Antimicrobial Materials for Local Drug Delivery

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Abstract In a vast number of medical treatments, the local drug delivery is of prime importance to achieve a favorable therapeutic effect since it enhances drug bioavailability. These systems provide biological and chemical protection for drugs, reduce toxicity, increase the concentration at the site of interest, and avoid systemic exposure. The development of local systems is of great interest in both prophylactics and intensive therapies, and their formulation will depend on the characteristics of the drug and motives for actions pursued. This chapter describes the use of carrier systems, routes of administration, release mechanisms and methods, and site of action.

Keywords Local drug delivery · Antimicrobial · Stimuli sensitive polymers · Liposome · Micelle

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1 Introduction

Controlled drug delivery systems can be designed for temporal control, local control, or both. The first consists of continuous drug release in therapeutic doses without reaching maximum levels, thus avoiding the side effects produced by large drug discharges. These systems represent an advantage for substances, which are quickly metabolized or eliminated by the body, and for therapies that need the release of drug at a controlled concentration for long periods. On another hand, local drug delivery systems allow drug release in a specific place of the organism or target side, which has the advantages of decreasing drug toxicity, and increasing drug effectiveness because these provide a high concentration where is required and avoid systemic exposure (Alt et al. 2015). Localized release of antimicrobial drugs can help overcome some of the drawbacks of systemic therapy, such as low concentrations at the target site of the injured tissue, and administration to avascular sites. Most bacterial infections in the body tend to form biofilms, which lead to persistent and extremely resistant to antimicrobials infections, mainly due to the difficulty of penetrating the barrier of polysaccharides that cover them. The use of release systems allows greater penetration into the biofilm and increasing drug efficiency (Berlanga and Guerrero 2016; Prasad et al. 2020).

2 Mechanisms of Drug Delivery

Drug delivery can be controlled by various mechanisms such as dissolution, diffusion, osmosis, swelling, and erosion; this depends on the composition of the system, the loading drug, and the use environment. Delivery systems may show different release mechanisms simultaneously, but usually, one mechanism is predominant. For example, most of the release systems present a dissolution mechanism, nevertheless it rarely constitutes the main mechanism. The most studied mechanisms for local drug delivery are diffusion control, solvent control, and chemical control (Anand et al. 2020; Prasad et al. 2017).

2.1 Diffusion-Controlled Systems

Diffusion is a mass transport phenomenon, fundamental for many natural processes. It is defined as the movement of a solute from a region of higher concentration to an adjacent region of lower concentration. In 1855, Adolf Eugen Fick presented the quantitative description of this phenomenon. He considered the unidirectionality of diffusion and related the diffusion flux with the gradient in solute concentration (Fick's First Law), according to the equation:

$$J = -D\frac{\partial c}{\partial x} \tag{1}$$

where the diffusion flux (J) is the amount of substance per unit area, per unit time; $\frac{\partial c}{\partial x}$ is the concentration gradient with distance; D is the diffusion coefficient, which is a measure of the mobility of the individual molecules of solute in a dissolvent; and the negative sign indicates that the flow direction is against the concentration gradient (Bruschi 2015).

In diffusion-controlled systems, the release occurs by permeation of the drug from inside the device to the medium, and the release rate is controlled by the diffusion rate. Although the diffusion occurs in all release mechanisms, it predominates when other processes are not involved in the control of drug release or their contribution is negligible. There are two types of diffusion devices, deposit and matrix systems.

2.1.1 Deposit or Reserve Systems

Deposit systems consist of drugs encapsulated in permeable membranes (thin or porous), where the release is given by the diffusion of the drug towards the outside of the membrane by affinity with the solvent, under the influence of a concentration gradient, following Fick's first law. These systems are one of the most used to date and ensure a relatively constant release rate, but present difficulty to deliver high-molecular-weight compounds and are expensive, due to requiring strict control in the thickness and the membrane area, because a failure could produce a massive release and overdose poisoning. Reserve systems can be classified for having either a nonconstant activity source or constant activity source. In the first case, drug concentration in the reservoir is less than its solubility, so released drug molecules are not replaced, and the reservoir's drug concentration decreases with time. Otherwise, in a constant activity source system, the depot is loaded whit an excess of drug that allows replacing the drug released and maintaining a constant concentration for more time (Yang and Pierstorff 2012), Fig. 1 shows a diagram of types of deposit systems.

2.1.2 Matrix or Monolithic Systems

In monolithic systems, the drug is evenly distributed in the polymer matrix and the migration occurs by diffusion of the drug through the support (Fig. 2). The release depends on the drug load concentration, the nature of components, and the geometry of the matrix. There are two types of monolithic systems: solutions and dispersions, in the first case, drugs are dissolved in the matrix; while in the second case, drugs are insoluble in the matrix and found as dispersed particles (Siepmann et al. 2012).

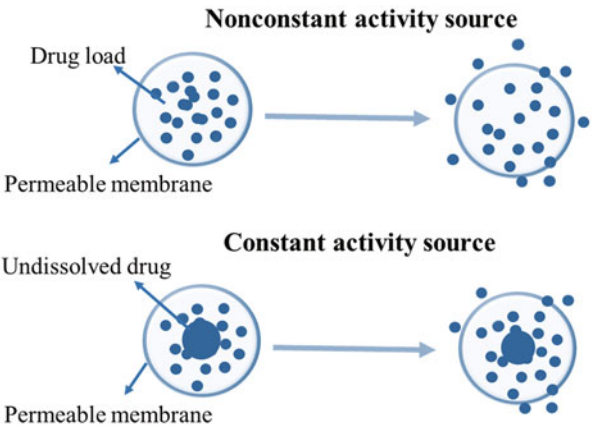

Fig. 1 Deposit systems with nonconstant activity and constant activity source

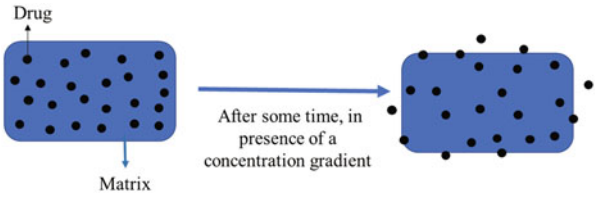

Fig. 2 Monolithic systems

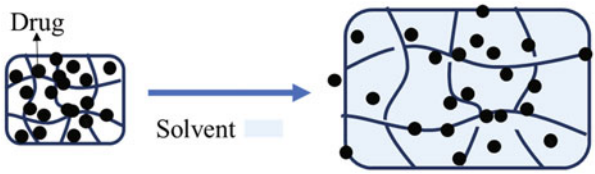

Fig. 3 Solvent controlled systems

2.2 Swelling Controlled Systems

In swelling controlled systems, the matrix, generally polymeric, absorbs solvent from the medium and swells affecting the release kinetics. The solvent enters the polymer and produces an expansion of volume and more space between polymeric chains, which is used to control the release (Fig. 3). The swelling mechanism is presented by sensitive polymers that change their swelling properties as a response to external conditions. The degree of swelling of the polymer depends on its hydrophilic/hydrophobic ratio, crosslinking grade, charge, and the ionic strength of the medium. The driving force for the swelling process is generally a balance of the osmotic and electrostatic forces favored by the entropy of the polymer in the solvent (Bruschi 2015).

