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Liposomal Encapsulation of Acyclovir: Enhancing Bioavailability, Targeted Delivery, and Therapeutic Efficacy in Herpesvirus Infections

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ABSTRACT
For years, acyclovir has remained the first-choice antiviral agent in the management of herpes viral infections due to its high specificity and excellent tolerability. However, severely low bioavailability, poor cell-type permeability, and lack of selective targeting contribute to significantly compromised therapeutic results. Despite various strategies adopted to overcome these barriers, the ideal oral route remains elusive for acyclovir even today.Liposome-encapsulated acyclovir is a promising, emerging approach for the treatment of herpesvirus infections. As the development of drug formulations necessitates translational assessments, preclinical studies on pharmacokinetics, biodistribution, excretion, and toxicity are essential to analyze the compatibility of the liposomal delivery system. Before liposomal acyclovir can be extensively used as a therapeutic drug, long-term consequences for nontarget cells and systems have to be investigated. Negatively interacting therapeutically useful agents, such as irradiation, with the liposomal delivery system should also be assessed. In all of the presented studies, an additional evaluation after the already mentioned time periods has not been conducted. Yet, liposome-based formulations can remain in certain organs for much longer, as shown for liposomal drugs. As one major cause of liposome retention in tissues is phagocytosis by macrophages, an organ-by-organ evaluation of liposome accumulation in macrophages is mandatory.

Keywords : Acyclovir, Herpesvirus, Liposomal, Encapsulation, Bioavailability.

INTRODUCTION

Acyclovir (ACV) is a widely used antiviral drug approved for the treatment of infections caused by various herpesviruses. Orally administered ACV is very scarcely absorbed, and thus high doses of the drug are required to achieve high plasma concentration. High doses of the drug may produce side effects, and long-term administration may induce drug resistance(1). The amphipathic nature of the drug compound, its poor solubility, high retention in the liver, rapid elimination, and the activity of various efflux transporters that pump out the drug from the cells prevent ACV from achieving therapeutic relevance. Strategies have been devised to solve these limitations, enabling a sustained systemic delivery of the drug and concentrating ACV at the infection site to further enhance its potency while minimizing the risk of induced drug resistance. Liposomal encapsulation has emerged as a very attractive alternative for improving the pharmacokinetics, plasma retention, oral bioavailability, and oral drug absorption of many drugs(2). Liposome protection against inactivation, such as the degradation of low molecular weight drugs by cellular enzymes, bypassing destabilization in the gastrointestinal tract, improved systemic availability by enhanced permeability and retention effect, and nanoscale optimized pharmacokinetics have been proven to be the most powerful benefits of liposomal drug delivery. The vesicle composition and the size of the system play crucial roles in increasing the selectivity of drug accumulation in inflammatory sites, thereby diminishing distribution in healthy tissues and potentially minimizing side effects in the treatment of disease(3). Liposomal drug encapsulation also facilitates intravenous and oral administration of compounds with limited applicability due to a narrow therapeutic index, along with the undoubted advantage of facilitating controlled drug release by physicochemical means or exposure to specific parameters (4).

Herpesvirus Infections

Herpesvirus is a ubiquitous family of DNA viruses that infect a wide variety of animals and humans. Within this family, the Alphaherpesvirinae and Gammaherpesvirinae subfamilies carry the most prominent members that cause infections in humans. The Alphaherpesvirinae family includes herpes simplex virus type 1 and 2, varicella-zoster virus, and some strains of the animal retroviruses it affects(5). The Gammaherpesvirinae subfamily of herpesviruses includes Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus, both of which can cause primary and latent infections. Herpesvirus has a high prevalence all over the world, and infection with this virus often leads to mild diseases characterized by skin rashes, blisters, and general malaise. However, chronic herpesvirus infections can cause severe acute diseases as well as cancer, meningitis, blindness, arthritis, encephalitis, and other complications, especially in newborns and immunocompromised individuals(6). Currently, antivirals are the mainstay of treatment, but potential drug resistance is a major threat for herpesvirus patients. Additionally, the use of existing antivirals is limited by poor bioavailability and severe adverse effects, thus halting the development of further complications and antiviral resistance. The development of alternative delivery systems, including liposomes, dendrimers, and polymer nanoparticles, as well as prodrugs developed using known chemical compounds, might be the solution for such limitations of existing antivirals(7).

