REVIEW ARTICLE

Antibiotic-Loaded Nano Drug Delivery Systems for the Treatment of Respiratory Tract Infections

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Abstract

Many antibiotics being currently used for the treatment of various infections face the problems such as short half-life, systemic toxicity, and increased susceptibility to bacterial resistance. Although, most antibiotic classes are administered systemically through oral or intravenous routes, a more efficient delivery system is needed for enhancement of the efficacy against the microorganisms and prevents the development of drug resistance. The exposure of subtherapeutic concentration of the antibiotics is considered as one among the major reason for the development of antibiotic drug resistance by the microorganisms. Incorporation of antibiotic drug-loaded nanoparticles for the treatment of respiratory tract infection shows a promising strategy to avoid rapid clearance from the lung and achieve sustained drug release. Many such reports are available, which scientifically exhibit the potential ability to achieve enhanced therapeutics response of antibiotics, when incorporated in an optimized nano-drug delivery system. This review discusses the approaches to be carried out for antibiotic loaded in nano-drug for enhancing the efficacy of antibiotics.

Key words: Antibiotic-loaded nanoparticles, antibiotics, nano-drug, respiratory tract infection

INTRODUCTION

Antibiotics are commonly administered systemically, generally through the oral or intravenous routes, to treat a variety of bacterial infections. While many common, non-life-threatening bacterial infections can be treated effectively with antibiotics, problems arise when germs are resistant to treatment or when the infection is severe.[1] Separately, implant-related infections are a severe health problem that makes already difficult and complex surgical operations even more challenging; biofilm accumulation at the implant site can lead to implant failure and infection, necessitating subsequent surgery to remove the infected implant.[2,3] Whether it is a common infection or an infection caused by an implant, the rising incidence of multidrug resistance bacteria like methicillin-resistant *Staphylococcus aureus* poses a significant therapeutic and prevention problem. Overprescribing broad-spectrum antibiotics (for example, to treat a viral infection with antibiotics) exacerbate the problem of resistant bacteria. Given the rise in antimicrobial resistance, novel antimicrobial delivery strategies with improved biocidal activity are urgently needed. Lower dose, less toxicity, longer release, and avoidance of systemic exposure are all advantages of local, controlled antibiotic release. Antibiotics specific for that strain can be provided at high doses without exceeding systemic toxicity, reducing side effects and preventing resistance, by localizing the medicine at the specific infection sites, such as in implant-related infections. The benefit of a regulated, sustained release method is obvious; polymeric delivery systems enable this desired treatment.[4-7] Respiratory system infections are a prevalent cause of sickness and a significant source of morbidity and mortality in cancer patients.[8] Upper and lower respiratory tract infections are commonly separated in respiratory tract infections. Infections in the upper respiratory tract primarily affect the nose, throat, and other nearby structures. Evidence of infection, respiratory symptoms, or physical examination findings suggesting lower respiratory

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tract disease and abnormal chest imaging are frequently used to characterize lower respiratory tract infections.[9] Bronchitis, bronchiolitis (as seen in young children), and pneumonia are all lower respiratory tract illnesses. Patients with underlying malignancies are more likely to develop otitis media and sinusitis. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most prevalent causes of infection in healthy people. *Staphylococcus aureus*, enteric Gram-negative bacteria, and anaerobes can all be found in patients with more chronic disease.[10]

RESPIRATORY TRACT INFECTIONS

There is a scarcity of information on the incidence and epidemiology of respiratory tract infections in cancer patients. Cancer was the second leading cause of death in the United States in 2006 (nearly 560,000 deaths), while influenza and pneumonia were ranked eighth (with over 56,000 deaths).[8] In national vital statistics reports, mortality is described as being caused by a single cause, despite the fact that a significant portion of mortality is caused by a combination of cancer and pneumonia. Chronic lower respiratory diseases (e.g., chronic obstructive pulmonary disease), which overlaps with lung cancer and pneumonia, are the fourth leading cause of death. In patients with febrile neutropenia, 15–30% of infections are subsequently diagnosed as pneumonia.[11]

