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Strategies and progresses for enhancing targeted antibiotic delivery

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ABSTRACT

Antibiotic resistance is a global health issue and a potential risk for society. Antibiotics administered through conventional formulations are devoid of targeting effect and often spread to various undesired body sites, leading to sub-lethal concentrations at the site of action and thus resulting in emergence of resistance, as well as side effects. Moreover, we have a very slim antibiotic pipeline. Drug-delivery systems have been designed to control the rate, time, and site of drug release, and innovative approaches for antibiotic delivery provide a glint of hope for addressing these issues. This review elaborates different delivery strategies and approaches employed to overcome the limitations of conventional antibiotic therapy. These include antibiotic conjugates, prodrugs, and nanocarriers for local and targeted antibiotic release. In addition, a wide range of stimuli-responsive nanocarriers and biological carriers for targeted antibiotic delivery are discussed. The potential advantages and limitations of targeted antibiotic delivery strategies are described along with possible solutions to avoid these limitations. A number of antibiotics successfully delivered through these approaches with attained outcomes and potentials are reviewed.

Contents

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1. Introduction

Bacterial infections are the main cause of mortality across the globe despite the availability of a wide range of antibiotics [1]. Improper and recurrent use of antibiotics results in the emergence of multidrug-resistant bacteria which impose a remarkable hazard for mankind [2]. World Health Organization (WHO) reported a very high prevalence of pathogenic bacteria that are resistant to available antibiotics [1]. Planktonic bacteria are usually motile and multiply rapidly, however, they can be targeted by antibiotics and influenced by environmental as well as host factors [3]. Biofilms are communities of unicellular organisms, adhered to a solid surface and enclosed by an exopolysaccharide matrix. Outer matrix inhibits the penetration of antibiotics and limits their interaction with enclosed bacteria. Hence, biofilms are more resistant to antibiotics than planktonic bacteria and are highly challenging to eradicate [4,5]. Biofilms do not undergo opsonization and phagocytosis, enabling the survival of bacteria within biofilms under stressed conditions. Host immunity is unable to cope with biofilms and immune cells become paralyzed with hindered phagocytosis [6]. It was revealed that 65 % of nosocomial infections are associated with biofilms which require more than $1 billion for the treatment per annum [4,7]. Certain bacteria reside inside the host cells and may transform to a non-replicating or slowly replicating state to cope with stress conditions in the host cell. Such bacteria are referred to as intracellular bacteria which present another challenge for antibiotic delivery [8,9]. Orally administered antibiotics are required to permeate across epithelial cells of the gastrointestinal tract to enter the bloodstream, topical antibiotics need to cross thick stratum corneum for penetration across the skin, while pulmonary antibiotics have to be absorbed through mucosa for respiratory tract infections [10]. However, antibiotics encounter another challenge if bacteria reside intracellularly as they are required to pass through the host cell membrane. Hence, localization of bacteria inside host cells protects bacteria and results in another barrier to antibiotics. After crossing the host cells, antibiotics must be delivered to the sub-cellular compartment containing the target bacteria. Moreover, an antibiotic must attain sufficient concentration for a specified period at the site of action in order to show its effectiveness [11].

Typical antibiotics have low therapeutic indices, non-specific modes of action, inconvenient routes of administration, and a wide range of side effects [12,13]. Moreover, two-thirds of approved antibiotics are unable to cope with intracellular pathogens, and various life-saving antibiotics have become ineffective [10,14]. Furthermore, pharmaceutical companies are reluctant to develop antibiotics due to economic concerns and regulatory impediments [15,16]. Hence, the development of new classes of antibiotics has lagged far behind our needs [13], as demonstrated by the limited number of antibiotic approvals during the previous decade. Currently, the antibiotic pipeline contains only 13 drugs in advanced phases of clinical trials. Even, there is no guarantee that these newly developed drugs will retain their effectiveness because bacteria are continuously developing various resistance mechanisms [17]. It is highly challenging to deliver an effective concentration of antibiotics at the site of infection [18]. Antibiotics administered through conventional drug delivery systems lack targeting effect and spread to various undesired sites leading to sub-lethal concen-

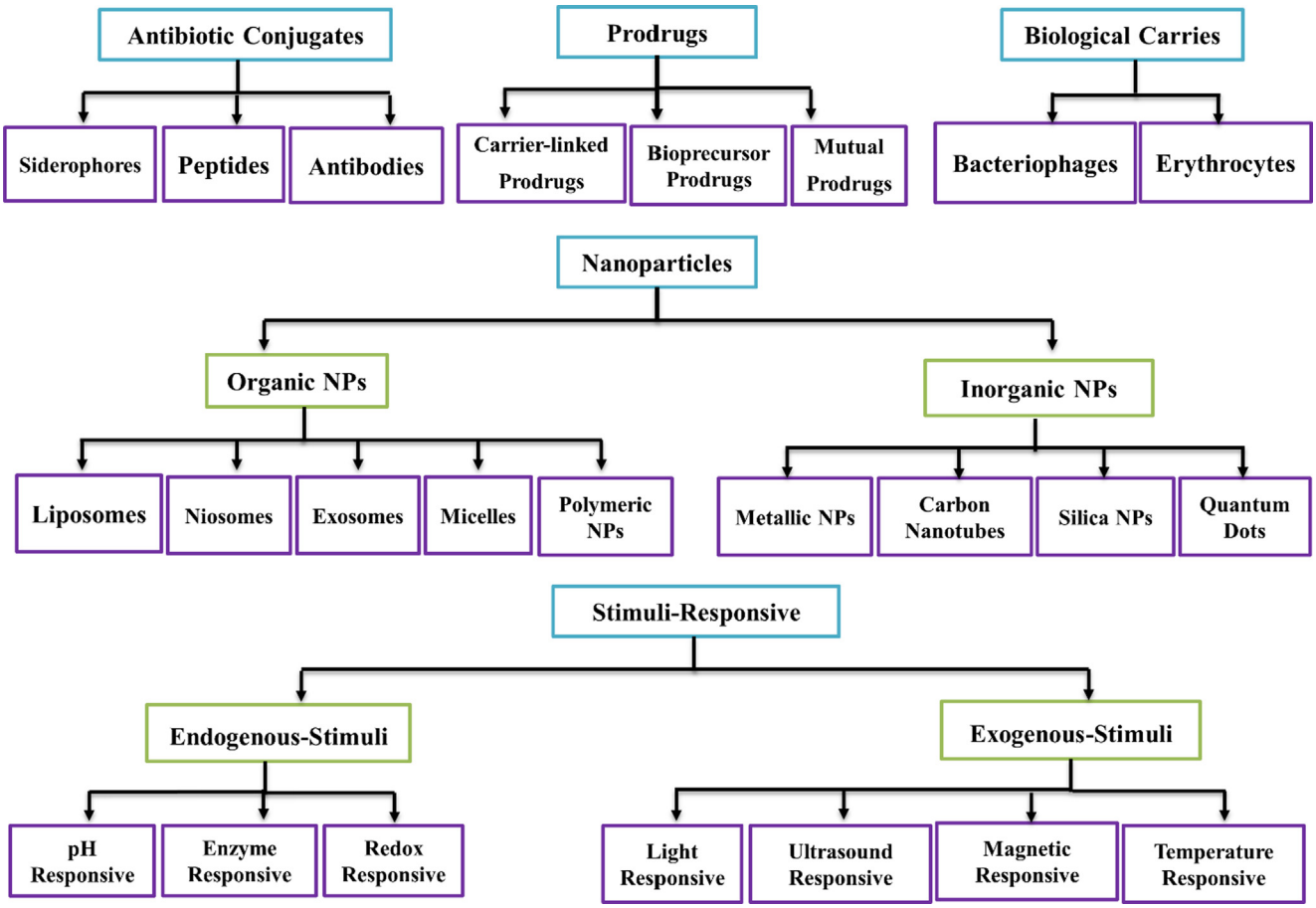


Fig. 1. Targeted antibiotic delivery strategies.

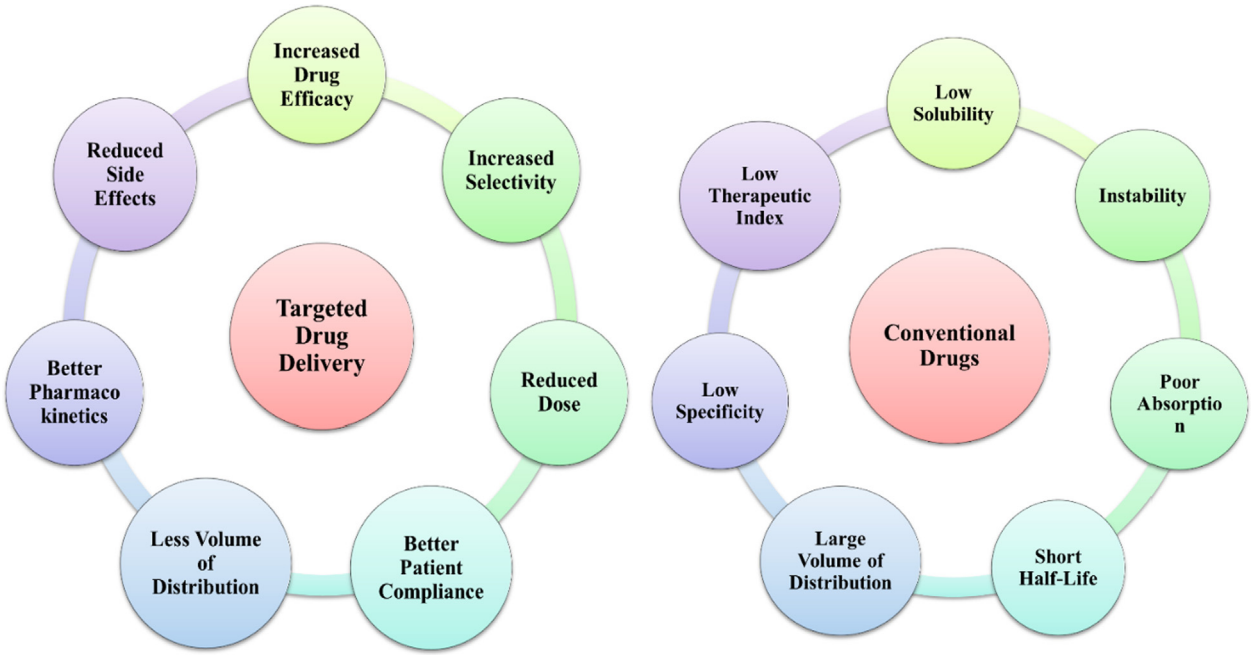


Fig. 2. Advantages offered by targeted drug delivery compared with conventional dosage forms.

tration at the site of action as well as side effects [19]. Moreover, various antibiotics are hydrophilic and are thus unable to penetrate the plasma membranes of infected cells [18]. To overcome these barriers, antibiotics are usually administered at high doses, resulting in both off-target toxicity and the emergence of drug resistance [20]. Though drug resistance is a multifaceted phenomenon, antibiotic delivery through conventional dosage forms is one of these attributable factors [19]. To counter the diminished pipeline of antibiotics, as well as limitations associated with conventional dosage forms, there is an urgent need to develop and adopt alternative strategies. Targeted drug delivery is an interesting strategy which intends to deliver antibiotics at the site of infection [21]. Various researches focusing on targeted antibiotic delivery have been explored by researchers. This review intends to provide an overview of these strategies (summarized in Fig. 1).

2. Targeted drug delivery

Targeted drug delivery is an advanced strategy which selectively transports drugs to sites of interest, thereby minimizing the relative drug concentration at undesired sites [22]. Targeted antibiotic delivery can extend the value of commercially available antibiotics by increasing their effectiveness, reducing potential side effects, and overcoming bacterial resistance mechanisms [19,23].

This approach provides several advantages as compared to conventional dosage forms (Fig. 2) [24]. A targeted drug delivery system should have four features: retaining, evading, targeting, and releasing. Drugs should be efficiently loaded in a suitable vehicle, which is capable of eluding the body's secretions. The system should possess a long residence time in the body, and deliver the drugs at the site of action within a time frame that allows for effective drug functioning [22]. A drug delivery system is generally designed based on two components i.e., target and drug carriers. The target refers to a diseased organ, tissue, or cell which requires therapy, while drug carriers are vectors responsible for the delivery of attached drugs at the target site [24]. Passive targeting and active targeting are two basic approaches for targeted drug delivery. Physicochemical features of pathogenic tissues facilitate the drug accumulation at the target site in passive targeting [25]. Macromolecules have a propensity to passively and preferentially retain at sites of increased vascular permeability and this phenomenon is termed as enhanced permeability and retention (EPR) effect [26]. Previously, EPR was only considered to be associated with tumor sites but later on increased vascular permeability was also noticed at the site of infections. After bacteria enter the body, lipopolysaccharide (LPS) from Gram-negative bacterial cell wall adhere to TLR (Toll-like receptor)-4 while lipoteichoic (LTA) acid from Gram-positive bacterial cell wall binds with TLR-2. It stimulates the immune system and results in the liberation of inflammatory mediators (TNF-α, IL-1β, and IL-6) which subsequently enhance vascular permeability.

Both LTA and LPS trigger the kallikrein-kinin system which is a main contributor to the EPR effect as it mediates the release of bradykinin [26–28]. Subsequently, bradykinin is involved in the direct activation of vascular permeability enhancement (VPE). The exact mechanism by which bradykinin promotes vascular permeability is not understood yet. Several bacterial proteases such as cysteine protease, protease elastase, and subtilisin (serine protease) also promote this cascade. Bradykinin-1 receptor (BKR-1) mediates the generation of nitric oxide which also promotes the VPE [26,29]. Matrix metalloproteinases (MMPs) stimulates the kallikrein-kinin mediated permeability by proteolytic degradation and inactivation of α1-proteinase inhibitors. Vascular endothelial growth factor (VEGF) also increases the vascular permeability at the infection site as activated VEGF receptor-2 (VEGFR-2) disrupts the endothelial junctions by the uncoupling of vascular endothelial (VE) cadherin–β-catenin. LPS is also involved in the up-regulation of BKR-1 and increases the generation of VEGF [26,30]. All these shreds of evidence refer that EPR is a common feature at the site of infection. Hence in passive targeting, drug carriers employ their intrinsic characteristics and selectively accumulate at the site of infections due to EPR effect, resulting in better therapeutic outcomes and reduced toxic concerns [25,26,31]. Dysfunctional lymphatic drainage is another characteristic of infection sites that promotes passive targeting [32]. Infections can also impair the lymphatic circulatory system as a result lymphatic flow is inade-

quate to retain tissue homeostasis which promotes interstitial fluid accumulation and leads to swelling [33]. Hence, increased interstitial pressure and tissue destruction are the main factors that cause reduction in lymphatic drainage at the site of infection [26]. A passive targeting strategy also involves drug release in response to certain endogenous or exogenous stimuli. Infectious sites contain a low oxygen level which mediates anaerobic fermentation leading to the production of lactic acid and acetic acids. As a result, the site of infections possesses a low pH (<6) than the physiological pH (~7.4). Antibiotics are conjugated to polymers through pH-sensitive bonds such as hydrazone bond which cleaves under acidic infectious conditions and ensure site-specific drug release [34]. Certain bacterial enzymes are highly expressed at the site of infection such as hyaluronidase and lipase which can be exploited for designing enzyme-sensitive antibiotic delivery systems [35,36]. Bacteria also release certain toxins such as alpha-toxin from S. aureus is employed to trigger the antibiotic release. This toxin perforates the liposomal membrane and entrapped antibiotics are liberated [37,38]. Antibiotic delivery systems have also been designed which are sensitive to exogenous stimuli such as light, magnetic field, heat, and ultrasound [39].

Active targeting involves conjugation of drug or drug carries with targeting moieties which interact with a specific type of receptors expressed on the cell surface and deliver the drug intracellularly by forming receptor-ligand interaction. Various receptors such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), mycobacterial membrane protein large5 (MmpL5), and immunoreactive trypsinogen A&B possess high-affinity binding sites and may be exploited for active delivery of antituberculosis drugs [40]. Moreover, various other components of the Gram-positive bacterial cell wall can also be exploited for active targeting as vancomycin selectively adheres with D-alanyl-D-alanine dipeptide subunit of peptidoglycan [41]. Similarly, teichoic acids are anionic substituents that can be selectively targeted by cationic polymers including quaternary ammonium polymers [42]. Moreover, certain proteins in Gram-positive bacterial envelop can act as antigens and bind with specific antibodies such as the protein A of S. aureus (Spa) interacts with staphylococcal protein A antibody (aSpa). Hence, antibody conjugation can facilitate the delivery of antibiotics to pathogenic sites [43]. In the case of Gram-negative bacteria, LPS interacts through electrostatic interactions with positively charged antibiotics such as colistin [44]. Moreover, bacterial lectins also serve as target sites and selectively bind with glycosylated polymers [45]. Certain proteins in Gram-negative bacteria such as anti-P. aeruginosa protein A (aPa) serves as antigens for corresponding antibodies [46]. Furthermore, inflammation caused by bacterial invasion involves a.

wide range of macrophages and inflammatory mediators. Polymer-based antibiotic delivery systems have been designed that interact with up-regulated receptors on the surface of macrophages. Hence, passive and active targeting approaches employ all these strategies to exploit changes in the infection microenvironment and ensure site-specific drug release [42].

3. Strategies for targeted antibiotic delivery

Resistant bacteria can inactivate antibiotics either by blocking the drug entrance at the site of action or by modification of antibiotics [47]. Successful delivery of an antibiotic is highly challenging, especially for Gram-negative bacteria as their cell walls are composed of a cytoplasmic membrane, peptidoglycan layer, and lipid bilayer [48,49]. The resistance development of Gram-negative bacteria towards various antibiotics can be attributed to the lipid bilayer [50]. Due to such defense mechanisms, alternative strategies are highly desired to cope with resistant bacteria.

3.1. Antibiotic conjugates

Site-specific release of antibiotics can be achieved by the conjugation of antibiotics with targeting agents including siderophores, peptides, and antibodies [51].

