

**A REVIEW ON PROMISING ANTIBIOTIC THERAPY BY NOVEL DELIVERY SYSTEMS**

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**ABSTRACT**

The introduction of a new moiety of drugs for antibiotics in the market is getting declined. Antibiotic resistance is a major threat to human health worldwide. Many life-saving antibiotic drugs are rendered ineffective. Resistant bacterial infections are difficult to treat because of the poor response to antibiotics. Hence, utilizing the novel methods/approaches for the development of formulation into its novel delivery can prevent bacterial resistance. This review article explores the various promising approaches for delivery of antibiotics in the form of liposomes, solid lipid nanoparticles, microspheres, dendrimers, inhaled antibiotics, and polymeric particles. These approaches of delivery have been proven to provide innovative and novel delivery of antibiotic by enhancing the therapeutic effectiveness, targeting at the site of action, enhanced activity, and penetrability at intracellular pathogens, thereby reducing side effects, toxicity, and the chances of bacterial resistance.

**Keywords:** Antibiotics, Liposomes, Solid lipid nanoparticles, Polymeric particles, Microspheres, Dendrimers, Inhaled antibiotics.

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**INTRODUCTION**

Infectious diseases continue to be one of the main reasons for mortality and morbidity [1]. Introduction of antibiotics in the medical field has made significant gains in the health status and enabled the development of modern medical procedures [2]. Antibiotics play an important role in ensuring safe surgical procedures, organ transplants, chemotherapy, and a great weapon against many infections such as plague, tuberculosis (TB), and pneumonia [2,3].

Antibiotic resistance is a global public health threat. Overconsumption and unnecessary use of antibiotics increased the rate of antibiotic resistance around the world. The use of antibiotics generates resistance to their effect, by decreasing their effectiveness in the prevention and cure of disease [4]. Modes of action and resistance mechanism of some antibiotics are given in Table 1. Among the resistance pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococcus*, vancomycin-resistant *S. aureus*, and penicillin-resistant *Streptococcus pneumonia* have become major clinical threats [5].

According to a report released by the World Health Organization on 30<sup>th</sup> April - 2014, antibiotic resistance globally reveals that this serious threat is no longer be regarded as an issue for the future but rather a current crisis that requires urgent interventions [7]. To overcome the antibiotic resistance, new antibiotics are being investigated, but the US Food and Drug Administration (FDA) reported that there is a gradual decline in the introduction of new antibiotic drugs. During the period of 2008-2012, the US FDA approved only two systemic antibacterial agents for use in humans while 16 drugs approved from 1983 to 1987 [5].

The development of novel and effective strategies for enhancing the drug therapy with current antibiotics is major focus areas of research priority [5]. Novel drug delivery system has some benefit in the delivery of antibiotics. The pharmaceuticals are averse to investing novel drug delivery strategy for efficient delivery of antibiotics. The novel drug delivery methods such as self-emulsifying drug delivery system, microspheres, inhaled antibiotics, liposomes, solid lipid nanoparticles, polymeric particles, dendrimers, nanoemulsions, and nanosuspension could be promising drug delivery systems for antibiotics [5,8].

**NOVEL DRUG DELIVERY METHODS****Liposomes as delivery systems for antibiotics**

Liposomes are concentric, bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are in the size range of 0.01-5.0  $\mu\text{m}$  in diameter and can act as a carrier for a variety of drugs [9,10]. The antibacterial activity and the pharmacokinetics properties of antibiotics can be enhanced by entrapping an antibiotic in liposomes. Lipid vesicles are used as drug carriers which have influence on drug distribution and reduction of toxic effects. Some antibiotics have limited application due to toxicity and weak biodistribution because of low penetrability, so the pharmacokinetic and pharmacodynamic properties can be modified by encapsulating a drug in lipid vesicles [11]. Improved pharmacokinetic and biodistribution, target selectivity, enhanced activity against intracellular pathogens, protection of antibiotic drugs against hydrolytic activity of enzymes, decreased toxicity, enhanced penetrability, and thereby increased residence time of the drug in macrophages are the main advantages of liposomes [12].

