hydrophilic and hydrophobic anti-TB drugs, including rifampicin, isoniazid, pyrazinamide, and amikacin. These nanoscale vesicles enable targeted macrophage delivery, sustained and controlled drug release, enhanced intracellular bioavailability, and reduced systemic side effects. Combination liposomal formulations, particularly inhalable and ligand-targeted systems, have demonstrated superior efficacy in preclinical studies, including reduced bacterial load, improved tissue penetration, lower hepatotoxicity, and potential dose reduction. This review highlights the current advances in liposomal nanocarrier technology for GTB management, emphasizing their potential to improve therapeutic outcomes, address multidrug-resistant strains, and facilitate personalized treatment strategies.

Introduction

Tuberculosis (TB)

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis (Mtb). It primarily affects the lungs (pulmonary TB) but can involve almost any organ system (extrapulmonary TB). TB remains one of the top infectious causes of death globally despite being preventable and curable. Overcrowding, malnutrition, HIV infection, inadequate treatment, and antimicrobial resistance continue to drive its persistence. Tuberculosis (TB) is an infectious disease caused by a bacterium called Mycobacterium tuberculosis. It mainly affects the lungs, but it can also spread to other parts of the body such as the brain, kidneys, bones, lymph nodes, and reproductive organs.

Etiology&Pathogenesis

TB is caused by the Mycobacterium tuberculosis complex (MTBC). These bacilli are aerobic, acid-fast, slow-growing organisms with a lipid-rich cell wall, contributing to drug resistance and persistence.

Pathogenesis Steps

1. Inhalation of droplet nuclei containing Mtb.
2. Alveolar macrophage uptake and intracellular survival by preventing phagolysosome fusion.
3. Granuloma formation—body walls off bacteria.
4. Latent TB infection (LTBI) if immunity keeps bacteria dormant.
5. Active TB disease if immune control fails.

Combination Liposomal Drug Therapy on Tuberculosis

Causes

TB spreads through the air, when a person with active TB of the lungs coughs, sneezes, laughs, or talks.

It is not spread by touching, sharing utensils, or shaking hands.

Types of Tuberculosis

1.Latent TB

- Bacteria are present in the body but inactive
- No symptoms
- Not contagious
- Can become active later

2. Active TB

- Bacteria multiply and cause symptoms
- Contagious
- Requires treatment

Symptoms

- Persistent cough for more than 2–3 weeks
- Coughing blood (sometimes)
- Fever
- Night sweats
- Weight loss
- Loss of appetite
- Chest pain
- Fatigue or weakness

Diagnosis

Doctors may use:

- Sputum test (for TB bacteria)
- Chest X-ray
- Mantoux/Tuberculin skin test
- IGRA blood test
- GeneXpert/CBNAAT test (detects resistance too)

Treatment

TB is treated with a combination of 4–5 antibiotics for 6 months or more, depending on the type:

- Drug-sensitive TB → 6 months
- Drug-resistant TB → 9–20+ months
- Treatment must be taken regularly to prevent resistance.

Prevention

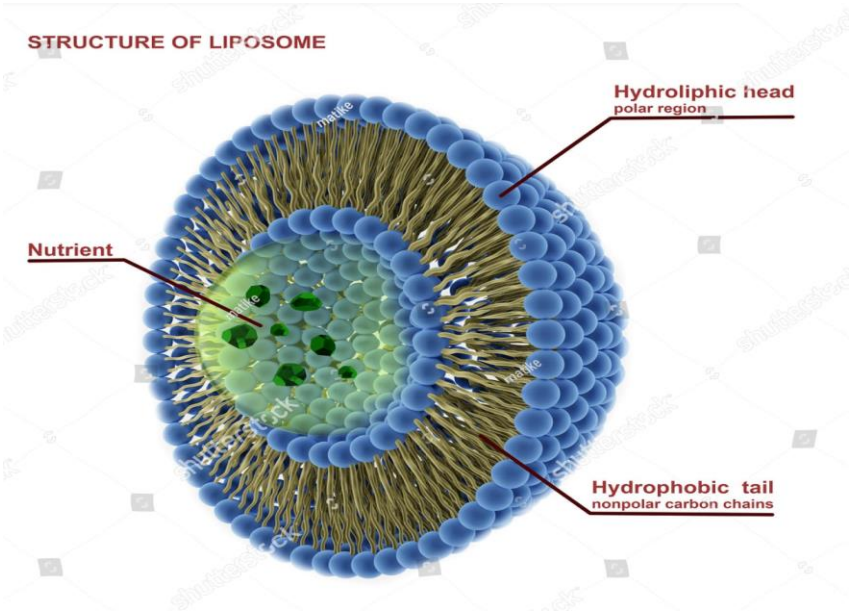
- BCG vaccine (given to infants)
- Avoid close contact with active TB patients
- Maintain good ventilation
- Use masks/scarves when coughing
- Complete full TB treatment