3.1.1. Antibiotic-siderophore conjugates

Iron is a vital nutrient for the functioning of a living cell and serves as a redox catalyst for cellular respiration and DNA replication [52]. Usually, the ferrous (Fe^{2+}) form of iron performs these functions, but it can be oxidized to the ferric (Fe^{3+}) form, which hinders the cellular processes. To overcome the limited availability of iron, microbes have developed unique mechanisms to extract iron [53,54]. Siderophores are tiny organic chelators produced by bacteria for iron uptake from the surroundings into the bacterial cytoplasm through specific membrane transporters [55]. The covalent linking of an antibiotic to a siderophore (termed as sideromycins) can serve as a gate in the bacterial cell wall to increase the permeability of antibiotics [56,57]. Bacteria possess siderophore receptor proteins that selectively identify the iron complexes of their native siderophores [58]. Hence, siderophore-antibiotic conjugates exploit the advantage of possessing high-affinity receptors that trigger their penetration into bacteria [57,59]. A therapeutic agent that cannot cross the bacterial membrane is attached to a siderophore. Siderophore–drug complex contains a siderophore, a linker, and a therapeutic agent (see Fig. 3a). Siderophore facilitates the iron-binding, while linker attaches a therapeutic moiety to the siderophore. Siderophore-drug conjugate is identified by cognate receptors, actively transported through the bacterial membrane through ferri-siderophore uptake pathways promote. After entering into bacteria, siderophore–drug conjugate reaches the cytoplasm while pathogen is killed through different actions: (1) by the release of therapeutic agents; (2) employing the whole complex as an antibacterial agent, and (3) by circumventing the iron formation [59,60]. Drugs whose targeting sites are located in the periplasm of bacterial cell walls, such as β-lactams, can bind directly to the target in the form of conjugates without the need for drug release. Such drugs do not need to be actively transported into the bacterial cytoplasm to exhibit antibacterial potential [26]. However, drug release is crucial from siderophore conjugates if a drug (norfloxacin) target is located in the cytoplasm, hence, a cleavable linker is used in such cases [26,61].

The cleavable linkers should be stable in the extracellular environment and cleaved only inside the cytoplasm. Different mechanisms may trigger cleavages such as hydrolysis, reduction, and enzyme-catalysis [57]. Ji and Miller et al. prepared siderophore-ciprofloxacin conjugates in which a quinone analog was employed as a precursor of the 'trimethyl lock" motif. It was proposed that quinone linkers may undergo reduction by hydride donors including NAD(P)H which are normally responsible for the reduction of Fe(III). Hydroquinone conjugate forms containing the "trimethyl lock" motif which subsequently cyclizes to form lactone derivative accompanied by the liberation of entrapped drug [62]. They also reported the use of esterase-cleavable trimethyl lock to trigger drug release from siderophore conjugates [63]. Different bacterial species synthesize unique siderophores which enable the selective targeting of bacteria and reduce the probability of resistance development [55]. Some of these sideromycins include albomycins, ferrimycins, danomycins, and salmycins [64,65]. Daptomycin's spectrum of activity is generally restricted to Gram-positive bacteria. However, Ghosh et al. prepared a daptomycin-siderophore conjugate which enabled the permeation of daptomycin across Gram-negative bacteria. Daptomycin conjugates were highly active against Acinetobacter baumannii. It was suggested that siderophores including bis-catechol monohydroxamate are identified by Gram-negative bacteria and facilitate the penetration of cova-

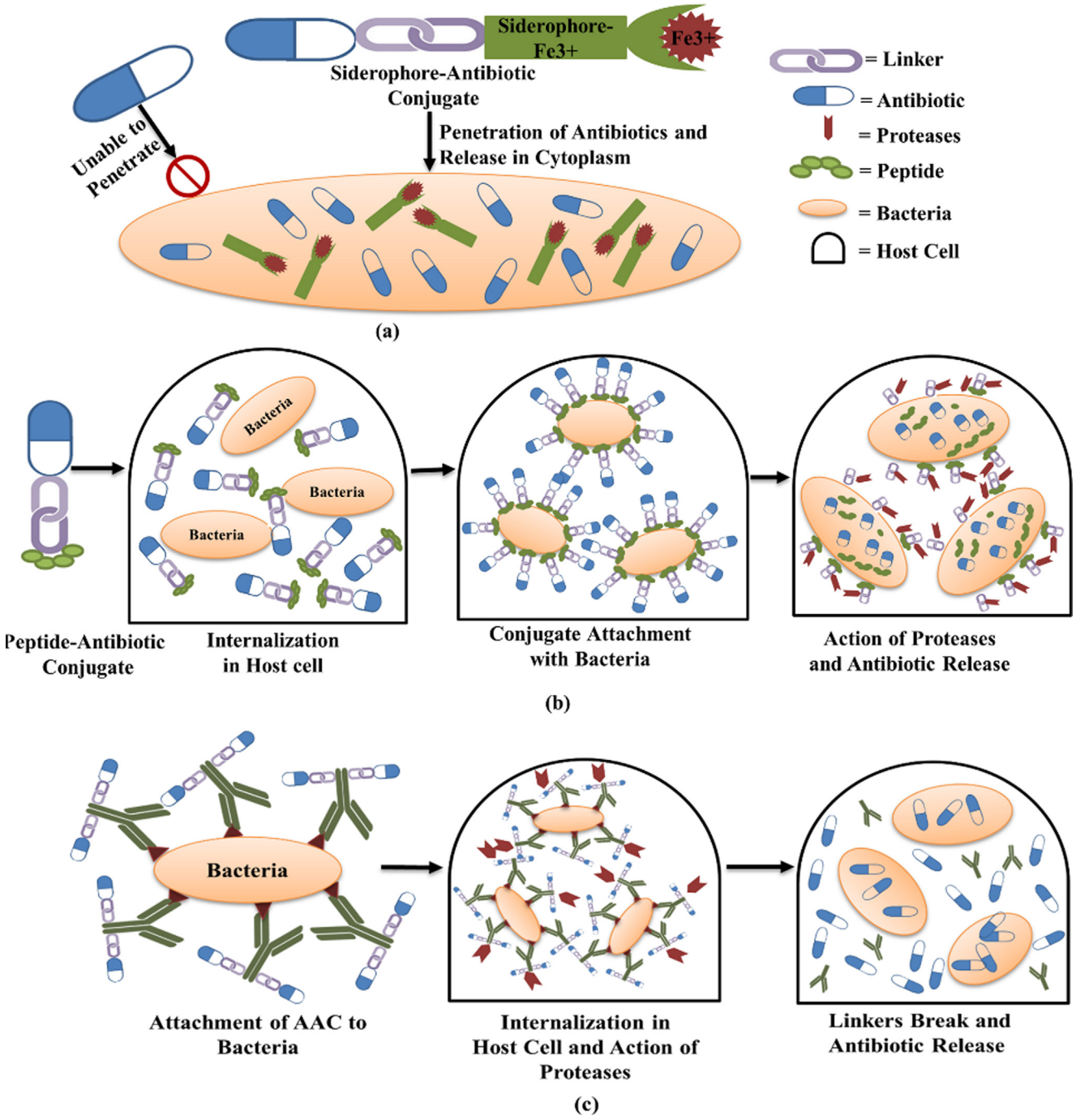


Fig. 3. The Trojan Horse strategy. Drug penetration across bacterial cells through (a) Siderophore-Antibiotic conjugation (b) Peptide-Antibiotic conjugation (c) Antibody-Antibiotic conjugation.

lently linked daptomycin. In such a way, existing antibiotics that function against Gram-positive bacteria can be repurposed for use against Gram-negative bacteria via siderophore conjugation [66]. A wide range of antibiotics, including cephalosporins [67], norfloxacin [68], ciprofloxacin [69], and spiramycin [70] have been successfully conjugated with siderophores. The effectiveness of siderophore-antibiotic-conjugates is compared with the free form of drugs in Table 1. The increased penetration of conjugated antibiotics results in improved antibacterial activity relative to bare antibiotics [55].

3.1.2. Antibiotic-peptide conjugates

Peptides are synthetic vectors that can be coupled with antibiotics to revamp the physicochemical characteristics and to enhance the inter-and intracellular distributions of antibiotics (see Fig. 3b) [71]. Antimicrobial peptides (AMPs) and cell-penetrating peptides (CPPs) are particularly important targeting agents for antibiotic delivery [72]. AMPs are also referred to as cationic antimicrobial peptides because they usually possess a net positive charge, which is attributable to their powerful interactions with anionic bacterial membranes. AMP binding breaks down

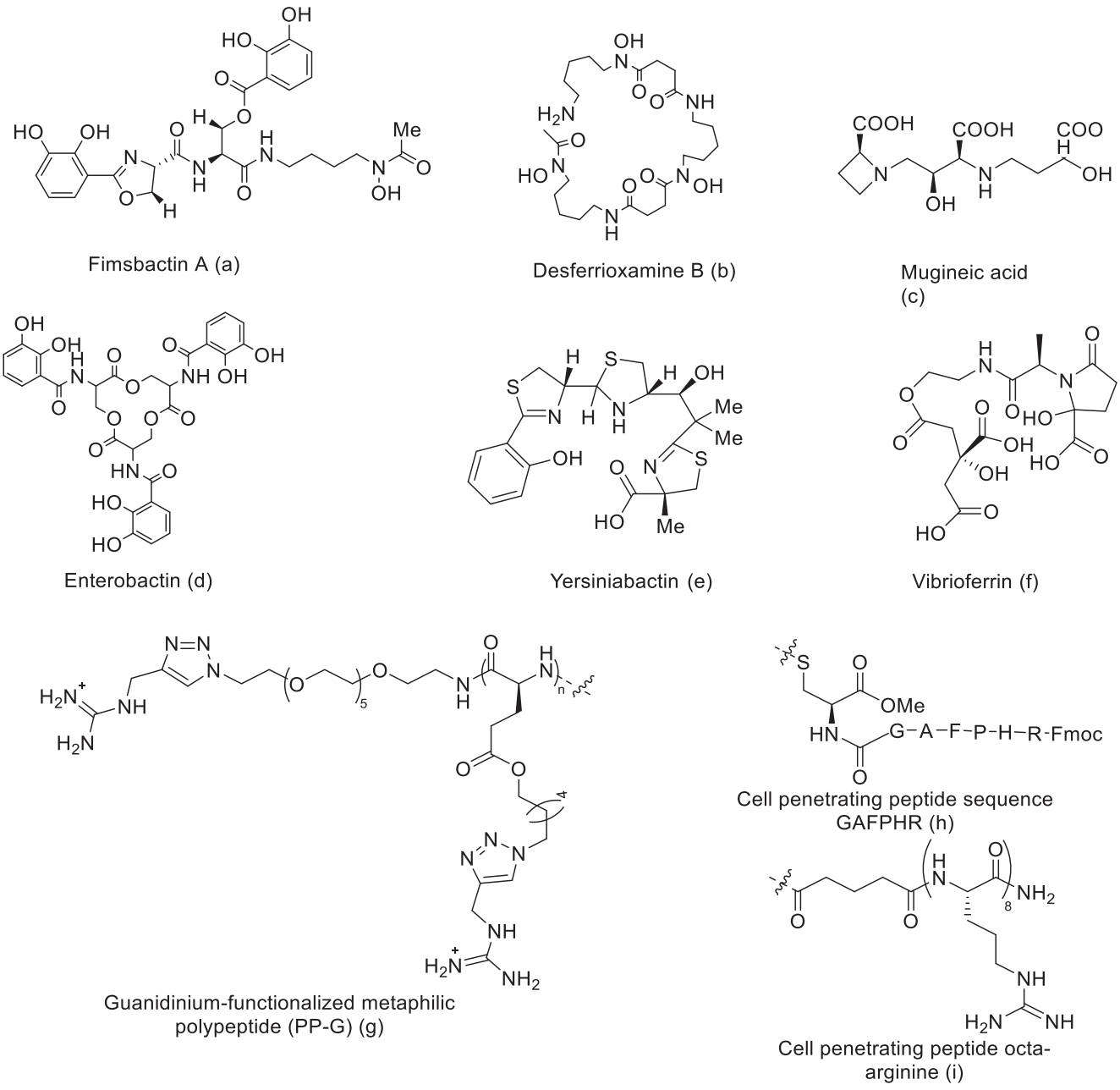
Table 1
Antibacterial efficiency of siderophore-antibiotic and peptide–antibiotic conjugates.

Antibiotic Conjugates	Conjugated Antibiotic	Targeted Pathogen	MIC, IC_{50} of Conjugates (μg/mL, μmol/mL *)	MIC[a], IC_{50} of Control (μg/mL, μmol/mL*)	References
Siderophore					
Fimsbactin	Daptomycin	Acinetobacter baumannii ATCC 17,961	0.4*	>*100	[83]
Biscatecholate–Monohydroxamate	Loracarbef	Acinetobacter baumannii ATCC 17,961	0.0078*	>128*	[84]
Desferrioxamine B	Loracarbef	Micrococcus luteus ATCC 10,240	0.001*	0.39*	[85]
Desferrioxamine B	Ciprofloxacin	Staphylococcus aureus SG511	31.25*	0.47*	
Desferrioxamine B	Nadifloxacin	Bacillus subtilis ATCC 6633	<0.1*	0.008*	
Tris-catecolate	Ampicillin	Pseudomonas aeruginosa KW799/wt	0.05*	>200*	[86]
Tris-catecolate	Amoxicillin	Pseudomonas aeruginosa KW799/wt	0.05*	>200*	
Bis-catechol	Cephalosporin +Oxazolidinone	Pseudomonas aeruginosa KW799/wt	0.2–0.4*	>50* >50*	[67]
Enterobactin	Ciprofloxacin	Escherichia coli UTI89, CFT073	0.1–1*	0.1–1*	[87]
Acylated Bis-Catecholate	Ampicillin	Pseudomonas aeruginosa SG 137	<0.005	>100	[88]
Acylated Bis-Catecholate	Amoxicillin	Pseudomonas aeruginosa SG 137	0.01	-	
Enterobactin	Ampicillin/ Amoxicillin	Escherichia coli CFT073, UTI89	0.01*	10*	[89]
Novel pyrazolidinone	Dihydroxy-phthalimide	Pseudomonas aeruginosa	1	8	[90]
Aminothiazolylglycyl-cephalosporin	SID	Pseudomonas aeruginosa	0.25–0.5	0.125->32	[91]
Tetra-acetyl-catechol	Teicoplanin	Acinetobacter baumannii ATCC BAA 1793	0.8–1.6*	>50*	[92]
Penta-acetyl–catechol–hydroxamate	Teicoplanin	Acinetobacter baumannii ATCC BAA 1793	0.8–1.6*	>50*	
Monocatecholate enterobactin	Ciprofloxacin	Pseudomonas aeruginosa DSM 1117			[69]
Triscatecholate enterobactin	Ciprofloxacin	Pseudomonas aeruginosa DSM 1117	16 4	0.25 0.25	
Vanchrobactin	Norfloxacin	Vibrio anguillarum RV22/MB12/MB84	0.097	0.006	[68]
Peptide					
MSI-78	7-ADCA	Acinetobacte baumannii	3.6*	470*	[93]
MSI-78	7-ACA		3.7*		
Polyamine	Chloramphenicol	MRSA GRE2272	7.0*	8.0*	[94]
Amphiphilic Lysine	Neomycin B	MRSA	32	256	[95]
Amphiphilic Lysine	Neomycin B	MRSA	128	256	
Amphiphilic Lysine	Neomycin B	MRSA	64	256	
P14LRR	kanamycin	Brucella abortus	4*	4*	[96]
α1H	Gentamicin	Escherichia coli K1 RS218	2	0.5	
α2H	Gentamicin	Escherichia coli K1 RS218	1	0.5	[97]
(Fxr)3FX(Fxr)	Nalidixic acid	MRSA	13*	47*	[71]
3	Nalidixic acid	MRSA	18*	47*	
Tripeptides	Triamino analogue of cholic acid	Escherichia coli ATCC 25,922	8	–	[98]
A short peptide transporter sequence derived from penetratin	Tobramycin	Escherichia coli MG1655	1.6	<1.6	[99]
Modified human lactoferrin 20–31 fragment; HLopt2	Levofloxacin	Staphylococcus epidermidis ATCC 12,228	4	6.2	[100]
	Ciprofloxacin		4		
Lactoferricin	Ciprofloxacin	Staphylococcus epidermidis ATCC 12,228	3.13	0.63	[101]
Polybasic peptides	Levofloxacin	MRSE CAN-ICU 61,589	128	>128	[102]
Hecate	Vancomycin	Vancomycin-resistant Staphylococcus aureus	5*	>80*	[78]

[a] The control drug is the corresponding antibiotic conjugated. MIC values with * are reported as μmol/mL while others are reported as μg/mL. **Abbreviations:** MIC, minimum inhibitory concentration; SID, (N-(2-((4-aminopyrimidin-5-yl) amino) ethyl)-1,5-dihydroxy-4-oxo-1,4–202 dihydropyridine-2-carboxamide); 7-ADCA, 7-aminodesacetoxycephalosporanic acid; 7-ACA, 7-aminocephalosporanic acid; MAAPC03, membrane-active antibiotic – peptide conjugate03; MRSA, methicillin-resistant Staphylococcus aureus; MSSE, methicillin sensitive Staphylococcus epidermidis.

the membrane potential, diminishes the ion gradient, disrupts the bacterial membrane, and facilitates the permeation of attached drugs across the bacterial wall [73–75]. AMPs can restrict the emergence of antibiotic resistance and facilitate antibiotic entry into host cells through endocytosis, phagocytosis, and macropinocytosis [72]. A unique characteristic of AMPs is that they selectively act on biological targets in contrast to typical antibiotics and thus can be utilized as a vehicle for the delivery of various bioactive leads [76].

CPPs are small peptides which form pores in the bacterial outer membrane and mediate the penetration of attached drug molecules [77,78]. CPPs are categorized into three main groups: cationic, amphipathic, and hydrophobic [79–82]. CPPs are being employed to deliver a wide range of bioactive leads including proteins, oligonucleotides, and nanoparticles which illustrates their potential as drug carriers [82,103,104]. Moreover, CPPs are the most attractive option for the delivery of non-cell-permeable antibiotics [97]. Conjugation of antibiotics to CPPs can enhance their cellular uptake resulting in improved antibacterial potential [71]. Wong and coworkers synthesized tobramycin-CPP conjugates, which showed a 10,000-times improved antibiotic activity. It was suggested that conjugates create negative Gaussian curvature (curvature induced in a membrane that reduces the free energy barriers for entry mechanisms such as endocytosis) in bacterial cell envelope which is topologically needed for membrane permeation through pore generation and blebbing [71,105,106].