**Improved pharmacokinetic and biodistribution and decreased toxicity**

Drug encapsulation in liposomal vesicles improves the pharmacokinetics and also protects antibiotics against the hydrolytic activity of enzymes and chemical and immunological deactivation. The liposomes which are given by intravenous administration are determined as foreign antigens by the immunological system and are opsonized. This causes the activation of non-specific defense mechanisms and the liposomes are taken up by the mononuclear phagocyte system (MPS), and this leads to lower blood clearance; this phenomenon is essential for intracellular pathogen eradication [12].

**Enhanced activity against intracellular pathogens**

For eradicating the intracellular pathogen, the liposomal drug delivery system is effective. For treating the diseases which is caused by intracellular bacteria, rigid conventional liposomal vesicles and polyethylene glycol (PEG) coated have been referred to improved drug retention in proper tissues, provided sustained release, and decreased toxicity [12].

An overview of various reported liposomal systems with the rationale for formulation development is provided in Table 2. Filipin is the first

antibiotic drug reported for liposomes in antibiotic drug delivery. Filipin is the polyene macrolide antibiotic, and it was reported that the hemolytic activity of filipin complex could be removed more effectively by liposomes [16]. Another research goal by Gregoriadis has been to overcome the failure of penicillin to penetrate cells of the reticuloendothelial system. He entrapped potassium benzylpenicillin in liposomes composed of egg lecithin, cholesterol, phosphatidic acid, and dipalmitoyl lecithin. These *in vivo* studies with rats showed lysosomal localization of penicillin-entrapped liposomes into the liver and spleen [19].

The cationic or anionic liposomes can be prepared using cationic or anionic ingredients in the liposomal formulations. The two antibiotics ciprofloxacin and vancomycin were encapsulated alone and in combination with liposomes to achieve a new antibiotic therapeutic approach against chronic staphylococcal osteomyelitis infections presenting in rabbits. Among all these formulations, enhanced antibacterial activity against *S. aureus* was observed for cationic liposomal formulation [20].

Surface modification of liposomes is another active area for delivery of antibiotics. It was reported that liposomes encapsulation of vancomycin offers increased pharmacokinetic and pharmacodynamic activity and decreased toxicity. When compared to the standard vancomycin formulation, the surface PEGylated liposomes deliver the drug more essentially to pathogens by depositing a higher concentration of drug into lung tissue. Liposome encapsulation decreases the drug distribution into the kidney and increases the drug accumulation in the lungs, liver, and spleen [21].

#### SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles are the most effective lipid-based colloidal carriers, introduced in the early 1990s. SLNs are one of the novel potential colloidal carrier systems as alternative materials to polymers which are

identical to oil in water emulsion. SLNs are in the submicron size range of 50–1000 nm and are composed of physiologically tolerated lipid components which are in the solid state at room temperature [22]. High-pressure homogenization, microemulsion technique, ultrasonication, solvent emulsification, spray drying, and double emulsion are the most commonly used technique for the preparation of SLN [23]. Many solid lipids such as stearic acid, glyceryl monostearate, glyceryl distearate, and decanoic acid have been used in preparing SLN. Various surfactants such as soy lecithin, egg lecithin, sodium cholate, sodium glycocholate, tween 20 and 80, and polaxamer 188, 182, and 407 are reported [24]. Proposed advantages of SLN include possibility of controlled drug release, high drug payload, excellent bioavailability, avoiding the use of organic solvent, no biotoxicity of the carrier, easy to scale up and sterilize, increased drug stability, and incorporation of lipophilic and hydrophilic drugs [25,26]. SLNs have some drawbacks such as particle growth, unpredictable gelation tendency, and unexpected dynamics of polymeric transitions [24]. Examples of solid lipid nanoparticles investigated for antibiotic delivery are mentioned in Table 3.