2.3 Chemical Control Systems

Chemical control systems show active participation of the matrix in the release process because of the release occurs by matrix erosion as a result of a chemical reaction. This rupture or eventual formation of a weak bond or its ionization can occur by hydrolysis or enzymatic action, and the release rate will depend on the chemical characteristics of the bond and the conditions of the medium. The immobilization of the drug can be physical or chemical (Fig. 4). For physical immobilization, the drug is embedded in the matrix and released after its erosion. On the other hand, in chemical immobilization, the drug is chemically linked at the matrix´s structure and form part of its, so the drug is released when it erodes. An advantage of these systems is that do not need to be retrieval after full drug released because they are biodegradable and easily assimilated by the organism (Rezk et al. 2019).

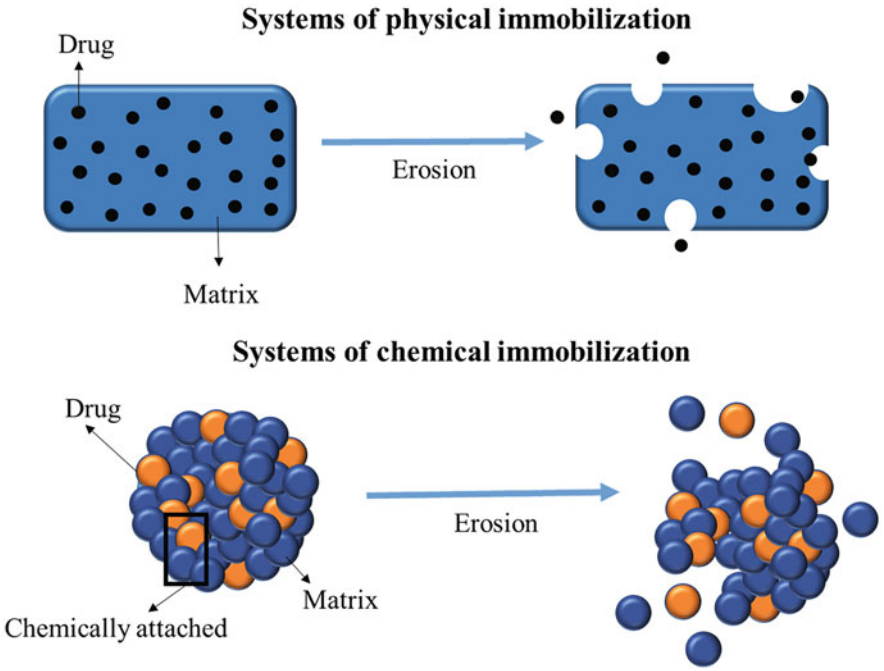

Fig. 4 Chemical controlled systems

3 Antimicrobial Drugs: Antibiotics

Antibiotics are antimicrobial agents, considered the most important drugs against bacterial infections. There is a wide variety of antibiotics among which stand out β-lactams, aminoglycosides, azoles, fluoroquinolones, macrolides, sulfonamides, and tetracyclines, which depending on their origin can be natural or synthetic (Figs. 5 and 6). This section describes general information about the chemical structure, mechanisms of action, and examples of active principles of these drugs.

3.1 β-lactams

β-lactams are cyclic amides of low molecular weight, with activity against Gram-positive and some Gram-negative bacteria. There is a wide range of antimicrobials as penicillin, cephalothin, clavulanic acid, and carbapenem types. Some bacteria strains can develop resistance against this class of compounds by enzyme synthesis, specifically a β-lactamase (Bush and Bradford 2016). Carbapenem is a sub-group