What is liposome

liposome (often misspelled as liposomae) is a tiny spherical vesicle made of lipid (fat) molecules, similar to the natural fats found in cell membranes.

Definition: A liposome is a nano-sized bubble made of lipids that can carry drugs inside the body.

Structure:



A liposome has:

Outer lipid bilayer (like a cell membrane)

Inner aqueous core (water-filled center)

Can carry:

Hydrophilic drugs (inside the water core)

Hydrophobic drugs (inside the lipid layer)

Why are liposomes important?

They are widely used in drug delivery, especially for:

Tuberculosis (TB) therapy

Cancer treatment

Antifungal drugs

Vaccines

Gene delivery

Advantages

1. Improved drug stability
2. Lower toxicity
3. Controlled and targeted release
4. Better absorption

Disadvantages

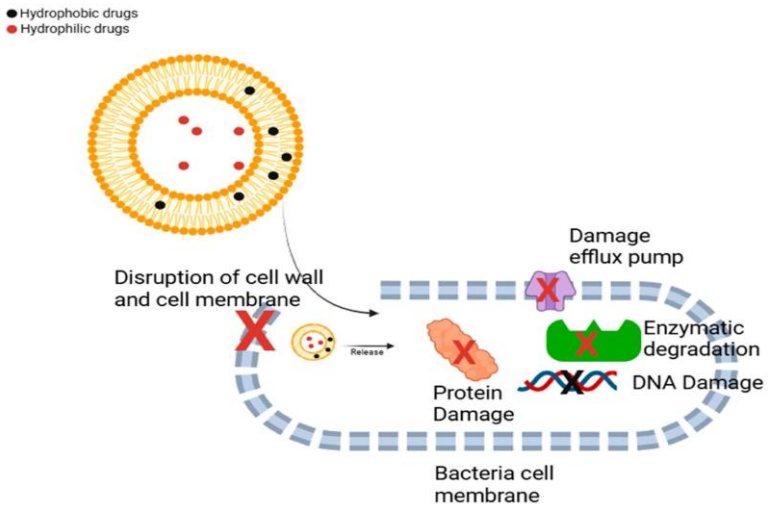
1. High Cost of Production
2. Stability Issues
3. Rapid Clearance from the Body
4. Low Drug Loading Capacity
5. Sterilization Challenges
6. Physical and Chemical Instability

Example

Liposomal amphotericin B, liposomal doxorubicin, liposomal vaccines.

Liposomes for TB Combination Therapy

Liposomal carriers are spherical vesicles made of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic anti-TB drugs.



Advantages:

•Each a need drug penetration into macrophages (where TB bacteria reside).

•Prolonged drug release, reducing dosing frequency.

•Reduced systemic toxicity, especially for drugs like rifampicin and isoniazid.

•Improved drug stability, bioavailability, and resid.

•Possibility of combination loading, allowing multiple drugs in a single carrier.

Combination Drugs Used in Liposomal Systems

Common first-line and second-line anti-TB drugs that can be co-encapsulated:

First-line Drugs

Rifampicin (RIF)

Isoniazid (INH)

Pyrazinamide (PZA)

Ethambutol (EMB)

Second-line Drugs

Levofloxacin

Amikacin

Ethionamide

Bedaquiline&Clofazimine (in current research)

Examples of Combination Liposomal Formulations

RIF + INH liposomes

RIF + PZA liposomes

RIF + INH + PZA triple-loaded liposomes

Amikacin + Levofloxacin liposomes for MDR-TB

Mechanism of Action of Liposomal Combination Therapy

1. Targeted Uptake by Macrophages

Liposomes are naturally phagocytosed by macrophages, delivering drugs directly to M. tuberculosis.

