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Clinical implications of novel polymer and lipid based drug delivery systems

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ABSTRACT



The use of lipids in drug delivery is not a new trend, some of the lipid dosage forms have been in use for a long time such as suppositories, creams, and emulsions. However, there has been much advancement in the designs of lipid carriers over the past decade. In the same way from the past two decades, new approaches in biodegradable and bio-reducible polymers have paved a way for many recent drug delivery systems. Applications of these novel drug delivery formulations have been promising clinically. However, each system has its pros and cons in various factors depending upon their use and intended route of administration. This review focuses on upbringing the challenges in the use of novel lipid and polymer drug delivery systems in clinical settings and few insights on how to overcome them.

Keywords: Novel drug delivery; Gene delivery; Liposomes; Polymerosomes; Solid dispersions.

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Review Article

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INTRODUCTION

In pharmaceutical technology, lipids and polymers have always been the vital components of drug delivery and dosage forms [1]. They can be used in many ways such as stabilizers, solubilizers, permeation enhancers, release rate modifiers, and also targeted systems. In the early day's lipids and polymers were derived from various natural sources but with advancements and development in chemistry, the drug formulators now use a variety of natural, semi-synthetic, and also completely man-made lipids and polymers manufactured in various types for use in different routes such as oral, topical, etc. Lipids and polymers have similar roles despite their structural differences and quality by design approach is followed to ensure safety of product [2]. New applications of lipids in fields such as gene

therapy and new methods of improving circulation in the body blood flow by stabilization are also being proven efficient [3].

Novel lipid-based nanoformulations such as nanostructured lipid carriers and solid lipid nanoparticles have been proven to be a recent breakthrough in many aspects. Nanofibres that are manufactured through electrospinning are also proving to be efficient in cancer diagnosis, tissue engineering etc [4,5,6]. However, when it comes to usage of these drug delivery systems through various routes in real-time clinical settings and hospitals, few challenges need to be addressed [7]. Certain side effects and adverse outcomes are being reported by the usage of these novel drug delivery systems in clinical settings. Although many of these drug delivery systems reach the clinical trials phase, some of them don't show expected and desirable results and can't succeed the phase 4 of clinical trials. Certain steps are followed by manufacturers to ensure the safety of using these drug delivery systems. High-performance liquid chromatography (HPLC) is used for the analysis [8,9,10].

Novel lipid based drug delivery systems

The main objective of using lipid-based drug delivery systems is to improve the bioavailability and to promote better solubility as well as the distribution of poor water-soluble drugs [11]. Lipid-based formulations can be efficiently designed to meet many requirements such as solubility, cost-efficacy, bioavailability, route of administration, and toxicity. Lipid-based drug delivery system can be used for routes including oral, topical, vaginal, parental, ocular, and also intranasal. For example proliposomal gel is used for rheumatoid arthritis for sustained

release of drug. [12,13] However the most preferred route is oral. A recent novel approach for the oral lipid drug delivery system is lipid nanocarriers. The recent developments are in motion in solid lipid nanoparticles (SLN's), Nanostructured lipid carriers (NLC's), Lipid drug conjugate (LDC's), Self nano emulsifying drug delivery system (SNEDDS) [14,15,16]. These nanoparticles have opened up a way for the treatment of cancer through options such as gene therapy through siRNA. High Profile Liquid Chromatography is used for quantitative and qualitative isolation of lipids. The main exponents for lipid-based formulations are: 1) Solubility, 2) Dispersion, 3) Digestion, 4) Absorption. [17,18]

Trends in novel lipid based drug delivery systems

Recent technological advancements in medicine and discoveries in pharmacology have made possible many new lipid-based drug delivery systems and paved a way for efficient treatment methods for cancers too [19]. Lipid-based drug delivery systems are nowhere to be considered as new because they have been in use for a very long time. But recent and main advancements have occurred over the past decade with breakthrough discoveries. [20]

Recent trends in the lipid-based drug delivery systems are nano particles with limelight focused upon solid lipid nanoparticles and nanostructured lipid carriers [21,22]. These two along with hybrid nanoparticles have gained much interest as drug delivery systems because of their capacity to hold and release drugs of Class 2 (High Permeability and Low Solubility)[23] and Class 4(Low Permeability and Low Solubility)[24] from the Biopharmaceutical Classification System (BCS). Many novel liposomal drug formulations are already in late-stage clinical trials for cancer treatment as they have been proven effective in improvising the efficacy and safety of chemotherapeutic agents for cancer treatment. [25] Specific targeted drug delivery is the main goal for any discovery and that is made possible by temperature-sensitive liposomes (TSL's) that helps in minimizing the clearance and non-specific uptake. ThermoDox (Celsion) is showing promising results in drug uptake and release rate in heated tumors. Magnetic resonance-guided focused ultrasound is being combined with TSL to promote better efficacy of localized chemotherapy. Protoposomes, defined as free flowing particles in a dispersed system can immediately convert into liposomal suspension as soon as it comes in contact with water. [26,27,28] Nanocarrier based delivery of platinum compounds for cancer treatment in the field with most extensive research and clinical trials under progress which would revolutionize the platinum chemotherapy. Some other innovations of lipids are, nanofibres which brought a revolution in tissue engineering. Also nano ethosomes which carry bioactive agents and help penetrate them deep into the layers of skin. [29]