Scheme 1. Chemical structures of siderophores (**a**-**f**) and peptides (**g**-**i**) employed for targeted antibiotic delivery.

Peptide conjugation to antibiotics such as chloramphenicol [94], neomycin B [95], kanamycin [96], gentamicin [97], ciprofloxacin [100], levofloxacin [102], and vancomycin [78] showed better therapeutic potential relative to the free form of antibiotics (see Table 1). Some representative examples of siderophores and peptides employed for targeted antibiotic delivery are given in Scheme 1 [107–114].

3.1.3. Antibiotic-antibody conjugates

Various bioactive leads capable of combating intracellular bacteria fail in clinical practice just because of their poor pharmacokinetic profiles. Antibody–antibiotic conjugation is a novel tactic for the delivery of antibiotics with unfavorable pharmacokinetic profiles [115]. Moreover, another factor for antibiotic failure is that pathogenic bacteria can survive within host phagocytic cells [116]. Antibody-antibiotic conjugates (AAC) can increase the effectiveness of antibiotics against intracellular infections [115]. Monoclonal antibodies bypass healthy tissues and selectively deliver the attached therapeutic agents at the site of infection [117]. Recombinant monoclonal antibodies (mAbs) interact with complementary antigens possessing high selectivity, binding ability, as well as long half-life. An antibody-drug conjugate is composed of an antibody capable of interacting with an overexpressed antigen, a therapeutic moiety, and a chemical linker group [118]. Lehar et al. developed an AAC (DSTA4637S) by the covalent linking of an anti-S. aureus antibody (THIOMAB^{TM}) to an antibiotic (dmDNA31, rifalogue) and using a protease cleavable valine-citrulline linker [115,119]. It was revealed that the antibody component of AAC (DSTA4637S) adheres to the S. aureus and host cells uptake the AAC opsonized bacteria, where intracellular proteases break the linker and liberate the antibiotic.

Thousands of AACs adhere to a single bacterium and release a large quantity of free antibiotics within the phagosome, leading to bactericidal action (see Fig. 3c). The conjugate was superior to

treating intracellular S. aureus infection as compared to free vancomycin, and rifalogue [115,120]. DSTA4637A was administered at 25 to 50 and 5 to 50 mg/kg doses in S. aureus-infected and healthy mice models to investigate pharmacokinetic (PK) and pharmacodynamic (PD) profiles. It was reported that DSTA4637A exhibited an identical pharmacokinetic profile in both models and remarkably reduced the bacterial load. Moreover, coupling of dmDNA31 with a THIOMAB^{TM} antibody increased the half-life ($t_{1/2}$) of dmDNA31 from the original 3–4 h to 4 days [119]. DSTA4637S is currently undergoing Phase I clinical trials to evaluate safety, tolerability and pharmacokinetics in volunteers infected with S. aureus [121]. During another study, an antibody was attached through ethylenediamine linker to different photosensitizers which liberate singlet oxygen upon irradiation with light and mediate death in neighboring cells. Although, singlet oxygen is highly reactive but possess a short lifespan that restricts its activity up to 1000 Å area of its generation. It was revealed that antibody selectively directs the reactive oxygen species formation at the site of infection and overcomes the limitation of a short lifetime [51]. Hence, these strategies can be employed for targeted antibiotic delivery to enhance its effectiveness.

3.2. Prodrug strategy for Site-Specific delivery of antibiotics

Prodrugs are inactive agents which are spontaneously or metabolically converted to their pharmacologically active forms inside the body [122]. This strategy avoids the shortcomings of existing antibiotics which are highly effective against resistant bacteria but possess poor pharmacokinetic properties [123]. Moreover, the prodrug approach can be employed for site-specific drug delivery and can assist in reducing side effects [124,125]. Prodrugs are categorized as: (a) Carrier-linked prodrugs contain a therapeutic agent conjugated to a carrier moiety which liberates the active drug upon enzymatic or chemical reaction inside the body [126,127] (b) Bioprecursor prodrugs contain a molecularly modified drug which is converted to its active form by the metabolic modification of functional groups [126] (c) Mutual prodrugs are conjugates of two therapeutically active agents which act as a promoiety for each other (see Fig. 4) [127]. Prodrugs address many of the problems associated with free drugs, including chemical degradation, poor water solubility, and rapid clearance from blood [128,129]. Prodrugs can improve the physicochemical characteristics as well as pharmacokinetic profile of antibiotics, and enhance their potential for the eradication of intracellular infections [129]. Prodrugs selectively deliver the drug at site of infection, avoid undesired effects, and antibiotic resistance development [51]. This drug delivery platform enables selective drug interaction with pathogenic microbes without harming the microbiota, and decreases the prevalence of secondary infections [130]. In addition, prodrug strategies can potentially enhance the bioavailability of poorly absorbed β-lactam antibiotics.

Metronidazole is a bioprecursor prodrug that penetrates the bacterial envelope through passive diffusion and its nitro group is reduced to nitro radicals by ferredoxins in anaerobic organisms. Anaerobic microbes possess redox potential for their electron transport components, which are attributable to the reduction of nitro group and production of toxic metabolites including N-(2-hydroxyethyl) oxamic acid and acetamide. Subsequently, toxic metabolites show cytotoxic and antimicrobial potential by interacting with DNA and forming adducts with guanosine [131–133]. Sultamicillin is a prodrug formed by attachment of ampicillin with sulbactam through formaldehyde as a linker motif. β-Lactamase enzyme generated by bacteria inactivates the ampicillin while this shortcoming is avoided by linking the ampicillin to a β-lactamase inhibitor i.e., sulbactam. Orally administered sultamicillin is efficiently hydrolyzed to sulbactam and ampicillin resulting in increased serum concentration of ampicillin. Sultamicillin shows better therapeutic potential and fewer side effects than ampicillin [127,134]. Cefuroxime axetil is an acetoxyethyl ester prodrug of cefuroxime which undergoes hydrolysis in the GI tract and serum.

During the prodrug activation process, axetil motif converts into acetic acid and acetaldehyde (Scheme 2) [135,136]. Chloramphenicol palmitate, a prodrug of chloramphenicol which was designed to mask the unpleasant taste of chloramphenicol. Pancreatic lipases promote the hydrolysis of the prodrug into its active form [136]. Some other prodrugs are summarized in Table 2 with an evaluation of their potential outcomes.

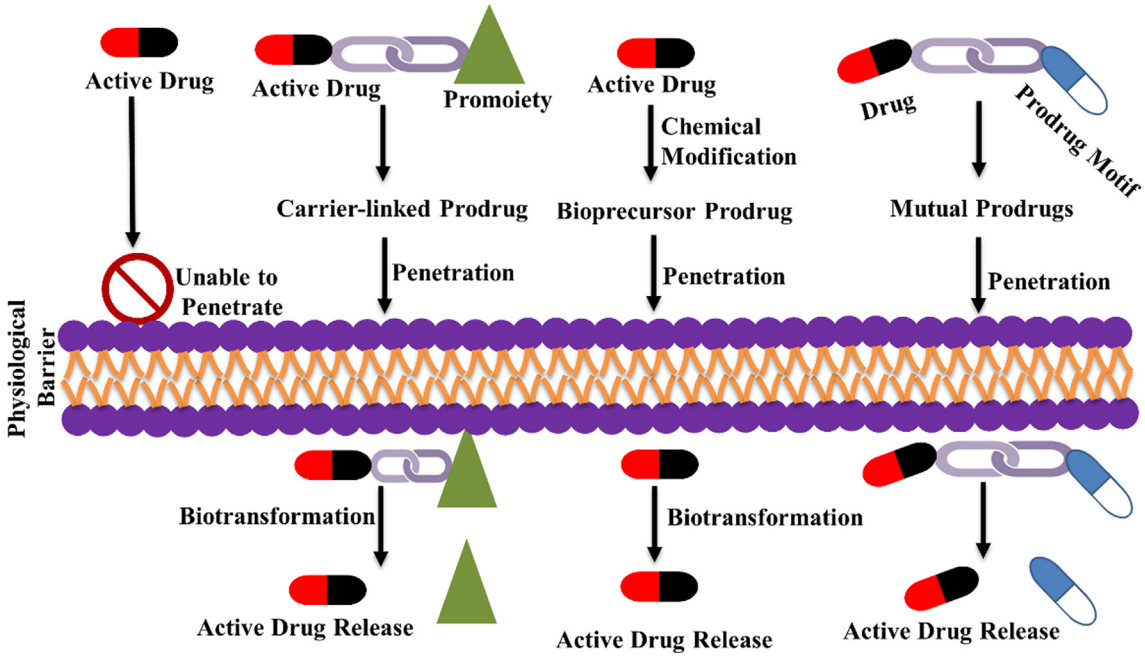
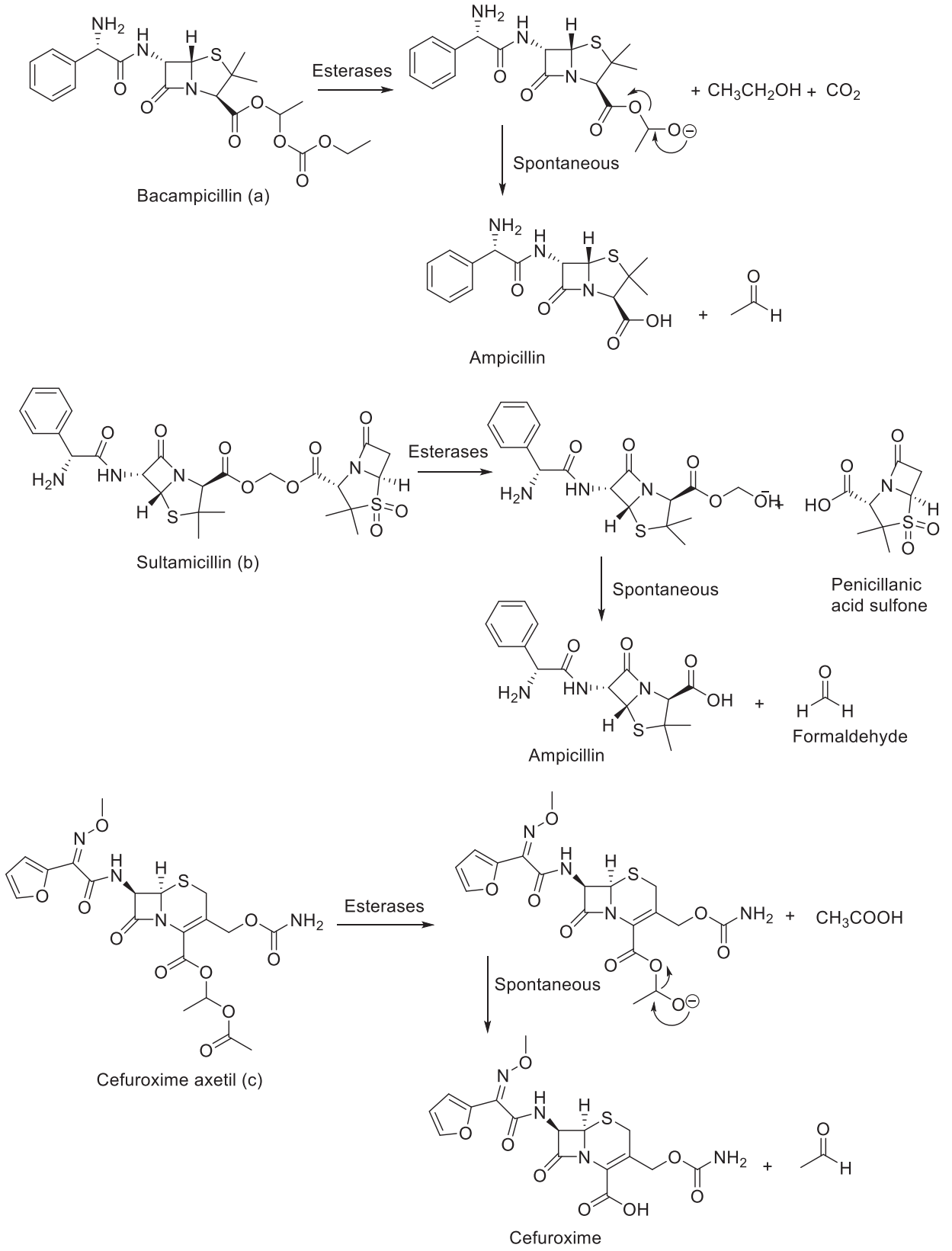


Fig. 4. Pictorial description of different prodrug strategies.



Scheme 2. Activation mechanism of some commercially available prodrugs Bacampicillin (a), Sultamicillin (b) and Cefuroxime axetil (c).

3.3. Nanocarriers for targeted antibiotic delivery

Loading antibiotics in different nanocarriers provides another approach for targeting intracellular pathogens (see Fig. 5) [96]. These carriers provide controlled and targeted drug release at the site of infection, as well as drug delivery to intracellular bacteria [149,150]. Ultimately, these factors improve the drug efficacy, facilitate the solubilization of hydrophobic compounds, and enable the simultaneous delivery of multiple therapeutic agents [151].

Table 2
An overview of prodrug strategy and evaluation of potential outcomes.

Prodrug	Parent Drug	Prodrug Design	Outcome Achieved	References
Cephalosporin-Ciprofloxacin was attached via the carboxylic acid at position-3 of	Fluoroquinolone Cephalosporin.	Ciprofloxacin Prodrug preferentially targeted the β-lactamase producing bacteria and avoided the interaction with bacteria that do not express β-lactamases.		[130]
Cephalosporin nitric oxide-donor prodrug (DEA-C3D)	Nitric oxide	Cefaloram at position-3 was linked with Diazeniumdiolate NO donor.	Prodrug was capable to scatter P. aeruginosa biofilms, while combination with colistin potentially eliminated the P. aeruginosa biofilms.	[137,138]
Norfloxacin prodrug	Norfloxacin	Macromolecular carrier was developed by dextran attachment with mannose and Norfloxacin was conjugated with macromolecular carrier.	Prodrug approach enabled norfloxacin to impart antimycobacterial potential which was inactive in its free form.	[139]
Cephalosporin nitric oxide-donor prodrug (PYRRO-C3D)	Nitric oxide	Cefaloram was attached with diazeniumdiolate PYRRO/NO.	Prodrug combined with azithromycin increased the vulnerability of azithromycin to Nontypeable Haemophilus influenzae (NTHi) biofilms.	[137,140]
Triclosan prodrug	Triclosan	Triclosan was conjugated with mono-(dimethylaminoethyl) glutarate through enzyme-sensitive ester bond.	Attachment of tertiary amine ester promoted the cellular uptake of triclosan and enhanced the activity against E. coli up to four-times.	[141]
Triclosan prodrugs NB2001 NB2030	Triclosan	Cephalosporin was core attached with Triclosan at C-3 position while Thienyl (NB2001)/ Tetrazole (NB2030) functionality at C-7 position.	Both prodrugs efficiently delivered the remarkably high amount of triclosan inside S. aureus and E. coli.	[142]
Tebipenem Pivoxil	Tebipenem	Pivaloyloxymethyl moiety was attached with carboxylic acid group of Tebipenem.	Prodrug approach enhanced the oral bioavailability of tebipenem.	[143,144]
Avibactam O-neopentyl ester prodrug	Avibactam	Neopentyl group was attached for sulfate group protection of Avibactam.	Charged sulfate group impedes the oral absorption of avibactum hence, sulfate protection strategy remarkably improved the bioavailability of avibactam.	[145]
Tedizolid phosphate	Tedizolid	Phosphate group was attached at C-5 hydroxymethyl group of Tedizolid	Phosphorylation of tedizolid enhanced the aqueous solubility as well oral bioavailability and circumvented the interaction of C-5 hydroxymethyl with monoamine oxidase (MAO).	[146]
Carvacrol lipophilic prodrugs WSCP18 WSCP19	Carvacrol	Prenylated groups were attached with hydroxyl group of Carvacrol via ether linkage.	Prodrugs exhibited biofilm eradication against S. aureus and Staphylococcus epidermidis.	[147]
PC190723 (Benzamide)	TXY436	A protonated form of Mannich base moiety was introduced at amide group of TXY436.	Prodrug approach potentiated the drug-like characteristics, pharmacokinetic profile and efficacy of TXY436.	[148]

Abbreviations: DEA-C3D, DiEthylAmin-Cephalosporin-3′-Diazeniumdiolate.

Liposomes are self-assembled vesicles which contain an aqueous core surrounded by single or multiple lipid bilayers of phospholipids [152,153]. Omri et al. prepared polymyxin B-loaded liposomes by using 1,2-dipalmitoyl-*sn-glycero*-3-phosphocholine (DPPC) and cholesterol. Concentration of polymyxin B was significantly higher in the lungs of infected animals treated with liposomal formulation than those treated with free polymyxin B resulting in better antibacterial potential. It was revealed that the lipid content of liposomes promotes the uptake by phagocytic cells at the site of bacterial residence. Hence, improved antibacterial activity exhibited by liposomal formulation might be due to the fusion of membrane phospholipids of liposomes with bacterial cells [154]. Liposomal formulations of other antibiotics, including cefepime, imipenem, ceftazidime [155], vancomycin [156], tobramycin [157], clarithromycin [158], and rifampicin [159] have demonstrated improved therapeutic outcomes (see Table 3).

Dendrimers are tree-like globular vehicles with a hollow core surrounded by branched layers and various terminal groups as shown in Fig. 5 [160–162]. Serri et al. revealed that polyamidoamine (PAMAM) dendrimers can increase the sensitivity of vancomycin against Gram-negative bacteria with a 64-fold reduction in MIC values. Cationic PAMAM dendrimers preferentially interact with anionic bacterial membrane resulting in membrane disruption which facilitates the drug penetration across bacterial surfaces [160]. González et al. prepared levofloxacin-loaded MSiNPs, a polycationic dendrimer, with poly(propyleneimine) covalently attached to the surface of nanostructures. It was revealed that electrostatic interaction arises between positively charged dendrimers and negatively charged bacterial envelope which promote the antibiotic uptake in Gram-negative bacteria. Levofloxacin was released from nanostructures in a controlled manner while biofilms were completely eradicated [163]. Other antibiotics including tobramycin [162], rifampicin [164], amoxicillin [165], and sulfamethoxazole [166] have also been encapsulated in dendrimers.