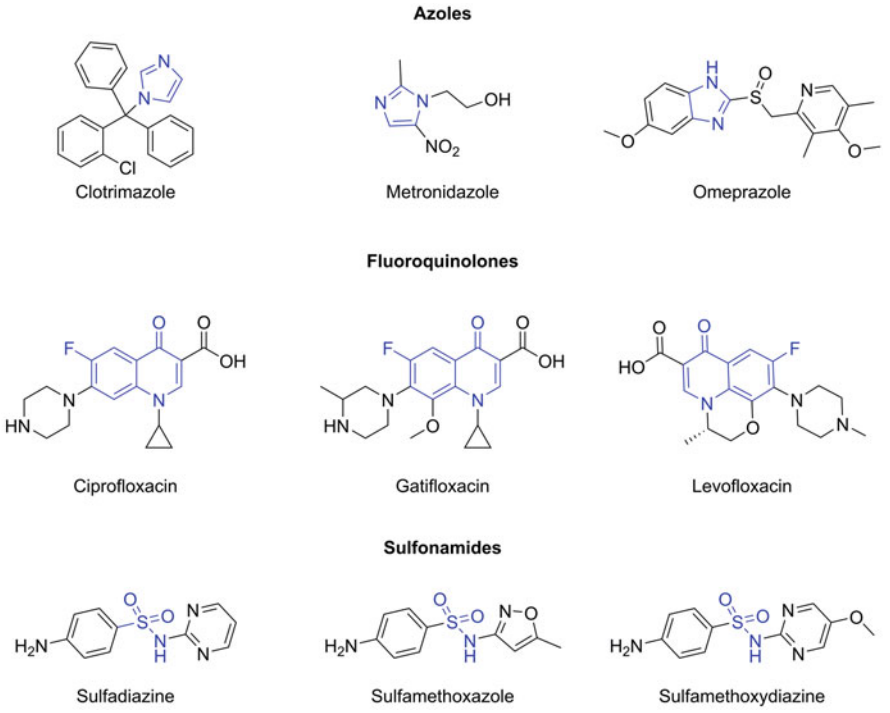

Fig. 5 Examples of synthetic antibiotics

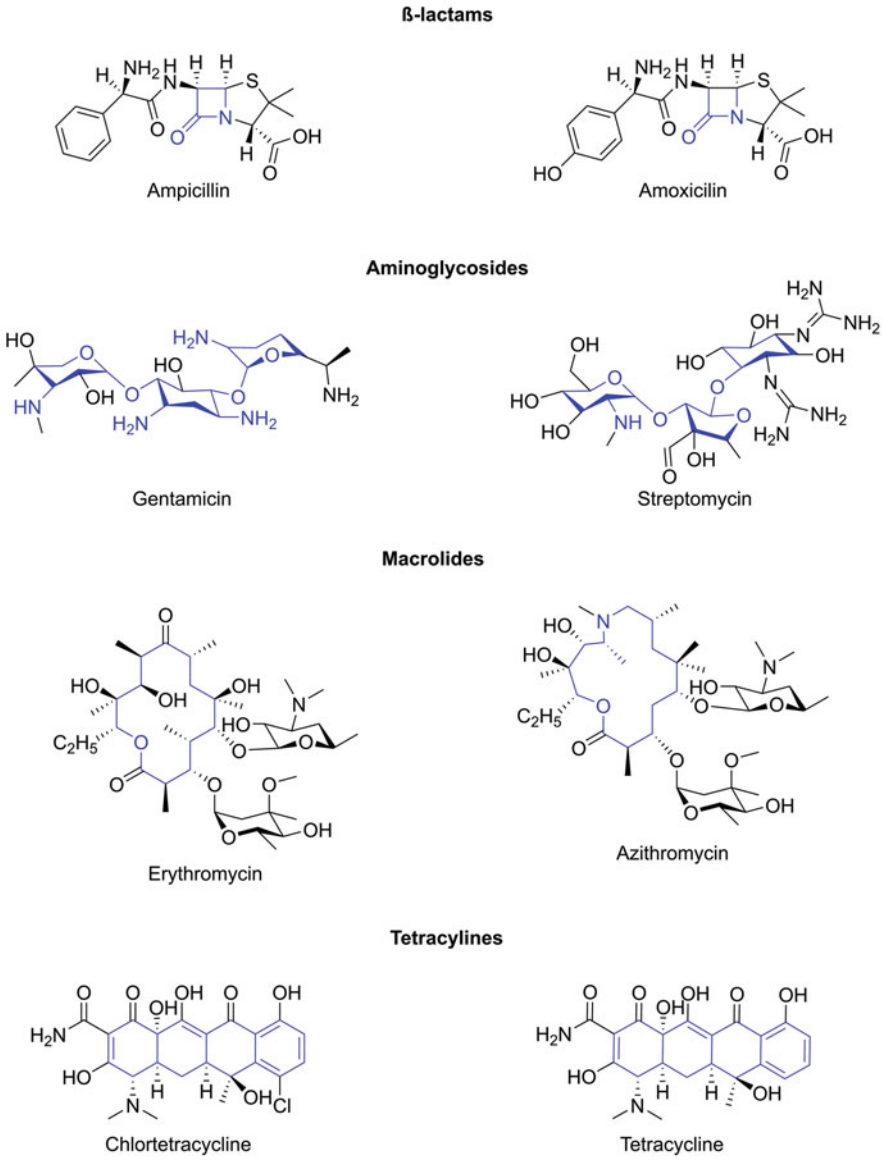

Fig. 6 Some examples of natural antibiotics

of broad-spectrum antibiotics with bactericidal activity characterized by their high resistance to beta-lactamases (Zhanel et al. 2007). The relatively low toxicity of β-lactams still makes them a good option.

3.2 Aminoglycosides

Aminoglycosides are natural origin antibiotics that are isolated from *Streptomyces* strains and contain in their structures two or more amino sugars. Some aminoglycosides of extending use are gentamicin, streptomycin, and neomycins. These are prescribed for the treatment of aerobic Gram-negative *Bacillus*, *Staphylococcus*, and *Mycobacterium tuberculosis*. Their mechanism of action includes protein synthesis inhibition (Kotra et al. 2000). A disadvantage of these antibiotics is that high drug concentrations are required to reach inhibition, and it is necessary to be careful with the dose because there is a small difference between a toxic dose and therapeutic effect dose. Another limitation of aminoglycosides is the administration, which must be via injection, otherwise, the body does not carry out a correct absorption.

3.3 Azoles

Azoles are compounds of low and medium molecular weight, which chemical structure contains one five-membered heterocyclic ring with one N and also another S, O, or N atoms. There is a vast number of bioactive molecules in this class of heterocyclic compounds, such as imidazoles, thiazoles, oxazoles, pyrazoles, isoxazoles, isothiazoles, etc. Some of those azoles can act as enzymatic inhibitors of cytochrome P-450 or through mechanisms involving reactive oxygen species (ROS) (Francois et al. 2006), the most important drugs of this class are mentioned below. The first example is the albendazole, an anti-parasitic drug, useful against giardiasis, trichuriasis, filariasis, neurocysticercosis or ascariasis, microsporidiosis, etcetera (Horton 2000). Another drug is metronidazole that is active against a wide range of microorganisms as *Bacteroides*, *Fusobacteria*, *Giardia lamblia*, *Clostridia*, *Eubacteria*, *Gardnerella vaginalis*, *Trichomonas*, *Entamoeba histolytica*, or *Balantidium* (Freeman et al. 1997). While, the omeprazole and its derivatives, including lansoprazole and pantoprazole, are used against nosocomial opportunistic bacteria like Gram-negative *Helicobacter pylori*, the bioactivity of these compounds is through a selective mechanism of proton-pump inhibition. Nonetheless, another group of azoles is mainly used in the treatment of fungal infections as tinea, chromomycosis, paracoccidioidomycosis, or cutaneous candidiasis. The most important commercial antifungal azoles are ketoconazole, fluconazole, voriconazole, clotrimazole, and itraconazole, which are effective against pathogenic fungi *Candida*, *Histoplasma*, *Coccidioides*, and *Blastomyces* (Mast et al. 2013).

3.4 Fluoroquinolones

These molecules are fluoroquinolones substituted with low molecular weight. These compounds are effective against Gram-negative bacteria. Mechanisms of action propose inhibition at DNA level, first- and second-generation quinolones act as inhibitors of the bacterial DNA gyrase, also the third- and fourth-generation quinolones act through a similar mechanism but more selective to the enzyme domain topoisomerase IV and can inhibit the growth of some Gram-positive bacteria (Hooper 1999). Some active principles are ofloxacin, moxifloxacin, levofloxacin, enoxacin, norfloxacin, gatifloxacin, and ciprofloxacin. Unfortunately, this group of drugs is contraindicated to patients with epileptic antecedents and limited for children and women during pregnancy.

3.5 Lincosamides

Lincosamides are a class of antibiotics that have in their molecular structure amides link to thio-sugars by peptide bonds. The first lincosamide, the lincomycin, was from a natural origin, but currently, it has been replaced by semi-synthetic derivatives as clindamycin and pirlimycin. These antibiotics show a bacteriostatic activity at low concentrations, but bactericidal activity at higher concentrations. Their action mechanism is the inhibition of protein synthesis of the 50S ribosomal subunit of the bacterial ribosome (Spížek and Řezanka 2017). And their range of use is against Gram-positive *Staphylococci* and *Streptococci*. Nevertheless, some bacteria strains can develop lincosamide-resistant, the most important type is the so-called MLS_B resistance, which consists of a monomethylation or dimethylation at an enzymatic level in the N6 exocyclic amino group of A_{2058} by a specific ribosome.

3.6 Macrolides

The first compounds of this kind were isolated from natural sources (e.g., erythromycin and azithromycin). Their general structure includes a macrocyclic lactone ring bonded to hexoses. Macrolides belong to a class of natural products named polyketides, and are mainly effective against Gram-positive bacteria genus as *Streptococci*, *Pneumococci*, *Staphylococci*, or *Enterococci*; Gram-negative as *Chlamydia*, *Bordetella pertussis*, *Haemophilus influenzae*, or *Legionella pneumophila*; and are used in the treatment of infections caused by *Mycoplasma pneumoniae*. The role of macrolides as antibiotics is inhibiting P-glycoprotein in bacterial protein synthesis during the translation process. Pathogen microorganisms are particularly susceptible to macrolide action during the replication process. Examples of synthetic macrolides are roxithromycin and clarithromycin drugs. Just as to other types of

antibiotics, microorganisms develop resistance to macrolides through enzymatic modification or the efflux pump mechanism.

3.7 Sulfonamides

It is a synthetic group of molecules derived from sulfanilamide, which show different pharmacokinetics and pharmacodynamics as well as a different mechanism of action, depending on the changes in their chemical structure that interact with different receptors (Hassanein 2019). Some sulfonamides show broad-spectrum activity inhibiting the metabolic cycles of the bacteria like *Streptococci* and *Bacilli*. Sulfonamides are indicated to treat urinary tract, eye, ear, intestinal, and lung infections. However, one part of the population becomes photosensitive after treatment or present an allergic reaction. Common antibiotic sulfonamides are sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfasalazine, and sulfamethoxydiazine. Due to sulfonamides are selective to the enzyme dihydropteroate synthase (DHPS) in the folic acid pathway, bacteria strains can mutate and develop resistance that way the sulfonamides lose their effectiveness (Sköld 2000).