Oral delivery of drugs is the most preferred route for drug administration. Tobramycin is an orally administered antibiotic drug, used against *seudomonas aeruginosa* infections in cystic fibrosis (CF). Tobramycin has a poor absorption by intestinal cells because of active exploration of the drug through p-glycoproteins (p-gp) an ATP-dependent drug efflux pumps. Tobramycin-loaded SLNs can significantly suppress the p-gp efflux pump by penetrating the intestinal linings through endocytosis instead of passive diffusion. Tobramycin-loaded SLNs show increased pharmacokinetic activity, enhanced drug distribution in the lungs, and less drug payload to kidney [33]. A research group developed the solid lipid nanoparticles of enrofloxacin for sustained release of drug. The study showed that only 18% of drug released within 2 h, followed by sustained release over 96 h [34]. This study showed that solid lipid nanoparticles are promising delivery for the sustained and prolonged release of drugs.

Table 1: Modes of action and resistance mechanisms of some antibiotics [6]

Antibiotic	Target	Mode of action
Penicillin, Cephalosporins	Peptidoglycan biosynthesis	Hydrolysis, efflux, altered target
Gentamycin, Streptomycin	Translation	Phosphorylation, acetylation, nucleotidylation, efflux
Azithromycin, Erythromycin	Translation	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Chloramphenicol	Translation	Acetylation, efflux, altered target
Ciprofloxacin	DNA replication	Acetylation, efflux, altered target
Trimethoprim, Sulfamethoxazole	C1 metabolism	Efflux and altered target
Rifampin	Transcription	ADP-ribosylation, efflux, altered target
Daptomycin	Cell membrane	Altered target
Colistin	Cell membrane	Altered target

Table 2: Overview of antibiotic liposomal development

Lipids used for liposomal preparation	Active Ingredient	Targeted Microorganism	Rationale for Formulation	Reference
1,2-dimyristoyl-Sn-glycero-3-phosphocholine and cholesterol	Gentamicin	<i>P. aeruginosa</i>	Improvement of killing time and prolongation of antimicrobial activity	Ref [13]
Phosphatidylcholine, cholesterol, and phosphatidylserine	Penicillin-G	<i>L. monocytogenes</i>	Treatment of intracellular infections	Ref [14]
Egg PC, diacetyl phosphate, cholesterol	Vancomycin and teicoplanin	MRSA	Treatment of intracellular MRSA	Ref [15]
Phosphatidylcholine, diacetyl phosphate, cholesterol	Filipin	None	Removal of hemolytic activity of filipin	Ref <sup>[16]</sup>
Soybean PC, cholesterol	Ampicillin	<i>M. luteus</i>	Improvement of drug stability and retention of antibacterial activity	Ref [17]
PC, cholesterol, and phosphatidylserine	Cephalothin	<i>S. typhimurium</i>	Intracellular killing of the microorganisms	Ref [18]

*P. aeruginosa*: *Pseudomonas aeruginosa*, *L. monocytogenes*: *Listeria monocytogenes*, MRSA: Methicillin resistant *Staphylococcus aureus*, *L. monocytogenes*: *Listeria monocytogenes*, *M. luteus*: *Micrococcus luteus*, *S. typhimurium*: *Salmonella typhimurium*

In addition to oral delivery of solid lipid nanoparticles, they are ideal for topical application because of their prolonged residence time on the stratum corneum and their occlusive property can induce film formation on the skin [35]. Vijayan *et al.* developed a SLN-based drug delivery system for neem oil to treat acne and pimples. Decrease in particle size and high entrapment efficiency showed that SLNs have an ability to incorporate a high quantity of neem oil. Their results revealed that SLNs of neem oil provide a sustained effect which satisfactorily produced the antibacterial action on acne microbes [36]. A research group prepared solid lipid nanoparticles containing curcuminoids for the development of topical delivery. The formulation containing SLN-curcuminoids showed good spreadability and stability. As a result of slow release, nano-encapsulated curcuminoids showed no permeation or penetration when assayed using pig ear skin during 18 h. The study concluded that the topical formulation is stable and can be used for the treatment of inflammatory reactions such as radioderms [37].

Another research area for SLNs is pulmonary delivery of antibiotics. Pulmonary delivery of antibiotics through SLN is used to treat TB, a lung infection caused by bacteria, *Mycobacterium TB*. The antitubercular drug such as rifampicin, isoniazid, and pyrazinamide when incorporated into SLNs showed increased bioavailability. Solid lipid nanoparticles of these drugs offer drug delivery to the lungs and lymphatic system [38].