Niosomes are non-ionic surfactant vesicles composed of an aqueous core and bilayer architecture sandwiched with lipophilic components (see Fig. 5) [167]. Barakat et al. prepared niosomes by employing Span 60, Tween 40, and cholesterol which were entrapped with vancomycin. Drug-loaded niosomes showed better potential for biofilm eradication than free vancomycin which might be due to the potential of vesicular systems to bind with bacterial biofilms and promote the penetration of entrapped drug across biofilm [168]. **Exosomes** are a subclass of extracellular vesicles which can cross different physiological barriers and can be exploited for the targeted delivery of therapeutic agents [169]. Yang et al. prepared exosomes (from RAW264.7 cells by centrifugation method) encapsulated with lysostaphin and vancomycin for targeted antibiotic delivery to intracellular pathogens. DBCO-

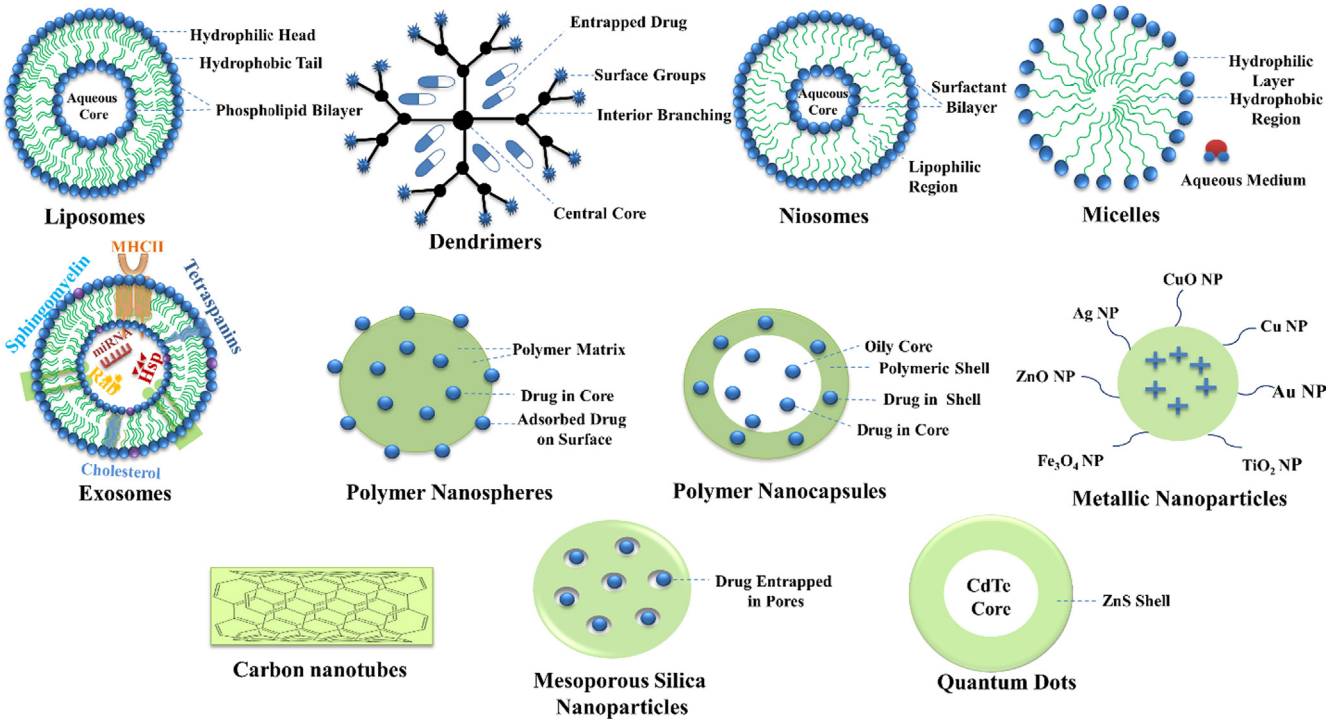


Fig. 5. Nanocarriers employed for the targeted antibiotic delivery.

mannosyl ligands were attached with exosomes which enabled them to preferentially interact with macrophages that express high levels of the mannose receptors resulting in antibiotic delivery to macrophages. This formulation was able to penetrate the target organs and annihilate intracellular methicillin-resistant Staphylococcus aureus (MRSA) [170]. In another study, Yang et al. revealed that linezolid entrapped exosomes (prepared from RAW264.7 cells using the ExoQuick-TC™ Kit) eradicated the intracellular MRSA to a greater extent than free linezolid. It was proposed that linezolid is released into the acidic environment of lysosomes and shows bactericidal activity inside lysosomes, while some drug content also crosses the intracellular endolysosomal membranes into the cytoplasm and shows antibacterial activity over there [171].

Micelles contain a hydrophobic core to entrap hydrophobic drugs and a hydrophilic outer layer which enhances the drug circulation time in blood (see Fig. 5) [172–174]. Guo et al. prepared polycationic micelles composed of polyethylenimine while tetracycline was loaded into the core of micelles. Electrostatic interactions between cationic micelles and anionic bacterial membrane enabled the penetration of drug carriers while subsequent enzymatic action was responsible for drug release resulting in eradication of intracellular drug-resistant E. coli (see Table 3) [175]. Chen et al. prepared ciprofloxacin-loaded micelles in which amphiphilic poly(ethylene glycol)- poly(ε-caprolactone) copolymers were attached with vancomycin as targeting ligands. Targeting ligands on micelle surface enabled the recognition of bacteria and prolonged the blood circulation of ciprofloxacin. This formulation minimized the bacterial burden and alveolar injuries in P. aeruginosa infected lungs to a greater extent as compared to free ciprofloxacin [41].

Polymer nanoparticles (PNPs) refer to nano-sized particles including nanospheres and nanocapsules which are composed of natural and synthetic polymers [176]. PNPs selectively deliver the antibiotics at infection sites and improve the efficacy of antibiotics against pathogenic microbes as shown in Table 3 [176]. Chitosan is the most widely used polymer which possesses positive charge and ionically interacts with the negatively charged bacterial cell. Furthermore, chitosan can cross bacterial cell walls and interact with negatively charged mRNA, leading to the inhibition of protein synthesis [177,178]. Scolari et al. prepared rifampicin and ascorbic acid entrapped alginate/chitosan NPs which showed a 2 to 8-fold reduction in MIC as compared to bare rifampicin. It was suggested that NPs interaction with bacteria can disrupt bacterial membrane and alters its permeability which permits the penetration of loaded drugs. The synergistic action of antibiotics causes leakage of intracellular contents from bacterial calls leading to bactericidal action [179]. Smitha et al. synthesized rifampicin-loaded chitin NPs which facilitated the accumulation of rifampicin in polymorphonuclear leukocytes. It was proposed that adherence of rifampicin loaded nanoparticles to bacterial membrane and localized release of rifampicin is attributable for improved antibacterial potential of nano formulation [180]. Cai et al. prepared nanostructured vehicles in which the outer layer was composed of rhamnolipids and phospholipids while the inner core contained amoxicillin and pectin sulfate (PECS). It was noticed that outer layer lipids can disrupt the biofilms by dissolving the extracellular polymeric substance (EPS). Subsequently, exposed free planktonic bacteria are killed by pectin sulfate which circumvents the binding of H. pylori, and amoxicillin which imparts the direct antibacterial activity [181].

Metallic nanoparticles (MNPs) such as silver, gold, and copper impart antibacterial activity mainly by interfering with cell membrane metabolism [182]. MNPs efficiently cross the bacterial membrane and interfere with enzymes, resulting in antibacterial action. MNPs also liberate reactive oxygen species (ROS) which disrupt the bacterial DNA and potentiate the bactericidal action [183]. Among MNPs, silver (Ag) NPs in particular are highly effective against a wide range of pathogenic microbes [183]. Synergistic effects of AgNPs were revealed for ciprofloxacin (see Table 3), methicillin, ampicillin, gentamycin, streptomycin, and vancomycin [184,185]. AuNPS loaded with levofloxacin, cefotaxime, ceftriaxone, ciprofloxacin, gentamycin, rifampicin, and vancomycin showed remarkably

Table 3
Targeted antibiotic delivery through different nanocarriers and comparison of antibacterial activity.

Drug Delivery System (DDS)	Encapsulated Antibiotic	Targeting moieties	Targeted Pathogen	MIC (μg/mL) of Formulation	MIC[a] (μg/mL) of Control	References
Liposomal						
Liposomal pyochelin–antibiotic (L-Pch-Ab)						
L-PCH-CPM	Cefepime	Pyochelin-siderophore	P. aeruginosa PS75	5.01	16.33	[155]
L-PCH-IPM	Imipenem		P. aeruginosa PS75	1.66	4.21	
L-PCH-CAZ	Ceftazidime		P. aeruginosa PS75	8.33	17.66	
Small unilamellar liposome vesicle (SUVETs)	Vancomycin	Phosphatidylethanolamine-fusogenic agent	E. coli	6–25	>512	[156]
			Klebsiella spp.	25–50	>512	
			P. aeruginosa	50	>512	
			A. baumannii	6–12.5	>512	
			E. coli ATCC 25,922	10.5	>512	
			P. aeruginosa ATCC 27,853	83.7	>512	
Nanoliposomes	Tobramycin-	1,2-dioleoyl-*sn-glycero*-3-phosphatidylethanolamine- fusogenic agent	P. aeruginosa ATCC 25,619	–	0.10	[157]
Liposomes (POS-Lipo-CAM)	Clarithromycin	Didecyldimethyl-ammonium bromide-cationic surfactant	P. aeruginosa-M13639-1	8	256	[158]
Nanostructured lipid carriers (NP-pRIF)	Rifampicin	Tuftsin modified- peptide	M. tuberculosis	0.48	1	[159]
Dendrimers						
PAMAM Dendrimers		Cationic polyamidoamine-membrane				
Generation 3 PAMAM	Vancomycin	disrupting agent	P. aeruginosa	78.1	5000	[160]
Generation 5 PAMAM	Vancomycin		P. aeruginosa	78.1	5000	
Micelles						
Polycationic Micelles		Polylactide-poly (ethylene glycol)	E. coli isolates			[175]
(PP-PEI/TC)	Tetracycline	-polyethylenimine-cationic polymer	EB1-1	4	>128	
			BE7-1	4	64	
			EB14	8	128	
Polymer						
Lipid polymer nanoparticles	Amoxicillin	Rhamnolipids-surface active agents	Helicobacter pylori	15.6	125	[181]
Polymer NPs Alginate/chitosan	Rifampicin	Chitosan-surface active agent	S. aureus	< 0.025	0.2	[179]
Chitosan nanoparticles	Vancomycin	Anionic gemini surfactant (AGS)-	S. aureus	7.81	–	[200]
DL_CSSNPs		surface active agent	MRSA	62.5		
Polymer NPs						
Rifampicin-chitin	Rifampicin	Amorphous chitin-cationic biopolymer	E. coli	20	35	[180]
PEGylated Nano-BAs (Nano-BA12K)	Bacitracin	Poly(D,L-lactic-*co*-glycolic acid)-	S. aureus ATCC29213	0.5	>128	[201]
		Lipopolysaccharide disrupting agent	S. pyogenes ATCC19615	0.5	>128	
			A. pyogenes ATCC19411	1	>128	
			E. coli ATCC25922	1	1	
			P. aeruginosa ATCC27853	2	1	
			S. typhimurium ATCC13311	2	2	
Polymer NPsPoly (lactic-*co*-glycolic acid)	Ciprofloxacin	Deoxyribonuclease I-targeting ligand	P. aeruginosa	0.0625	0.39	[202]
PLGA-NPs	Cloxacillin	Poly(d,l-lactide-*co*-glycolide) acid-polymer	methicillin-susceptible strain (Newman)methicillin-resistant strain (USA300)	0.00625	0.035	[200]
				0.2	1	
PLGA-NPs	Azithromycin	Poly (lactide-*co*-glycolide)-polymer	E. coli	0.78	6.25	[203]
			S. aureus	0.39	3.12	
Poly(D,L-lactic-*co*-glycolic acid)	Rifampin	Anti-protein A (anti-Staph)-targeting ligand	S. aureus	0.016	0.008	[204]

Table 3 (*continued*)

Drug Delivery System (DDS)	Encapsulated Antibiotic	Targeting moieties	Targeted Pathogen	MIC (μg/mL) of Formulation	MIC[a] (μg/mL) of Control	References
Polystyrene NPs	Penicillin-G	Carboxylic acid group-targeting ligand	E. coli	12	17.5	[205]
COO^--NPs			P. aeruginosa	15.2	24.9	
			S. typhimurium	4	15.7	
			P. vulgaris	5.8	16.8	
			K. pneumoniae	13.6	28.3	
			S. aureus	5	10	
			MRSA-252 (MDR)	20.5	> 100	
			CA-MRSA (MDR	17	38.6	
			HA-MRSA	6.7	12.6	
			MSSA	4	16.5	
Polystyrene NPs	Penicillin-G	Sulfate group-targeting ligand	E. coli	11.9	17.5	[205]
$SO4^-$-NPs			P. aeruginosa	16.8	24.9	
			S. typhimurium	4.5	15.7	
			P. vulgaris	6.4	16.8	
			K. pneumoniae	15	28.3	
			S. aureus	5	10	
			MRSA-252 (MDR)	12.1	> 100	
			CA-MRSA (MDR	18.9	38.6	
			HA-MRSA	8.3	12.6	
			MSSA	5.5	16.5	
Metallic Nanoparticles						
Gold (Au) NPs			K. pneumoniae			
LEV-NPs	Levofloxacin	Bacterial exopolysaccharide-biopolymers	S. aureus	1.125	>10	[186]
CTX-NPs	Cefotaxime		E. coli	1.125	>10	
CTR-NPs	Ceftriaxone		E. coli	0.281	>10	
CIP-NPs	Ciprofloxacin			0.140	>10	
Chitosan (CS) NPs			P. aeruginosa			
Ciprofloxacin- CSNPs	Ciprofloxacin	Chitosan-cationic polymer	(*P*1)P. aeruginosa (*P*1	0.6	–	
Gentamicin-CSNPs	Gentamicin			0.3	-	[206]
Carbon nanotubes						
MSiNPsCol@MSN@LL-(LL37)	Colistin	LL-37 peptide-targeting ligand	P. aeruginosa	0.6	4	[20]

[a] The control drug is the corresponding antibiotic delivered. **Abbreviations**: NEG-Lipo-CAM, negatively charged liposomal clarithromycin; POS-Lipo-CAM, positively charged liposomal clarithromycin; NEU-Lipo-CAM, uncharged liposomal clarithromycin; PAMAM, polyamidoamine; CR-MRSA, ciprofloxacin-resistant methicillin-resistant S. aureus; PP-PEI, polylactide-poly (ethylene glycol)-polyethylenimine (PLA5K-PEG2K-PEI2K); NPs, nanoparticles; MSiNPs, mesoporous silica nanoparticles.

reduced MICs against various bacterial strains relative to the corresponding free antibiotics [186,187]. Titanium oxide (TiO_2) NPs entrapped with penicillin, amikacin, ampicillin, gentamycin, and cloxacillin demonstrated improved antibacterial potential compared to free antibiotics [188]. Grumezescu et al. prepared amoxicillin entrapped Fe_3O_4 nanoparticles which showed approximately 3–4 fold reduced MIC values for S. aureus and E. coli, respectively. Nanoparticles showed positive zeta potential (~70 mV) being suitable for electrostatic interaction with the negatively charged bacterial cell surface. Moreover, nanocarriers were found to be well circulated through the host body and localize only in target sites or organs [189]. Patra et al. demonstrated that ciprofloxacin-loaded zinc oxide NPs (ZnONPs) possess improved antibacterial potential over free ciprofloxacin. It was demonstrated that ZnONPs disrupt the cell membrane by generating reactive oxygen species (ROS) which enables the permeation of ciprofloxacin in a bacterial cell and stops bacterial growth [190]. Tyagi et al. compared the antibacterial activity of ciprofloxacin-loaded zinc oxide nanoparticles (ZnONPs) with bare ciprofloxacin. Nanoconjugates showed improved activity against Streptococcus spp. and E. coli up to 2.8–2.9 fold as compared to free ciprofloxacin. Same mechanism of action was proposed as described in the previous study [191].

Carbon nanotubes (CNTs) are single or multiple layers of graphene rolled to form cylindrical shapes [192]. CNTs can be classified as single-walled nanotubes (SWNTs), multi-walled nanotubes (MWNTs), and C60 fullerenes. SWNTs and C60 fullerenes are promising drug carriers because of their unique diameter (1–2 nm) which is approximately half of the diameter of the DNA helix [193]. SWNTs and MWNTs can penetrate the cell either through direct interaction with the cell membrane or through endocytosis. Fullerenes can protect the injured mitochondria by generating free radicals and facilitate the tissue-specific targeting of mitochondria which can be exploited for the delivery of drug molecules [194]. Syed et al. prepared a drug delivery system in which SWCNTs were non-covalently attached with doxycycline and methicillin. It was revealed that antibiotic entrapped SWCNTs are less toxic to mammalian cells, enable drug delivery at the site of infection, and potentiate the antibacterial effect of methicillin with slightly enhanced activity of doxycycline. It is a well-known fact that SWCNTs can disrupt bacterial membranes while a significant amount of SWCNTs was found to be associated with bacterial cell walls in the present study. It was revealed that SWCNTs promote bacterial accumulation as well as internalization and improve the antibacterial potential of conjugated drugs. Moreover, non-covalent linkage also enhances the probability of antibiotic release inside bacterial cells [195]. Carver et al. employed SWNTs and nanographene oxide (NGO) as carriers for tetracycline to a resistant strain of E. coli. It was revealed that SWNTs are better carriers for tetracycline as compared to graphene oxide, which might be due to the needlelike shape of SWNTs [196].