2. Sustained Release

Combination-loaded liposomes release drugs slowly, keeping therapeutic levels for longer periods.

3. Reduction of Drug Resistance

Using multiple drugs together reduces risk of mutant selection.

4. Enhanced Lung Bio distribution

Inhalable liposomal formulations deliver drugs directly to pulmonary tissues.

Examples of Liposomal Combination Formulations

Drug Encapsulated	**Type of liposome**	**Outcome**
Rifampicin + Isoniazid	PEGylated liposome	Increased lung targeting, reduced hepatotoxicity
Rifampicin + Pyrazinamide	Cationic liposome	Enhanced intracellular uptake and sustained release
Isoniazid + Ethambutol	Multilamellar liposome	Improved drug stability and therapeutic index
Rifampicin + Levofloxacin	Stealth liposome	Synergistic effect against MDR-TB strains

Methods of Administration

1. Inhalable Liposomal Formulations (Most effective)

Nanoliposomes delivered via nebulizer

Lung targeting → minimal systemic toxicity

2. Intravenous Liposomal Injections

Used for severe or MDR-TB

3. Oral Liposomal Suspensions

Emerging field, but stability challenges exist

Research Evidence

Key outcomes from studies:

Liposomal RIF–INH showed 2× higher intracellular drug concentration in macrophages.

Combination liposomes reduced bacterial load in lungs faster than free drugs.

Inhalable liposomal formulations reduced required doses by 50–70%.

Animal models show reduced liver toxicity compared to conventional therapy.

Challenges of Liposomal Combination Therapy

Stability issues in conventional storage

High cost of production

Need for scalable industrial manufacturing

Variability in encapsulation efficiency for multiple drugs

Regulatory challenge

Future Prospects

Liposomal triple-drug inhalable formulations for once-weekly dosing

Targeted liposomes using ligands (mannose, antibodies)

Liposomes combined with polymeric nanoparticles (hybrid nanosystems)

Personalized liposomal therapy for drug-resistant TB

Liposomal Drug Delivery in Tuberculosis

Liposomal drug delivery is an advanced nanocarrier-based approach designed to improve the delivery, efficacy, and safety of anti-tuberculosis drugs. Liposomes are spherical vesicles composed of lipid bilayers that can carry both hydrophilic and hydrophobic drugs. They help deliver anti-TB drugs directly to the infected tissues—especially in the lungs, macrophages, and granulomas, where Mycobacterium tuberculosis hides.

Use Liposomes in TB Treatment

Traditional TB therapy faces problems such as:

Long treatment duration (6–24 months)

High doses leading to toxicity

Poor patient compliance

Drug resistance (MDR-TB, XDR-TB)

Difficulty in drug penetration into macrophages and granulomas

Liposomal systems solve these challenges by improving drug targeting and reducing side effects.

How Liposomes Work in TB

1. Macrophage Targeting

M. tuberculosis lives inside alveolar macrophages.

Liposomes are naturally taken up by macrophages → improving drug concentration at infection site.

2. Controlled and sustained release

Liposomes slowly release anti-TB drugs → fewer doses needed.

3. Improved penetration into granulomas

Liposomes can enter necrotic tissues where TB bacilli hide.

4. Reduced toxicity

Liposomes lower the side effects of drugs like isoniazid, rifampicin, and amikacin.

Anti-TB Drugs Successfully Loaded into Liposomes

Rifampicin (RIF)

Isoniazid (INH)

Pyrazinamide (PZA)

Ethambutol (EMB)