Current Treatment Modalities and Limitations

The limitations of conventional acyclovir therapy have prompted efforts to identify formulations capable of enhanced target delivery. Nongeneric prodrug synthesis, colloidal aggregates, polyelectrolyte re-coating methods, and biomimetics are promising formulations described for improved acyclovir effectiveness. However, technological limitations make these methods unviable for translation to clinical settings, as the pharmaceuticals suffer from diminished efficacy, unacceptable side effects, or unwanted interactions compared to the free drug and do not mimic the natural antiviral defense(8). Conventional antiviral agents and acyclovir constitute short-term therapeutic modalities that necessitate prophylactic or high/systemic doses to elicit a protective immunity-linked response for the prevention of recurrent infections caused by the establishment of latency, commonly occurring in immunocompromised populations(9).

Acyclovir causes different toxic side effects, such as sperm damage and infertility, neurologic side effects, skin scarring, and skin infection, implicating its need for repeated doses. The bioavailability of acyclovir in tissues is low, and fluctuating doses are frequently required in a responsive treatment regimen. Furthermore, acyclovir has varied solubilities in different solutions and at neutral or acidic pH; it is not conducive to delivery in liposomes constructed from such solvents. High, repeated oral doses can induce detrimental gastrointestinal disturbances and can impair immune function in immunocompromised patients, and intravenous administration causes pain and discomfort. In addition, the main dose-limiting factor is viral resistance to acyclovir, which occurs due to prolonged periods of therapeutic acyclovir use and increased clinical dosing and duration of medication usage(10) .

Liposomal Drug Delivery Systems

Lipid- and polymer-based nanotechnology has been employed in several successful formulations to improve the safety, biocompatibility, and bioavailability of medications. Nanosized liposomes largely possess the necessary and favorable attributes of a drug delivery system, including biocompatibility, biodegradability, long systemic circulation time, and the ability to encapsulate lipophilic as well as hydrophilic compounds(11). Additionally, they have the capability to escape reticuloendothelial system recognition, permitting therapeutically beneficial concentrations of drugs to reach and accumulate in target areas and thus enhance their biological action. These attributes have allowed the use of liposomes as an artificial carrier for drug transport to enable controlled and sustained drug release, tumor targeting, and modulation of encapsulated drug activity at the site of release. The capability to incorporate compounds or unfavorable drugs using cost-effective formulations has triggered additional interest and expectation in liposomal drug delivery systems(12).

The key applications of liposomes in pharmacotherapy include their carrier function for the transportation of lipophilic drugs, their use as artificial microorganism/adjuvant vaccines, and their use as antileishmanials for antileishmanial therapy. Notably, more liposomes have been used to encapsulate several favorably charged compounds, including proteins, peptides, nucleic acids, and/or genes. These favorable attributes, therefore, allow liposomes to function as a carrier for intracellular accumulation, to protect genetically or chemically altered contents from degradation, to improve cell targeting, and to selectively deliver the genetically altered contents. The present review underscores the significant role of liposomes in aiding formulation and payload modifications in order to enhance its targeted delivery and thereby improve its therapeutic impact on herpesvirus infection(13) .

Basic Principles of Liposomal Encapsulation

Despite the current advances in formulations and therapeutic strategies, the treatment of herpesvirus infections remains a major need for novel drugs and efficient drug delivery systems. Liposome-based delivery systems

have garnered significant attention in therapeutics, pharmaceuticals, diagnostics, and gene delivery, mainly due to their immense potential in enhancing the bioavailability of drugs, promoting targeted delivery, and improving therapeutic efficacy. In addition, surface-modified liposomal constructs provide excellent opportunities for targeted drug delivery systems(14). The present chapter reviews the potential application and therapeutic benefits of liposomal encapsulation of acyclovir in various formulations to enhance the efficacy of antiviral therapy and their potential in the management of various herpes simplex, swine influenza, and feline herpesvirus infections. 1. Introduction Vesicular systems represent efficient carriers for various drugs and therapeutic agents, mainly due to their unique microenvironment, lipid membrane envelopes, and the ease with which the surface can be modified. They have the potential to provide intracellular and sustained delivery of therapeutic agents, control release rate and duration, and protection from degradation(15). Of all the various drug delivery systems, liposomes are the most common and successful systems, mimicking cellular and subcellular membrane constructs. Their ability to improve the bioavailability of both hydrophilic and lipophilic drugs and to entrap drug molecules has garnered significant attention to address complex diseases. Liposomal encapsulation is significant in drug delivery systems, as it allows for the distribution of the drug to various target sites at the desired time while avoiding rapid release after administration and metabolic instability(16).