Silica nanoparticles (SiNPs) possess an exceptionally large surface area covered with polar silanol groups which facilitate the adsorption of water and enhance the stability of bioactive molecules. Moreover, SiNPs can be employed for site-specific drug delivery because of their potential to interact with nucleic acids [197]. The attachment of stimuli-responsive agents within the pores of SiNPs can enhance the potential for drug delivery at the site of interest [194]. Clemens et al. demonstrated that attachment of cationic polyethyleneimine (PEI) to mesoporous silica nanoparticles (MSiNPs) can selectively deliver the entrapped isoniazid at the site of infection as it improves the cellular uptake and promotes the flee of therapeutic agents from acidifying endosomes into the cytoplasm. This resulted in 2–4 times enhanced activity against M. tuberculosis as compared to free isoniazid [198]. Subramaniam et al. revealed that rifampicin-loaded MSiNPs of 100 nm size can potentiate the effectiveness of rifampicin to a greater extent than that of 40 nm nanoparticles. It was revealed that drug-loaded MSiNPs efficiently accumulate inside macrophages by phagocytosis or endocytosis and potentiate the effectiveness of rifampicin. Furthermore, it was demonstrated that after cellular uptake, smaller nanoparticles are more susceptible to exocytosis than larger nanoparticles which might be the possible reason for less promising results of 40 nm nanoparticles [199].

It was revealed that drug-loaded MSiNPs efficiently accumulate inside macrophages by phagocytosis or endocytosis and potentiate the effectiveness of rifampicin. Furthermore, it was demonstrated

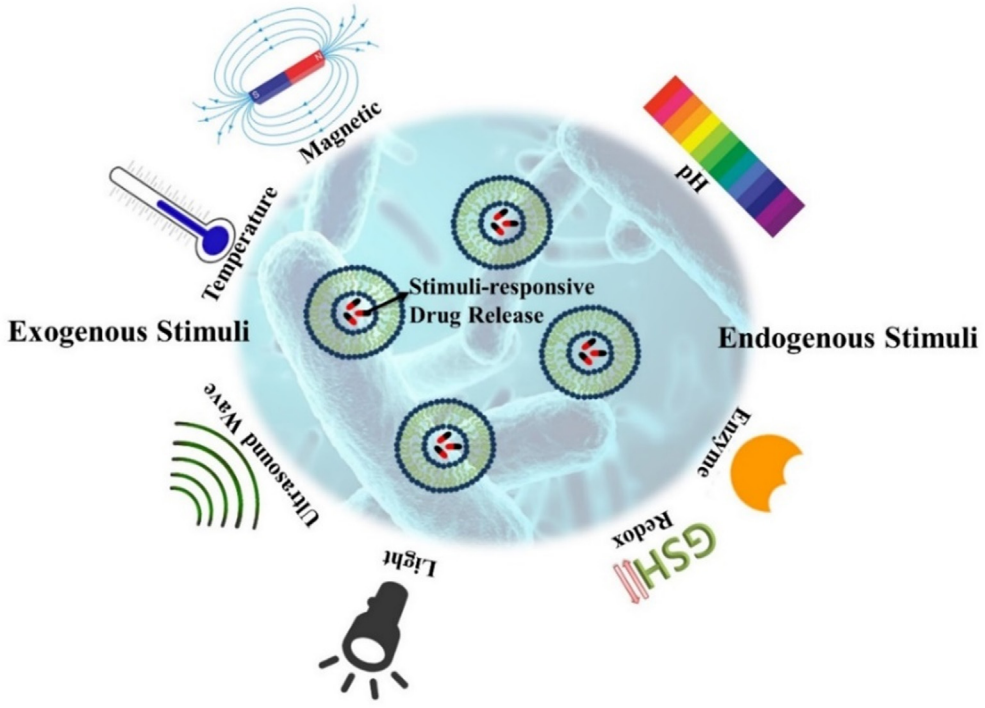
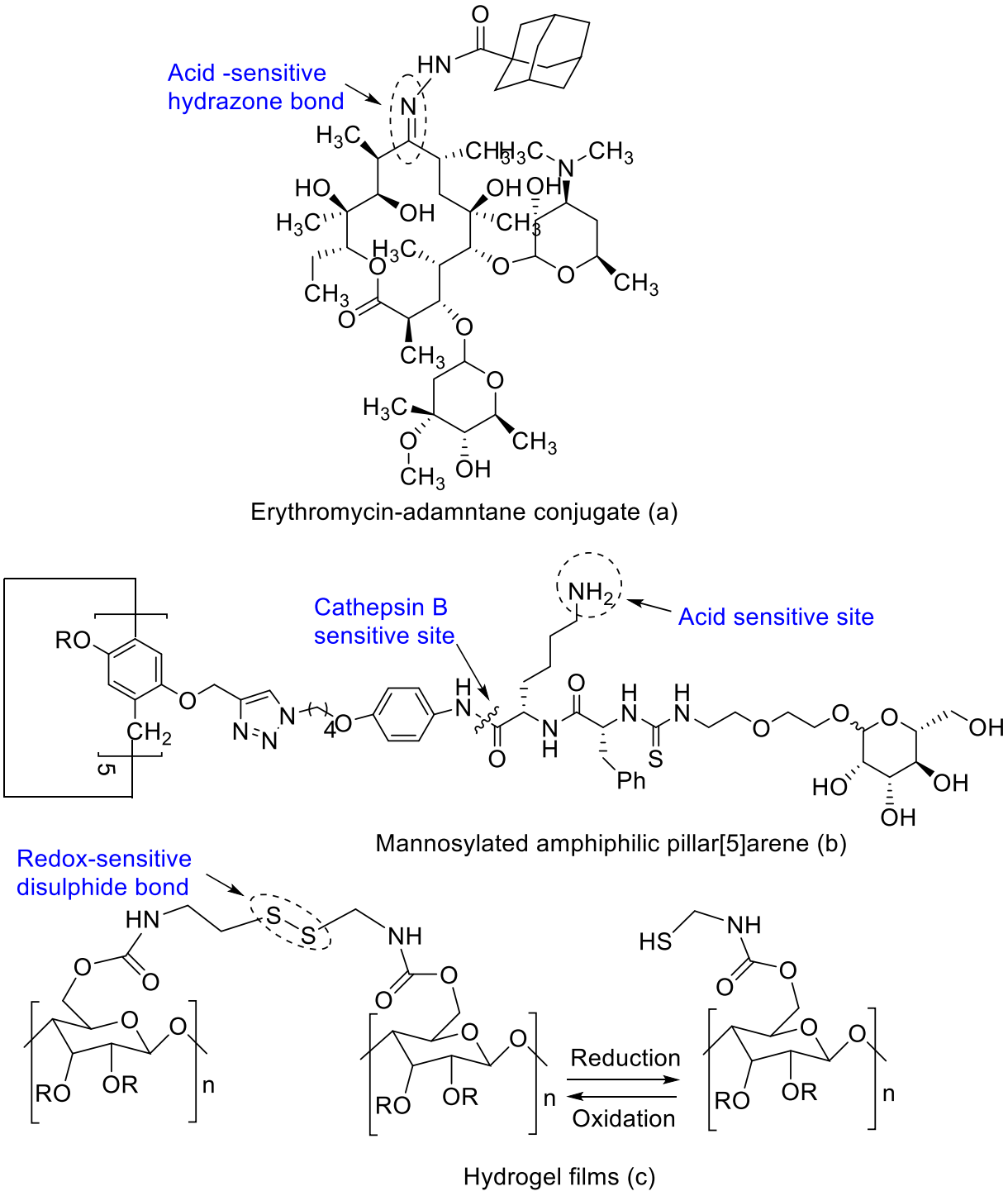


Fig. 6. Various types of stimuli which can be exploited to mediate antibiotic release from drug carriers at the target site.



Scheme 3. Demonstration of acid-sensitive, enzyme-sensitive, and redox-sensitive sites in Erythromycin-adamntane conjugate (a), Mannosylated amphiphilic pillar [5]arene (b), Hydrogel films (c).

that after cellular uptake, smaller nanoparticles are more susceptible to exocytosis than larger nanoparticles which might be the possible reason for less promising results of 40 nm nanoparticles [199]. Rathnayake et al. designed structured vehicles which contained a colistin entrapped MSiNPs core with a liposomal shell and attached to PA (Pseudomonas aeruginosa)-targeting LL-37 peptide. It was notified that liposomal layer degrades by the action of lipase present at the site of P. aeruginosa infection and releases the entrapped colistin. Hence, nano assembly showed 6.7-fold more effectiveness than free colistin due to site-specific drug release in the presence of bacteria [20].

Quantum Dots (QDs) are semiconductor nanoparticles (2–10 nm in size) developed from II to VI or III-V group atoms of the periodic table with a size smaller than the excited Bohr radius [207,208]. Quantum dots (QDs) contain semiconductor inorganic core and an outer aqueous organic coated shell (see Fig. 5) [194]. Carbon Quantum dots (CQDs) enter into bacteria through the cationic surface and induce the formation of intracellular reactive oxygen species (ROS), resulting in a non-uniform cell framework and bactericidal action [209]. Dowoo et al. prepared silicon quantum dots (Si QDs) which were conjugated with amoxicillin through covalent linkage. It was demonstrated that drug delivery system

Table 4
Stimuli-responsive drug carriers for site-specific release of antibiotics.

Stimuli-Responsive System	Antibiotic Entrapped	Stimuli-Responsive Motif	Nanocarrier	Targeted Pathogen	Outcome Achieved	References
pH-responsive	Vancomycin	Fatty acids-derived lipids	Liposomes	S. aureus and MRSA	Liposomal formulation of vancomycin showed 1.8-fold less log10 CFU/mL of MRSA than free vancomycin	[239]
pH-responsive	Vancomycin	N-(2-Morpholinoethyl) oleamide	Solid lipid nanoparticles	MRSA	Formulation released the vancomycin in a pH-dependent manner and reduced the MRSA burden up to 4.14-fold as compared to free vancomycin	[240]
pH-responsive	Amoxicillin	Poly (γ-glutamic acid) (γ-PGA) and arginine conjugated with chitosan	Colloidal nanoparticles	Helicobacter pylori	Amoxicillin was swiftly liberated at 7.0 pH which exists at the site of H. pylori infection and exhibited better activity (37.8 %) than bare amoxicillin (17.7 %)	[241]
pH-responsive	Tetracycline	Modified montmorillonite nanosheets	Nanosheets	S. aureus, E. coli	A significant amount of tetracycline was released in the intestine by retaining the antibiotic potential	[242]
pH-responsive	Erythromycin	Polyethylene glycol, Chitosan	Mesoporous silica nanoparticles (MSiNPs)	–	Polymer coating of MSiNPs enabled the controlled drug release at the pH of inflammatory sites (pH 5.5)	[243]
pH-responsive	Doxycycline	Calcium carbonate ($CaCO_3$)	Mineralized nanoparticles	Prevotella intermedia	The formulation released doxycycline under acidic conditions appropriate for oral plaque biofilms, showed complete eradication of biofilms	[244]
Thermo-/ pH-responsive	Ciprofloxacin	Poly (NIPAAm-MAA-VP)Poly (methacrylic acid)	Gel	P. aeruginosa	Nanopreparation of ciprofloxacin (4.687 mg/mL) showed 4-fold reduced MIC than CIP solution (18.78 mg/mL)	[245]
pH-responsive	Tobramycin	Heparin, chitosan	Micelles	S. aureus	Formulation provided a sustained drug release under acidic conditions (pH 4.3), showed promising antibacterial potential, and damaged the biofilms	[246]
pH-responsive	Ciprofloxacin	Sodium alginate attached with 3-amino-7-chloro-2-nonylquinazolin4(3H)-one ACNQ	Polymeric nanoparticle	P. aeruginosa	Nanoformulation efficiently accumulated into P. aeruginosa biofilms and eradicated these biofilms as compared to the free ciprofloxacin	[247]
pH-responsive	Vancomycin	Oleylamine (OLA) and poly amidoamine	Lipid-dendrimer hybrid NPs	MRSA	Vancomycin was delivered intracellularly with improved anti-MRSA activity	[248]
Enzyme responsive (Lipase)	Carvacrol	poly(ε-caprolactone) polymer (PCL)	Nanoparticles	MRSA	Formulation improved the penetration of carvacrol and improved anti-MRSA activity up to 2-fold	[249]
Enzyme responsive (Trypsin)	Ciprofloxacin	Poly-L-lysin	nanogels	S. aureus	Formulation showed on-demand drug release, however antibacterial activity of ciprofloxacin reduced to a significant extent	[250]
Enzyme responsive (Hyaluronidase)	Polyhexanide	Hyaluronic acid	Nanoparticles	S. aureus, E. coli	Nanoformulation released polyhexanide upon hyaluronidase action and showed promising antibacterial potential against both pathogens	[251]
pH/Enzyme responsive (Lysosomal acid and cathepsin B)	Vancomycin	Mannose	Pillar[5]arene vesicle	MRSA	Formulation interacted with macrophages efficiently reduced the bacterial load	[23]
Enzyme responsive (Phospholipase A2)	Doxycycline	1,2-Distearoyl-*sn-glycero*-3-phosphocholine, 1,2-dioctadecanoyl-*sn-glycero*-3-phospho-(10 -*rac*-glycerol)	Liposome	Helicobacter pylori	Liposomes demonstrated "on-demand" drug release proportional to bacterial load at the infection site	[252]
Enzyme responsive (Butyrylcholinesterase)	Cyclodextrin	Myristoylcholine chloride	Supramolecular nanoparticles	–	Supramolecular nanoparticles were exploited as vehicles for site-specific drug release	[253]
Redox-triggered	Moxifloxacin	Disulfide snap-tops	Mesoporous silica nanoparticle	Francisella tularensis	Moxifloxacin loaded nanoformulation prevented the weight loss, significantly reduced the bacterial load as compared to bare moxifloxacin	[254]
Redox-responsive	Gentamicin, Tobramycin, and Neomycin	Disulfide bonds	Alginate nano hydrogels	S. aureus, E. coli	Reduction responsive disulfide bond containing hyperbranched polymers (SS-HP) of aminoglycosides were biocompatible with excellent antibacterial activity	[255]
Photothermal-responsive	Ampicillin Cefepime	rGO-containing poly (acrylic acid)	Polymeric nanofiber mats	S. aureus	Formulation released the antibiotics in a controlled manner upon NIR irradiation and exhibited efficient wound-healing	[256]
NIR light-responsive	Vancomycin	Polypyrrole	Microspheres	MRSA	Microspheres released vancomycin upon photoexcitation while photothermally-triggered hyperthermia showed synergistic antibacterial activity with vancomycin	[257]
Ultrasound-mediated	Gentamicin	–	Liposomes	Ralstonia insidiosa	Gentamicin entrapped liposomes showed an 80 % reduction in bacterial load. Ultrasound exposure enhanced the liposome-capture density to biofilms up to three-time magnitude	[258]
Ultrasound-mediated	Levofloxacin	–	Nanoparticles	Mycobacterium smegmatis	Nano formulation efficiently penetrated inside macrophages and showed ten times better activity against M. smegmatis as compared to bare levofloxacin	[259]

Table 4 (*continued*)

Stimuli-Responsive System	Antibiotic Entrapped	Stimuli-Responsive Motif	Nanocarrier	Targeted Pathogen	Outcome Achieved	References
Magnetic field	Ciprofloxacin	Iron-oxide NPs	Polymeric microspheres	S. aureus	Sustained drug release was attained up to 19 days and microsphere showed increased antibacterial effect under the influence of magnetic field	[260]
Magnetic field	Amoxicillin	Iron-oxide NPs	Xanthan/Fe_3O_4/ Albumin Patches	S. aureus, E. coli	Application of magnetic field triggered amoxicillin release, and growth of E. coli was efficiently inhibited under magnetic field than S. aureus	[261]
Temperature-responsive	Ofloxacin	N, *N*-methylene bisacrylamide	Hydrogel	–	Drug carriers release ofloxacin at high temperature and inhibit drug release at low temperature	[262]
Temperature-responsive	Imipenem	Stearic acid, Lauric acid	Nanoparticles	MRSA	Temperature elevation cleaves the drug carriers, disrupted the bacterial membranes, and enabled the permeation of imipenem. Nanoformulation reduced the MRSA load to a greater extent than free imipenem	[263]

In Abbreviations: CFU, colony-forming unit; Poly (NIPAAm-MAA-VP), poly (*n*-isopropylacrylamide-methacrylicacide-vinylpyrrolidone); NIR, near-infrared.

is capable to release amoxicillin in a controlled manner by the hydrolysis of amide moiety [210]. Li et al. synthesized various calcined gentamicin-derived CQDs at varying temperatures. One of these, CQD180 was highly effective against planktonic bacteria and capable to rupture S. aureus biofilms. Moreover, CQD180 possessed less drug resistance potential and didn't impart toxic impacts on mammalian cells. It was revealed that CQD180 penetrates bacterial membranes because of its cationic surface and generates intracellular ROS resulting in disruption of cell morphology and ultimate bacterial death [209].

3.4. Stimuli-responsive approaches for targeted antibiotic delivery

Nanocarriers are the most widely employed vehicles for the delivery of antibiotics [10]. Targeted antibiotic delivery potential can be further improved by the coupling of nanocarriers with a stimuli-responsive drug release approach [39]. Stimuli-responsive drug delivery systems preferentially recognize the distinct environment at the infection site (endogenous stimuli) and also respond to the exogenous stimuli [211]. This strategy circumvents the untimely release of antibiotics and enhances their transportation to the infection site. Hence, stimuli-responsive nanocarriers overcome the limitations of typical formulations of antibiotics as well as enhance the potential of nanocarriers for targeted drug delivery [212,213]. Different types of stimuli-responsive systems are shown in Fig. 6.

3.4.1. Endogenous Stimuli-Responsive nanocarriers

Intrinsic features of pathogenic sites differ from healthy tissues which can be exploited for site-specific drug release [214]. These intrinsic stimuli-responsive nanocarriers include:

3.4.1.1. pH-responsive nanocarriers. Pathogenic sites may possess a distinct pH value from physiological conditions i.e., 7.4. Infection sites possess an acidic environment due to the generation of acetic acid and lactic acid during bacterial glycolysis [215]. This feature has enabled the development of pH-responsive nanocarriers which selectively liberate the antibiotics upon detection of acidic pH at the infection site. These nanocarriers stabilize the antibiotics in blood circulation, minimize their release in healthy tissues, and reduce the emergence of antibiotic resistance [39,213,216,217].