3.8 Tetracyclines

This class of molecules has a polycyclic structure of four six-membered rings linearly fused, and functionalized with oxo, hydroxyl, and amine groups; some tetracyclines also contain halide, methyl, or amide groups. First tetracyclines were isolated from *Streptomyces* but currently, semi-synthetic derivatives are more used. Tetracyclines show bacteriostatic and bactericidal activity, through mechanisms of protein synthesis inhibition, and are easily absorbed via oral. Also, some of these broad-spectrum antibiotics such as tetracycline, chlortetracycline, oxytetracycline, minocycline, and doxycycline show also activity against protozoan parasites. Bacteria strains develop resistance by many paths as efflux pump, site mutation in RNA, or ribosomal protection.

4 Antimicrobial Pharmacokinetics and Pharmacodynamics

The interaction between antimicrobial drugs and the body produces different effects at the local and systemic levels. The reactions and action mechanisms of drugs from administration until eliminate are explained by their pharmacokinetics and pharmacodynamics parameters. The following provides information about each stage concerning these processes and the use of antibiotics.

Pharmacokinetics studies the movement of the drug within the body and the changes until it leaves the body. Pharmacokinetics has four phases: (a) absorption, (b) distribution, (c) metabolism, and (d) excretion (Levison and Levison 2009).

a. Absorption comprises the drug passage from the administration to the systemic circulation. Absorption depends on the concentration and the lipid-soluble/water-soluble equilibria at the molecular level. Drug transport in biological membranes may be direct (used for lipid-soluble antimicrobial), through pores (used for water-soluble antimicrobials) or by passive and active diffusion. Passive diffusion does not need expenditure of energy; on the other hand, active transport goes to counter-gradient and energy is required, this energy is obtained from the hydrolysis of ATP. Both facilitated diffusion and active diffusion use a transport protein to pass through the cell membrane. Finally, pinocytosis is another way in which high-molecular-weight antimicrobials penetrate the bacterial membrane, in this mechanism the antimicrobial is deposited in vesicles.
b. In the case of the drug distribution, the antimicrobial is already in the bloodstream and from there it is distributed to the target organ, at this stage, drugs may be free or protein-bound, acidic drugs often bond to albumin, and alkaline drugs to β-lipoprotein and acidic α1-glycoprotein. The free antimicrobial is the only one with an activity that is capable of diffusing into the target organ, while the protein-bounded antimicrobial is unable to pass to the target organ and acts as a reservoir. The antimicrobial-cell bond is reversible in a dynamic equilibrium, where liposoluble antimicrobials have the greatest opportunity to reach both extracellular and intracellular bacterial targets. Useful pharmacokinetic parameters for local dosage are (1) volume of distribution (Eq. (2)), (2) loading dose, (3) maintenance dose, (4) steady-state volume of distribution (Weiss 1984).

$$Vd = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} \tag{2}$$

c. In the phase of metabolism occurs the biotransformation of the drug, through a sequence of chemical reactions by enzymatic action. The purpose of this step is to turn the antimicrobial into a more water-soluble metabolite to be retained in the target organ. Metabolism takes place in organs such as the lung, kidney, digestive system, bloodstream, but is in the liver where most drugs are metabolized. The drugs metabolize in phases I and II reactions (Gibson and Skett 1996). In the phase I reactions or non-synthetic reactions (oxidation, reduction, hydrolysis, decarboxylation), metabolites can be active, inactive, or toxic; normally, a phase I metabolism may be necessary to form a prodrug (metabolized active drug). In phase II or synthetic reactions (acetylation, ethylation, methylation, conjugation), the drug or its phase I metabolite is combined with an endogenous substance, producing usually inactive metabolites. The second objective of metabolism reactions is to transform the drug into a more water-soluble substance

to continue the cycle in the process of urinary elimination by filtering through the kidney, through cytochrome CYP P450 mechanisms (White 2000).

d. Excretion is the elimination of drugs or their metabolites from the body (Kok-Yong and Lawrence 2015). The main liquid excretion is through the kidney and comprises three processes glomerular filtration, tubular secretion, and passive tubular reabsorption. The second route of elimination is hepatobiliary that is used to eliminate high-molecular-weight drugs or metabolites, which is produced by active transport and on some occasions, it is useful to treat biliary infections, in this case, the drugs are eliminated through the feces. Another route of excretion is pulmonary excretion, where the inhaled drugs are eliminated. Finally, the excretion maybe by secondary routes as sweat, salivary, or lacrimal. The capacity of an organ to eliminate a drug is variable, in general, the factors that alternate the renal or hepatic capacity have repercussions in the velocity of excretion drug interfere in the effect of the drug.

Pharmacodynamics studies the interaction of the drug with cellular receptors and the mechanisms of action through which it acts. Drugs may be classified as agonists (produce a response) and antagonists (block a response). Receptors, which are macromolecules responsible for chemical signaling between and within cells, play a principal role in antimicrobial activity. If the antimicrobial bonding a receptor (chemical target) occurs a change in its cellular function, this interaction may be reversible or irreversible, the response that receptor triggers may be changing in ion flux, enzyme activity, and protein production and structure. Antimicrobial efficacy and potency (minimum inhibitory concentration and minimum bactericidal concentration) are indicators of activity (Dafale et al. 2016). Overall, the efficacy is the capability of a drug to modify response processes and produce a biological response after binding to a receptor. In the case of antimicrobial efficacy, it is defined as the capability to inhibit proliferation or kill the pathogenic microorganism. The potency is a measure of drug activity; it is defined as the amount necessary to achieve an effect. Extrapolating to antimicrobials is the amount necessary (dose) to achieve the bacteriostatic or bactericidal effect.

5 Antibiotic Administration Routes

Antibiotic administration comprises enteral (oral), parenteral (intravenous and intramuscular), topical, ophthalmic, and ototopical routes. The correct choice of drug administration is as important as the choice of the antibiotic, being these factors to fight successfully against infections caused by microorganisms such as bacteria, fungi, protozoa, viruses, and other pathogens, which are responsible for various diseases that unbalance the homeostasis in the human body. Even when any person is susceptible to become afflicted by pathogens, the vulnerable groups such as children, major adults, and immunocompromised people are who have a higher risk to develop an infection and posteriorly to get sepsis, this can eventually diminish

Table 1 Advantages and disadvantages of drug administration routes

Route	Advantages	Disadvantages
Oral	Administration and dosage is easily controlled Controlled release	Effect and delivery are not achieved as fast as with other routes Unpredictable absorption Drug resistance developed faster
Intravenous	Delivery at the systemic circulation immediately	Preparation requires special cares and specialized personal Cannulae are prone to infection Drugs may cause local reactions.
Intramuscular	Fast delivery and effect Good absorption	Preparation requires special cares Injections hurt causing bruises
Topical	Localized delivery Non-invasive	Irritation Slow absorption Penetration limited
Ophthalmic	Localized delivery Fast delivery and effect	Irritation Penetration limited Limited drug available
Ototopical	Localized delivery No systemic side effects	Limited drug available May cause local sensitivity reactions

the quality of life and in the worst scenario to be fatal. Opportune therapy is critical to enhancing the chances of recovery because when the antibiotic is administered in time, it may be controlled and stopped the bacterial proliferation. Nevertheless, the use of antibiotics must be prudent and discretional to avoid or minimize complications and side effects. A therapy must focus on how antibiotics are administrated to perform the more effective, selective, and localized drug delivery. Table 1 shows the most important advantages and disadvantages of each route of administration.

