TOPICAL REVIEW

A brief overview about the use of different bioactive liposome-based drug delivery systems in Peritoneal Dialysis and some other diseases

Sandeep Kumar Singh, Umesh Kumar, Anupam Guleria and Dinesh Kumar
Centre of Biomedical Research, SGPGI Campus, Lucknow-226014, India
E-mail: sks.1247@gmail.com

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Abstract
Peritoneal dialysis (PD) is a promising way of treatment used for patients suffering from End-Stage Renal Failure (ESRF). Liposomes are nanocarriers comprised of lipid bilayers encapsulating an aqueous core. Liposomes are extensively used as drug delivery systems and several liposomal nanomedicines have been approved for clinical applications. Nanomedicine constitutes a new direction in peritonitis prevention using peritoneal dialysis (PD). In case of PD; there is a more risk of bacterial infection in the peritoneal cavity along with subcutaneous tunnel and catheter existing site. These infections are the most common complications associated with prolonged peritoneal dialysis (PD) therapy. To prevent such complications, patients used to treat with suitable antibiotic. Nanocarriers consist of assembly of nano-sized vehicles planned to deliver encapsulated/loaded bioactive(s) to the specific target (tissues or organs) and have provided prominent improved therapeutic efficacy for PD patients. The advantage of bioactive loaded nanocarrier has the efficient capacity to deliver at target specific site in PD. This review focuses mainly on the current use of different liposomal encapsulated bioactive compounds in drug delivery systems in the case of PD and other human diseases and briefly highlights the importance and use of different liposomal encapsulated antimicrobial agents to improve the PD technique.

Nomenclature
ESRF End-Stage Renal Failure.
HAI Healthcare associated infections
HD Hemodialysis.
IP Intraperitoneal.
LUVs Large unilamellar vesicles
MDR Multidrug-resistant
MRSA Multidrug-resistant Staphylococcus aureus.
NDDS Novel drug delivery system
PD Peritoneal dialysis.
PEG Polyethylene Glycol
RRT Renal replacement therapy.
siRNPs Silica-containing redox nanoparticles.

Peritoneal dialysis (PD)
Peritoneal dialysis (PD) is an unshakable renal replacement therapy (RRT) used for the treatment of the patients suffering with end-stage renal failure (ESRF). In developing countries like India, PD is mostly used for a patient
suffering with severe acute kidney injury to provide support and easy treatment. It is highly cost-effective and offers the advantages of having a supple lifestyle, steady hemodynamics, and better conservancy of residual renal function. However, PD therapy is usually related to a high-risk infection of the peritoneum; subcutaneous tunnel and catheter exit site as well as the successively formed microbial biofilm [1–4]. These recurrent microbial infections lead to the wedged of the peritoneal membrane, the condition referred to as infectious peritonitis which is the leading reason behind the death and morbidity rate in PD patients [1, 3]. Further due to the weak immune system, the PD patients repeatedly demand a higher dose of antibiotic to tenacity the infectious condition. But, the continuous intraperitoneal supply of higher dose of antibiotic and their absorption by the peritoneum lead to harmful effects including glitches of the peritoneal cavity, hepatotoxicity along with multiple drug resistance (MDR) [5]. Thus, this is a very demanding and urgent situation to amend the PD technique so that the incidence of these life-threatening and serious episodes of infectious peritonitis can be reduced.

Nanotechnology and its importance in medical science
Nanotechnology is the study of very tiny structures [6]. General meaning of nano is very small or miniature size. Nanotechnology is the design, production, and application of structures, devices, and systems by manipulation of size and shape at the nanometer scale [7]. Nowadays Nanotechnology is very advance field with its application in the field of medicines and pharmaceuticals.

Nanotechnology deals with materials in the size of 0.1 to 100 nm; however, it is also very important that these materials should display different properties such as magnetism, chemical reactivity, optical effects, electrical conductance and physical strength, from bulk materials as a result of their nano size [8]. Nano-medicines can be enriched with characteristics different from traditional drugs by encapsulating drugs in nanocarriers or modifying nanodrugs [9, 10].