Moreover, pH-triggered nanocarriers are protonated under acidic conditions and attain a positive charge which interacts with negatively charged bacterial membrane. These electrostatic interactions enhance the accumulation of antibiotics at the site of interest, reduce the antibiotic dose, and avoids undesired effects [32,34]. Cyphert et al. prepared conjugates by the covalent linking of adamantane-1-carbohydrazide to the erythromycin through a pH-sensitive hydrazone bond (Scheme 3a). Since S. aureus infection sites possess lower pH compared to physiological conditions, therefore, hydrazone linkage breaks under acidic infectious conditions and selectively releases the erythromycin while imparting reduced systemic toxicities. Moreover, modified erythromycin remains in tissues for a prolonged interval as it is more hydrophobic than free erythromycin and shows improved therapeutic outcomes [218]. Kalhapure et al. prepared an anionic gemini surfactant (AGS) which is a twin-chain anionic amphiphile and facilitates the formation of pH-responsive drug delivery systems. Subsequently, vancomycin entrapped chitosan nanoparticles containing AGS were prepared which selectively liberated the antibiotic at an acidic pH at the site of MRSA infection and exhibited a significantly lower MIC value (7.81 μg/mL) at acidic pH relative to its MIC at physiological pH (62.5 μg/mL). Moreover, an in vivo study demonstrated that the designed nanocarriers are approximately 8-time more efficacious than free vancomycin. It was elaborated that ionization of AGS is reduced at the site of infection due

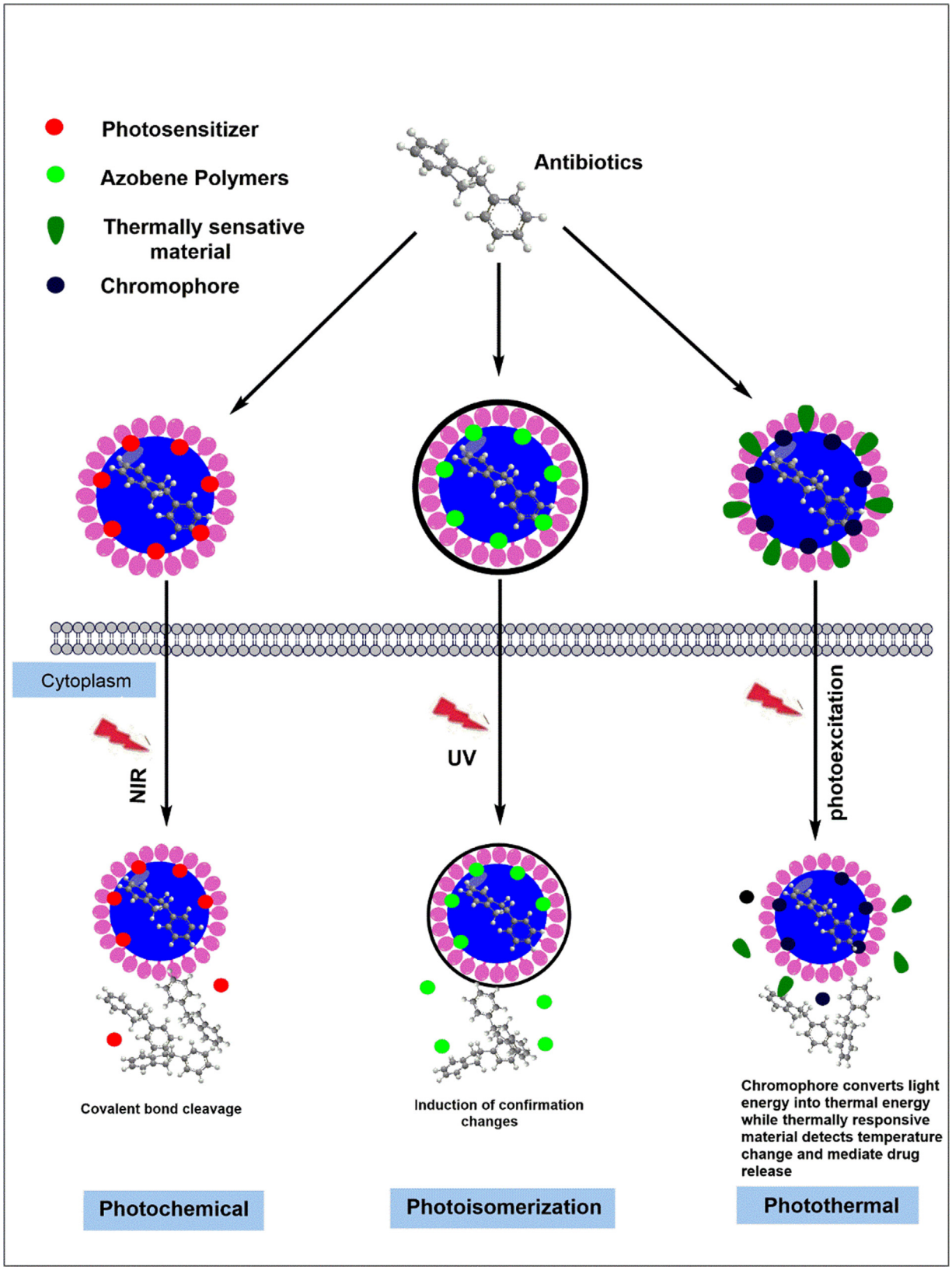


Fig. 7. Three strategies for light-mediated drug release.

to the acidic pH followed by the binding of protonated amino groups to the negatively charged bacterial membrane. It results disruption of nanocarriers and liberation of vancomycin [200]. Munir et al. prepared cefazolin-loaded hydroxyapatite nanocarriers (opHANPs) which exhibited increased drug release at low pH and superior antibacterial activity against resistant strains compared to pure cefazolin. In the case of bone and joint infections, the pH of bone tissues is lower than physiological pH of bone

matrix because of bacterial load. opHANPs selectively rupture in an acidic environment and facilitate the release of antibiotics at the site of infection. Moreover, the tiny size and the cationic feature of opHANPs also promote the disruption of bacterial membrane resulting in improved antibacterial potential [219]. Lutwyche et al. prepared gentamicin liposomes composed of dioleoylphosphatidylethanol-amine (DOPE). It is a well-known fact that DOPE exists as a hexagonal-II phase confirmation in aqueous media and is unable to form a bilayer structure. Hence, it was stabilized into liposomes through the incorporation of bilayer forming lipids such as *N*-succinyl-DOPE. This stabilizing lipid has a negatively charged head which is neutralized under the acidic environment of endosomes leading to the destabilization of bilayers. As a result, liposomes fuse with adjacent membranes and liberate their payload i.e., gentamicin into the endosomal compartment of cell leading to the efficient killing of intracellular L. monocytogenes and S. typhimurium [220,221]. More studies on stimuli-responsive antibiotic delivery are described in Table 4.

3.4.1.2. Enzyme-responsive nanocarriers. Enzymes play a vital role in various physiological processes. Thus, dysregulation in the normal functioning of enzymes can mediate various abnormal processes resulting in pathogenic conditions. Moreover, these altered enzymes can serve as biological triggers for drug transport as they could modulate the breakdown of nanocarriers to liberate the therapeutic agents [222]. High specificity and bio-selectivity of enzymes for their substrates can be exploited for site-specific release of a payload, which minimizes undesired effects. Moreover, the biocatalytic feature of enzymes facilitates the efficient release of therapeutic agents and reduces the required dose to attain desired therapeutic outcome [223]. Enzyme-triggered drug delivery systems enable the drug release through a cascade of enzyme-facilitated events. Enzyme-cleavable linkers are conjugated with drug-loaded nanocarriers, whose polymeric coverings are disrupted upon enzymatic action, resulting in the liberation of the entrapped therapeutic moiety as well as intracellular drug delivery.

Moreover, lipid- and enzyme cleavable polymer incorporating drug carriers can be designed which liberates the payload upon enzymatic action on the polymer. The catalytic action of enzymes generates different by-products which in turn facilitate drug release [213,222,223]. Peng et al. prepared mannosylated amphiphilic pillar[5]arene-based nanostructures which self-assemble into supramolecular vesicles to entrap vancomycin (Man@AP5-Van) and preferentially interact with macrophages via mannose receptor-mediated phagocytosis. (Scheme 3b). After the invasion in macrophages, Man@AP5-Van undergoes protonation under lysosomal acidic conditions, and the Phe-Lys linker is broken by cathepsin B. This results in disruption of nanocarriers and liberation of vancomycin which efficiently circumvents the intracellular MRSA growth and imparts the least cytotoxic effects [23]. Paul et al. prepared Alcalase-coated nanogels encapsulated with ciprofloxacin which were sensitive to protease. It was demonstrated that nanostructures efficiently penetrate the extracellular matrix of biofilms and deliver a high dose of payload to bacterial cell walls. They investigated the potential of nanogels for eradication of various biofilm-forming bacteria including S. aureus, P. aeruginosa, S. epidermidis, and E. coli. Nanogels minimized the biofilm load up to 6-fold and a significant reduction in bacterial cell density was noticed [224]. Various examples of enzyme-triggered antibiotic release are shown in Table 4.

3.4.1.3. Redox-responsive nanocarriers. Redox-responsive drug carriers possess redox potential and exploit GSH concentration differences between infectious and healthy cells, as well as intracellular and extracellular compartments. The level of GSH is approximately 100–1,000 times higher in infected cells than in healthy cells [213,225]. Moreover, the intracellular level of GSH (1–10 mM) is three orders higher as compared to its blood concentration (2–10 μM) [226,227]. Thus, these nanocarriers exhibit stability in healthy tissues but liberate the entrapped therapeutic agents in pathogenic tissues upon detection of higher GSH levels [228–230]. Redox-sensitive nanocarriers provide a promising strategy for the management of bacterial infections with selective targeting and sustained drug release [231]. Wang et al. prepared pH and redox dual-responsive hydrogel films by integrating chitosan (CS) microspheres into carboxymethyl cellulose (CMC) hydrogel through disulfide cross-linker i.e., cystamine dihydrochloride (CYS). Subsequently, tetracycline hydrochloride (an antibiotic) was incorporated in this formulation. Antibiotic was released at a slow rate under physiological pH conditions, while an increased release rate was observed under acidic conditions. Moreover, hydrogels were sensitive to redox conditions due to the presence of disulfide bonds (Scheme 3c). This formulation exhibited promising antibacterial potential against E. coli and S. aureus [232]. Lu et al. synthesized chlorhexidine entrapped redox/pH-responsive, silver functionalized MSiNPs. By taking advantage of GSH-mediated matrix degradation potential, nano-formulation showed subsequent release of chlorhexidine and silver ions mediated by reductive and acidic environment. The mechanism of chlorhexidine release may involve the protonation and cleavage of carboxyl groups in acidic conditions. Nano-formulation was more effective for restricting the growth of Streptococcus mutans biofilm than bare chlorhexidine. Moreover, nano-formulation minimized the toxic effects of chlorhexidine in oral epithelial cells [233].

3.4.2. Exogenous Stimuli-Responsive nanocarriers

Multiple energy sources can serve as exogenous stimuli to mediate drug release from nanocarriers at the desired site. Exogenous stimuli-responsive nanocarriers include:

3.4.2.1. Light-responsive nanocarriers. Light-sensitive drug carriers have attained remarkable considerations for site-specific drug delivery [234]. Light-triggered drug release is noninvasive, allows high spatial and temporal control over the release, and can sequentially liberate multiple drug molecules [235]. Light-mediated drug release can work through three different approaches (see Fig. 7). (a) Photochemical: light-responsive drug carriers utilize photosensitive agents which break covalent bonds upon photoexcitation and mediate the release of entrapped drugs at pathogenic sites [214,235–237]. Various photosensitive moieties can be incorporated, including *ortho*-nitrobenzyl, coumarin, and pyrene derivatives, etc. [235]. Light of different wavelengths, including ultraviolet (UV), visible, and near-infrared (NIR) can be employed for photoexcitation [234]. NIR is most appropriate for photoexcitation because of its safety and high tissue penetration power [214,237].

(b) Photoisomerization: light-triggered drug release is achieved by inducing reversible conformational changes in drugs mediated by UV and visible light irradiation. Azobenzenes are usually employed for such reactions since they undergo transitions from trans to cis conformations and vice versa upon UV and blue light irradiation, respectively [235]. (c) Photothermal: drug carriers contain chromophores which generate heat upon photoexcitation and trigger thermally sensitive agents to mediate the drug release [235]. Liu et al. designed a functionalized MSN-based drug delivery system encapsulated with ampicillin (MSNs@C-dots/RB/Amp) containing C-dots as a fluorescence probe and photosensitizer rose bengal (RB) which liberates singlet oxygen to perform photodynamic therapy. Ampicillin-loaded MSNs@C-dots/RB exhibited remarkable antibacterial activity against E. coli upon irradiation

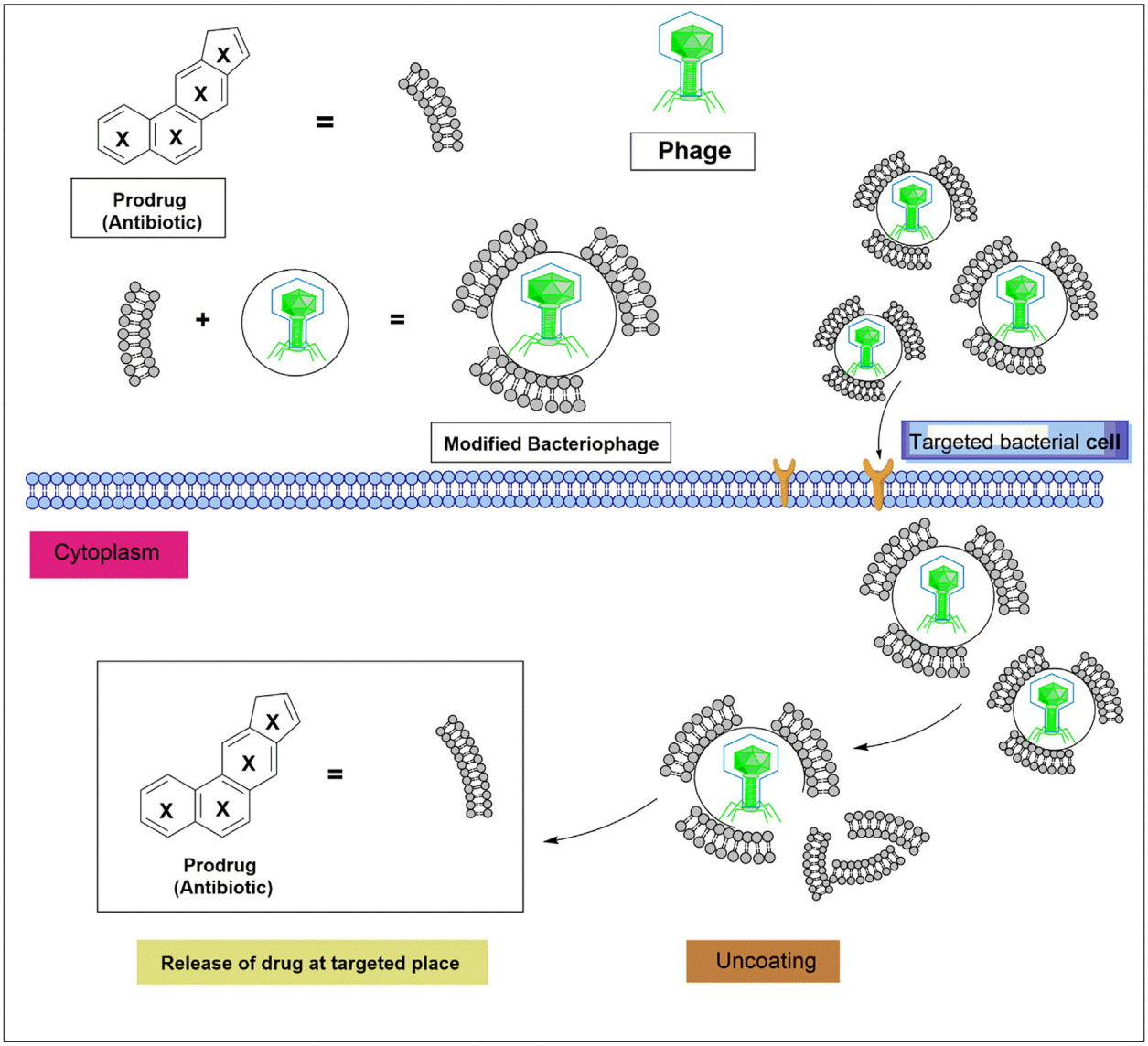


Fig. 8. Schematic representation of targeted antibiotic release through bacteriophages which involves the insertion of ligand on the surface of phage, penetration in the bacterial cell, followed by uncoating and release of therapeutic agents.

by green light as bacterial colonies were not observed on agar plate [238].

3.4.2.2. Ultrasound-responsive nanocarriers. Ultrasound waves are high-frequency sound waves, which facilitate the activation of nanocarriers for controlled drug delivery at pathogenic sites. The intensity of ultrasound can be adjusted for different applications [236]. Ultrasound waves are noninvasive, possess high tissue penetration power, and improve spatiotemporal control for site-specific drug delivery which minimizes the unwanted effects [214,234]. Ultrasound waves mediate drug release through thermal and physical forces triggered by the radiation phenomenon [234].

Ultrasound exposure to a medium may form gas-filled bubbles, a phenomenon referred to as cavitation. Cavitation cleaves drug carriers to mediate drug release and enhances intracellular drug penetration [39,264]. Dong et al. investigated the effect of ultrasound-triggered microbubbles combined with vancomycin in rabbits implanted with S. epidermidis infected catheters. It was revealed that ultrasound-microbubbles-vancomycin combination reduced the bacterial load (from 6.44 $\log_{10}$ CFU per catheter to 3.49 $\log_{10}$ per catheter) to a greater extent than ultrasound and vancomycin in conjunction. Thus, it was concluded that ultrasound mediated microbubbles improved the antibacterial potential of vancomycin against S. epidermidis biofilms without imposing toxic effects. It has been reported that the ultrasound waves induce local fluctuations in pressure and velocity which generate pores in bacterial envelop and facilitate passive transport [265].

