REVIEW ARTICLE

Polymeric Fluoroquinolone Microparticles for Pulmonary Drug Delivery: A Review on Characteristics, Drug Release Profile, and Antibacterial Study

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ABSTRACT

Polymeric microparticles have recently gained significant attention as promising carriers for antibiotic administration to the pulmonary route, especially the antibiotics from the fluoroquinolone class. The versatility and efficiency of fluoroquinolones, combined with the stability, biocompatibility, and tunable protection provided by polymeric encapsulation in microparticles, contribute to the effectiveness of fluoroquinolone microparticles in achieving desirable characteristics, particularly precise and controlled drug release in the lungs. Such characteristics, drug release profile, and antibacterial activities are mainly influenced by the physics and chemistry of the fluoroquinolones-polymer system as a whole, formulation parameters, and solvent usage. Therefore, this review provides a comprehensive summary of studies and research conducted between 2012 and the present, focusing on the characteristics, drug release profile, and antibacterial investigation of fluoroquinolone microparticles that utilize polymeric formulations for the purpose of delivering drugs to the lungs.

Keywords: Microparticles, Fluoroquinolones, Pulmonary drug delivery, Drug release, Antibacterial.

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INTRODUCTION

Fluoroquinolones, a class of broad-spectrum antibiotics, have become indispensable in the realm of antibacterial treatment, rivaling the significance of β-lactams. They provide a flexible treatment choice for various infections, including respiratory tract infections, gastrointestinal infections, skin infections, urinary tract infections, and sexually transmitted diseases.[1,2] Over time, the development of numerous synthetic fluoroquinolones with structural modifications has expanded their efficacy, allowing them to effectively combat both gram-positive and gram-negative bacteria. Based on the exceptional tissue penetration, excellent pharmacokinetics, and high oral bioavailability, fluoroquinolones have been found to be widespread use in various clinical settings, especially when treating respiratory infection cases.[1,3]

The clinical use of fluoroquinolones for treating respiratory infections is common, with administration occurring through both oral and intravenous routes. However, this approach has certain limitations. One such limitation is the unfavorable pharmacokinetic profile of fluoroquinolones in the lower respiratory tract. Additionally, these drugs exhibit lower solubility and tissue permeability, which further impact their efficacy in the targeted respiratory organ. Moreover, the first-pass metabolism in the liver that fluoroquinolones undergo before becoming bioavailable in the respiratory system poses risks of side effects.

Such limitations could be alleviated by delivering the drug through the pulmonary route, mainly through inhalation. The administration of fluoroquinolones via inhalation could be achieved with the form of microparticles, small particles with diameters ranging from 1 to 5 μm. The utilization of microparticles as a drug delivery system offers several advantages. First, the large surface area of microparticles allows for efficient drug absorption and rapid onset of action. When inhaled, the microparticles deposit in the lungs, where they can directly interact with the target tissues, delivering the drug locally. This targeted delivery helps minimize systemic side effects and enhances therapeutic efficacy.[4]

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Microparticles can be designed with natural polymers to release drugs in a controlled manner while also being readily biodegradable, with low immunogenicity and toxicity in the body, allowing for sustained release and prolonged therapeutic effect. Different formulations and techniques using natural polymers can be utilized to modify the characteristics and release kinetics of the drug from the microparticles, ensuring optimal drug encapsulation efficiency, particle size, and release kinetics. This review aims to comprehensively analyze the characteristics, drug release profile, and antibacterial study of fluoroquinolone microparticles utilizing polymeric formulation for pulmonary drug delivery.[4]

Fluoroquinolones

Fluoroquinolones are synthetic compounds derived from nalidixic acid, it falls within the category of compounds known as 1,8-naphthyridine. They possess a 4-quinolone nucleus with a specific structure. The structure of quinolone comprises a bicyclic system with substituents positioned at different locations, including N-1, position 3 (carboxyl group), position 4 (keto group), position 6 (fluorine atom), and position C-7 (often a nitrogen heterocycle moiety). There are no substituents at position 2, but there can be various 1-methyl-2-alkenyl-4(1H) groups.[1,5]

Fluoroquinolones function by impeding the transcription and replication mechanisms of bacterial DNA, which are essential for the normal operation of the cell. During the processes of DNA replication and transcription, the double-stranded DNA needs to unravel and transform into a single-stranded configuration, a task facilitated by enzymes known as DNA gyrase or DNA topoisomerase. This is composed of a pair of A subunits (gyrA) and a pair of B subunits (gyrB). Bacterial DNA gyrase introduces negative supercoiling twists in the DNA strands. The enzyme is inhibited by quinolones and fluoroquinolones through their binding to the A subunit, preventing bacteria from replicating or synthesizing proteins. This disruption of DNA gyrase activity hinders bacterial growth and survival.[5]

Microparticles

Microparticles are tiny solid particles ranging from 1 to 1000 μm.[6] Microparticles deliver macromolecules of drugs by various routes and control drug release, thus providing a constant drug concentration in the blood or drug targets to specific cells or organs.[7] Microparticles offer numerous advantages. They are formulated to protect drugs from environmental degradation, mask bitter tastes, preserve volatile components, reduce side effects, and enhance drug targeting.[8]