### POLYMERIC PARTICLES

Polymeric particles made up of natural and synthetic polymers show high stability *in vitro* and *in vivo*, good biocompatibility, and multifunctionality. The antibiotics in polymeric particles allow slow, sustained release of drug and improve antibacterial efficacy against biofilm-related infectious disease [39]. The commonly used natural polymers are human or bovine serum albumin, gelatin, collagen, alginate, chitosan, and starch. Synthetic polymers such as poly ( $\alpha$ -hydroxy acids), polyanhydrides, polylactide, poly lactide-co-glycolide (PLGA), and poly (fatty acid dimer-sebacic acid) are reported [40]. Encapsulated polymeric particles of antibiotics offer advantages such as improved pharmacokinetic and biodistribution and enhanced antibiotic penetration into bacterial biofilm. It also helps to overcome tissue and cellular barriers by effective targeting or responding to bacterial infected microenvironment [39].

### Improved pharmacokinetics and biodistribution of antibiotics

Several problems such as poor absorption on oral administration and drug aggregation after intravenous administration can be overcome by delivery of antibiotic as polymeric particles. An antibiotic encapsulated in polymeric particles alters the tissue distribution and plasma pharmacokinetic of the drug and increases the concentration of antibiotics at the site of infection, thus enhancing drug bioavailability [39]. After intravenous administration, the polymeric particles interact with blood cell constituents that are captured by macrophages of the MPS, and this is rapidly cleared from the blood [41]. PLGA polymer used in the polymeric particles could successfully deliver drugs to MPS tissue for the treatment of infectious disease caused by intracellular pathogens in the liver and spleen [40].

An example of polymeric particle system used for antibiotic therapy is given in Table 4. Formulation development of poly( $\epsilon$ -caprolactone) nanospheres containing amphotericin B coated with non-ionic surfactant poloxamer 188 exhibits greater therapeutic efficacy against *Leishmania donovani* when compared to the free drug [50]. PLGA acid considered as one of the most widely used polymers for antibiotic delivery. Formulation development of ciprofloxacin hydrochloride PLGA PNPs were prepared by W/O/W emulsification solvent evaporation method using a factorial design to study different parameters on particle size, zeta potential, and drug entrapment efficiencies. Their results revealed that there was a decrease in particle size and increase in drug entrapment efficiencies and the antibacterial activity of polymeric particles was found to be comparable to free drugs against *P. aeruginosa* and *S. aureus* [51]. However, 100% of the drug was not released after 24 h, so these researches recognized that PLGA being negative might have low interactions with the anionic mucus of ocular infections. Then, they extended the study and incorporated cationic polymers into this PLGA formulation. In this study, they investigated the effect of positively charged polymers, namely, Eudragit® RS 100 and RL100 on physical properties, release profile, and antibacterial activity. They concluded that the PNPs are active against *P. aeruginosa* as well as against *S. aureus* to a lesser extent. Eudragit® RL containing particles were more active against microorganisms than Eudragit® RS [52]. A further paper by the same researchers has been developed to examine whether the cationic Eudragit® containing poly(lactide-co-glycolide) nanoparticles can adhere to *P. aeruginosa* and *S. aureus*. Flow cytometric measurements were performed to examine the adhesion of particles to microorganisms. Their results showed that Eudragit NPs showed more bacterial adhesion with test organisms when compared with PLGA-NPs [53]. This becomes a new research area for the delivery of antibiotics based on surface charge difference between bacteria and PNP formulation. In another study, azithromycin- and rifampicin-loaded PLGA nanoparticles have been prepared, and this showed an enhance in the delivery of azithromycin and rifampicin to intracellular chlamydial infections which is caused by *Chlamydia trachomatis* and *chlamydia pneumoniae* [54]. Drug entrapment efficiency and drug encapsulation can be enhanced using different polymer ratio. It was reported that a combination of PLC and PLGA in a ratio of 80:20 improved the entrapment efficiency by 32% as compared to PLC and PLGA ratio of 60:40 [49]. Ungaro *et al.* formulated a PLGA nanoparticle for pulmonary delivery of tobramycin; they mentioned the importance of hydrophilic polymers such as chitosan, alginate, and polyvinyl alcohol for attaining optimal drug entrapment and release profiles [55].