UPPER RESPIRATORY TRACT INFECTIONS

The upper respiratory tract comprises mouth, nose, throat, and larynx commonly known as voice box and trachea. The following are some of the commonly occurring respiratory tract infections common cold, sinusitis, pharyngitis, laryngitis, and laryngotracheitis.[12,13]

Nasopharyngitis (common cold)

The inflammation occurring in the nasal passages is known as common cold it is caused by virus. The majority of these infections are self-limiting and go away on their own. The common cold has a different frequency depending on your age group. The majority of viruses that cause the common cold belong to six different families of viruses; they are as follows: Rhinovirus, influenza A/B/C, parainfluenza, respiratory syncytial virus (RSV), coronavirus, and adenovirus.[14] Clinical findings are generally always used to diagnose a common cold. The basic symptoms of flu are compared with the common cold which serves as the key to distinguish common cold from other virulent viral illness such as the influenza. In rare circumstances, virus can be cultivated from nasal washings or identified using enzyme-linked immunosorbent test or radioimmunoassay techniques.[15]

Acute sinusitis (AC)

AC is a condition in which the nasal mucosa becomes inflamed.[16,17] A recent national health survey, about one out of every seven persons is affected and diagnosed each year. It is generally a matter of symptom length to tell the difference between a common cold and AS. Common colds usually last 7–10 days, whereas AS can linger up to 4 weeks.[18] The following are the some of the symptoms of nasal congestion and discharge, face pain over the sinuses, impaired sense of smell, and cough, which are comparable to those of a typical cold.[19,20] If any of the following symptoms or indicators are present, a bacterial origin is usually suspected and diagnosed:

- Nasal discharge with a foul odor
- Pain in the maxillary teeth or in the face
- Tenderness in one side of the maxillary sinuses
- Symptoms worsening after a period of improvement.[21]

PHARYNGITIS

One of the most common conditions seen by a family physician is pharyngitis. A physical examination and appropriate laboratory tests are the best ways to differentiate between various causes of pharyngitis. It is critical to determine the etiology of pharyngitis, particularly Group A b-hemolytic streptococcus, to avoid potentially fatal consequences.[22,23]

LOWER RESPIRATORY TRACT INFECTIONS

Evidence of infection, respiratory symptoms, or physical examination findings suggesting lower respiratory tract disease and abnormal chest imaging are frequently used to characterize lower respiratory tract infections.[24] Bronchitis, bronchiolitis (as seen in young children), and pneumonia are all lower respiratory tract illnesses. Patients with underlying malignancies are more likely to develop otitis media and sinusitis.

Nosocomial pneumonia

Serious nosocomial infections are more common in immunocompromised patients due to a variety of causes. These include changes in natural host defenses as a result of immunosuppressive medication and prescribed antibiotics in the context of increasing nosocomial pathogen exposure from extended stays in health-care facilities.[25,26] Gram-negative rods are multidrug-resistant and non-fermenting, such as *Pseudomonas* spp. The discovery of several new respiratory viruses, including human metapneumovirus and human coronaviruses, has heightened awareness of respiratory viruses and their significance in this susceptible population. Rapid diagnosis combined with prompt antiviral

therapy has been found to reduce illness severity in cases of RSV and influenza infection.[27]

Preparation of antibiotic-loaded nanoparticles (ANPs)

The use of ANPs as a carrier system for medication and gene delivery has been well described in the literature. ANPs have been prepared in a variety of ways since they were initially characterized in 1978.[28]