Microparticles are typically classified into two categories: microspheres and microcapsules. In microspheres, the drug is uniformly dispersed within a matrix system, where it can be either suspended or dissolved. On the other hand, microcapsules consist of heterogeneous particles surrounded by a membrane shell, creating a core-shell structure that forms a drug reservoir.[9]

There are multiple techniques accessible for the production of microparticles, such as emulsion-solvent evaporation (including o/w, w/o, w/o/w), phase separation methods (like nonsolvent addition and solvent partitioning), solvent precipitation method, emulsion extraction process, spray drying, jet milling technique, fluidization, and interfacial polymerization.[7]

Pulmonary-Based Drug Delivery

Polymers are attractive options for delivering drugs to the lungs. They provide convenient methods for encapsulating drugs in different forms like nano-embedded microparticles, microparticles, and nanoparticles. Moreover, polymers can slow down the absorption of drugs into the bloodstream, allowing for increased drug retention in the lungs. This is beneficial for treating lung-related diseases since it ensures that the drug remains in the lungs longer than immediately absorbed. Considerable investigation has been undertaken on the utilization of both natural and synthetic polymers as carriers or additives in dry powder inhalers (DPIs), which are employed for administering medications to the respiratory system. They improve the aerodynamic characteristics of the particles, prevent particle clumping, and improve particle dispersion and deposition in the lungs.[10]

Natural Polymers for Drug Delivery System

Natural polymers are extensively utilized in the drug delivery system to control release kinetics, mask taste, and provide protection and stabilization. Polysaccharides, which are the dominant type of natural polymers, are biocompatible and do not have any harmful side effects. These natural polymers are also biodegradable, cost-effective, readily available, and environmentally friendly compared to their synthetic counterparts.[11]

However, the use of natural polymers is not without its challenges. These polymers are prone to microbial contamination, and batch-to-batch production can vary due to various physical factors. Natural polymers are also susceptible to heavy metal contamination and uncontrolled hydration rates, and their release kinetics may suffer from the "burst effect" phenomenon or high initial drug release after administration. Chitosan, alginate, carrageenan, and gelatin are among the natural polymers that have been widely used and extensively researched to date.[12]

Alginate

Alginate is a polysaccharide variety discovered in brown algae. It has gained significant attention in drug delivery systems, particularly in the field of microparticle-based drug delivery. Alginate offers several desirable properties, making it an ideal choice for this application. A significant characteristic of alginate is its potential to establish gel-like structures in the presence of divalent cations, such as calcium ions. This gelation process occurs when alginate comes into contact with calcium ions, leading to the formation of a three-dimensional network. This gel network provides structural integrity to the microparticles, enabling them to encapsulate

drugs effectively. The gelation process of alginate can be easily controlled, allowing for the customization of microparticle properties. By varying the concentration of calcium ions or the alginate composition, the microparticles' size, shape, and drug release kinetics can be finely tuned. This versatility enables tailored drug delivery systems to meet specific therapeutic requirements. Furthermore, alginate is biocompatible, biodegradable, and non-toxic, making it suitable for biomedical applications. These properties ensure that alginate-based microparticles are well-tolerated within the body and can be safely degraded over time. As a result, alginate microparticles are often used as carriers for various drugs, including small molecules, proteins, and nucleic acids.[13]

Chitosan

Chitosan is a naturally derived polysaccharide obtained from chitin, this substance is found in the exoskeleton of crustaceans like shrimp, crabs, and lobsters. Due to its distinctive properties and potential applications, it has garnered considerable interest in the field of drug delivery. Chitosan possesses several characteristics that make it attractive for drug delivery systems. Firstly, it is biocompatible, biodegradable, and non-toxic, making it suitable for use in biomedical applications. It is well-tolerated by the body and can be metabolized and eliminated without causing significant harm. The ability of chitosan to stick to the lungs and extend drug release is attributed to its cationic charge, which contributes to its mucoadhesive properties. Additionally, chitosan particles have the capability to interact with macrophage mannose receptors, leading to enhanced phagocytosis. Researchers have created chitosan microparticles specifically designed to transport different anti-TB drugs, including rifabutin, rifampicin, isoniazid, ethionamide, and ofloxacin, to the lungs.[7,14]

Gelatin

Gelatin is a natural biopolymer that originates from collagen found in animal tissue. While gelatin has not been extensively studied for drug delivery, particularly for pulmonary administration, it possesses several properties that make it suitable for formulating microparticles for inhalation and pulmonary delivery. One significant advantage of gelatin is its biocompatibility. It is well-tolerated by the body and has a long-established safety record in pharmaceutical and food applications. Gelatin microparticles have demonstrated low cytotoxicity and minimal immune response, which makes them appropriate for inhalation and pulmonary administration. The surface characteristics of gelatin microparticles can undergo modifications to improve or enhance their stability and control drug release. For instance, incorporating crosslinking agents or utilizing surface modification techniques can improve the mechanical strength and regulate the release kinetics of the encapsulated drugs. Researchers have created gelatin microparticles containing therapeutic drugs with the purpose of actively targeting alveolar macrophages. Since macrophages have mannose membrane receptors, mannosylated gelatin microparticles demonstrate notably higher drug concentrations inside the cells compared to non-mannosylated microparticles.[15,16]