Advantages of Liposomal Delivery Systems

There are several advantages to utilizing liposomal delivery systems to effectively deliver therapeutic drugs. One of the main benefits of using these carriers is that they have an enhanced ability to accumulate in infected tissues when compared to free drugs, owing to their increased uptake by immune cells post-injection. Another advantage is that the encapsulation of a therapeutic drug can prevent it from being metabolized by the body, or in the case of potent antimicrobials, contain the drug in the vehicle until it is at the infection site in order to reduce its toxicity profile(17).

Liposomes can also protect their cargo from cleavage by protease action, maintaining the therapeutic agents in circulation for a prolonged period of time and allowing the agent to spread through the inflamed skin during topical administration. Moreover, drugs and bioactives entrapped in liposomes show enhanced penetration into the epidermis and dermis, ensuring higher local bioavailability. Another positive aspect is that liposomes can concurrently deliver multiple drugs, not only enhancing patient convenience, but also reducing the chances of drug resistance and promoting drug synergism for improved therapeutic action. Ultimately, liposomes possess an inherent biodegradability, safety, toxicity profile, and biocompatibility with other natural biomaterials that can be incorporated into the bilayer, endowing liposomes with the option for tailored modification(18) .

Liposomal Encapsulation of Acyclovir Formulation and Characterization

Encapsulation of acyclovir into liposomes makes in vivo drug disposition action different. These include manipulation of the enhancement or otherwise abrogation of drug bioavailability and the control or modification of the release of the drug from the assimilated organ. A huge variety of liposome-based formulations of acyclovir are available[(19)]. Liposomes containing acyclovir were prepared by using the conventional thin-film hydration method. Using the solvent reflux method, a PEG-mediated nanoemulsion was prepared as a further drug carrier for acyclovir. Additionally, if we consider the acyclovir group of molecules as a category, three-quarters of the acyclovir liposomal vehicles were developed. As a result, they may play an important role in revealing the relationship between the characteristics of the prototypal liposomal-acyclovir formulation, such as polydispersity index, encapsulation efficiency, release rate, liposome size, and so on. They also have crucial importance for further optimizing each factor in order to reach the lowest value possible, because optimal formulation or drug properties are obtained by matching these various traits appropriately (20).

The liposomes of acyclovir are generally prepared by various encapsulation techniques, including solvent evaporation or thin-film hydration and so on. Acyclovir can be loaded either within the lipid bilayer or by entrapping within the internal aqueous space. The major formulation components, such as phospholipids, determine a liposome's size, zeta potential, and drug encapsulation efficiency (21). The method also represents the size of the prepared liposomes, either in the nanometer range or micrometer. As a result, various methods require a particular solvent or diluent for liposome formulation preparation. The investigation of an overlooked and important shared perspective among the acyclovir liposomal vehicles is that the acyclovir-crystal-liposome precipitation after the hydration step in formulation development issues has been a very common, otherwise mild problem at the bench scale level, but quite serious and incontestable and huge issue on scaling to industrial production. However, the agglomeration of drug crystals has been more likely to occur than encapsulating molecule-containing drug crystals, because for the solvent evaporation approach, drug crystals provide a much easier surface to form aggregates than free crystalline acyclovir (22).

Formulation Components and Techniques

Liposomal Acyclovir Encapsulation: Lipids, surfactants, and stabilizers used to formulate acyclovir liposomes create a hydrophobic/hydrophilic bilayer environment inside the system, thus making them appropriate to

encapsulate a hydrophilic drug such as acyclovir in the core. Surfactants and stabilizers account for integrity during preparation by providing a stable bilayer(23). Encapsulation of an antiviral drug in a liposomal carrier system and its targeted release to cells infected with herpesvirus have immense potential in the actual chronic therapy of viral infections. Various preparation techniques create liposomes with advantages and limitations in the desired particle characteristics. Different common techniques are employed to prepare liposomes, such as mechanical agitation for the large-scale production of multi-lamellar vesicles, sonication for extra small, widely distributed unilamellar vesicles, and polycarbonate membrane extrusion for liposome unification(24). Advanced technologies for the preparation of pristine liposomes have gained broad interest, such as the supercritical fluid method, microfluidizationto prepare small and large unilamellar vesicles for drug targeting, reverse-phase evaporation technique, application of proliposomes containing hydrogenated soy phosphatidylcholine in a monodispersed, lipid-stabilized aqueous submicron particle form for oral and IV administration, and ultrasonicated liposomes for gene delivery(25). The choice of encapsulation method is important to manipulate the drug-release profile and stability and is governed according to the desired size of the entrapments sampled, drug properties, and dehydration temperature specific for each formulation in preparation. In the different processes of liposome entrapment preparation, the most important aspect is the optimization of the mixture of the entrapment components, such as lipid, cholesterol, buffer of the external aqueous phase, and percent organic-aqueous phase ratios, in order to improve the efficiency of the system for the targeted therapy of herpesvirus infections(26).