Nanotechnology can benefit chemical catalysis due to the extremely large surface to volume ratio. The various applications of nanoparticles in catalysis range from fuel cell to catalytic converters and photocatalytic devices. There are various applications of nanotechnology in different field including in Health and Medicine, Electronics, Transportation, Energy and Environment, Space exploration etc [11].

Nowadays there are serval human disease like cancer, diabetes, Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, cardiovascular diseases and other various serious inflammatory or infectious diseases constitute a high number of serious and complex illnesses which are posing a major problem for the mankind [8]. So, there is diverse role and importance of nanomedicine in diagnosis and treatment of the various diseases mentioned above and many more. Using the nanomedicine, the damaged tissue can be repaired or reproduced. Nanomedicine is an application of nanotechnology which works in the field of health and medicine. Nanomedicine makes use of nano materials, and nano electronic biosensors. In context of the review, nanotechnology have an important application in the use of drug delivery for specific site in particular disease. So, the targeted medicine reduces the drug consumption and treatment expenses, making the treatment of patients cost effective.

Nanocarriers based drugs and importance of liposome
Nanocarriers are a cluster of nano-sized vehicles device to transport loaded bioactive compounds or substances to the specific target (tissues/organisms) and also showed awfully evolved therapeutic efficacy in PD patients [12]. An array of nano-carriers such as nanoparticles, micelles, dendrimers, liposomes, carbon nanotubes, gold carriers, solid lipid carriers, viral carriers and magnetic carriers integrating cytotoxic therapeutics have promising ways of delivery system used for several human diseases [13]. Among these, this chapter focuses on liposomal mediated therapeutic approaches for the treatment of complications related with PD patients. Furthermore, liposomal mediated drug delivery systems may aid as potential way of drug delivery to resolve multiple issues associated with PD therapy such as to eradicate intraperitoneal infections and microbial biofilms in an efficient and timely manner and to advance the efficiency of peritoneal dialysis for complete elimination of drug metabolites and harmful endotoxins from the patient body after the treatment. Recently liposomes are being utilized in making effective drugs against cancer and imitating microorganisms of host cells [14, 15]. The important and most attractive features of liposomes are the encapsulation of both hydrophilic and lipophilic drugs and improved therapeutic index of the drugs and minimizing their adverse effects [16]. Moreover, liposome supposed to be a good vehicle for drug delivery because of its compatible physicochemical properties like biodegradability, biocompatibility, and low cytotoxicity [17]. All these features are desirable for enhancing dialysis efficiency and treatment against the alarming intra-peritoneal infections in PD patients. The major advantage of liposomes to assist drug delivery is that it effectively helps in the delivery of encapsulated compounds to the specific sites while minimizing systemic toxicity [18].
Complications associated with PD