Desolvation

The desolvation procedure involves adding a desolvating substance (e.g., alcohol or acetone) to an aqueous antibiotic solution to dehydrate the antibiotic molecules, causing them to shift conformation from stretched to coil. A crosslinking process is then required to harden the native particles.[29] However, the heterogeneity in antibiotic molecular weight using natural antibiotics results in big particles with a wide size range. Coester *et al*. demonstrated that adding a second desolvation process improves the creation of smaller and more homogeneous nanoparticles. In the first desolvation process, the high molecular weight (HMW) antibiotic was precipitated to remove the low-molecular-weight (LMW) antibiotic, and then, the HMW antibiotic was redissolved. Ofokansi *et al*.[30] created a new streamlined one-step desolvation method that eliminates the need for an initial desolvation phase to remove the LMW antibiotic component. Before desolvation, the pH of the antibiotic solution was adjusted to neutral values of 7.0, well over the pI, to ensure that antibiotic molecules were sufficiently uncharged to be sensitive to desolvation while also sufficiently charged to prevent aggregation. Furthermore, a 37°C preparation temperature was used to ensure that the antibiotic's molecular weight distribution remained reasonably stable during incubation.[31] ANPs with sizes ranging from 253 to 479 nm and a polydispersity index of 0.073 were discovered. Despite its widespread use in the preparation of ANPs, the desolvation approach has two major drawbacks: The use of organic solvents and the use of toxic cross-linkers.

Coacervation phase separation

Coacervation is the separation of a homogenous solution of charged macromolecules into a polymer-rich dense phase at the bottom and a clear solution above.[32] Coacervation is generally aided by the addition of natural salt or alcohol, resulting in the required nanoparticles. Slow addition of sodium sulfate to aqueous antibiotic solution including surfactant (Tween 20), followed by addition of isopropanol to dissolve the precipitate by sodium sulfate, resulted in ANPs (600–1000 nm).[33] A second aliquot of sodium sulfate was added until the solution became murky, indicating antibiotic aggregate development. After that, distilled water was added until the solution became transparent, and ANPs were cross-linked with glutaraldehyde (GA).

Emulsification-solvent evaporation

ANPs (100–400 nm) were generated using a solvent evaporation approach based on a single W/O emulsion in this process. The oil phase, for example, organic solution of polymethylmethacrylate[34,35] or paraffin oil,[15] was mixed with vigorous shaking with the aqueous phase containing both antibiotic and polymer followed by crosslinking with GA[12-14] or genipin.[36] Insulin-loaded ANPs (250 nm) were recently prepared under mild conditions using an unique water-in-water emulsion approach that may guarantee insulin bioactivity.[37] To summarize, a pre-warmed antibiotic solution containing insulin was added dropwise to a poloxamer solution while stirring to generate an emulsion, which was subsequently chilled to 5°C to enhance nanoparticle formation and crosslinking.

Nanoprecipitation

The nanoparticles were found to be narrowly distributed, with a mean size of 251 nm and a polydispersity of 0.096. The interfacial turbulence induced during solvent displacement has been used to explain how nanoparticles originate. As a result of the reciprocal miscibility of the solvents, a violent spreading occurs. Solvent droplets, most likely nanometric in size, are ripped from the interface. The stabilizing agent quickly stabilizes these droplets until the solvent has diffused completely and the protein has solidified.[38,39] Nanoprecipitation has a number of advantages, including the fact that it is a simple, quick, and simple procedure to use. Small nanoparticles with a limited unimodal distribution are frequently produced using this method. Furthermore, it does not require high temperatures, sonication, or extended shearing speeds, and it is characterized by the absence of oily-aqueous interfaces.