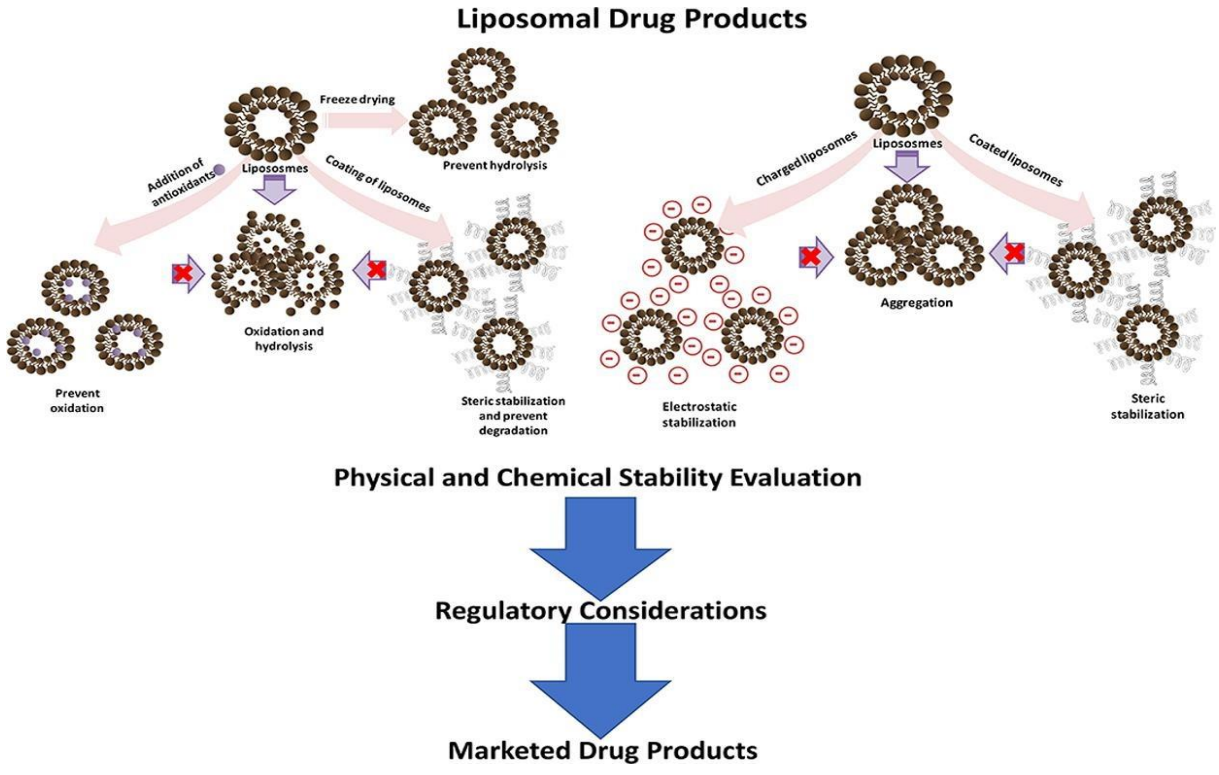
Amikacin

Ciprofloxacin

Ofloxacin

Bedaquiline (recent research)

Clofazimine



Advantages of Liposomal Drug Delivery for TB

• Advantages	• Explanation
Targeted delivery	Delivers drugs directly to infected macrophages.
Lower dose required	Higher bioavailability of drug.
Reduced toxicity	Safer delivery of toxic drugs (e.g., amikacin).
Bypassed drug resistance	Increases intracellular drug concentration.
Better stability	Protects drug from degradation.
Improved patient compliance	Long-acting liposomes reduce dosing frequency.

Types of Liposomes Used in TB Therapy

1. Conventional Liposomes

Used for hydrophilic drugs like INH and PZA.

2. PEGylated (Stealth) Liposomes

Long circulation time

Good for chronic TB therapy

3. Targeted Liposomes

Mannose-coated liposomes target macrophage mannose receptors.

Good for pulmonary TB and genital TB.

4. pH-Sensitive Liposomes

Release drug in acidic intracellular compartments (phagolysosomes).

Mechanism in TB Infection Site

1. Liposome circulates → reaches lungs

2. Macrophage phagocytoses liposome

3. Liposome fuses with macrophage membrane

4. Drug released inside phagosome

5. Drug kills intracellular M. Tuberculosis

Applications in Different TB Types

✓ Pulmonary TB

Inhalable liposomal rifampicin and isoniazid

Higher lung concentration, fewer side effects

✓ Genital TB

Targeted liposomes improve penetration into reproductive tissues

Enhanced delivery of rifampicin, isoniazid

✓ Drug-Resistant TB

Liposomal amikacin or bedaquiline

Better intracellular penetration

Genital Tuberculosis (Genital TB):

Genital Tuberculosis—also called Genitourinary Tuberculosis—is a form of tuberculosis that affects the male or female reproductive organs. It occurs when Mycobacterium tuberculosis infects the reproductive tract, usually through the bloodstream from a primary TB infection (typically lungs).It is common in developing countries, especially among women of reproductive age, and is an important cause of infertility.