Carrageenan

Carrageenan refers to a collection of high molecular weight hydrophilic sulphated polysaccharides. It is made up of D-galactose and 3,6-anhydro-galactose (3,6-AG) units connected by alternating α-1,3 and β-1,4-glycosidic bonds. This anionic polysaccharide contains ester-sulphate groups ranging from 15 to 40%. Carrageenan can be categorized into six distinct forms based on factors like its solubility, extraction source, and sulfate content. These forms are kappa (K-), lambda (λ-), iota (ι-), mu (μ-), beta (β-), nu (ν-), and theta (θ) carrageenan. The main types commonly used in commercial and pharmaceutical applications are K-carrageenan, λ -carrageenan, and ι-carrageenan. Typically, they can be acquired individually or as a precise blend, as many seaweeds consist of hybrid variations of carrageenan. The distinguishing factor among kappa-, iota-, and Lambda-carrageenan refers to the count of ester-sulphate groups present in each recurring disaccharide unit: one, two, and three, respectively. The chemical structures of carrageenan are diverse and influenced by factors such as algae sources, seaweed life stage, and extraction process. Carrageenan exhibits multiple characteristics that render it suitable for pulmonary drug delivery systems. Firstly, it has mucoadhesive properties, allowing it to interact with the mucus layer lining the respiratory tract. This mucoadhesive behavior enables prolonged residence time of drug-loaded carrageenan particles in the lungs, enhancing drug absorption and local therapeutic effects. Moreover, carrageenan has been investigated for its immunomodulatory properties. Research has demonstrated its ability to exhibit anti-inflammatory properties and the ability to enhance the immune response. These properties make carrageenan an attractive candidate for the treatment of respiratory conditions characterized by inflammation or immune dysfunction. However, it is important to note that the safety and biocompatibility of carrageenan have been subject to some debate, particularly regarding its potential for inducing inflammation or allergic reactions in certain individuals. Further research is needed to fully understand and address these concerns.[17]

Synthetic Polymers for Drug Delivery System

Synthetic polymers have demonstrated favorable outcomes compared to natural polymers due to their ease of synthesis and cost-effectiveness. Various synthetic polymers, including poly (lactic-co-glycolic acid) (PLGA), polyanhydrides, and poly (lactic acid) (PLA), have shown promising effects in terms of biocompatibility and versatility.

PLGA

PLGA (poly(lactic-co-glycolic acid)) is a polymer with both biodegradable and biocompatible properties, attracting considerable interest in drug delivery and tissue engineering domains. It is a copolymer synthesized from lactic acid and

glycolic acid, these monomers occur naturally in nature. PLGA offers several advantages as a polymeric encapsulation material for therapeutic drugs. Its controlled drug release capabilities can be achieved by adjusting parameters such as the content of glycoside units, initial molecular weight, stereochemistry (D- or L- composition), or end-group functionalization. PLGA, a commonly used biodegradable polymer, is highly suitable for encapsulating a wide range of therapeutic agents, encompassing small molecule drugs, DNA, proteins, and other substances. This is mainly due to its excellent biocompatibility.[10]

Pulmonary Drug Delivery

Pulmonary drug administration is a promising approach for delivering medications, benefiting both general and localized treatments. Incorporating polymers into medical applications enhances delivery systems, allowing customization for desired therapeutic outcomes. Polymer-based drug delivery systems enable sustained release and precise targeting of specific cells or organs, improving treatment efficacy while minimizing side effects. Microparticles have gained significant attention in pulmonary drug delivery research, demonstrating high effectiveness in treating conditions like infectious diseases, COPD, and asthma.[18]

One of the key benefits of microencapsulation is its ability to protect drugs against pulmonary metabolism. Encapsulating the drug within the microparticles makes it less susceptible to degradation and breakdown, ensuring its stability until it reaches the targeted site of action within the lungs. This safeguarding effect enables optimal drug delivery and enhances the therapeutic impact of the treatment.[18]

Additionally, microencapsulation allows for sustained and prolonged drug release. The controlled release mechanism of microparticles ensures a steady and consistent supply of the drug over an extended period. This prolonged release improves patient compliance and reduces administration frequency, resulting in a more convenient and effective treatment regimen. Furthermore, the use of extended-release microparticulate formulations can potentially minimize long-term side effects. By regulating the drug's release profile, it is possible to balance therapeutic efficacy and minimize adverse reactions. This approach offers a significant advantage in managing chronic conditions where long-term medication is required, as it reduces the likelihood of undesirable complications associated with prolonged drug exposure.[19]