Intraperitoneal infections (Peritonitis) are the most abundant type of complication associated with interminable peritoneal dialysis (PD) therapy used for treating patients with ESRF and is the cause of significant morbidity and mortality rate in PD patients. Infectious peritonitis is technique failure and due to which the patient shift to haemodialysis [1, 3]. In recent years, the number of infections related to antibiotic-resistant bacteria has increased and also the intraperitoneal infections caused by such drug-resistant bacteria remain critical. *Staphylococcus aureus* is the predominant bacterial infection associated with PD. The Center for Disease Control and Prevention (CDC) announced that the number of multidrug-resistant *Staphylococcus aureus* (MRSA) infections increased annually from 127,000 to 278,000 between the years 1999 and 2005 [19]. Likewise, the number of annual MRSA-related deaths elevated from 11,000 to 17,000 over the same time duration [6]. Also, the increase of MRSA is accredited primarily to the overexpose and inappropriate use of antibiotics. In current clinical practice, the events of PD associated infections if diagnosed on appropriate time, are cured by the proper use of suitable antibiotics. The ESRF patients remaining on PD generally require higher dose of antibiotic to resolve the infection condition due to their weak immune system, which may lead to deadly outcome such as hepatotoxicity, peritoneal malfunctioning and MDR. Even after strong antibiotic treatment, the peritonitis does not resolve for several patients and they are transferred to permanent or temporary haemodialysis (HD) depend on the situation. As the number of ESRF patients relying on PD is growing continuously worldwide (because of scarcity of the kidney(s) necessary for the transplantation and several other reasons and limitations), the PD associated infections are also emerging as most prominent situation and imposing extra load on dialysis-centers/nephrology-wards to tackle such life-threatening events of infectious peritonitis and in coming days, it is a serious issue for future and one of the most complicated and deadly healthcare associated problems. The situation is even more miserable and destructive in the developing countries like India, where most of the ESRF patients residing on PD die because of intraperitoneal (IP) infections either due to unavailability of proper treatment, poor socioeconomic status of patients and limited number of dialysis centers [1, 3, 20, 21]. Therefore, spontaneity of existing PD technology is important, particularly, to reduce the frequency of PD associated infections and thereof the episodes of infectious peritonitis.

Nanocarriers and liposomal encapsulation of antimicrobial agent targeting infectious biofilm

Nanotechnology based products and solutions have extensively being utilized for biomedical applications and particularly, are of great focus as an approach to kill or reduce the activity of various microorganisms and associated infections. There are well-documented studies in the literature where such commodity including nanomedicines have been involved in the diagnosis and treatment of diseases including renal disorders [22–26]. There is also an increasing evidence of bioactive nanocarriers which has been expected to improve the PD technique by the use various ways: (a) anti-microbial solution spraying, preventing infection at Catheter Exit-Site [27] (b) nano-carriers for TNF-β–1-SiRNA to prevent the peritoneal fibrosis [28], (c) redox nanoparticles (siRNPs) of silica for high-performance PD through scavenging Reactive Oxygen Species to overcome the oxidative stress [29], and (d) antimicrobial nanomaterials to reveal infection resistant properties to the PD fluid [30]. Another promising approach to improve the current practiced PD therapy can be anticipate by using liposomal encapsulated antibiotic treatment. Liposomal encapsulation of antibacterial agents has very important role in other human diseases too, several antimicrobial agents have been used in various other disease also for targeted drug delivery using liposome.

It has been already reported that fusogenic liposomes comprised cholesterol hemisuccinate were effective to enhance the antimicrobial activities of vancomycin drug against a range of vancomycin-resistant, Gram-negative bacteria [31].

Furthermore, it was shown by previous study that when specific antibiotic encapsulated with liposome were administered then several antibiotic-resistant Gram-positive and Gram-negative bacteria have been demonstrated to lose their resistance and potentially contributed to the fucogenicity and the provide a strong protection by the encapsulation [31–33]. Liposomes have also been shown potential antimicrobial application when used to encapsulate the antimicrobial agents against *P. aeruginosa* biofilms infections [34]. Another study by Beaualc et al strongly supported the concept of effectiveness of antibacterial drug encapsulated with liposome. He showed that Fusogenic liposomes which composed of Dipalmitoylphosphatidylcholine (DPPC) and dimristoylphosphatidylglycerol (DMPG) were effective to carried the tobramycin specifically site of mucoid pulmonary *P. aeruginosa* biofilms infection [35]. It was clearly shown that liposomal tobramycin effectively acted against the biofilms, whereas naked drugs was ineffective. So, we can say that liposomal encapsulation of any antimicrobial drug is more effective and potential to prevent the microbial infections and improve the human health issue.
Advantages of liposome used as drug delivery system

