CHAPTER 21

Novel Drug Delivery Systems

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Abstract

Novel Drug Delivery Systems (NDDS) represent advanced approaches to delivering pharmaceutical compounds in ways that enhance therapeutic efficacy, improve patient compliance, and reduce side effects. This section explores various innovative drug delivery technologies and their applications in modern pharmaceutical practice. Controlled release systems, including matrix tablets, reservoir devices, and osmotic systems, are examined for their ability to maintain therapeutic drug levels over extended periods. Targeted drug delivery approaches, such as nanoparticles, liposomes, and antibody-drug conjugates, are discussed in the context of improving drug specificity and reducing systemic toxicity. Transdermal delivery systems, including patches and iontophoretic devices, are explored for their potential in providing non-invasive, controlled drug administration. Pulmonary drug delivery systems, such as dry powder inhalers and metered-dose inhalers, are addressed, highlighting their importance in respiratory therapeutics. The principles of mucoadhesive drug delivery for improving gastrointestinal and nasal absorption are examined. Advanced technologies like 3D printing in pharmaceutical manufacturing and its potential for personalized medicine are briefly discussed. Challenges in developing NDDS, including formulation complexities, scale-up issues, and regulatory considerations, are addressed

Keywords: *Controlled release, Targeted delivery, Nanocarriers, Transdermal systems, Personalized medicine, Smart therapeutics*

Learning Objectives

After completion of the chapter, the student should be able to:

- Define novel drug delivery systems and their advantages over conventional dosage forms.
- Classify different types of novel drug delivery systems and their applications.
- Explain the principles of controlled release and targeted drug delivery.
- Describe various technologies used in developing novel drug delivery systems.
- Discuss the formulation considerations for different novel delivery systems.
- Analyze the challenges in developing and manufacturing novel drug delivery systems.
- Evaluate the future trends and potential of novel drug delivery technologies.

Novel drug delivery systems can include those based on physical mechanisms and those based on biochemical mechanisms. Physical mechanisms also referred as controlled drug delivery systems include osmosis, diffusion, erosion, dissolution and electro transport. Biochemical mechanisms include monoclonal antibodies, gene therapy, and vector systems, polymer drug adducts and liposomes. Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) Passive and (ii) Active targeting.

Therapeutic benefits of some new drug delivery systems include optimization of duration of action of drug,

decreasing dosage frequency, controlling the site of release and maintaining constant drug levels

Classification of novel drug delivery systems (NDDS)

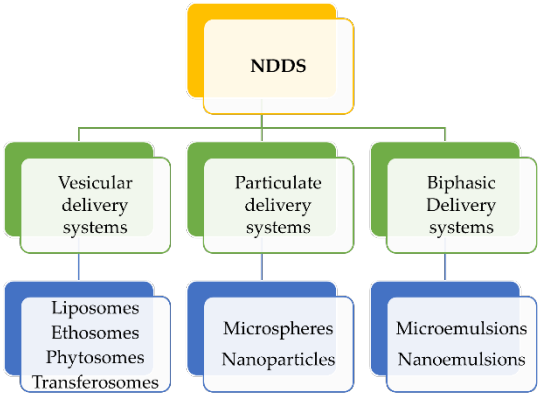

Figure Classification of NDDS

1. Phytosome
2. Liposome
3. Nanoparticles
4. Emulsions
5. Microsphere
6. Ethosome
7. Solid lipid nanopartical
8. Niosomes
9. Proniosomes
10. Transdermal Drug Delivery System
11. Dendrimers
12. Liquid Crystals
13. Hydrogels

PHYTOSOME

Phytosomes are lipid compatible molecular complex which are composed of "phyto" which means plant and "some" meaning cell-like. Complexing the polyphenolic phytoconstituents in the molar ratio with phosphatidyl choline results in a new herbal drug delivery system, known as "Phytosome". Phytosomes are advanced forms of herbal products that are better absorbed, utilized to produce better results than those produced by conventional herbal extracts. Phytosomes show better pharmacokinetic and therapeutic profiles than conventional herbal extracts. Phytosomes are not specifically regulated by the FDA as a distinct category. They are generally considered dietary supplements or nutraceuticals, which do not require pre-market approval from the FDA. The FDA regulates dietary supplements under the Dietary Supplement Health and Education Act (DSHEA) of 1994. Manufacturers are responsible for ensuring the safety of their products before marketing. They must register their facilities with the FDA but don't need FDA approval to sell their products. The FDA can take action if a product is found to be unsafe or if it makes false or misleading claims. While phytosomes don't require pre-market approval, they must comply with Good Manufacturing Practices (GMPs) for dietary supplements.