Dry powder inhaler (DPI) formulations consisting of small drug particles have emerged as a prominent option in pulmonary drug delivery. With their size range of 1 to 5 μm, these DPI formulations enable the deposition of drug particles deep into the lungs, particularly in the alveoli. This targeted delivery enhances drug absorption and distribution within the lungs, optimizing treatment outcomes. The small size of the drug particles in DPI formulations facilitates increased intracellular drug concentration in macrophages. Macrophages play a crucial role in the immune response within the lungs and are often involved in the clearance of pathogens and foreign particles. By enhancing drug uptake by macrophages, the treatment duration can be reduced, leading to faster recovery and improved patient outcomes. Additionally, this targeted approach can help prevent the development of multi-drug resistance, a significant concern in the management of infectious diseases.[18,19]

Table 1 encompasses a range of studies that have explored the incorporation of fluoroquinolones into microparticle formulations, resulting in diverse characteristics. These variations are attributed to factors such as drug and polymer properties, formulation parameters, particle size and morphology, solvent selection, and drug-polymer interactions. Considering that inhalation and passive diffusion are the main mechanisms of drug delivery and absorption in the lungs, where small molecular weight drugs are absorbed more rapidly than macromolecular drugs, it becomes crucial to emphasize particle size and morphology characteristics. Drugs with a molecular weight lower than 1000 Da display a brief absorption half-life and demonstrate favorable bioavailability. Despite the thinness of the alveolar wall, macromolecular drugs can still be absorbed through the gaps between cells or engulfed by alveolar macrophages and transported to the lymphatic system before entering the bloodstream.[14]

The aerodynamic diameter, which depends on particle size and density, is a crucial factor influencing the trajectory of particles in the lungs. Particles ranging in size from 0.5 to 1.0 μm accumulate on the walls of the respiratory bronchioles and alveoli. particles smaller than 0.5 μm are expelled out of the respiratory tract due to Brownian motion, resulting in approximately 80% of them being discharged. Consequently, Particles sized between 1.0 to 5.0 μm exhibit the highest rate of deposition in the bronchioles and alveoli, making them ideal for inclusion in pulmonary inhalation preparations.[15,20]

Drug Release Mechanism

The concept of "drug release mechanism" can be described with slight variations depending on the perspective, depending on whether it refers to the transportation or release of drug molecules (known as the true release mechanism) or the process that governs the release rate (known as the rate-controlling release mechanism).[21] Within this section, the latter definition, which pertains to the mechanism of the rate-controlling release, is utilized to offer a more precise categorization of release mechanisms. Understanding the mechanism that controls the rate of release is vital during the design of drug delivery systems, as it offers insights into how the drug release rate can be adjusted.[21] Understanding the release mechanisms is crucial to ascertaining the rate's control process. Additionally, it is worth mentioning that the mechanisms of release have the potential to undergo change throughout the course of drug release, and multiple mechanisms can concurrently influence the overall detected drug release mechanisms (Figure 1).[22]

Diffusion

Diffusion is a commonly observed drug release mechanism that can occur through various mediums, such as a porous matrix, non-porous matrices, or polymer membranes. Diffusion functions as a mechanism that controls the rate of drug

release. Nonetheless, it also plays a role in situations where another release mechanisms are predominant and regulate the processes that control the rate. In instances of pure diffusion-controlled release, the drug release kinetics adhere to Fickian diffusion kinetics, demonstrating a reduction in the rate of drug release over time.[9]

Surface Erosion

Surface erosion pertains to a mechanism of drug release where the polymer's chemical bonds degrade more rapidly than the diffusion of water into the polymer matrix. As a consequence, erosion predominantly transpires on the outer surface of the matrix. The drug encapsulated within the matrix is concurrently released throughout this erosion procedure, indicating that surface erosion governs the drug's release irrespective of its physicochemical attributes.[23] One benefit of this process is the capacity to regulate the release rate through the manipulation of the erosion characteristics of the delivery system. Surface erosion-controlled mechanisms are usually used in controlled drug delivery systems as they ideally enable linear, zero-order release kinetics. This differs from bulk-eroding matrices, which display non-linear kinetics. However, a challenge associated with this process is to ensure that the