Novel polymer based drug delivery systems

Polymer-based drug delivery systems have gained major advancements in the past two decades. It can be defined as a formulation used to introduce a drug into the body. Biodegradable and bio reducible polymers have made possible a choice for many new drug delivery systems. [30] For polymer-based drug delivery systems natural polymers such as polysaccharides, dextrin, chitosan (obtained from shellfish) [31], arginine, alginate (derived from brown seaweed known as Phaeophyceae), Zein (found in corn) and hyaluronic acid are used. Synthetic polymers such as dendrite polymers, 2-hydroxyethyl methacrylate, PLGA (elastomeric copolymer) and N-isopropyl acrylamide are used. Targeting polymeric drug delivery and biomimetic and bio-related polymeric systems are also used in polymeric based drug delivery.[32,33,34] The polyethyleneimine derivatives are used as a system for non-viral vectors for gene delivery also polyethyleneimine copolymer. Polyvinylpyrrolidone (PVP) is also being studied as excipient from conventional to controlled delivery systems for COVID-19 inhibition.[35] Systems for viral vectors are DNA conjugates and RNA conjugates for gene delivery. In situ gel is an effective polymer based drug delivery system for ophthalmic purposes.[36]

Trends in novel polymer based drug delivery systems

Smart polymers can be said as the current breakthrough in the drug delivery system from the past decade. The ultimate aim for a manufacturer of any drug or any invention of formulation and drug delivery system is to provide a site-specific or targeted drug for anything, recent advancements in the polymeric drug delivery system have made this possible. For example Alginate is multifunctional with its uses ranging from impression making in dentistry and also in preparation of reflux inhibiting medications.[37,38] Zein another natural polymer is used for targeted drug delivery, gene delivery and also vaccinations. Smart polymers are gaining momentum, and researchers are interested as the discoveries in the chemistry by scientists are paving a way for innovation of controlled release drug systems and drugs that sense environmental and biological changes. [39,40] The smart polymers such as pH-sensitive polymers, temperature-sensitive polymers, polymers with dual stimuli responsiveness, phase-sensitive polymers, and light-sensitive smart polymers are the major discoveries in the past 10 years that made possible a ton of new efficient ways for treatment. Biomimetic and bioinspired systems are used to improve the biocompatibility during drug delivery. [41] Dendrimers, these polymers with well defined molecular weight and multi-branching are showing promising results for further aspects of polymeric drug delivery systems. The viral and non-viral vectors for polymeric gene delivery are promising for cancer treatment and have the potential to be an important tool for human gene therapy too. Okra

thioglycolic acid is used as a mucoadhesive polymer and is multifunctional.^[42] Chitosan a naturally obtained polymer is also proven to be effective in weight loss.^[43]

Clinical implications by using lipid/ polymer drug delivery systems

Although Lipid and Polymeric drug delivery systems are considered as one of the greatest advancements in the past decade there are many challenges when it comes to real-time clinical setting. Many of these new delivery systems are not being successful in phase 4 clinical trials.^[44,45]

Disadvantages and limitations of lipid based drug delivery systems

Every system has pros and cons to go with. There are certain disadvantages for lipid-based drug delivery systems, some of them are:

1. **API Instability:** API Instability is seen in certain formulations; research is still ongoing to consider the factors that promote API stability.^[46]
2. **Excipient shell compatibility issues:** This compatibility issues and interactions may have effects on bioavailability, stability, and chemical also physical factors of the drug or dosage.^[47,48]
3. **Uncontrolled drug precipitation post-dosing:** This may have normal therapeutic failure or serious effects on the patients by either embolization ranging from thrombophlebitis or multiple organ failure and even death.^[49]
4. **Inadequate drug loading in the lipid drug delivery system:** This is also a major setback in the formulation of the lipid-based drug delivery system which may lead to inefficient therapeutic effects.^[50, 51]
5. Drug burst release by erosion mechanism.^[52]
6. Drug expulsion.^[45]
7. Accumulation of lipids in the liver and spleen may cause pathological alteration with certain lipid nanoparticles.^[53]
8. Enhanced permeability and retention effect (EPR) may vary significantly from one human patient to another.^[4]

Disadvantages and limitations of polymeric based drug delivery systems

1. Insufficient literature of toxicological assessment^[54]
2. Can be only used for lipophilic drugs^[55]
3. Low drug loading capacity^[56]
4. Elimination and mechanism depending upon the materials and generation^[57,58]
5. High cost for their synthesis^[52]
6. Chances of cellular toxicity^[36]
7. Difficult to maintain the integrity of synthetic and natural polymers in the body in genetic engineering or in vivo treatments^[53]
8. Complex and multistep process^[38, 52]

Safety, efficacy, and success rate of lipid and polymer based drug delivery system

The new approaches to drug delivery system in terms of polymer and lipid-based are successful in the clinical trials phase with in vivo and genetic engineering advancements.^[56] Post-marketing surveillance report, however, vary in some of these drug delivery systems as the EPR and other factors vary from human to human and also a lot of other factors needs to be characterized to formulate a successful system that works for all the humans similarly.^[59] To ensure the safety of these drug delivery systems the formulators and manufacturers make sure to strike off the factors that may arise any further complications.^[60] However more literature and more trials need to be done to determine the factors that may promote or demote the efficacy of the drug in the patients and prevent any unwanted adverse effects.

CONCLUSION

Since their discovery lipids and polymers have advanced rapidly technologically from being used as an apparatus for cell membranes to versatile drug carriers. These drug delivery systems have emerged as a promising strategy for new-age drug delivery systems including potential cancer treatment. Many formulations are being investigated in different phases of clinical trials and awaiting approval while many others are already been approved and commercially available. However, the post surveillance reports show certain setbacks. Further studies and clinical trials are warranted to completely optimize their potential as drug delivery systems and to overcome the setbacks and challenges these two drug delivery systems are facing in the real-time clinical settings.

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