As illustrated in figure 1, the clear advantages associated with liposomes include its ability (a) to encapsulate both water-soluble and lipid-soluble compounds/drugs, respectively, within their aqueous spaces and membrane bilayer, (b) to protect degradation of the drugs in the body, (c) to surface engineer these entities for targeted drug delivery without causing harm to healthy cells and (d) to provide sustained release owing to their prolonged retention time; particularly, large unilamellar vesicles (LUVs) of size >1000 nm exhibit optimal peritoneal retention inside the peritoneal cavity [36]. All these characteristics are greatly enticing for promoting dialysis efficiency and treatment of alarming intraperitoneal infections in PD patients. The efficacy of currently available antibiotics can be enhanced in the form of liposomal formulations. Liposomes have successfully been used in the delivery of anticancer, antibacterial and antifungal drugs in vitro and in vivo [37]. So, nowadays researcher are focusing to find the suitable natural antibacterial liposomal encapsulated drug for the treatment of PD patients. Therefore, this area should be explored for future drug discovery targeting liposomal based nanoparticle for the treatment of peritonitis.

Use of liposomal based drugs as antimicrobial agents

Healthcare associated infections (HAI) along with multidrug-resistant (MDR) bacteria remain to be a global risk, highlighting a vital need for novel antibiotics. While many researchers are putting their efforts to come up with some new antibiotics, others are focused on improving the efficiency of antibiotics currently available in the form of liposomal formulations [38]. Liposomes owing to their ability to encase both lipophilic and hydrophilic drugs- are emerging technologies for the rational delivery of chemotherapeutic drugs in the treatment of various human pathologies including cancer, critical bacterial/viral infections [39]. Their use overture enhanced pharmacokinetic properties controlled and uninterrupted release of drugs and, more importantly, reduced systemic toxicity. Liposome based delivery of antibiotics have also been researched extensively and intensively in last two decades to enhance their antimicrobial activity and pharmacokinetic properties [40–44]. Nowadays, there are various liposome based pharmaceutical products available in the market for their use in veterinary and human healthcare [39, 45], some of the commercially available liposome based drugs are mentioned in figure 2 and also illustrated with the active components along FDA approved year which involved in drug delivery in various disease conditions (table 1). Also, in table 2, we mentioned the Drugs which are in different phase of clinical trial with agents/target (table 2).

The effect of lipid composition, liposome coated with polyethylene glycol (PEG) charge has been investigated on the peritoneal holding of liposomes [82]. Further the use of liposomes as a detoxicant for drugs and endogenous metabolites to enhance the efficacy of peritoneal dialysis has also been reported [83, 84]. However, so far, no scientific studies have been reported on (a) the design of liposomal antibiotic formulations for the treatment of intraperitoneal infections associated with PD therapy, (b) whether the liposomal antibiotic formulations remain stable in all the variants of PD fluids available in the market, (c) what should be the maximum non-toxic dose for their clinically safe intraperitoneal use and (d) whether they preserve their efficacy and adequacy when used intraperitoneally along with PD fluid. Apart from the commercially available antimicrobial liposomal encapsulated drug there are several natural plants extract (table 3) which are extensively...
Table 1. List of different types of commercially available liposome-based drugs against various disease conditions with active agents.