5.1 Oral

The oral route is the most known and widely used. The antibiotic ingested by oral route pass to the intestinal system where it is posteriorly absorbed to the target organ. There are some therapeutics advantages such as easy ingestion, do not require previous care or cleaning in the zone of administration, and preparation and dosage can be well-regulated. Oral administration is mainly used in respiratory, gastrointestinal, dermatological, and genitourinary infections. This route has good penetration to almost any organ. Some bactericidal compounds show a good activity when they are administrated via oral, examples are lincosamides as lincomycin and clindamycin; macrolides as erythromycin; sulfonamides as sulfamethoxazole; or first-generation cephalosporins as cephalexin. However, some studies in mice have suggested that oral administration has a higher effect on antibiotic resistance amplification and development in gut microbiota (Zhang et al. 2013). Drugs coat with polymer or embedded in a matrix can protect and avoid the gastric release. For

example, plant-based polysaccharides have been used for the oral administration of colonic drugs for the treatment of infections. The colonic microflora secretes a series of enzymes capable of hydrolyzing the glycosidic bonds of the polysaccharides, which allows a localized release, by the erosion of the matrix (Paderni et al. 2012; Wilson 2013).

5.2 Parenteral

Parenteral drug administration is defined as any reconstituted powder, suspension, emulsion, or solution formulation supplied to the body by injection, which can be subcutaneous, intramuscular, and intravenous. Occasionally, parenteral dosage forms can also be administered by intrathecally, intracisternal, intraspinal, and intraepidermal injection to achieve a local effect (Birrer et al. 2001). This route is the most common for drug administration since it allows close interaction between the delivery system and the body. In the case of antibiotics administration, intravenous and intramuscular injections are preferred (Osmani et al. 2014).

5.2.1 Intravenous

The intravenous is the fastest way to reach the target, where a direct inoculation of the antibiotic is dosage by a needle into the bloodstream. The intravenous route is very useful for infections in the nervous system such as meningitis, myopathies, or osteotendinous system because practically the intravenous route targets any infected organ since it has a systemic effect on the human body (Harper et al. 2018). A prompt antibiotics administration through this route is adequate to counter bacterial proliferation and reducing the probabilities of sepsis. It is highly recommended to commence antibiotic therapy within the first hours after the diagnosis of sepsis and septic shock (Brown and Semler 2019). Nevertheless, a previous preparation and application by specialized personal must be effectuated, besides a meticulous and well-controlled dosage, rate, and composition must be watched out during all the therapy. Otherwise, an overdose or incorrect dosage may cause adverse consequences. Drugs such as carbapenems (include imipenem), lincosamides, second-generation cephalosporins as ceftriaxone, amikacin and gentamicin, and metronidazole, whose properties are not only antibacterial but also antifungal, are some examples of drug administrated by this route.

5.2.2 Intramuscular

The intramuscular route consists of the direct inoculation of the drug directly in muscle tissue. It is used to combat primary and secondary pathologies (Gordetsky et al. 2018). Antibiotics available for intramuscular injection are considered an

economical alternative to intravenous injections (under appropriate conditions) because the absorption of antibiotics through intramuscular is fast besides a previous preparation in the zone of application require less care as by intravenous (Milkovich and Piazza 1991). However, given the anatomical proximity to the neurovascular bundles, the connections with nerves and blood vessels may get damaged, possibly causing hematomas at the puncture site and even necrotic tissue.

Examples of infections that may be treated by intramuscular injection are from the bacterial origin Gram-positive bacteria like *Staphylococcus aureus*, responsible for abscesses and gastroenteritis; or *Streptococcus pneumonia* that causes pneumonia; and Gram-negative such as *Neisseria gonorrhoeae* responsible of gonorrhea and *Escherichia coli* associated with urinary infections. Also, the intramuscular route is used in treatment for diseases of the respiratory, skeletal, circulatory, and genitourinary systems. In general, this route of administration is prescribed in the body zone with good penetration of the active substance and with adequate irrigation at the site of inoculation. Using this route of administration, third-generation cephalosporins are dosed to treat pseudomonas infections, including folliculitis skin, tissue infections, or pneumonia.

Parenteral drug delivery systems offer an easy administration and if they are in situ, the number of applications may be decreased, at a lower dose, and minimizing side effects. Therefore, the development and improvement of new injectable systems have received much attention in recent years. For example, in the use of micelle (lipid nanoparticles) solutions for the administration of antibiotics and anticancer drugs (Lu et al. 2008); the injection of thermoplastic matrices that allow a local drug administration in the sites of surgical interventions (Schwach-Abdellaoui et al. 2002); or in the use of liposomes for controlled release such as liposomal amphotericin B, which is used for the treatment of fungal infection, being the first licensed liposomal formulation (Patel and Patel 2010).

5.3 Topical

The topical route of administration consists of applying the antimicrobial drug directly on integuments, in such a way that a local effect is produced only in the zone. It is mainly used for dermatological diseases as abscesses, cutaneous infections, or cellulite. Via the topical route, the drug can be absorbed for longer periods and in and controlled way, which is sometimes more convenient, especially for patients who are incapable to take drugs via oral. Thus, comparing the administration through the topical route with the oral and parenteral routes, the topical is the lesser invasive and decreasing the risk caused by ingestion. Most of the topical antimicrobials act with a bacteriostatic effect as 50S ribosomal subunit inhibitors such as fusidic acid, metronidazole, or clindamycin. Also, other common antimicrobials as neomycin, bacitracin, silver sulfadiazine, mupirocin, or polymyxin are applied topically (Thornton Spann et al. 2004). Another advantage of topical administration is that combo drugs with analgesics may be incorporated in the same medicine,

achieving a local effect, and without compromising the integrity of the patient. For example, topical administration of analgesics lidocaine or capsaicin (patches or cream), or antidepressants as selegiline (patches) act locally as receptors of ion channels (Leppert et al. 2018).

5.4 *Ophthalmic*

The ophthalmic administration aims to reach the receptors of the eye when occurs an ocular infection. Antibiotics are delivered in the form of eye drops, directly applied in the ocular globe, but also it is possible to find ophthalmic antibiotics in ointment or hydrogel. Ocular diseases, such as conjunctivitis, caused by the Gram-negative bacteria *Haemophilus influenzae* may be treated using erythromycin ophthalmic ointment or gentamicin ophthalmic solution. Although, it is estimated that only 5–10% of ophthalmic antibiotics cross the corneal barriers (Dubald et al. 2018), drug delivery by ocular route produces a better bioavailability in the target than via the oral route. Regarding ophtalmic administration, the chloramphenicol works through the inhibition of the 50S ribosomal subunit in bacteria strains as *Escherichia coli*, *Staphylococcus aureus*, or *Streptococcus pneumoniae*.

5.5 *Ototopical*

The otic route has a local effect on the area to be treated and no systemic side effects. The antimicrobial is placed on the ear canal producing bacteriostatic or bactericidal activity depending on the antibiotic type and dose administered. It is mainly used as an adjunct in pathologies such as acute otitis media that is associated with the etiological agents *Moraxella Catarrhalis*, *Streptococcus Pneumoniae*, and *Haemophilus Influenzae*. An example of antimicrobials administrated via this localized route is broad-spectrum fluoroquinolones such as ciprofloxacin (Mosges et al. 2011). However, many antibiotics are contraindicated via this route because can damage the ears. Ototoxic drugs include antibiotics as gentamicin, neomycin, streptomycin, and vancomycin.

6 Methods to Local Controlled Release

The release mechanism will depend on the release system, which is determined by the therapeutic requirements of the application and the objective of the drug, focusing on maximizing drug effectiveness and stability, and decreasing its toxicity and the manifestation of side effects. Localized release concentrates drug at the site of action instead of dispersing throughout the body, which improves the

effectiveness of the therapy. Many materials allow formulating this type of systems, among which stand out liposomes, micelles, stimulus sensitive polymers, and their combination.