Table 1: Fluoroquinolone microparticles physical characteristics

No	*Form*	*Drug*	*Polymer*	*Method*	*Result*	*References*
1	Microspheres	Ciprofloxacin	Sodium Alginate	Ionotropic gelation	Particle size : between 1.23 ± 0.07 µm and 1.43 ± 0.09 µm Moisture Content (MC) : ranged from (2.44 ± 0.48)% to (3.00 ± 0.24)% Drug Loading (DL) : ranged from (2.82 ± 0.21)% to (4.13 ± 0.30)% Eficiency Entrapment (EE): ranged from (30.05 ± 2.37)% to (74.53 ± 5.48)%	[26]
2	Microspheres	Ciprofloxacin	Kappa Carrageenan	Ionotropic gelation	Particle size: 1.4 to 1.6 µm EE: lowest 10.54%, highest 28,69% DL : from 13 to 18%	[27]
3	Microparticles	Ciprofloxacin	Chitosan	Ionic gelation	Particle size: 720,9 ± 153,3 µm Zeta potential : 32,3 ± 3.9 Loading efficiency: 87.4 ± 1.6%	[28]
4	Microparticles	Ciprofloxacin	Gelatin	Single-step Spray-drying	Particle size : 2.61 ± 0.70 µm to 2.79 ± 0.80 µm MC : < 2% DL : 1.0 ± 0.03% to 4.73 ± 0.44% EE: 94.6–100%	[29]
5	Microspheres	Levofloxacin	Chitosan	Spray drying	Particle size: 8.2 ± 2.6 µm Yield: 79% DL: 43.2 ± 0.5% EE: 108 ± 1% Mass Median Aerodynamic Diameter (MMAD): 8.4 ± 2.3 µm	[30]
6	Microspheres	Levofloxacin	PLGA	Spray drying	Particle size: 5.0 ± 1.7 µm Yield: 50.0 ± 4.9% DL : 10.5 ± 1.4 wt%	[31]
7	Microspheres	Levofloxacin	PLGA	Double emulsion - Solvent evaporation	Particle size: 4,3 µm to 17.5 ± 1.0 µm DL : 0,30 wt.% to 18,4 wt.% EE : 0.9 to 44.4%	[32]
8	Microspheres	Levofloxacin	PLGA	Solvent evaporation	Particle size: 2.86 ± 0.26 µm DL : 40.85% EE : 77.8% MC : 3.96 ± 0.41% MMAD : 2.13 ± 1.24 µm	[33]
10	Microspheres	Moxifloxacin	PLGA	Solvent evaporation	Particle size: 3.16 µm DL : 21.98% EE : 78.0% MMAD : 2.85 ± 1.04 µm	[34]
11	Microspheres	Ofloxacin	Chitosan	Water-in-oil emulsification	Particle size: 1–6 µm DL : 27%	[35]

drug's diffusion rate does not surpass the erosion rate. When the diffusion rate of the drug exceeds the erosion rate, the release mechanism transitions from being governed by surface erosion to being governed by diffusion. For instance, the introduction of pores can modify the release mechanism, causing a shift from surface erosion-controlled release to diffusion-controlled release. In situations where polyanhydrides, a significant level of hydrophilicity or a high degree of drug loading tends to transition the release process from surface erosion-controlled to diffusion-controlled. Conversely, increased hydrophobicity and reduced drug loading facilitate surface erosion-controlled release from polyanhydrides by augmenting the interaction between the drug and the polymer matrix.[9]

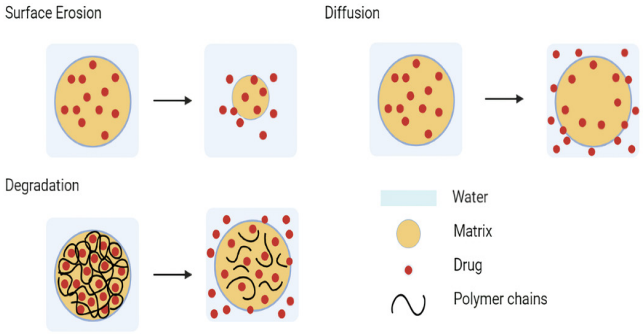

Figure 1: Drug release mechanism

Degradation

Degradation refers to the breaking of chemical bonds.[23] It can contribute to regulating drug release from different delivery systems, for instance, bulk-erosing polymers and hydrogels. Nonetheless, release controlled by degradation is commonly linked to release controlled by diffusion and is generally not the sole mechanism involved throughout the entire drug release process. For instance, in bulk-eroding delivery systems, drug release occurs in three distinct phases: an initial burst phase, a diffusional release phase, and finally a rapid release phase due to matrix degradation and erosion. Likewise, within crosslinked hydrogels, the breakdown of crosslinks causes an expansion of the mesh size, leading to a higher rate of release for macromolecules. This transition shifts the drug release mechanism from being governed by diffusion or swelling to being governed by degradation. Furthermore, as the polymer network loosens due to degradation, water absorption and polymer expansion are amplified, resulting in an accelerated drug release rate.[9,22] Table 2 displays the drug release profiles of studies involving the utilization of fluoroquinolone microparticles, some of which exhibit the characteristic "early burst release" and biphasic-phase release while still demonstrating controlled and gradual release over time.