| S. No. | Name of drugs | FDA approved year | Active agents | Indication | References |
|--------|---------------|-------------------|---------------|------------|------------|
| 1.     | Doxil®        | 1995              | Doxorubicin   | Kaposi’s sarcoma | [17, 46, 47] |
| 2.     | DaunoXome®    | 1996              | Daunorubicin  | Leukemia    | [48, 49]   |
| 3.     | Depocyt®      | 1999              | Cytarabine    | Neoplastic meningitis | [17, 50, 51] |
| 4.     | Mepact®       | 2004              | Mifamurtide   | Osteosarcoma | [52, 53]   |
| 5.     | Onivyde™      | 2015              | Irinotecan+fluorouracil+folic acid | Pancreatic adenocarcinoma | [54, 55] |
| 6.     | Myocet®       | 2000              | Doxorubicin+cyclophosphamide | Metastatic breast cancer | [17, 56, 57] |
| 7.     | Marqibo®      | 2012              | Vincristine   | Non-Hodgkin’s lymphoma and leukemia | [17, 58, 59] |
| 8.     | Exparel®      | 2011              | Bupivacaine   | Used for pain management | [60, 61] |
| 9.     | DepoDur™      | 2004              | Morphine sulfate | Used for pain management | [62, 63] |
| 10.    | Inflexal® V   | 1997              | Inactivated hemagglutinin of A or B influenza virus | Influenza | [39] |
| 11.    | Epaxal®       | 1993              | Inactivated hepatitis A virus (strain RG5B) | Hepatitis A | [39, 64, 65] |
| 12.    | Abelect®      | 1995              | Amphotericin B | Invasive fungal infection | [17, 39, 66] |
| 13.    | Ambisome®     | 1997              | Amphotericin B | Invasive fungal infection | [17, 39, 67] |
| 14.    | Amphotec®     | 1996              | Amphotericin B | Fungal Infection | [68, 69] |

Table 2. Liposomal drugs under various clinical trial phase.

| S. No. | Name of drug | Clinical trial phase | Agents/Target | References |
|--------|--------------|----------------------|---------------|------------|
| 1.     | BP1001       | Phase I              | Antisense protein/Grb-2 | [70] |
| 2.     | INX-0076     | Phase I              | Topotecan Sphingosomes | [39] |
| 3.     | LEM-ETU      | Phase I              | Mitoxantrone/TOPO II inhibitor | [71] |
| 4.     | Aroplatin    | Phase II             | L-NDDP/Platinum | [72] |
| 5.     | OSI-211      | Phase II             | Lurtotecan/antineoplastic | [73] |
| 6.     | S-CK2D602    | Phase II             | TOPO I inhibitor | [74] |
| 7.     | Arikace      | Phase III            | Amikacin/Ribosomal inhibitor | [75] |
| 8.     | Liprostin    | Phase III            | PGE-1/Prostaglandin Receptor | [76] |
| 9.     | Thermodox    | Phase III            | Doxorubicin/antimitotic | [77] |
| 10.    | Cyclophosphamide | Phase III     | Nitrogen mustard/antineoplastic | [78] |
| 11.    | Atu027       | Phase I              | siRNA/Solid tumors | [79] |
| 12.    | Irinotecan SN-37 | Phase II              | Camptothecin/DNA damage | [80] |
| 13.    | CPX-351      | Phase III            | Cytarabine/daunorubicin/DNA polymerase inhibitor | [81] |
Table 3. List of some natural plants having antimicrobial bioactive components effective against various microorganisms.

| S. No. | Natural source     | Antimicrobials                        | Microbes effected                                                                 | References |
|--------|--------------------|---------------------------------------|----------------------------------------------------------------------------------|------------|
| 1.     | *Angelica lucida L*| Coumarins                             | *S. mutans, S. viridans*                                                         | [85]       |
| 2.     | *Cirsium hypoleucum*| Flavones                              | Multidrug Resistance (MDR), *pneumoniae*                                        | [86]       |
| 3.     | *Allium sativum*   | Allicin, Organosulphur compounds      | *MDR E. coli, C. albican, Campylobacter jejuni, Giardia lamblia, Entamoeba histolytica* | [87, 88]  |
| 4.     |                    | Tannins, Flavonoids, Terpenoids, Saponins, | *B. subtilis, S. aureus viridians, E. coli, MDR E. coli, Shigella sonnei, K. pneumoniae, C. albican* | [89, 90]  |
| S. No. | Natural source | Antimicrobials | Microbes effected | References |
|-------|----------------|----------------|-------------------|------------|
| 5.    | 
|       | **Lawsonia inermis** | Quinones | MDR *Pseudomonas aeruginosa* | [91] |
| 6.    | 
|       | **Curcuma longa** | Curcuminoid (A phenolic compound), turmerone, curclone, Essential oil, curcumin, turmeric oil | *S. aureus*, *S. typhi*, *E. coli*, *B. cereus*, *P. aeruginosa*, *B. subtilis*, *B. coagulans*, *P. digitatum*, *A. niger*, Antifungal and antiviral activity | [92] |
| 7.    | 
|       | Saponins, Canavanine | | *Enterococcus faecium*, *S. aureus*, Antifungal | [93] |
Table 3. (Continued.)