Bioavailability Enhancement Strategies

Although acyclovir is the most effective drug for the treatment of herpesvirus infection, conventional methods of acyclovir delivery offer low bioavailability due to the presence of various factors delaying its gastrointestinal absorption and undergoing extensive first-pass metabolism. In order to tackle these hurdles, several innovative strategies have been combined with nanoparticle technologies(27). The addition of a permeation enhancer offers an approach to overcome the difficulties of poor acyclovir solubility in gastrointestinal fluids. Liposomal acyclovir can be simply prepared by rehydrating lipid films with an aqueous medium containing various permeation enhancers. Optimization of oral formulations based on liposomes is critical for improved physical stability, associated with resistance to gastrointestinal disintegration and aggregation(28). Lipids utilized in liposomal formulations may possess the potential to offer a synergistic role in enhancing both acyclovir solubility in gastrointestinal fluids and relative molecular drug stability. Optimized liposomal formulation of acyclovir enhances residence time and minimizes systemic clearance after oral or parenteral administration in rats, substantiated by improvements in the acyclovir pharmacokinetic profile. After considering the characteristics of liposomal acyclovir, liposomal systems with diverse levels of mechanical and digestion stability may be desirable to control the release rate at the site of drug absorption in the gastrointestinal tract(29). Improved solubility of encapsulating components is also potentially useful to enhance the solubility of acyclovir in the buccal cavity. There are no clear advantages of including reduced in vitro cytotoxicity. Poor epithelial penetration and rapid systemic clearance of acyclovir from buccal tissues limit the buccal route of acyclovir delivery. However, there are a few case studies that illustrate successful buccal acyclovir delivery(30). Intragastric administration of a liposomal preparation that releases free acyclovir rapidly enhanced the therapeutic effect. The technological development of oral acyclovir drug delivery systems that achieve economically significant improvement in the dollar cost of therapy may be worthy of investigation. The emergence of viral resistance, particularly in immunocompromised herpesvirus patients under long-term therapy, necessitates an innovative oral acyclovir formulation offering improved therapeutic effects. An oral combination therapy of growth hormone and insulin did not influence hepatic acyclovir first-pass metabolism but offered a therapeutic outcome significantly better than with the single drug treatments(31).

Challenges in Oral Delivery

Several studies have reported the oral bioavailability of acyclovir to be poor owing to a multitude of physiological barriers. Hydrophobic drugs, such as acyclovir, are poorly absorbed from various sites of the gastrointestinal tract because of their low solubility in highly aqueous media, such as gastrointestinal fluids, mucus, and epithelial membrane. Furthermore, acyclovir is unstable at acidic pH and is rapidly deaminated in the liver. First-pass metabolism may also result in a decreased bioavailability of drug substances and could result in pharmacotoxicological effects. Various bioequivalence studies have also shown the plasma concentration, half-life, and volume of distribution of acyclovir to be inconsistent between the formulations based on their release patterns and characteristics(32). Properties of the drug and the physicochemical properties of the carrier system usually affect the release kinetics, release behavior, and the amount of drug dispersed in in vitro dissolution media. The latter can also have an impact on estimated drug permeability depending on the dissolution medium composition. Low bioavailability in the case of acyclovir and famciclovir may also lead to the intake of larger doses, which can decrease patient adherence and the success of therapy given the chances of toxicity and side effects, specifically in sensitive individuals(33).

Therapeutic Efficacy Studies of Liposomal Acyclovir in Preclinical Models

The therapeutic efficacy of liposomal acyclovir has been evaluated in various experimentally infected animal models.In most studies, all three liposomal formulations of acyclovir administered at equivalent doses of acyclovir exhibited more potent activity than free acyclovir for the reduction of viral replication in the target organs or tissues, blood, and/or body fluids under the same infection conditions(34). Moreover, therapeutic efficacy is important in drawing a clinical conclusion. In addition, the improvement of illness score, prolongation of survival time, and depth of serous water in lung tissue should be taken into consideration in comparative studies. Such typical therapeutic efficacy studies for liposomal antiviral drugs have been fully described. Taken together with those findings, liposomal acyclovir formulations have the potential to enhance the therapeutic responses typical of infection sites(35). A schematic model that combines prophylactic and therapeutic responses has been proposed for antiviral liposomes. Based on the viral shedding pattern, the inhibition of exogenous viral shedding prolonged the survival time of infected mice and reduced deaths compared to those in mice treated post-infection(36). In accordance with the reduction of the exogenous viral shedding, liposomal antiviral drug treatments suppressed the growth of the inoculation virus and virus spread to the local organs. Subsequently, liposomal antiviral drugs augmentatively inhibit endogenous virus release, which is related to the shortening of tool-switching time from the exogenous route to the endogenous route in the viral shedding pattern (37).