Advantages of phytosome

1. Phytosome increases the absorption of active constituents, so its dose size required is small.
2. There is appreciable drug entrapment and improvement in the solubility of bile to herbal constituents, and it can target the liver.
3. In Phytosome, chemical bonds are formed between phosphatidylcholine molecules, so it shows good stability.

4. Phytosome improves the percutaneous absorption of herbal phytoconstituents

Types of Phytosomes

Standard phytosomes: These are the most common type, consisting of a plant extract or its constituents bound to phosphatidylcholine. They typically have a 1:1 or 1:2 molar ratio of the herbal extract to phosphatidylcholine.

Lipid-soluble phytosomes: These are designed for lipophilic plant constituents. They may incorporate additional lipids to enhance solubility and absorption of highly lipophilic compounds.

Water-soluble phytosomes: These are formulated for hydrophilic plant extracts or constituents. They may include additional hydrophilic components to improve water solubility and stability.

Preparation Methods

1. Solvent evaporation method:
- The plant extract and phospholipids are dissolved in an organic solvent (e.g., dichloromethane or ethanol).
- The solvent is then evaporated, leaving behind a thin film of phytosome complex.
- This film is hydrated with water or a buffer to form phytosome vesicles.
2. Anti-solvent precipitation method:
- The plant extract and phospholipids are dissolved in a suitable solvent.
- This solution is then added dropwise to an anti-solvent (typically water) under constant stirring.
- The phytosome complex precipitates out and is collected by filtration or centrifugation.
3. Rotary evaporation method:

- Similar to the solvent evaporation method, but uses a rotary evaporator.
- The plant extract and phospholipids are dissolved in a solvent in a round-bottom flask.
- The solvent is removed under reduced pressure using a rotary evaporator.
- The resulting film is hydrated to form phytosomes.

Evaluation/Characterization Tests

1. Particle size and zeta potential analysis:
    - Typically done using dynamic light scattering (DLS) techniques.
    - Particle size affects the bioavailability and stability of phytosomes.
    - Zeta potential indicates the surface charge and predicts stability.
2. Entrapment efficiency:
    - Determines how much of the plant extract or active compound is incorporated into the phytosome.
    - Usually measured by separating free drug from entrapped drug and analyzing using spectrophotometry or HPLC.
3. In vitro drug release studies:
    - Assess how the phytosome releases the entrapped compound over time.
    - Often conducted using dialysis membrane methods or Franz diffusion cells.
4. Transmission electron microscopy (TEM):
    - Provides high-resolution images of phytosome structure and morphology.
    - Can confirm vesicle formation and size distribution.
5. Fourier transform infrared spectroscopy (FTIR):

- Used to study the interaction between the plant extract and phospholipids.
- Can confirm complex formation by showing shifts in characteristic peaks.

6. Differential scanning calorimetry (DSC):
    - Provides information on the thermal behavior of phytosomes.
    - Can indicate changes in melting point or crystallinity, confirming complex formation.

Marketed Products

- Siliphos (Silybin phytosome)
- Greenselect Phytosome (Green tea extract)
- Meriva (Curcumin phytosome)

LIPOSOMES

Liposomes are tiny pouches made of lipids, or fat molecules surrounding a water core widely used for clinical cancer treatment. Several different kinds of liposomes are widely employed against infectious diseases and can deliver certain vaccines. During cancer treatment they encapsule drugs, shielding healthy cells from their toxicity, and prevent their concentration in vulnerable tissues such as those of patient kidneys and liver. Liposomes can also reduce or eliminate certain common side effects of cancer treatment such as nausea and hair loss. They are form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within phospholipid bilayer according to their affinity towards phospholipids. The first FDA-approved liposomal drug was Doxil in 1995. Since then, several liposomal

formulations have been approved, with review times typically ranging from 6-10 months for priority review and 10-12 months for standard review. Doxil (liposomal doxorubicin) was approved in 1995 for AIDS-related Kaposi's sarcoma.

The FDA considers liposomal formulations as new drug products, even if the active ingredient is already approved. Liposomal drugs often qualify for expedited review programs due to their potential for improved efficacy or reduced toxicity. The 505(b)(2) regulatory pathway is commonly used for liposomal formulations of approved drugs. The FDA has issued guidance documents specific to liposomal drug products to aid in their development and approval

Advantages of liposomes

1. The high biocompatibility.
2. The easiness of preparation.
3. The chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds.

The simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components.

Preparation Methods

1. Thin-film hydration method:
    - Lipids are dissolved in organic solvent, which is then evaporated to form a thin film.
    - The film is hydrated with an aqueous solution, forming MLVs.
    - Further processing (e.g., sonication, extrusion) can produce SUVs or LUVs.