Intracellular bacterial infections are very difficult to treat because of poor penetration of antibiotic drug and due to its lesser bioavailability. A research group developed biocompatible, nano-sized tetracycline encapsulated O-carboxymethyl chitosan PNPs using ionic cross-gelation technique to eradicate intracellular *S. aureus* infection. There were six-fold increases in antibacterial activity over that of the free tetracycline against intracellular *S. aureus* [56]. For targeted delivery of lectin-conjugated gliadin binding to carbohydrate receptors on *Helicobacter pylori*, cell wall shows the inhibitory effect with two-fold

**Table 3: Overview of antibiotic solid lipid nanoparticle development**

Formulation	Drug	Targeted microorganism	Activity	References
Compritol 888® ATO	Vancomycin	<i>S. aureus</i> , MRSA	Enhanced encapsulation efficiency and antibacterial activity	Ref [27]
Stearic acid, sodium taurocholate	Tobramycin	<i>Pseudomonas aeruginosa</i>	Increased tobramycin bioavailability	Ref [28]
Stearic acid, phosphatidylcholine, and sodium taurocholate	Ciprofloxacin hydrochloride	Gram-positive and Gram-negative bacteria	Prolonged drug release	Ref [29]
Tetradecanoic acid	Enrofloxacin	<i>S. aureus</i>	Sustained drug release and enhanced antibacterial activity	Ref [30]
Stearic acid	Norfloxacin	<i>E. coli</i>	Enhanced antibacterial activity	Ref [31]
Hydrogenated castor oil	Tilmicosin	<i>S. aureus</i>	Sustained drug release, enhanced antibacterial activity	Ref [32]

*P. aeruginosa*: *Pseudomonas aeruginosa*, MRSA: Methicillin-resistant staphylococcus aureus, *E. coli*: *Escherichia coli*

higher than gliadin nanoparticles [57]. The synthesis of pH-sensitive nanoparticles for the delivery of antibiotics through ring-opening metathesis copolymerization has been developed by Pichavant *et al.* A pH-sensitive  $\alpha$ -norbornenyl-poly(ethylene oxide) macromer was used for the synthesis of polymeric derivatives. The drug gentamicin was linked through pH-sensitive imine bond to a polymer, and polymeric nanoparticles were found to be non-cytotoxic when performed neutral red and (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assays. The performance of MIC measurements on *Staphylococcus epidermidis* at different pH values revealed that there was no significant inhibition of growth at pH 7, whereas a decrease in conditions of pH 4 and 5 was observed [58].

## DENDRIMERS

Dendrimers are hyperbranched polymers with precise nanoarchitecture and low polydispersity, which are synthesized in a layer-by-layer fashion around a core unit, resulting in a high-level control of size, branching points, and surface functionality. The highly dense surface of functional groups allows the synthesis of dendrimers with specific and high binding affinities to a wide variety of viral and bacterial receptors. Polyamide dendrimers (PAMAM) are the first and most popularly studied dendrimers. PAMAM is non-immunogenic and biocompatible compounds and water soluble. PAMAM are regarded as carriers or drugs such as antibacterial and antifungal which have a capacity to improve their solubility, drug permeation, and therapeutic efficiency [59]. Based on the types of linkages and chemical moieties present, dendrimers are classified into four types: Glycol dendrimers [60], peptide dendrimers [61], janus dendrimers [62], and metallodendrimers [63].

Dendrimers are synthesized either by convergent or divergent method. In the divergent method, dendrimers grow from a multifunctional core molecule to the outward through a repetition of coupling and activation steps. The core molecules react with monomer molecule to give first-generation dendrimers. Then, the periphery of the molecules reacts with additional monomers to give several generations. Divergent method is ideal for the large-scale production of dendrimers. Side reactions and incomplete functionalization can occur when the number of generation increases. The purification of the final product is difficult in case of divergent approach. In contrast, the convergent approach is synthesized stepwise, from the periphery and progressing inward. This approach begins with coupling end groups to each branch of the monomer and followed by the activation of single functional group. The dendrons, growing branched polymeric arms are large particles; they are attached to a multifunctional core molecule. Dendrimers thus synthesized by this method can be easily purified [64]. Dendrimers with their role in antibiotic drug delivery are provided in Table 5.