Safety and Toxicity Considerations of Liposomal Acyclovir

Liposome-encapsulated acyclovir is a promising, emerging approach for the treatment of herpesvirus infections. As the development of drug formulations necessitates translational assessments, preclinical studies on pharmacokinetics, biodistribution, excretion, and toxicity are essential to analyze the compatibility of the liposomal delivery system(38). Before liposomal acyclovir can be extensively used as a therapeutic drug, long-term consequences for nontarget cells and systems have to be investigated. Negatively interacting therapeutically useful agents, such as irradiation, with the liposomal delivery system should also be assessed. In all of the presented studies, an additional evaluation after the already mentioned time periods has not been conducted. Yet, liposome-based formulations can remain in certain organs for much longer, as shown for liposomal drugs. As one major cause of liposome retention in tissues is phagocytosis by macrophages, an organ-by-organ evaluation of liposome accumulation in macrophages is mandatory(39).

The disadvantageous situation of acute drug toxicity may change when applying drugs in liposomal formulations. For conventional acyclovir, an upper limit of 30-50 mg/kg was determined as the no-observed-adverse-effect level in rodent studies, based on kidney lesions. In cynomolgus monkeys, at least, an acceptable safety margin can be established between the therapeutically relevant dose and higher doses that can be tolerated without causing acute nephrotoxic effects(40). In patients with mycophenolate mofetil-treated transplants, acyclovir leads to kidney damage due to a competitive active tubular secretion inhibition and also nephrotoxicosis. In liposomal carriers, no pharmaceutically relevant active tubular secretion is found, so that nephrotoxic and kidney-damaging effects of liposomal acyclovir are not necessarily transferred, and liposomal concentration may be translated(41). Based on these preliminary conclusions, after subsequent detailed safety/toxicity testing stages including administration over several weeks to healthy non-immunocompromised monkeys, comprehensive genotoxicity assessments, and investigations into the effects of liposomal acyclovir on the immune response, additional subchronic studies in HIV-1/AIDS and HCMV-positive animals would be required to confirm the superiority of effective dosage schedules of liposomal acyclovir over those of standard acyclovir for resistant strains(42).

Current Status and Future Directions

For future research in the clinical development of liposomal acyclovir for herpesvirus management, the results of ongoing clinical trials and possible outcomes in terms of the efficacy of the formulated agent could provide potential hope for use in clinical settings. The literature has greatly expanded our understanding of the mechanisms of drug delivery to enhance bioavailability, prolong systemic circulation, and improve the targeting of drugs, resulting in improved therapeutic efficacy and reduced related toxicity. However, very little work has been done to investigate whether it is possible to encapsulate a drug using a novel drug delivery system to enhance its bioavailability and therapeutic efficacy for the treatment of this infection. High costs and the lack of supervised trials are some limitations faced in this research. In clinical settings, it is challenging to gain participation due to forgetfulness, lack of tracking, and the high mobility of inhabitants. Additionally, although recent testing has been successful, it has been conducted with a small sample size; hence, the conclusions at this stage are rather premature(43).

A future study should consider a multi-center study of liposomal acyclovir involving the participation of two or more geographic settings to achieve general applicability in other herpesvirus-related disorders. In the near future, it is our vision that modifications to the experimental conditions could include the formulation of a combination treatment in the same formulation, such as ZnONPs-liposomal acyclovir or liposomal acyclovir-

gentamicin combination treatment. Incorporation of antibiotics in antimicrobial formulations for co-administration is an area that is less exploited. It could be projected that such combinations will bring a shift in clinical medicine in order to manage herpesvirus co-infected cases. Additionally, formulations coated with vaginal fluid mimicking fluid, with the aim of developing in situ gelling vaginal formulations, could be a valuable area of research. We can further improve the prepared liposomal formulations targeting acyclovir for vaginal administration. This will be a valuable personalized medicine approach for the delivery of this formulation to the relevant subjects that need chemoprophylaxis during HRV reactivation(44).

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