Table 2: Fluoroquinolone microparticles: *In-vitro* drug release profile

No	*Form*	*Drug*	*Polymer*	*Medium*	*Result*	*References*
1	Microspheres	Ciprofloxacin	Sodium Alginate	Phosphate buffer saline (pH 7.4)	Slowing rate of release as the concentration of alginate and $CaCl_2$ decrease	26
2	Microparticles	Ciprofloxacin	Chitosan	Phosphate buffer saline (pH 7.4)	On average, microparticles exhibit a release rate of 0.5% drug within the first 24 hours and 0.02% every 24 hours thereafter.	28
3	Microparticles	Ciprofloxacin	Gelatin	Phosphate buffer saline (pH 7.4)	The release pattern of CPx gel-microparticles containing varying drug quantities exhibited an initial burst release during the initial 6 hour period, there is a rapid release of the microparticles, which is then followed by a slower release rate. The entire release was accomplished within 24 hours.	29
4	Microspheres	Levofloxacin	Chitosan	Phosphate buffer Salin (pH 7.4)	All formulations showed immediate drug release profile	30
5	Microspheres	Levofloxacin	PLGA	Phosphate buffer Salin (pH 7.4)	There was a burst release in the first 30 minutes, afterward gradual release up until 72 hours. At 72 hours, about 75% of the drug content is released	31
6	Microspheres	Levofloxacin	PLGA	Phosphate buffer saline (pH 7.4)	Burst release in the first 30 minutes as much as 35–40%. Subsequently, there is a gradual release of the substance, reaching a maximum of 75% within a span of 72 hours.	32
7	Microspheres	Levofloxacin	PLGA	Acetate buffer (pH 4.4) and phosphate buffer (pH 7.4)	13% of the drug was released from the microspheres within 8 hours. Levofloxacin microspheres exhibit a biphasic release pattern with fast burst release (~21%) at the first 12 hours, afterward continued drug release for up to 15 days	33
8	Microspheres	Moxifloxacin	PLGA	Phosphate buffer (pH 7.4) and acetate buffer (pH 4.4)	The release profile of drugs from PLGA microspheres exhibits a biphasic pattern. It commences with an initial burst release of approximately 20% during the initial 12 hour period, which is then followed by a sustained release that persists for up to 360 hours.	34

Table 3: Fluoroquinolone microparticles: Antibacterial activity

No	*Form*	*Drug*	*Polymer*	*Bacteria*	*Result*	*References*
1	Microspheres	Ciprofloxacin	Sodium Alginate	*S. aureus* *E. coli*	Inhibition diameters : *S. aureus* (15.05 ± 0.07 mm and 15.30 ± 0.36 mm) *E. coli* (15.37 ± 0.38 mm and 15.92 ± 0.28 mm)	[26]
2	Microparticles	Ciprofloxacin	Chitosan	*E. coli* (ATCC 25922) *P. aeruginosa* (ATCC 27853) *S. aureus* (ATCC 29213)	Minimum Inhibitory Concentration (MIC) : *E. coli* : 0,93 µg/mL *P. aeruginosa* : 4.27 µg/mL, *S. aureus* : 17.8 µg/mL	[28]
3	Microparticles	Ciprofloxacin	Gelatin	*S. aureus* (ATCC29213) *E. coli* (NCTC8196)	MIC : *S. aureus* : 0.25 µg/mL *E. coli* : 0.008 µg/mL	[29]
4	Microspheres	Levofloxacin	Chitosan	*P. aeruginosa* (CF2_2004) *P. aeruginosa* (CF7_2005)	Inhibition diameters & MIC : *P. aeruginosa* (CF2_2004) : 20 mm & 0.625 mg/L *P. aeruginosa* (CF7_2005) : 24 mm & 0.625 mg/L	[30]
5	Microspheres	Moxifloxacin	PLGA	*M. tuberculosis*	MIC: 0.8 µg/mL	[34]

Fluoroquinolones Antibacterial Activity

Antibacterials are compounds used to control the growth of harmful bacteria. The inhibition mechanism of antibacterial compounds against bacterial growth can manifest as the disruption of cell walls, inhibition of nucleic acid and protein synthesis.[24] Fluoroquinolones, being one of the most commonly used antibacterial compound owes its antibacterial activity to the presence of pharmacophore structure of 4-pyridone-3-carboxylic acid with a ring substitution at 5 or 6 positions, which in turn is part of its 4-quinolone nucleus. Now that significant research advancements regarding the consequences of modifications on the nucleus, various modification efforts were made to enhance the antibacterial effectiveness. In the lead optimization of the original 1,8-naphthyridine core, two primary strategies were pursued. These strategies involved modifying the 6-fluoro and 7-piperazinyl quinolone components. In the initial stage of lead optimization, modifications were made to the side chains, including the replacement of a nitrogen atom with a carbon atom at position -8. These modifications led to the development of fluoroquinolones such as 1-cyclopropyl (ciprofloxacin) and 1,8-cyclo compounds like sparfloxacin and clinafolxacin. These compounds exhibited significantly enhanced effectiveness against gram-negative bacteria.[25]

Fluoroquinolones hinder the duplication and transcription of DNA in bacteria, ultimately leading to the demise of the cells.[5] They can either hinder the functioning of DNA gyrase, a crucial enzyme called topoisomerase II that utilizes ATP hydrolysis, alternatively to hinder the detachment of gyrase from DNA or impede its separation. The topoisomerases were susceptible to the bactericidal effects when they interacted with the DNA. In the course of replication and transcription procedures, helicase enzymes are responsible for unwinding or untwisting the DNA double helix. This can result in excessive supercoiling in the remaining DNA double helix. The remaining double helix experiences a tension that needs to be alleviated in order to proceed with the process. The enzyme topoisomerase II assists in the relaxation of tightly coiled DNA by breaking and rejoining both DNA molecule strands and resealing them. Bacterial gyrase and mammalian topoisomerase differ significantly, resulting in quinolones and fluoroquinolones exhibiting approximately 1000 times greater preference for targeting bacteria compared to the corresponding enzyme found in humans.[5,25]