| S. No. | Natural source | Antimicrobials | Microbes effected | References |
|--------|----------------|----------------|-------------------|------------|
|        |                |                |                   |            |
| 8      | *Medicago sativa* |                |                   |            |
|        | *Raphanus sativum* | RsAFP2 (Antifungal peptide) | *C. albicans* | [94] |
| 9      | *Syzygium aromaticum* | Eugenol, Essential oil. | *S. aureus*, *S. mutans*, *Candida albicans*, *L. acidophilus*, and *Saccharomyces cerevisiae*, *K. pneumoniae*, MDRE. coli, | [95] |
| 10     | Antimicrobial peptides (AMPs) | | *E. faecium*, *S. aureus* | [93] |
| S. No. | Natural source       | Antimicrobials     | Microbes effected                                      | References |
|-------|----------------------|-------------------|--------------------------------------------------------|------------|
| 11    | *Onobrychis sativa*  |                   | MDR *Staphylococcus aureus*                            | [96]       |
| 12    | *Mentha longifolia*  | Essential oil     | MDR *Staphylococcus aureus*                            | [96]       |
| 13    | *Zingiber officinale*| Gingerol          | *P. aeruginosa, Enterobacter spp., E. coli, Klebsiella spp., Proteus spp., Bacillus spp.* And *S. aureus* | [97, 98]   |
| 14    | Flavonoid, Polyphenol|                   | *E. coli, S. Typhi, MDR Pseudomonas aeruginosa,*      | [97]       |
Table 3. (Continued.)

| S. No. | Natural source | Antimicrobials | Microbes effected | References |
|--------|----------------|----------------|-------------------|------------|
|        | Allium cepa    |                |                   |            |

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being used as antimicrobial component are equally important and we can focus to encapsulate these natural antimicrobial components using liposome and could be used as suitable drug target in clinical settings for the treatment of PD.

**Conclusion**

Peritoneal dialysis therapy -widely used in nephrology clinics for curing the patients suffering with end-stage renal failure- is often related with a severe risk of infection of the peritoneum, subcutaneous tunnel and catheter exit site. The infections develop because of persistent colonization of sporadic microbial contaminations owing to inherently weak and sabotaged immune system of ESRF patients continuing on PD. The infection causes the serious condition; peritonitis. In situations when the infectious peritonitis does not resolve, the intravenous antibiotics or catheter removal may become necessary. So continuous supplementation of traditional antimicrobial agents are the owning of multiple drug resistance and hostile side effects. So, to prevent such peritonitis condition, we should target specific site with suitable and effective drug release using liposomal encapsulation of antibiotics. Along with PD, there are several human diseases where there is effectively drug target and release is required which can be possible by using nanomedicine treatment approaches. So this chapter is focuses to discuss and explain the benefit and significance of liposomal mediated drug delivery system for the treatment of critical microbial associated infections during long term PD. The improvisation using liposomal formulations will help a lot the PD patients in two ways: (a) it will provide them a improved quality of life by reducing the incidence of infectious peritonitis and (b) it will reduce the financial burden on such PD patients through compromising their visits to hospitals. So far, the liposomal drugs are not in clinical practice for treating the PD associated infections. This chapter will provide the road map for the researcher to explore the therapeutic approaches of liposomal encapsulated drugs in the treatment of PD associated complications in future clinical settings.

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**Data availability statement**

All data that support the findings of this study are included within the article (and any supplementary files).

**ORCID iDs**

Sandeep Kumar Singh https://orcid.org/0000-0002-0022-6240

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