6.1 Liposomes and Micelles

Liposomes are spherical vesicles constitute by a lipid bilayer, which is composed of cholesterol and natural phospholipids, due to which presents biocompatibility, biodegradability, and low toxicity, besides allows encapsulating hydrophobic and hydrophilic agents (drugs, nucleotides, proteins). Figure 7 shows the general structure of a liposome where each phospholipid presents a hydrophilic part, "head," consisting of a phosphate group, and two hydrophobic "tails" of fatty acids. The properties of the liposome will depend on its lipid composition, size, surface charge, and preparation processes. In general, unsaturated lipids with greater hydrophilic character produce more permeable and less stable bilayers, and hydrophobic saturated lipid's bilayers are rigid and impermeable (Akbarzadeh et al. 2013). For their high compatibility and versatility, the liposomes are widely used as a carrier in cosmetic, food, farming, and pharmaceutical industry, especially as a way to manage unstable molecules (Sercombe et al. 2015). Besides, liposomes can be functionalized to respond to specific chemical markers and external stimuli.

There are many methods for liposome preparation but all of them involve four stages. First, separation of lipids from an organic solvent, then dispersion the lipid in

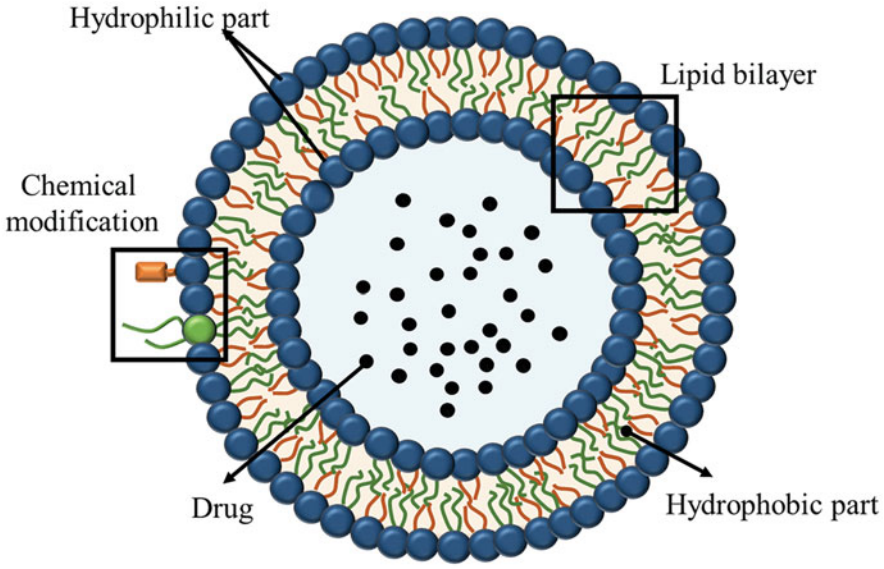

Fig. 7 Structure of a liposome

aqueous media, and finally, the purification and characterization of the product. Depending on the method, the liposome diameter can vary from 25 nm to 2.5 μm, and they may have unilamellar (single phospholipid bilayer) or multilamellar (onion structure) assembly. These parameters affect the durability and drug loading capacity of the liposome. Two ways are known for drug loading in liposomes: passive load, in which the drug is incorporated at liposome during its formation, and active load, where load occurs after liposome formation. The passive process is used for hydrophobic drugs, like amphotericin B taxol or annamycin, two antibiotics that have no permeability across the membrane (Daraee et al. 2016).

Some strong antibiotics need to be released into the cytoplasm or cell nucleus to have a greater effect. However, many of them have low permeability in the cell membrane making it difficult to admire. The release of these drugs through liposomes is a very attractive possibility, since allowing a direct attack to the site of interest. Kunisawa et al. developed fusogenic liposomes, which are conventional liposomes, functionalized with an inactive virus, in this case, Sendai virus, giving it the ability to release nanoparticles in the cell cytoplasm through the mechanism of fusion of the virus, which increases the concentration of nanoparticles in the cytoplasm compared to administration with conventional liposome, in in vitro tests. This type of gene functionalization of liposomes opens the way for devices capable of regulating intracellular pharmacokinetics and more effective carriers (Kunisawa et al. 2005). Liposomes are good alternatives as carriers since their interaction with cells occurs naturally, and they easily access it because of the similarity of their membranes. Although achieving cell differentiation is difficult, current researches are being advanced using a stimulus sensitive functionalization to control the site of release. Cancer or bacterial and fungal advanced infections therapies can be very toxic, and treatment efficiency is limited by low concentration of drugs that can be achieved without produce severe side effects. This is the case of doxorubicin HCl and amphotericin, two very toxic drugs that have shown good results to be administered with liposomes as carriers (Lopez-Berestein et al. 1985; Olusanya et al. 2018).

There are three types of liposomal drug delivery systems: conventional liposomes, which are formed by a lipid bilayer that can be cationic, anionic, or neutral which main disadvantage is that they present rapid elimination in the bloodstream, limiting their therapeutic efficacy. The second one, the sterically stabilized liposomes, generally are modified with hydrophilic polymers like polyethylene glycol (PEG) that improve the stability and increase the time of blood circulation (Ning et al. 2007). Finally, ligand-targeted liposomes are the more recent developed; these are modified to show selectivity over specific ligands (antibodies, peptides, proteins, carbohydrates) and have been studied as an alternative for intensive therapy where the selection of ligand-target depends on infection or cancer class and its location due to the expression of receptors is particular for each one of them (Saraf et al. 2020).

Micelles are systems constituted by amphiphilic units, which in aqueous solution produce a self-assemble core-shell structure, when their critical micellar concentration (CMC) is exceeded, allowing hydrophobic drug encapsulation (Kwon and

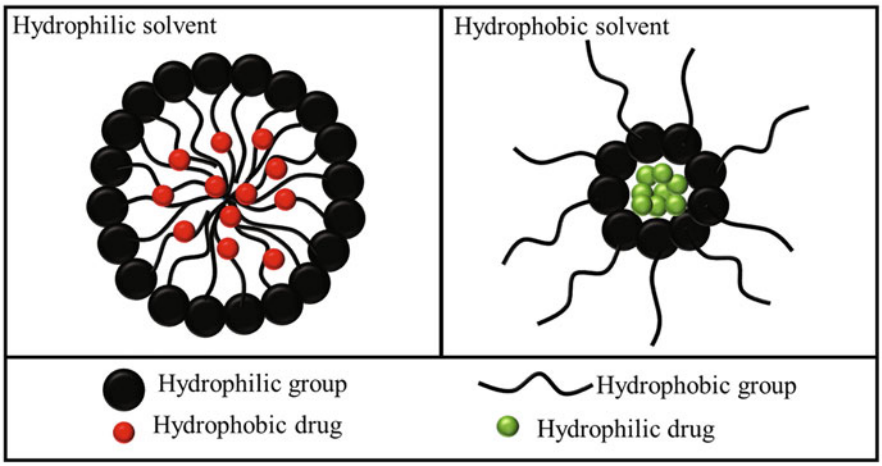

Fig. 8 Schematic structure of micelles in a hydrophilic and hydrophobic solvent

Okano 1996). Figure 8 shows the structure of micelles in hydrophilic and hydrophobic solvents, micelles can organize depending on the environment. These systems have a longer lifetime in the bloodstream and more load capacity than liposomes, however, the facility to penetrate membranes and biocompatibility are lower, and only can load hydrophobic drugs. The self-assembly process is thermodynamic and reversible. It is the product of an entropy increase by the liberation of the water that was around hydrophobic blocks; as a result, micelles are very stable systems over their CMC although dissociate below this (Gong et al. 2020).