Additionally, it has been discovered that fluoroquinolones possess the ability to impede the *in-vitro* functions of topoisomerase IV, which shares a resemblance in structure to DNA gyrase. Topoisomerase IV plays a vital role in the separation of chromosomal DNA during the division of bacterial cells, and it is probable that it serves as the primary target for the activity of fluoroquinolones in gram-positive bacteria. This process is in accordance with apoptosis instead of necrosis.[25] Table 3 presents studies that have investigated the antibacterial activity of fluoroquinolone microparticles. It could be seen that most studies have achieved the right microparticle formulations that preserve low fluoroquinolone dosages required to achieve the minimum inhibitory concentration (MIC) in antibacterial activity studies.

CONCLUSION

This review study explores a range of studies known to date that have incorporated fluoroquinolones into microparticle formulation, primarily focusing on its physical characteristics, drug release profile, and antibacterial activity of the formulations. It has been determined in those studies that various formulations of polymer-based microparticles possess diverse physical characteristics. However, many of them have achieved a size range of 1.0 to 5.0 µm, ensuring the lungs'

highest deposition rate. Additionally, it has been shown that certain formulations exhibit a steady-slow release profile, while others demonstrate early burst-release and biphasic characteristics. Furthermore, these microparticle formulations preserve low fluoroquinolone dosages required to achieve the MIC in antibacterial activity studies.