3.4.2.3. Magnetic-responsive drug carriers. As compared to other exogenous stimuli, magnetism is an attractive strategy to mediate the drug release as it does not physically interact with the human body. Moreover, due to spatial focusing, magnetic stimuli facilitate drug permeation across biological barriers [230]. Superparamagnetic iron oxide nanoparticles (SPIONs) possess the potential for targeted drug release. SPIONs-based drug delivery systems mainly contain magnetite nanoparticles with an organic or inorganic covering which depends on guidance by an external magnetic field to

arrive at their target sites. Locally employed external magnetic field to the target organ promotes the accumulation of drug-loaded magnetic nanoparticles at the site of action [266]. Subsequently, drug release is triggered via two mechanisms: induction of hyperthermia (Magnetothermal Release) [267], and drug targeting guided by a magnetic field (Magnetic Release) [214,268]. As a result, these carriers selectively interact with target cells which minimizes the required dose and avoids unwanted effects [266]. Magnetic drug carriers enhance the blood-circulation span of drugs by reducing their clearance [266]. Mohapatra et al. prepared microspheres composed of chitosan which were attached with poly-ethylene glycol dimethacrylate (PEGDMA) and incorporated with magnetic nanoparticles (MNP). Subsequently, vancomycin was entrapped into microbeads which were exposed to a 25 mT fluctuating magnetic field (109.9 kHz for 30 min). It was reported that application of magnetic field enabled vancomycin release from microbeads in an amount above the MIC while the drug release from microbeads in the absence of applied magnetic field remained below the MIC, demonstrating that magnetic stimuli can mediate the drug release in a controlled manner depending upon the duration exposed and intensity of the magnetic field. It was concluded that these microspheres are capable of liberating their payload in higher concentration for a prolog interval and may help us to retain antibiotic concentrations at the target while preventing systemic toxicity [269]. Geilich et al. employed iron oxide polymersome (IOPs) for loading of methicillin in the core and SPIONs in the outer layer. The formulation was incubated with S. epidermidis and subsequently exposed to a magnetic field which facilitated the methicillin release inside biofilms. A preparation containing 40 μg/mL SPION and 20 μg/mL of methicillin completely eradicated the biofilms without imposing any harm to mammalian cells. It was elaborated that biofilms treated with methicillin loaded IOPs exhibit efficient bacterial killing inside the magnetic field and little bactericidal action outside the magnetic field. Hence, application of an external magnetic field is needed to attain the full therapeutic outcome of the IOPs [270].

3.4.2.4. Temperature-responsive drug carriers. Temperature-sensitive carriers are frequently employed for stimuli-responsive drug release to treat various pathogenic infections [271,272]. Such drug carriers contain a temperature-sensitive motif which liberates the payload upon detection of a certain temperature. Thermoresponsive nanocarriers retain the entrapped drug at normal body temperature and release the payload upon detection of locally heated infection sites [234,273]. Temperature-sensitive systems can also release the payload at locally cooled sites which enhances the porosity of nanocarriers, resulting in diffusion of payload at the site of interest. Thermosensitive nanocarriers can be functionalized with receptor affinity ligands to improve selectivity for site-specific drug delivery [234]. Boo et al. prepared a temperature-sensitive poly(*n*-isopropylacrylamide) functionalized hyaluronic acid (HApN) hydrogel encapsulated with gentamicin. The potential of gentamicin-loaded hydrogel was investigated for fracture healing and anti-S. aureus activity in a rabbit model. The formulation showed promising anti-S. aureus activity while infected humeri exhibited necrosis and an absence of callus formation. It could be anticipated that the humeri of the rabbits treated with the gentamicin-entrapped hydrogel would heal after a prolonged time span [274]. Some studies on temperature-sensitive carriers are depicted in Table 4.

3.5. Biological carriers for targeted antibiotic delivery

Currently, many studies have been carried out for the development of bio-inspired drug carriers including bacteriophages and blood cells.

3.5.1. Bacteriophages

Viruses naturally act as gene carriers and deliver biological information among various species. Nowadays, multiple viruses are being exploited for drug delivery and among these bacteriophages are mostly used [275]. Bacteriophages invade bacterial cells and interrupt bacterial metabolism resulting in bacterial death. Targeted drug-loaded phages provide a new group of bioconjugated delivery systems which combines biological and chemical components into a modular nano-metric drug delivery system [13]. Phages are extremely selective for their target and their self-regulating system such as the potential to limit propagation in specific cells enables them to be employed as modifiable carriers for site-specific drug delivery [276,277]. A massive quantity of drugs can be entrapped into the phage through genetic manipulation and chemical interaction. Therapeutic agents are either attached to protein coats of phages through chemically and genetically engineered linkers or entrapped inside the core (see Fig. 8). Target selectively is attained through a targeting moiety such as an antibody that is displayed on the phage surface and triggers drug release upon the interaction of phage particles with the host cell [13,277–279].

Phage-derived carriers are highly effective for the elimination of biofilms [275,277]. Drug conjugation with phage-based drug carriers provides improved antibacterial activity, selective bacterial targeting, and minimizes the side effects [21,277]. As drug carriers, bacteriophages possess a high capacity for drug loading and can be rapidly cleared by the host reticuloendothelial system (RES) [277,280–282]. Bacteriophages can efficiently propagate inside the host which enables them to impart a sustained antimicrobial potential. Moreover, bacteriophages are safe, non-toxic, and well-tolerated because of their host-specific character [283]. Vaks et al. prepared chloramphenicol-conjugated filamentous phage-based drug carriers attached to an antibody. In this study, the phage particles provided a drug-carrying vehicle that was manipulated to exhibit a targeting motif such as an antibody on its surface which selectively interacts with pathogens. Chloramphenicol was attached to esterase sensitive linker and subsequently conjugated to the phage particles. The controlled drug release was attained through serum esterase activity. This drug delivery system reduced the immunogenicity, toxicity, and enhanced the half-life of chloramphenicol. It was demonstrated that toxicity and side effects of therapeutic agents can be circumvented by conjugation with phages, as potential side effects of free chloramphenicol were not observed during this study [284]. Yacoby et al. prepared a Phage-A12C-based drug delivery system for chloramphenicol which showed 20-fold higher anti-S. aureus activity relative to bare chloramphenicol. In this system, filamentous phage served as a drug carrier grafted with targeting agents i.e., S. aureus-specific peptides. Chloramphenicol was conjugated to lysine moieties on the phage coat through an ester bond. In the conjugated form, chloramphenicol served as a prodrug having no cytotoxic effect while the drug was released in active form as soon as the phage interacts with S. aureus at the target site.

Hence, the enhanced antibacterial potential of chloramphenicol can be attributed to the selective adhesion of phages to target bacteria, leading to site-specific drug release [285]. Photosensitizers are light-activated antibacterial agents which are employed for the treatment of topical infections. Embleton et al., employed bacteriophage for the site-specific delivery of tin(IV) chlorin e6 (SnCe6) photosensitizer to S. aureus. They prepared a conjugate by the covalent attachment of SnCe6 to S. aureus bacteriophage 75 and investigated the potential of this compound to eradicate S. aureus infection upon exposure to red light. It was noticed that methicillin- and vancomycin-intermediate strains of S. aureus were killed to a large extent while healthy human epithelial cells remained viable. Furthermore, conjugate showed improved bactericidal activity as compared to free SnCe6 [279,286].

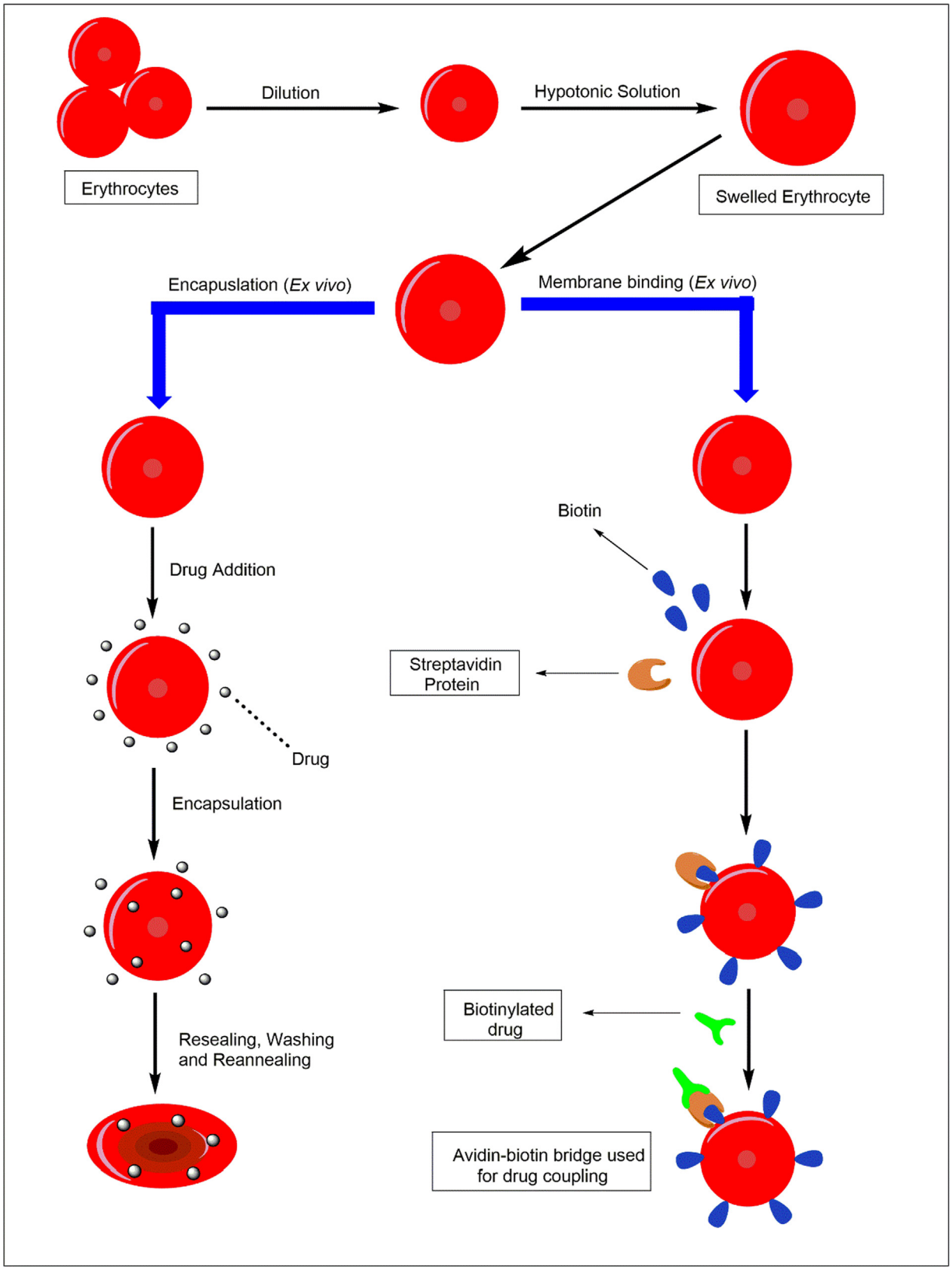


Fig. 9. An overview of erythrocyte-based antibiotic delivery by using encapsulation and membrane-binding methods for the loading of biologically active compounds.

3.5.2. Erythrocytes

Erythrocytes are the most abundantly found blood cells that are produced in the bone marrow and play a role in oxygen transport [287]. Erythrocytes are promising carriers for drug delivery and they are mainly isolated from mammalian (monkeys, pigs, cattle, dogs, goats, sheep) RBCs. Generally, the blood sample is collected

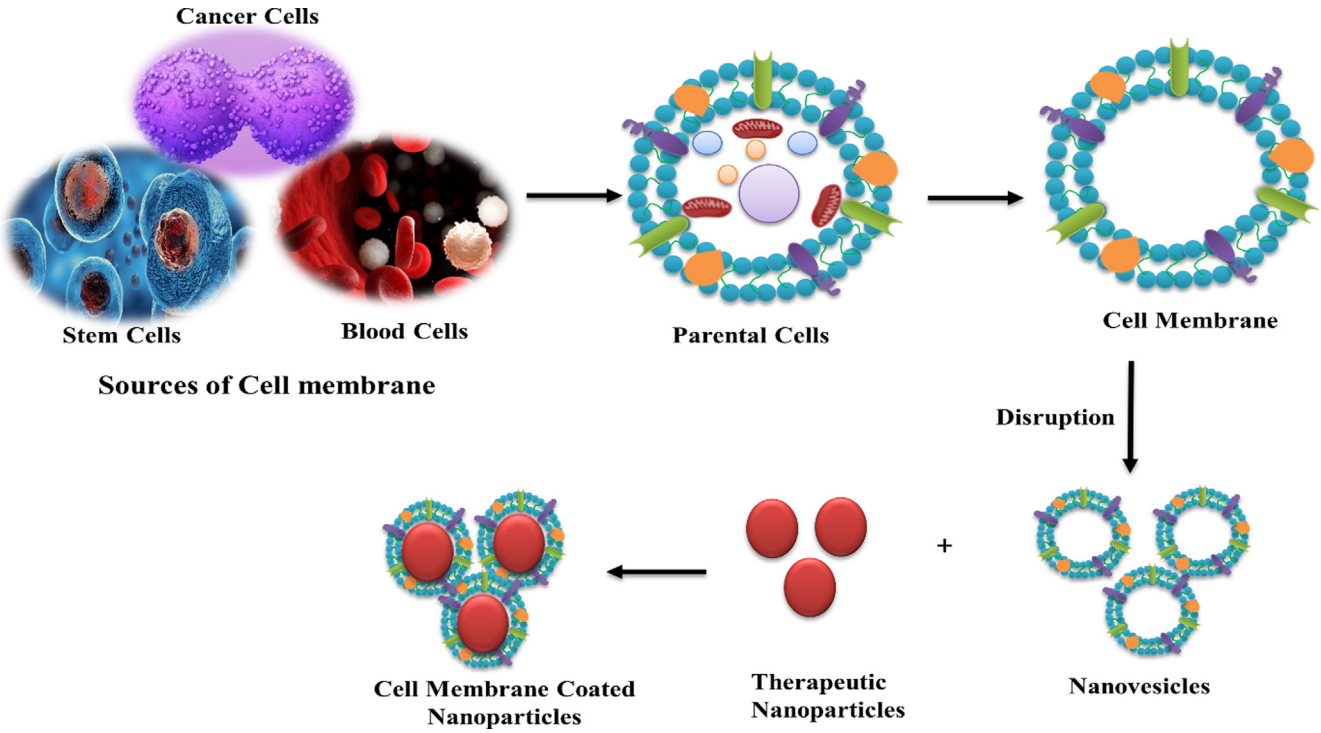


Fig. 10. Pictorial depiction for preparation of cell membrane-derived vesicles entrapped with therapeutic nanoparticles.

from an organism, erythrocytes are separated from plasma and washed by centrifugation. Drugs are loaded in erythrocytes by employing different physical and chemical approaches (see Fig. 9) [288]. Erythrocytes serve as a controlled drug release system when re-injected to the organism and prevent the inactivation of entrapped drugs by endogenous factors [289,290]. Moreover, erythrocytes can be modified with antibodies, glutaraldehyde which improves their target selectivity and prolongs circulation half-life [288]. Erythrocytes can be conjugated with a wide range of therapeutic agents and can entrap a relatively high quantity of drugs as well. Erythrocytes reduce alterations in drug concentration at a steady state and enhance the drug dosing duration [289,291,292].

Erythrocytes can efficiently deliver payloads to the reticuloendothelial system (RES), can be phagocytosed by macrophages, and are capable to liberate the drug in a controlled manner. Ultimately, a large quantity of entrapped antibiotics can be delivered to intracellular microbes [293,294]. Moreover, erythrocytes are biocompatible, biodegradable, non-immunogenic, and possess a prolonged lifetime [289]. Eichler et al. prepared anti-Rh antibody-labeled erythrocyte drug carriers encapsulated with gentamicin which were efficiently delivered to the RES. Antibody coating of gentamicin-loaded erythrocytes served as a targeting agent to the reticuloendothelial system. It was revealed that the rate of RES clearance of erythrocytes should be maximized to attain rapid RES targeting. This objective can be fulfilled by antibody coating of the carrier cells [295]. Jain et al. designed an isoniazid and magnetite entrapped erythrocyte-based drug delivery system which liberated the drug at zero-order kinetics. It was demonstrated that isoniazid can be selectively delivered at the site of infection by employing drug-loaded magnetic cells under the influence of an external magnetic field [296]. Millán et al. revealed that amikacin-loaded rat erythrocytes provide controlled drug release, prolong the plasma lifespan of amikacin, and facilitate drug penetration across target tissues.

It was reported that upon phagocytosis of erythrocytes, amikacin was released in a sustained manner accompanied by RES targeting. The possible reason for sustained drug release might be the fact that erythrocytes do not undergo diffusion across the cell membrane because of their polar nature while the drug may be liberated through a process of cell lysis [297,298]. In addition, human erythrocytes entrapped amikacin exhibited a long drug release period of up to 48 h and proved the potential of human erythrocytes for antibiotic delivery to the monocyte-macrophage system. It was referred that a higher RES targeting of amikacin can be achieved when drug-loaded erythrocytes are phagocyted by cells of the monocyte-macrophage system. Modifications of carrier erythrocyte membrane can facilitate the uptake by monocyte-macrophage system and help to attain a higher intracellular concentrations of amikacin [299].

3.5.3. Cell membrane-derived vesicles

Cells are structural and functional units of organisms, with different biomarkers present on the plasma membrane which facilitates the recognition, signal transduction, and various other functions. Hence, embedding a cell membrane on the surface of NPs can impart the potential to interact with the surrounding environment [300]. Cell membranes-derived vesicles have recently emerged as a promising tool for biomimetic nanoengineering in which the core material of NPs is covered with membrane derived from a cell including red blood cells, white blood cells, platelets, cancer cells, and stem cells [301,302]. Cell membranes coated on NP's surface contain receptors which enable the targeting of specific cells by considering the homotypic (identical cell types) or heterotypic (different cell types) adhesions. Moreover, cell membranes escape from the recognition of the immune system as these are self-antigens present on nanoparticle surfaces which enables to attain high targeting efficiency [302]. For the preparation of cell membrane-derived vesicles; parental cells are disrupted by using a hypotonic buffer. Subsequently, the mixture is subjected to centrifugation for the separation of cell membranes from other cellular components. Isolated cell membranes are cleaved through sonication or homogenization to attain nanovesi-

cles of the desired size (see Fig. 10). Cell membrane-derived vesicles contain a hollow core which is loaded with therapeutic nanoparticles through extrusion, sonication, or electroporation [300,303]. Moreover, certain bacteria secrete different spherical proteoliposomes with ~ 20 nm to ~ 400 nm diameter which are termed bacterial membrane vesicles (MVs). MVs are categorized into extracellular vesicles (EVs) derived from Gram-positive bacteria and outer membrane vesicles (OMVs) derived from Gram-negative bacteria.