Targeted intracellular drug delivery is a main research area for dendrimeric nanostructures. It was studied that Erythromycin, a macrolide antibiotic when conjugated with PAMAM dendrimers (GH-OH-link NH<sub>2</sub>) resulted in sustained release of the drug [71]. A research group synthesized conjugate of azithromycin with G4 PAMAM conjugate shows a sustained release of drug over 16 h and approximately 90% of the drug was released from the formulation and azithromycin readily entered the chlamydia-infected HEP-2 cells and inclusion. This study concluded that the dendrimers can efficiently deliver drugs to growing intracellular *C. trachomatis* even if the organism is in the persistent form [67]. Sulfamethoxazole PAMAM dendrimers with ethylenediamine core have been prepared to enhance its solubility, *in vitro* drug release, and antibacterial activity. The results revealed that when compared to water solubility of drug, it showed increased in solubility by 40 folds in G<sub>3</sub> PAMAM dendrimers solution, and the dendrimer drug was more potent against *E.coli* [70].

## MICROSPHERES

Microspheres are small spherical particles with diameter of 1 $\mu$ m to 1000 $\mu$ m and are free-flowing powders consisting of proteins or synthetic polymer. Microspheres are monolithic sphere or therapeutic

agent distributed throughout the matrix either as a molecular dispersion of particles [72]. The prime advantages of microsphere include controlled and prolonged therapeutic activity with reduction in dosing frequency. The drug encapsulated matrix system thus helps in enhancing the solubility of poorly soluble drug, with reduction in toxicity and irritant effects in the GIT. This encapsulation provides protection of drug from enzymatic and photolytic cleavage also [73]. Less reproducibility, difference in release rate from one to another, and low drug loading for controlled release parenteral are the main disadvantages of microspheres.

Tetracycline-loaded chitosan microspheres were prepared to develop a stomach-specific drug delivery system to increase the efficacy of tetracycline antibiotic against *H. pylori*. Ionic cross-linking and precipitation technique have been established for preparing tetracycline microspheres. The aim of this study was to increase the local concentration of tetracycline in the stomach so as to eradicate *H. pylori* infection. This study concluded that tetracycline was stable in acidic medium for about 12 h and the entire drug content was released in the acidic pH. The results from this study suggest the use of chitosan microspheres for the encapsulation of antibiotic drugs and may be effective against *H. pylori* when it is administered locally in the stomach [74]. Cefixime-loaded microspheres showed sustained release of drug, high loading yield, and increased encapsulation efficiency [75].

Microspheres containing antibiotics have been investigated for their bactericidal activity with tetracycline-loaded chitosan microsphere against *Pseudomonas aeruginosa* biofilms. The result shows 60% of drug release in the first 6 h and continued for 24 h. The researchers concluded that the use of tetracycline chitosan microspheres may be a new strategy for the development of drug delivery system to increase the efficacy of tetracycline against biofilm-associated *P. aeruginosa* infections [76].

## INHALED ANTIBIOTICS

Inhaled antibiotics are the valuable tool in treating diseases such as CF, TB, non-CFB (non-CFB), and pneumonia. Compared to orally and parenterally given drugs, an inhaled drug dose goes directly to the targeted area. Inhalation therapy of antibiotic results in less systemic adverse effect compared to other routes of delivery. An inhaled antibiotic provides higher local drug concentration because the administered dose directly reaches the respiratory tract. There is a growing interest in the inhaled route for administration of drug [77]. A research group conducted a meta-analysis of randomized trials to study the efficacy and safety in patients with non-CF B. According to Cochrane airways group register of trials from inspection to March 2014, 12 trials with 1264 patients and eight trials on 590 patient's data have registered. Drugs like ciprofloxacin, gentamycin, aztreonam, amikacin, colistin and tobramycin were used for 4 weeks to 12 months. After the survey, they reported that the inhaled antibiotics may provide an effective therapy with stable non-CF B and chronic bronchial infection [78].