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REFERENCES

1. Appelbaum PC, Hunter PA. The fluoroquinolone antibacterials: past, present and future perspectives. Antimicrobial Agents and Chemotherapy. 2000;16:5-15.
2. Guneysel O, Onur O, Erdede M, Denizbasi A. Trimethoprim/Sulfamethoxazole Resistance in Urinary Tract Infections. Journal of Emergency Medicine. 2009;36(4):338-341. doi: 10.1016/j.jemermed.2007.08.068.
3. Blondeau JM. Expanded activity and utility of the new fluoroquinolones: A review. Clinical Therapeutics. 1999;21(1):3-40. doi: 10.1016/S0149-2918(00)88266-1.
4. Borghardt J, Kloft C, Sharma A. Inhaled Therapy in Respiratory Disease: The Complex Interplay of Pulmonary Kinetic Processes. Canadian Respiratory Journal. 2018:1-11. doi: 10.1155/2018/2732017.
5. Brar RK, Jyoti U, Patil RK, Patil HC. Fluoroquinolone antibiotics: An overview. Adesh University Journal of Medical Sciences & Research. 2020;2(1):26-30. doi: 10.25259/aujmsr_12_2020.
6. Jyothi N, Roy H, Prasanhti NL, Vajrapriya VS. A Brief Review of Microparticle Drug Delivery System. World Journal of Pharmacy and Pharmaceutical Sciences. 2016;5(7):701. doi: 10.20959/wjpps20167-7209.
7. Madhav NVS, Kala S. Review on microparticulate drug delivery system. International Journal of PharmTech Research. 2011;3(3):1242-1254.
8. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. Scientific Pharmaceutics. 2019;87(3). doi: 10.3390/scipharm87030020.
9. Mönkäre J. Novel Materials for Controlled Peptide Delivery: Mesoporous Silicon and Photocrosslinked Poly(ester anhydride)s. 2015. doi: 10.13140/RG.2.1.1928.3923.
10. Sabuj MZR, Islam N. Inhaled Antibiotic-loaded Polymeric Nanoparticles for The Management of Lower Respiratory Tract Infections. Nanoscale Advances. 2021;3:4005-4018.
11. Rajeswari S. Natural Polymers: a Recent Review. World Journal of Pharmacy and Pharmaceutical Sciences. 2017;June:472-494. doi: 10.20959/wjpps20178-9762.
12. Singh J. Natural Polymers Based Drug Delivery Systems. www.wjpps.com. 2016;5(4):805. doi: 10.20959/wjpps20164-6453.
13. Abourehab MAS, Rajendran RR, Singh A, Pramanik S, Shrivastav P, Ansari MJ, Manne R, Amaral LS, Deepak A. Alginate as a promising Biopolymer in Drug Delivery and Wound Healing: A Review of the State-of-the-Art. International Journal of Molecular Sciences. 2022;23(16):9035.
14. Guan X, Zhang W. Applications of Chitosan in Pulmonary Drug Delivery. In: Tyagi RK, Garg N, Shukla R, Bisen PS, editors. Role of Novel Drug Delivery Vehicles in Nanobiomedicine. IntechOpen; 2020.
15. Miranda MS, Rodrigues MT, Domingues RMA, Torrado E. Exploring Inhalable Polymeric Dry Powders for Anti-tuberculosis Drug Delivery. Materials Science and Engineering C. 2018.
16. Nii T. Strategies Using Gelatin Microparticles for Regenerative Therapy and Drug Screening Applications. Molecules. 2021;26(22):6795. doi: 10.3390/molecules26226795.
17. Pacheco-Quito E, Ruiz-Caro R, Veiga M. Carrageenan: Drug Delivery Systems and Other Biomedical Applications. Marine Drugs. 2020;18(11):583.
18. Pham DD, Fattal E, Tsapis N. Pulmonary drug delivery systems for tuberculosis treatment. International Journal of Pharmacy. 2015;478(2):517-529. doi: 10.1016/j.ijpharm.2014.12.009.
19. Kaur M, Kaur H, Kaur IP. Advances in Inhalation Drug Delivery Systems: Formulation Strategies for Efficient Pulmonary Drug Delivery. Current Drug Delivery. 2020;17(7):606-622. doi: 10.2174/1567201817666200608123134.
20. Lim YH, Tiemann KM, Hunstad DA, Elsabahy M. Polymeric Nanoparticles in Development for Treatment of Pulmonary Infectious Diseases. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2016;8(6).
21. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems—A review. International Journal of Pharmacy. 2011;415:34-52.
22. Zhang H, Bei J, Wang S. Preparation and drug release behaviors of 5-fluorouracil loaded poly(glycolide-co-lactide-co-caprolactone) nanoparticles. Journal of Applied Polymer Science. 2007;106:3757–3767.
23. Göpferich A. Mechanisms of polymer degradation and erosion. Biomaterials. 1996;17:103–114.
24. Avcu E, Bastan FE, Guney M, Yildiran YA, Ur Rehman MA, Boccaccini AR. Biodegradable Polymer Matrix Composites Containing Graphene-Related Materials for Antibacterial Applications: A Critical Review. Acta Biomaterialia. 2022;151:1-44. doi: 10.1016/j.actbio.2022.07.048.
25. Sharma P, Jain A, Jain S. Fluoroquinolone antibacterials: A review on chemistry, microbiology and therapeutic prospects. Acta Poloniae Pharmaceutica. 2009;66(6):587-604.
26. Hariyadi DM, Hendradi E, Kurniawan DT. Alginate Microspheres Encapsulating Ciprofloxacin HCl: Characteristics, Release and Antibacterial Activity. International Journal of Pharma Research & Health Sciences. 2019;7(4):3020–3027. doi: 10.21276/ijprhs.2019.04.02.
27. Hariyadi DM, Hendradi E, Sharon N. Development of carrageenan polymer for encapsulation of ciprofloxacin HCl: In vitro characterization. International Journal of Drug Delivery Technology. 2019;9(1):89-93. doi: 10.25258/ijddt.9.1.14.
28. Kucukoglu V, Uzuner H, Kenar H, Karadenizli A. In vitro antibacterial activity of ciprofloxacin loaded chitosan microparticles and their effects on human lung epithelial cells. International Journal of Pharmacy. 2019;569:118578. doi: 10.1016/j.ijpharm.2019.118578.
29. Silva DM, Vyas HKN, Sanderson-Smith ML, Sencadas V. Development and optimization of ciprofloxacin-loaded gelatin microparticles by single-step spray-drying technique. Powder Technology. 2018;330:201–209. doi: 10.1016/j.powtec.2018.02.029.
30. Gaspar MC. Optimization of levofloxacin-loaded crosslinked chitosan microspheres for inhaled aerosol therapy. European Journal of Pharmaceutical Sciences. 2015;93:65–75. doi:

10.1016/j.ejps.2015.07.010.
31. Gaspar MC. Pulmonary pharmacokinetics of levofloxacin in rats after aerosolization of immediate-release chitosan or sustained-release PLGA microspheres. European Journal of Pharmaceutical Sciences. 2016;93:184–191. doi: 10.1016/j.ejps.2016.08.024.
32. Gaspar MC, Pais AACC, Sousa JJS, Brillaut J, Olivier JC. Development of levofloxacin-loaded PLGA microspheres of suitable properties for sustained pulmonary release. International Journal of Pharmacy. 2019;556:117–124. doi: 10.1016/j.ijpharm.2018.12.005.
33. Al Hagbani T. Pulmonary Targeting of Levofloxacin Using Microsphere-Based Dry Powder Inhalation. Pharmaceuticals. 2022;15(5):1–18. doi: 10.3390/ph15050560.
34. Vishwa B. Pulmonary targeting of inhalable moxifloxacin microspheres for effective management of tuberculosis. Pharmaceutics. 2021;13(1):1-17. doi: 10.3390/pharmaceutics 13010079.
35. Park JH, Jin HE, Kim DD, Chung SJ, Shim WS, Shim CK. Chitosan microspheres as an alveolar macrophage delivery system of ofloxacin via pulmonary inhalation. International Journal of Pharmacy. 2013;441(1–2):562–569. doi: 10.1016/j.ijpharm.2012.10.044.