Recently, it has grown studies about the use of micelles to improve the efficacy of some drugs since they have a local carrier behavior (Guo et al. 2020). Sonawane et al. designed polymeric micelles for vancomycin load, used an amphiphilic block copolymer, which contains a hydrazone bond cleavable by pH (Sonawane et al. 2017). Polymeric micelles were achieved with a CMC of 6 μg mL^{-1} and reached an entrapment efficiency of 39.61% with a 3.6% load. Showing an improved release of the pH-dependent drug and antibiotic activity against strains of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (Sonawane et al. 2020).

6.2 Stimuli Sensitive Polymers

Stimuli sensitive polymers or smart polymers can produce reversible changes in their conformation when be exposed to small variations in their environment. These variations may be physical such as temperature, light, magnetism, and electricity, or chemical such as pH, ionic strength, and presence of bioactive chemical species (antigens, enzymes, etc.) (Qiu and Park 2001). Smart polymers have been widely used for the development of local drug delivery systems since these may respond to

the environment in the target site (Alvarez-Lorenzo et al. 2016). Localized drug delivery systems for infections have the advantage that infection sites show a chemical environment that differs significantly from finding in the organism, characterized by a lower pH (<7.1) and overexpression of enzymes and toxins (Simmen et al. 1994).

According to their physical form, stimuli sensitive polymers can be classified in: free linear chains in solution, covalently cross-linked gels, and grafted chains (Kumar et al. 2007; Bajpai et al. 2016). The first are polymer chains that collapse after a stimulus is applied, which produces precipitation of polymer in solution forming a different phase. Many of these materials change at physiological conditions, minimizing invasive injectable systems for implants or scaffold, and they are widely used in bioseparation processes. Covalently cross-linked gels are microscopic or macroscopic networks that show a change in their separation when be subjected to a stimulus. They are the most investigated for their high storage capacity, which mainly depends on the porosity of the material. They can be synthesized with different pore sizes, generate interconnected pore systems or multi-sensitive interpenetrated networks (Maleki et al. 2016; Zhu 2019). Often, they are used for flow control, biological sensors, and drug delivery systems (Liechty et al. 2010). For example, Boppana et al. fabricated a pH-sensitive interpenetrated network of polyacrylamide-g-locust bean gum (PAAm-g-LBG) that allows intestinal targeted delivery of ketoprofen, in vitro studies, showed a release around 90% in phosphate buffer of pH 7.4 in comparison with 10.6% in pH 1.2 buffer, this system could reduce side effects of ketoprofen (Boppana et al. 2019). Finally, grafted chains allow the production of intelligent surfaces. In this case, the chains collapse on the surface, providing it with hydrophilic or hydrophobic characteristics depending on the conditions of the environment. The change produced will depend on the percentage of modification and the size of the grafted layer (Rubio et al. 2017).

6.2.1 Thermosensitive Polymers

Thermosensitive materials are polymers that are characterized by having a critical solution temperature (T_c), to which occurs a change from a hydrophilic to a hydrophobic state or vice versa. There is a conformational transition from the open coil to globule (Gandhi et al. 2015; Teotia et al. 2015). To present this property polymer structure requires having an amphiphilic composition with a balance in the proportion of hydrophilic and hydrophobic molecules. Hydrophilic part interacts with the solvent through intermolecular forces (hydrogen bridges, dipole-dipole, and ion-dipole interactions) allowing open coil structure, while hydrophobic allows the auto-association of the chains for the formation of globules during the transition (Le et al. 2018; Zarrintaj et al. 2019). Two cases of sensitivity occur lower critical solution temperature polymers and upper critical solution temperature polymers.

Lower critical solution temperature (LCST) polymers show hydrophilicity at temperatures below T_c, and hydrophobicity above it (Clark and Lipson 2012); this change in the properties of the material occurs for its transition of open coil form to

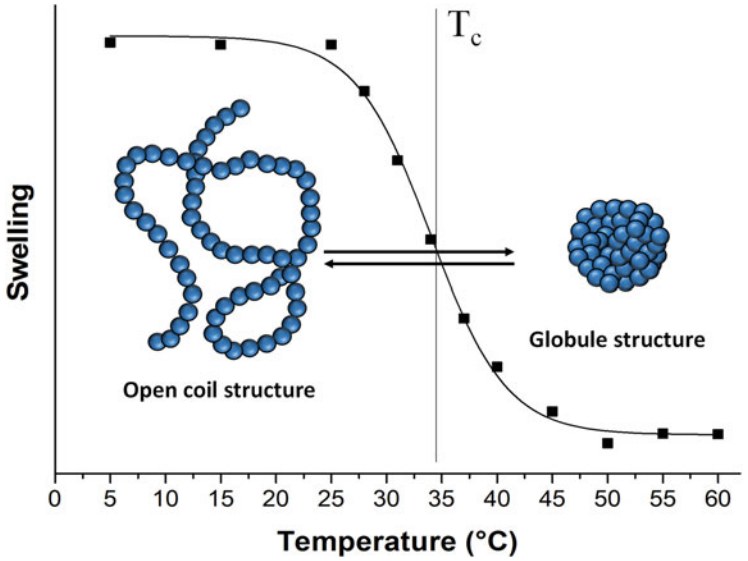

Fig. 9 Critical temperature of a LCST polymer

globular shape, as a result of an increase in the entropy of the system that exceeds enthalpy contribution of the water-polymer intermolecular interactions and leading stabilization to the system by intramolecular hydrophobic forces (Kamath et al. 2013). Figure 9 shows the model behavior of these materials. T_c only depends on the concentration or molecular weight under limit conditions (very diluted or very concentrated), under standard conditions it is related to the hydrophobic/hydrophilic balance in the polymer structure and can be modified by forming copolymers; the binding of hydrophilic monomers increases T_c while the binding to hydrophobic monomers decreases it (Gandhi et al. 2015). These materials are widely used in biomedical applications since their T_c is close to body temperature. Examples of polymers with LCST are poly(*N*-isopropylacrylamide) (PNIPAAm) (Do Nascimento Marques et al. 2015) and poly(*N*-vinylcaprolactam) (PNVCL) (Yang et al. 2020).

Higher critical solution temperature (UCST) polymers are insoluble at temperatures below T_c, but solubility increases at exceeded it. Owing to the forces that maintain the polymer-solvent interactions are broken, as a result, the transition from globular structure to open coil is observed (Seuring and Agarwal 2012). These materials are uncommon in biomedical applications since their T_c is normally at temperatures greater than 50 °C (Clark and Lipson 2012; Blackman et al. 2019). However, currently works look for the formation of copolymers that allow increasing the application range. Poly(methacrylic acid) (Illescas and Burillo 2009) and zwitterionic polymers (Yang et al. 2010) are examples of polymers with this behavior.

For antimicrobial local drug delivery, these systems have been used in implants where the corporal temperature is used as stimuli or as a coating of carriers capable of producing hyperthermia or together with laser irradiation-assisted photothermal therapy (Muñoz-Muñoz et al. 2015; Amoli-Diva et al. 2017). For example, Ramstad et al. synthesized photothermal response polymersomes using a diblock polymer of PNIPAAm and poly(lactic-co-glycolic acid), and gold nanoparticles. In which the gold nanoparticles embedded in the membrane of the system respond to infrared radiation generating highly localized hot spots that result in a rapid change of the amphiphilicity of PNIPAM, which produces holes in the membrane, triggering the release of the drug on the site of interest (Amstad et al. 2012).