Causes (Mycobacterium tuberculosis)

Genital TB is caused by the TB bacteria spreading from:
Lungs (most common)
Lymph nodes
Bones
Kidneys
Spread occurs through bloodstream or lymphatic system.

GENITAL TB IN FEMALES

Organs commonly affected
1. Fallopian tubes (90–100% cases)
2. Endometrium (uterus)
3. Ovaries
4. Cervix
5. Vagina / Vulva (rare)

Symptoms in Women

Many women have no symptoms (silent disease) until infertility appears.
Common symptoms:
Infertility (most common)
Irregular periods or absent periods
Pelvic pain
Heavy or light menstrual bleeding
Persistent vaginal discharge
Painful intercourse
Lower abdominal pain

General TB symptoms:

fever
night sweats
weakness
weight loss

Complications

Blocked fallopian tubes
Damage to uterus (thin endometrium)
Ovarian adhesions
Chronic pelvic inflammatory disease
Infertility
Ectopic pregnancy
Pregnancy loss

GENITAL TB IN MALES

Organs commonly affected
1. Epididymis (most common)
2. Testes
3. Prostate
4. Seminal vesicles
5. Vas deferens

Symptoms in Men

Painful swelling in scrotum
Testicular pain
Scrotal ulcers (rare)
Blood in semen
Infertility
Painful urination
Chronic prostatitis
Low semen count or azoospermi

DIAGNOSIS OF GENITAL TB

Tests for Women

Endometrial biopsy (gold standard)
Menstrual blood TB-PCR
Ultrasound / TVS
Hysterosalpingography (HSG):
Shows blocked tubes, “beaded tubes”
Hysteroscopy / Laparoscopy
TB PCR, GeneXpert
ESR, Mantoux test
Chest X-ray (to detect pulmonary TB)

Tests for Men

Semen analysis
TB PCR (semen sample)
Ultrasound of scrotum
Biopsy of epididymal mass
Urine TB PCR

TREATMENT OF GENITAL TB

First-line treatment

Anti-TB Therapy (ATT) – 6 months course

1. Intensive Phase (2 months):

Isoniazid (H)
Rifampicin (R)
Pyrazinamide (Z)
Ethambutol (E)

2. Continuation Phase (4 months):

Isoniazid (H)
Rifampicin (R)

Ethambutol (E)
If MDR-TB (Drug-resistant TB)
Longer treatment (9–20 months)
Special drugs: levofloxacin
bedaquiline
linezolid
cycloserine
Surgery (rare cases)
Removal of blocked tubes
Drainage of pus
Removing masses in testes/epididymis

GENITAL TB&FERTILITY

In Women

Genital TB is a major cause of infertility because it:
Blocks fallopian tubes
Damages endometrial lining (thin uterus)
Forms adhesions in pelvis
Even after treatment, fertility may not return if damage is severe.
Many women may need:
IVF (Test tube baby)
Surrogacy (if uterus is damaged)

In Men

Decreased sperm count
Blocked sperm ducts
Azoospermia
Assisted reproductive techniques (ART) may be required.

PREVENTION

Early detection and treatment of pulmonary TB
Good nutrition and immunity
Avoiding untreated chronic infections
Regular medical checkups for infertility
Screening in high-risk populations

Conclusion

Liposomal drug delivery represents a transformative approach for the management of genital tuberculosis by overcoming the limitations of conventional therapy. These nanocarriers enhance targeted delivery to infected macrophages, improve drug penetration into reproductive tissues, allow sustained release, and reduce systemic toxicity. Combination liposomal formulations of first- and second-line anti-TB drugs, including rifampicin, isoniazid, pyrazinamide, and amikacin, demonstrate higher intracellular drug concentrations, faster bacterial clearance, and improved patient compliance. Emerging strategies, such as inhalable formulations, PEGylated or ligand-targeted liposomes, and hybrid nanosystems, offer promising avenues for treating drug-resistant and extrapulmonary TB. Despite challenges related to cost, stability, and large-scale manufacturing, liposomal nanocarriers hold considerable potential to revolutionize TB therapy, particularly for GTB, by enabling precise, effective, and personalized treatment regimens.

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