



## Stealth Liposomes in Human Welfare: An Overview

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### ABSTRACT

Liposomes are artificially made vesicles which has a lipid bilayer and can be used as a drug carrier molecule for the treatment of various cancers and other diseases. Conventional liposomes have short half-life because of rapid uptake by reticuloendothelial system which leads to decrease in the concentration of liposomes and drug efficacy. Liposomes when coated with polyethylene glycol leads to decreased uptake by the macrophages. This is called as stealth effect which prolongs the half-life of liposome in the circulation and in turn improves drug effectiveness. The liposomes coated with polyethylene glycol are also called as sterically stabilized liposomes or stealth liposomes. This review focuses on the characteristics, methods of preparation, applications, advantages and limitations of stealth liposomes.

**Keywords:** Liposomes, polyethylene glycol, reticuloendothelial system, stealth effect.

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### INTRODUCTION

Liposomes are microscopic vesicles which are spherical in shape and enclosed by a double layer of phospholipids. Liposomes can be filled with drugs and can be used to deliver drugs for cancer and other bioactive molecules to the site of targeted action. Many liposomal drugs are already under clinical use. Long circulating liposomes are produced by modifying the composition of lipids, size and charge of conventional liposomes. These conventional liposomes are modified using molecules like sialic acid or glycolipids.

The development of stealth liposomes started with the insertion of polyethylene glycol (PEG) in liposomal formulations. The inclusion of PEG on the surface of the liposomes extends the blood-circulation time of the liposomes and reduces its uptake by the reticuloendothelial system (stealth technology).<sup>1</sup> With the introduction of the stealth technology, a large number of liposomal drug formulations were developed with high target efficacy. Stealth liposome is composed of a phospholipid bilayer and stabilized by PEG which can be used to deliver drugs to a target cell.<sup>2,3</sup>

### Characteristics of stealth liposome

1. The membrane of stealth liposome is composed of cholesterol, sphingolipids and phospholipids which is similar to the composition of host cell membrane.
2. The phospholipid bilayer consists of hydrophilic head (made up of phosphoric acid and glycerol) and hydrophobic tail (made up of fatty acid chain). Stealth liposome has PEG as an outer coating.
3. Stealth liposomes are colloidal in nature
4. Their size ranges from 50 to 5000nm.
5. The size and shape of the stealth liposome can be modified based on the drug and polymer.
6. They are stable in nature and they are not taken up by the reticuloendothelial system

### Methods of preparation

The preparation of stealth liposomes are similar to the methods of preparation of the conventional liposomes. But one important step in the preparation of stealth liposomes is PEGylation. PEGylation is the process in which the polymer is attached to the membrane of the liposome. The various methods for preparation of stealth liposomes are as follows<sup>4</sup>

1. Hand shaken method
2. Probe sonication method
3. Bath sonication method
4. Detergent deletion method
5. Liposome extrusion method
6. Reverse phase evaporation method
7. Freeze dried rehydration method



8. Micro fluidization method

9. Solvent injection method

### Polymers used in stealth liposomes

#### **Polyethylene glycol (PEG)**

PEG is mainly used in preparation of stealth liposome. PEG is hydrophilic in nature. In the final step of preparation of stealth liposome PEG is added which covalently attaches to the outer surface of the liposomal membrane thereby producing long circulating liposomes. Polyethylene glycol has the following characteristics as an ideal polymer:

- A. It is biodegradable and biocompatible.
- B. It is nontoxic and do not produce any inflammatory response.
- C. It is permeable to the lipid bilayer of the host cell membrane.
- D. It is not recognized completely or partially by mononuclear phagocytic system (MPS).

The other polymers used in stealth liposomes are<sup>5, 6, 7, 8</sup>

1. Polyacrylamide
2. Poly -2-methyl-2-oxazoline)
3. Polyglutamic acid
4. Polyglycerol
5. Polyvinylpyrrolidone
6. Poly N-2-hydroxypropyl methacrylamide

### Applications of stealth liposomes

**Stealth Liposome in Targeted delivery:**-Targeted liposomes are developed to increase drug accumulation in the target tissues thereby producing greater therapeutic activity. Targeting moieties can be monoclonal antibodies or ligands, peptides, growth factors or glycoproteins.<sup>9</sup> The anti-HER2 antibody named trastuzumab was the first human monoclonal antibody for metastatic breast cancer.<sup>10</sup> Folic acid containing liposomes are being used for targeting of doxorubicin, daunorubicin and cisplatin to the cancer cells.<sup>11</sup> Transferrin ligand attached liposomes are used for delivery of anticancer drugs, proteins and genes to the cancer cells.<sup>12</sup> Haloperidol containing stealth liposomes are being used to target genes to breast cancer cells.<sup>13</sup> L-peptide attached stealth liposome are used to deliver targeted anticancer drugs to the nasopharyngeal cells.<sup>14</sup>

**Stealth liposome in cancer therapy:** Stealth liposomes are useful in the treatment of cancer as they have long circulation time and targeted delivery. These liposomal drug retention within the cancer cells is generally high because of the poor lymphatic drainage in the cancer cells. The stealth liposome have enhanced permeation and increased retention effect. DOXIL is brand name of the drug doxorubicin by Seques pharma Ltd. It is a stealth liposome formulation available for treatment of ovarian cancer and kaposi's sarcoma.<sup>15</sup>

**Stealth Liposome in Vaccines:** There are various liposomal vaccines which are under clinical trials. Epaxal is a liposomal based hepatitis A vaccine which has inactivated hepatitis A virus anchored to their phospholipid bilayer.<sup>16</sup> Liposome based malaria vaccine has shown to produce higher level of anti-malarial antibody in healthy human volunteers.<sup>17</sup> Liposomal mycobacterium tuberculosis vaccine promotes T cell mediated immunity in human subjects is under investigation.<sup>18</sup>

**Stealth Liposome in Diagnostic Imaging:** Long circulating liposomal vesicles can be used as carrier molecules for various contrast agents used in computed tomography imaging, magnetic resonance imaging, gamma-scintigraphy and sonography. The liposomal vesicles used in diagnostic imaging has several advantages like they can deliver the contrast agent to the specified target site and also they help in enhancing the contrast signal. Gadolinium-containing sterically stabilized PEGylated liposomes are used as highly potent contrast agents in Magnetic resonance imaging.<sup>19</sup>

**Stealth liposome in gene transfection:** Stealth liposomes are used as transfecting vectors in cationic form. The encapsulation of gene in liposomal vesicles protects the DNA against degradation in the lysosome compartment. Many cationic liposomal formulations have been tested for gene delivery. The clinical use of cationic liposomes have various limitations like rapid clearance, large particle size, immunostimulation and complement activation. To overcome these limitations PEGylated cationic liposomes are introduced to prolong the circulation time in vivo and decrease immunostimulation and complement activation.

### Advantages of Stealth liposomes

1. Increased bioavailability
2. They provide sustained slow release of drugs.
3. Nontoxic and biodegradable
4. They provide targeted drug delivery in cancer therapy

### Limitations of stealth liposomes

The chemical interaction of stealth liposome with the cell membrane of the host cell and release of bioactive drug in the surrounding region of target tissues are the main limitations with stealth liposomes which can be improved by use of detachable PEG and intracellular delivery of vesicles.

### CONCLUSION

Stealth liposomes play an important role in targeted drug delivery, more effectively than the conventional liposomes. PEG coated liposomes with increased circulation time can be targeted with monoclonal antibodies and various ligands to deliver the bioactive molecules accurately to the target tissues. Stealth liposomes are of great interest of research in gene therapy and vaccination.



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