These vesicles can be directly isolated and transformed into nanovesicles and subsequently employed for the entrapment of NPs [300,304,305]. MVs-based delivery systems attain cargo protection due to the shielding effect of MVs, controlled release via the barrier function of MVs phospholipid bilayer, and homotypic targeting potential due to the identical structures of MVs with bacterial membranes [305].

Angsantikul et al., developed a biomimetic drug delivery system for the treatment of Helicobacter pylori infection. Initially, plasma membranes of gastric epithelial cells (e.g., AGS cells) were isolated and embedded onto PLGA polymeric cores. AGS-NPs contain cell surface antigens which are employed by H. pylori to bind and colonize the host as a result these conjugates exhibited preferential adhesion with H. pylori. Subsequently, AGS-NPs were loaded with clarithromycin which exhibited proficient antibacterial potential and significantly reduced the H. pylori burden without imparting any adverse events [306]. Rifampicin is usually employed for the eradication of S. aureus and tuberculosis infections. However, this drug poorly penetrates across the double-membrane structure of Gram-negative bacteria, resulting in less effective antibacterial activity. Wu et al., prepared a biomimetic nano delivery system (Rif@MSN@OMV) containing rifampicin entrapped MSiNPs as core which was covered with OMVs isolated from Escherichia coli. MSiNPs served as a reservoir for rifampicin entrapment while OMVs covering enhanced the stability of MSiNPs and circumvented the premature drug release. Furthermore, OMVs promoted the uptake of MSiNPs only in E. coli, but not in S. aureus due to the homotypic targeting potential of OMVs. As a result, nano drug delivery system showed the complete eradication of E. coli at an equivalent rifampicin dose while bare rifampicin exhibited poor antibacterial potential. A single dose of this nano delivery system improved the survival rate of infected mice and demonstrated good biocompatibility [307]. Gao et al., fabricated biomimetic NPs in which extracellular membrane vesicles isolated from S. aureus were coated on PLGA NPs (NP@EV) while NPs embedded with PEGylated lipid bilayer (i.e., NP@Lipo) were taken as control. It was revealed that NP@EV is efficiently uptaken by S. aureus-infected macrophages as compared to NP@Lipo. Furthermore, NP@EV showed remarkably higher accumulations within S. aureus infected organs of the mouse relative to healthy mouse resulting in efficient eradication of bacterial infection. These findings refer that the extracellular membrane covering of NP@EV imparts the active targeting potential on NPs [308].

4. Limitations of targeted antibiotic delivery approaches and possible solutions

Antibiotic-siderophore conjugation is a promising strategy for targeted antibiotic delivery at the site of action, however, this approach is associated with certain limitations. For non-β-lactam antibiotic-siderophore conjugates, penetration across the inner bacterial membrane might be challenging, as a suitable linker is required for siderophore–antibiotic conjugates but difficult to find. A non-cleavable linker can cause loss of antibiotic activity if drug targets are specifically located in the cytoplasm, while a releasable linker is more appropriate which should be stable in the extracellular environment and capable of delivering antibiotics at the site of infection SPS:refid::bib309[309]. Moreover, this approach could generate potential toxicity and side effects due to a deficit of selectivity and uncontrolled cell penetration [60]. Further efforts are needed for the synthesis of natural siderophores and the development of linkers for antibiotic-siderophore conjugates [310].

Peptides can trigger immune responses and poorly penetrate across physiological barriers. In addition, they have a shorter half-life in vivo and are susceptible to denaturation as well as degradation [311]. Clinical applications of peptides are restricted due to their inherent characteristics including cytotoxicity, stability, and bioavailability [312]. These shortcomings can be avoided by the chemical modifications of peptides such as the substitution of L-amino acids by D-amino acids, cyclization of AMPs, and lipidation (linking fatty acid chains to the amine groups), which could prevent the breakdown of peptides by proteases. More strategies are still under development to circumvent the limitations of peptide conjugation [313].

Antibody-antibiotic conjugates are complex agents and their preparation is quite challenging. Further efforts are required to develop strategies that can enable the attachment of multiple antibiotics with a single antibody without producing aggregation issues and not having any negative impacts on the pharmacokinetic profile of AACs [314].

Prodrugs have demonstrated successes in clinical applications but not been widely employed on commercial scales [128], as prodrugs require delicate design to achieve the desired pharmaceutical properties and efficacy. In addition, prodrugs and inert prodrug motifs can occasionally be converted to toxic metabolites. Furthermore, prodrug activation sometimes utilizes cell constituents such as glutathione (GSH), resulting in GSH deficiency [315]. After lead optimization, prodrugs are usually taken into account as the last strategy if a therapeutic agent has remarkable pharmacokinetic issues. Based on the evidence that the number of marketed prodrugs has increased in previous few years, the prodrug approach should also be considered at initial phases of lead optimization. Moreover, further investigations should be carried out to restrict the pre-systemic drug metabolism and efflux-limited drug absorption in the case of prodrugs [316].

Liposomes possess certain limitations such as poor stability of vesicles in the bloodstream as well as during storage and less encapsulation efficiency (3–8 %) specifically for hydrophobic drugs. Lipids can degrade at high temperatures and are amenable to oxidation as well as hydrolysis [151]. Stability issues of liposomes can be overcome by adding antioxidants to inhibit the oxidation of phospholipids. Moreover, hydrolysis can be restricted by manufacturing liposomal formulations at neutral pH while liquid liposomal preparations should be freeze-dried [317]. Residues of toxic solvents are usually present in final preparations while large-scale synthesis of liposomes is expensive [152,153]. High membrane permeability and drug leakage from the lipid vesicles are noticed during the storge of liposomes. However, leakage can be avoided by increasing the phospholipid content with saturated and longer fatty acids chains and by the addition of cholesterol which form rigid bilayers [317]. In the future, development of liposomes with imaging probes can be helpful to attain real-time delivery and monitoring of biological signatures hence, resulting in better therapeutic outcomes [318].

Dendrimers are associated with potential limitations such as being genotoxic, triggering immune responses, producing oxidative stress, and imparting detrimental impacts on cellular components [140]. Toxicity is a major concern associated with dendrimers as all components of dendrimers including (core, surface groups, branches) are attributable to toxicity. Dendrimers mainly interact with biological membranes and rupture these

membranes leading to cell death [319]. Various strategies such as modification of dendrimers with biocompatible poly(ethylene glycol) can reduce toxic impacts of dendrimers [320].

It is highly challenging to purify and obtain **exosomes** in large quantities because mammalian cells liberate only a minute amount of exosomes, though exosome-mimetic vesicles could be an alternative strategy [321]. Purification of exosomes is a complex process and the yield is extremely low. This problem is being avoided by the synthesis of good manufacturing practice adherent mesenchymal stem cells-derived exosomes. The actual phenotype and morphology of exosomes can disrupt during purification as exosomes may form aggregates [169]. Generally, a centrifugation period beyond 4 h should be avoided to circumvent the formation of compact aggregates [322]. Scaling-up strategies of exosomes are still needed to develop [169].

Niosomes have certain limitations such as physical instability, aggregation, and hydrolysis of encapsulated drugs [323]. Niosomal formulations may drip from the site of application because of their liquid nature [324]. Fabrication of certain niosomes needs special types of equipments [325]. Moreover, sterilization of niosomes is a challenging task as sterilization heat is deleterious for niosomal preparations. Dry heat and steam sterilization are inappropriate for niosomes because Tc, which is comparatively lower than the temperature needed for heat sterilization, and may lead to the leakage of drugs from niosomes [325]. Further studies are needed to avoid these problems and to prepare niosomal formulations at a commercial scale [326].

Micelles possess certain limitations such as low drug entrapment efficiency [327]. Micelles may show stability issues in the physiological environment which circumvents their potential as a drug carrier. Micelle-based formulations undergo dilution when injected into the systemic circulation which promotes their disintegration resulting in premature release of entrapped therapeutics into the bloodstream, lowering the drug efficacy and mediating toxicity concerns. Despite many investigations on the modification of micelle structures, further studies are still required to address the stability issues without limiting the feasibility of micelles for commercial-scale production [328].

Polymer nanoparticles have poor entrapment efficiency for hydrophilic compounds which can be leaked during the emulsification process. PNPs possess cytotoxicity and degradation problems [329]. Scale-up preparation of PNPs is a quite challenging task while toxicological investigations of PNPs reported in the literature are still insufficient [330].

Metallic nanoparticles are thermodynamically unstable, toxic, irritant, and carcinogenic [331]. Inorganic materials including noble metals, silica, and carbon (carbon nanotubes) have poor biodegradation potential which limits their in vivo applications. It is expected that biodegradable inorganic materials possessing high biocompatibility e.g., calcium phosphate-based nanocarriers can overcome these limitations [332].

Carbon nanotubes are non-biodegradable, immunotoxic, tend to aggregate, and impart toxicological impacts on the lungs [333]. Practical applications of CNTs still need further efforts due to certain issues regarding their stability, aggregation, and bioavailability. Hence, further investigations are required to successfully apply CNTs for the eradication of bacteria [334].

Mesoporous silica nanoparticles are less-degradable as well as compatible and have poor drug loading potential. The presence of negative charge on MSiNPs is another barrier as the biological membranes also possess a negative charge which mediates repulsion and results in poor drug delivery potential. However, this shortcoming can be avoided by attaching polymers on the surfaces of nanoparticles [335]. There is an intense need to develop cost-effect sources of silica and other agents needed for functionalization. Moreover, potential hazard guidelines should be established to ensure safety precautions [336].

Quantum dots possess complex surface chemistry [337]. QDs exhibit aggregation when coming in contact with cells which interrupts the functioning of cells [338]. In a few cases, bioconjugation of quantum dots can cause problems in delivery to target cells. Metabolism and excretion of quantum dots are not completely understood, further investigations are needed on this aspect [339].

Stimuli-responsive drug delivery systems have a promising potential to overcome the limitations associated with typical antibiotic therapy including resistance development and toxic effects. However, this approach is still undergoing initial phases of development and multiple challenges are still needed to overcome.

pH-responsive drug delivery systems possess somewhat low specificity and selectivity because the pH value of pathogenic sites may not always be distinct from healthy sites [230]. Although, pH-responsive nanostructures show promising efficacy in vitro however, their in vivo performance may not be the same under complex pathological conditions. In vivo effectiveness of pH-responsive nanostructures may be limited due to the low intensity of stimuli. Breakdown of some pH-responsive chemical bonds needs a prolonged time span which restricts the response speed of nanostructures. From the expect of material design, extremely pH-sensitive polymers should be developed which can detect even minor differences between pathogenic and healthy tissues [332].

In the case of **enzyme-responsive** carriers, enzyme expression levels vary among patients so it cannot be confirmed whether enzymes are adequately expressed in the target population. Moreover, it is necessary to consider whether the breakdown of enzyme-responsive substrates and polymers is possible in the complex physiological environment of the living body [230]. A wide range of dysregulations are noticed in enzyme activities during various pathogenic conditions and even at different phases of one disease. Hence, an understanding of spatial and temporal patterns is required for developing effective drug delivery systems. Moreover, there are various overlapping substrates between closely associated enzyme families hence, specific designs should be considered for improving drug delivery efficacy [222].

Until now, **redox-sensitive** antibiotic delivery systems have been applied on liposomes, micelles, and dendrimers [340–343]. However, limited literature is available regarding redox-responsive nanocarriers targeted delivery of antibiotics. Synthesis of these nanocarriers is highly complex and requires multistep tedious processes [213]. Other problems associated with this approach include stability issues and premature drug leakage because cysteine and GSH reside in the extracellular environment. This issue can be avoided by employing several disulfide linkages generated by adjusting the number of disulfide cross-links [344].

UV–vis light is associated with safety issues, possessing poor tissue penetration power possibly due to high absorption and scattering across the skin which limits its application to superficial infections [39,235]. Moreover, laser power density above 1 W cm^{-2} imparts toxic impacts on human health. These issues can be avoided by employing near-infrared (NIR) lasers which have less absorption and scattering power but deeper penetration potential while imparting the least photo-toxic impacts [344]. Hence, the development of NIR irradiation-sensitive drug release systems should be promoted [39].

High-intensity **ultrasound** waves can impart harmful effects on tissues upon prolonged exposure [235]. Moreover, ultrasound waves are highly attenuated by bones. Currently designed ultrasound systems employ magnetic resonance imaging and enable the delivery of drugs across the skull to targeted sites of brain [345].

Magnetism is inconvenient because a complex apparatus setup is required to generate the magnetic field, which requires appropriate focus and intensity. However, this problem can be avoided by developing a cheap magnetic-field generator [39,235]. Moreover, magnetism is an expensive approach as noble metal agents are susceptible to degradation [344].

Temperature-sensitive drug delivery approaches may cause superficial tissue damage upon the application of heat to enable the drug penetration in deep tissues [235]. Temperature-responsive carriers are limited in their potential sensitivity to the surplus of stimuli that characterize a particular pathogenic condition. Hence, the actual potential of thermo-responsive systems can be realized by combining with other stimuli-responsive moieties. A great extent of advancements is notified in multi responsive drug delivery systems and more investigations are expected in near future [346].

A systematic approach addressing all the challenges of stimuli-responsive approach can pave the path for innovative therapeutic avenues [39]. Accuracy over the stimulus is needed to improve while external stimuli are required to attain tissue penetration in a better manner without causing any damage. Moreover, ultimate clinical translation of stimuli-responsive drug release needs comprehensive investigations of biocompatibility [344].

Bacteriophages are associated with certain limitations such as the absence of multiple chemically distinct amino acids on phages' surfaces can circumvent their modification potential [277,347]. Bacteriophages can interact with eukaryotic cells, pass through epithelial cells and cerebrospinal fluid thus leading to the misfolding of proteins. They possess a high risk for commensal bacteria and are capable to disrupt the resident flora. Other drawbacks associated with phages include high transduction potential, phages can carry toxin genes and virulence factor genes. Moreover, lytic phage transformation into lysogenic form can impair their potential to lyse bacteria, bacterial endotoxins, and exotoxins. Phage toxicity can trigger a robust immune response in the body leading to the release of cytokines [348]. These problems can be avoided by utilizing phages having a narrow host range, phages with the least transduction potential of bacterial DNA, phages that do not contain toxin genes in their genome, and phages that do not exhibit lysogeny, and by manufacturing purified formulations (free from toxins) of phages [348,349].

Erythrocytes possess alterations in composition and mechanical characteristics relative to synthetic carriers [287]. Hence, erythrocytes can exhibit some native alterations in drug loading potential while entrapped drugs can be leaked from erythrocytes. Moreover, some conjugated drug molecules can affect the physiology of these biocarriers. Erythrocytes require specific storage requirements as they are living cells and need to be carefully handled to avoid contamination [289,350–352]. The plasticity of erythrocytes is decreased during the entrapment process thus they are susceptible to mechanical and osmotic damage [287]. Loaded therapeutics can alter the physiology and pharmacokinetics of erythrocytes. Preparation of carrier erythrocytes requires a sterile environment as a result large-scale production of erythrocytes is a complicated process. This problem can be avoided by developing high output automatic tools [353]. Other problems associated with the use of erythrocytes can be avoided by improving the experimental methods, and by employing different mathematical models of carrier erythrocytes (CEs) to investigate the effects of the entrapped therapeutics on erythrocyte metabolism [353]. It is expected that we will notice rapid advancements in the coming era to design innovative drug delivery systems based on erythrocytes. Moreover, other plasma constituents such as fibrinogen, haptoglobin, and hormones should be investigated as drug carriers [287].

Large-scale fabrication of **cell membrane-derived vesicles** is a quite challenging task. Cell membranes are highly complex which hinders their synthetic production. The development of cell membrane-based therapeutic agents is a multi-step time-taking process which needs quality-control procedures. As a result, patients have to wait for cell isolation and product development, and their treatment plans may be delayed. However, such delays can be avoided by using allogenic (donor) cells which provide a readily available source of cell membranes for treatment when required. However, antigen matching should be carried out to circumvent host immune responses. Moreover, natural cell membranes are amenable to certain nonspecific chemical modifications [205].

5. Conclusion and future prospects

Antibiotics have served as effective agents for the treatment of various life-threatening infections. However, bacteria are becoming resistant to circumvent the effects of antibiotics. Furthermore, MDR pathogens are emerging at a faster rate than the development of new antibiotics. Hence, smart drug delivery systems are highly needed to combat resistant pathogens. The current review has explored a wide range of targeted antibiotic delivery systems which demonstrated the promising potential for site-specific antibiotic release. In most cases, antibiotic-entrapped drug delivery systems showed better antibacterial activity than free antibiotics. However, most of these drug delivery systems were investigated through in vitro studies. Detailed in vivo studies exploring the absorption, distribution, metabolism, and excretion of the biomaterials employed for the fabrication of drug delivery systems are still missing. These studies will help to estimate the effectiveness and biocompatibility of drug delivery systems inside the complex physiological environment of the body. Moreover, in-depth investigations are still required for mechanisms involved in site-specific antibiotic delivery.

The momentum for the clinical translation of targeted drug delivery systems is comparatively slow as a limited number of targeted antibiotic delivery systems have progressed into clinical trials. Currently, Arikayce™ liposomal preparation of amikacin completed phase II trials for the treatment of Bronchiectasis [354]. Vivagel is a dendrimeric antibiotic formulation of 1 % SPL7013 Gel which has completed phase III trials for the treatment of bacterial vaginosis [355]. Clinical translation of targeted drug delivery systems is quite challenging as surface functionalization is usually required which involves the attachment of various targeting agents. Hence, the preparation of targeted drug delivery systems is a laborious, multi-step, and complex process. Subsequently, it increases the cost and imposes issues for large-scale good manufacturing production. Effective clinical translation requires an interdisciplinary approach to design innovative protocols, assays and infrastructure for the preparation of site-specific drug carriers.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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