Reverse phase microemulsion

Aqueous antibiotic solution was added to a solution of the surfactant, sodium bis(2-ethylhexyl) sulfosuccinate (AOT) in n-hexane, then GA was added to crosslink the nanoparticles followed by n-hexane evaporation to collect ANPs.[40] When the surfactant AOT is dissolved in non-polar solvents like hexane, it forms reverse micelles in which the hydrophobic tails of the surfactants are assembled toward the bulk non-polar solvent and the hydrophilic head is directed away from the bulk solvent inside enclosing an aqueous core in which the aqueous solution of antibiotic and cross-linker is dissolved, resulting in ANP formation and crosslinking inside the inner aqueous core of reverse. Because reverse micelles' inner aqueous cores are in the nanometer range, the ANPs produced inside these nanoreactors have an average diameter of 37 nm. The size of nanoparticles may be adjusted by modifying the size of the aqueous micellar core,[41] which is an advantage of using this sort of microemulsion system for nanoparticle creation. The nanoparticles' entrapment efficiency for fluorescein

isothiocyanate-dextran as a fluorescent marker was determined to be over 90%.

In vitro characteristics of antibiotic nanoparticles

Drug loading

Drugs or genes contained in ANPs may be entrapped in the nanoparticles' matrix during manufacture or adsorbed onto the produced nanoparticles' surface. Hydrophilic pharmaceuticals can be successfully loaded into ANPs by incubating the drug in an aqueous gelatin solution for a long enough period of time before nanoparticle production to facilitate drug-protein interaction. Physical trapping, electrostatic attraction, and covalent conjugation are all possible methods for drug loading into ANPs.[42] Hydrogen bonding and hydrophobic interactions between the medication and the polymer have also been documented. After allowing ANPs to expand in a freshly produced drug solution, electrostatic interactions between positively charged DXR and the negatively charged FeO and COO coating layers allowed DXR to be integrated into magnetic ANPs. Furthermore, it was proposed that DXR covalently binds to the protein matrix through GA crosslinking.

Due to competition between the amino group of DXR and the amino groups of the antibiotic chains during the crosslinking process, DXR-loaded ANPs have more free amino groups than unloaded ones.[43] Another study found that the rivalry between the carboxylic groups of gatifloxacin and the aldehyde groups of GA to react with the amino groups of antibiotic molecules reduced gatifloxacin loading efficiency into cross-linked ANPs when compared to uncross-linked ANPs.

Drug release

Desorption, diffusion, and biodegradation of ANPs are three common routes for drug release from ANPs. The rate of drug release from ANPs has been demonstrated to be influenced by a variety of circumstances. The antibiotic crosslinking density was found to have a substantial impact on the drug release rate from the nanoparticulate matrix. Another impact is the presence of proteolytic enzymes, which speeds up ANP biodegradation and thus drug release.[44,45]

Particle size and surface charge

The majority of ANPs generated using the procedures described above had mean diameters ranging from 200 to 400 nm. The particle size has a big impact on colloidal stability, drug encapsulation efficiency, loading capacity, drug release and biodistribution profile, cell internalization kinetics, and so on. Several organizations have looked into the effect of several parameters on the size of ANPs, such as temperature, pH, degree of crosslinking, antibiotic type, and kind of desolvating agent. A-NP will be diluted 100 times by deionized water, and particle size will be detected by Dynamic Light Scattering (DLS) (ELSZ-2000 particle range analyzer, Otsuka Electronics, Otsuka, Japan). Zeta potential of developed antibiotic-NP will be detected by means of a Malvern Zetasizer Nano ZS (Malvern Instruments, UK). The principle is based on DLS. Zetasizer estimates the intensity variation of scattered light and relates it to the particle range with the assistance of an autocorrelation function. The measurements were performed in triplicates.[42,46] Another, recent study carried out in Malaysia had also clearly indicated that the development of antibiotic resistance in outpatients was reported, which reinstates the need for research to defend the development of antibiotic resistance.[47]

CONCLUSION

Increased drug resistance among respiratory infections is linked to antibiotic usage and improper antibiotic medication selection. Antibiotic treatment of children with URTI is not supported by existing evidence from randomized studies due to lack of efficacy and low complication rates. Lower respiratory tract infections are the leading cause of morbidity and mortality in immunocompromised patients of all types.

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