Nanosystems such as liposomes, solid lipid nanoparticles, and polymeric nanoparticles are commonly used for preparing inhalable carrier systems for pulmonary drug delivery. Other carrier systems such as magnetic nanoparticles, gold nanoparticles, nanocrystals, and effervescent nanoparticles are currently in research to study the effect of antibiotics on delivery. Polymeric nanoparticles are widely used because they possess properties such as carrier suitability with the drugs, tissue or cell targeting, protection from therapeutic degradation, sustained release mechanism, aerosol transformability, less toxicity, and stability during aerosolization [79].

## Marketed formulation

Many of the novel-based formulation are in clinical use, and some of them are in pipeline.

Some of the marketed formulations of antibiotics through novel delivery approaches are provided in Table 6.



Table 4: Overview of antibiotic polymeric particle development

Formulation	Drug	Targeted microorganism	Activity	Reference
Alginate nanoparticle PLGA	Rifampicin, isoniazid	<i>M. tuberculosis</i>	High drug payload, high therapeutic efficacy	Ref [42]
	Azithromycin	<i>S. typhi</i>	Sustained release, Increased efficiency against <i>S. typhi</i>	Ref [43]
Glycosylated polyacrylate nanoparticle	$\beta$ -lactum/ciprofloxacin	<i>S. aureus</i> and <i>Bacillus anthracis</i>	Improved bioavailability. Higher therapeutic efficacy	Ref [44,45]
Polyisohehexylcyanoacrylate	Ampicillin	<i>S. typhimurium</i>	Increased potency of ampicillin bound NPs than free ampicillin	Ref [46]
PLGA	Ciprofloxacin	<i>E. coli</i>	Inhibit the growth of bacteria <i>in vivo</i>	Ref [47]
Polyethylcyanoacrylate	Pefloxacin mesylate and ofloxacin	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>E. faecalis</i>	Enhancement of antimicrobial activity	Ref [48]
PLGA and PCL	Doxycycline	<i>E. coli</i>	Increased drug entrapment efficiency, sustained release with enhanced antibacterial activity	Ref [49]

*P. aeruginosa*: *Pseudomonas aeruginosa*, *M. luteus*: *Micrococcus luteus*, *S. typhimurium*: *Salmonella typhimurium*, *B. anthracis*: *Bacillus anthracis*, *M. tuberculosis*: *Mycobacterium tuberculosis*, *E. coli*: *Escherichia coli*, PLGA: Poly lactide-co-glycolide, PCL: Poly( $\epsilon$ -caprolactone)

Table 5: Dendrimers for antibacterial drug delivery

Drug	Dendrimer	Role of dendrimer	Reference
Silver sulfadiazine	PAMAM	Solubility enhancer forming a nanoparticle system with enhanced antimicrobial properties for the topical treatment of burn-wound infections.	Ref [65]
Erythromycin and tobramycin	PAMAM	To investigate the effect of dendrimers on antibacterial activity of two drugs with different solubility profile	Ref [66]
Azithromycin	PAMAM	Conjugation with a drug to act as a carrier for efficient intracellular delivery to address chlamydia infections	Ref [67]
Nadifloxacin and prulifloxacin	PAMAM	Drug carrier to enhance solubility without affecting antibacterial activity	Ref [68]
Triclosan	PPO-PAMAM	Micellar carrier with high drug loading and controlled release for hydrophobic drug.	Ref [69]
Sulfamethoxazole	PAMAM	Solubility enhancer to obtain increased antimicrobial activity with sustained release	Ref [70]

PAMAM: Polyamide

## CONCLUSION

Most of the antibacterial drugs are very difficult to administer because of their cytotoxicity to health issues, poor water solubility, and bacterial resistance. Novel drug delivery systems such as liposomes, inhaled antibiotics, solid lipid nanoparticles, polymeric particles, microspheres, and dendrimers are able to overcome these issues and provide drug delivery to bacterial infection sites. The ability of the novel drug delivery system is to enhance solubility, stability, drug entrapment efficiency, targeted drug release, and sustained release and to overcome antibiotic resistance.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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