6.2.2 pH-Sensitive Polymers

pH-sensitive polymers consist of chains with ionizable groups (cationic or anionic), which have charges depending on the conditions of the medium. Anionic polymers generally have acid groups in their structure, which undergo partial dissociation in aqueous solution. The grade of dissociation depends on the pH of the medium, acid strength, bond polarity, molecule size, and conjugate base stability. The dissociation process occurs because, under determinate conditions of the medium, the ion form is more stable by solvation forces (Rizwan et al. 2017). On the other hand, cationic polymers have structures with amines, which protonate at pH below their pKa. This process of protonation/deprotonation occurs as a result of pH variations and produces chains with equal charges that repel, triggering an increment in the swelling to reduce stress. So cationic polymers such as chitosan (Noel et al. 2008) and polyethyleneimine (Li et al. 2020) show a greater swelling at acidic pH (lower than their pKa). While anionic polymers such as carboxymethyl chitosan and poly (acrylic acid) (Pertici et al. 2019) swell at basic pH (higher than their pKa). This swelling change is very sharp, in narrow ranges of 0.2–0.3 pH units (Gupta and Damodharan 2019).

For antimicrobial treatments, pH sensitivity is one of the best tools, since infections might induce an acidic microenvironment (low pH) as a result of their metabolic activities and immune response, which allows a specific and local response of the material (Simmen et al. 1994). Taking this into account many studies have been performed (Cheng et al. 2015; Cao et al. 2019). Polymeric micelles of poly(ethylene glycol) (PEG) and poly(β-amino ester) were synthesized to be used as carriers of triclosan, a potent antibacterial, and fungicidal agent, for the treatment of staphylococcal biofilms. Poly(β-amino ester) is a pH-sensitive polymer, which undergoes protonation at low pH, close to that of infectious foci while remaining neutral at physiological pH. It was observed that the micelles achieved a penetration of the biofilm, accumulating inside due to electrostatic interactions and allowing the localized release of the drug by diffusion. Besides, the system maintains stability in plasma conditions and increasing the effectiveness of the treatment (Liu et al. 2016). Similarly, polymeric nanoparticles of 2-(dimethylamino) ethyl methacrylate (DMAEMA), butyl methacrylate (BMA), and 2-propylacrylic acid (PAA) showed

positive results for the treatment of cariogenic biofilms, from the pH-controlled release of farnesol, a hydrophobic antibacterial drug. This system reduced both the number and severity of carious lesions in comparison with free drugs. In addition, formulation directs the release and protects the drug (Horev et al. 2015).

6.2.3 Magnetic Sensitive Materials

Magnetic sensitive materials are ferromagnetic or ferrimagnetic materials that respond at an external magnetic field. For drug delivery systems exist two ways to use these materials magnetic hyperthermia and magnetic deformation of gels. In both cases, the formulation can be guided at a target site with a magnetic field (Gutfleisch 2001; Liu et al. 2019).

When ferromagnetic or ferrimagnetic materials are subjected to magnetization and demagnetization processes, in the presence of an alternating field, show heating by energy dissipation, this process is called magnetic hyperthermia (Obaidat et al. 2015). The loss of energy can be given for two phenomena: hysteresis and parasitic currents. Energy losses by hysteresis are the result of the difference between the energy transferred to the field during magnetization and the energy returned in demagnetization, and energy losses by parasitic currents are induced by variations in the magnetic flux and can be reduced with an increase in the resistivity of the material. Magnetic hyperthermia can be used as a local treatment for some types of cancer (Mallory et al. 2016), magnetic nanoparticles are put inside the tumor and exposed at the alternating magnetic field, which increases tumor temperature and can shrink them (Kumar and Mohammad 2011). However, the use of magnetic hyperthermia to stimuli a thermosensitive system is more common. In these systems, magnetic particles are placed in thermosensitive material (polymer, liposome, micelle) and when hyperthermia occurs, the release system is activated (Chen et al. 2019, 2020), Figure 10 shows a schema of this phenomena.

In general, localized hyperthermia treatment in combination with encapsulated drugs can result in higher accumulation of the drug in the target site (Kong et al. 2000; Farr et al. 2018). For example, chitosan microbeads crosslinked with polyethylene glycol dimethacrylate and embedded with magnetic iron oxide

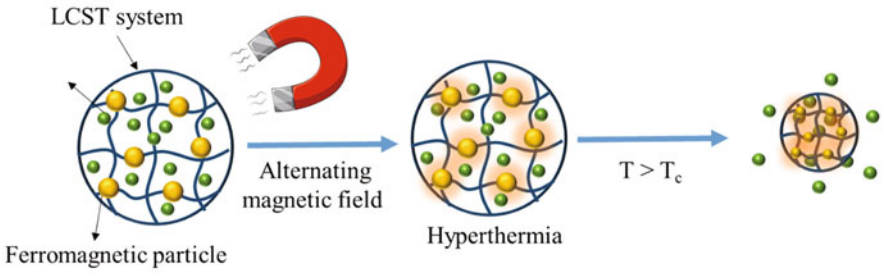

Fig. 10 Schema of a thermosensitive system stimulate by magnetic hyperthermia

nanoparticles were used for controlling vancomycin delivery and studying the influence of magnetic stimulation over this. The system showed greater release when subjected to an external magnetic field generating hyperthermia that destabilizes the polymer and allows greater diffusion of the drug (Mohapatra et al. 2018). Sirivisoot and Harrison also used iron oxide nanoparticles to generate hyperthermia, in this case, nanoparticles were embedded in polycaprolactone microspheres to increase the release of ciprofloxacin, showing improvements in *Staphylococcus aureus* inhibition (Sirivisoot and Harrison 2015).

Another way of using magnetism in sensitive stimulus systems is with magnetic gels, in which nanometric-sized magnetic particles are dispersed in a highly elastic polymer matrix. These systems are characterized in that the magnetic particles couple the shape of the elastomer to the external magnetic fields, since the forces acting on the particles are transmitted directly to the polymer chains, resulting in a deformation that occurs instantaneously and disappears sharply when apply or delete external fields (Zrinyi 2014).

6.2.4 Ionic Force Sensitive Polymers

Ionic strength sensitivity is a characteristic of polymers with ionizable groups in their chains, which also generate pH sensitivity. The ionic strength in a solution is a measure of the concentration of ions present. Ionizable groups at a certain pH dissociate forming ions that increase the ionic strength of the solution (Rasool et al. 2010). In the sensitive stimulus systems, whether cationic or anionic, an increase in swelling is observed by having ionized groups, since equal charges are generated that repel forming a larger interstitial space. By exposing systems to ion-rich environments, they can interact with chain ions by stabilizing them and decreasing swelling (Cabane et al. 2012). Another type of ionic strength sensitive system is zwitterionic polymers that have both anionic and cationic characteristics. These zwitterionic materials exhibit an agglomeration behavior because of attractive interactions between species with opposite charges, which can be decreased by ion presence. So, the polymer can be insoluble in deionized water but soluble in the presence of a critical concentration of electrolytes (Laschewsky 2014; He et al. 2016). Pimenta et al. studied the modification of intraocular lenses with zwitterionic polymers as an alternative for prolonged local administration of moxifloxacin for the prevention of post-operative acute endophthalmitis. Finding effective results against *Staphylococcus aureus* and *Staphylococcus epidermidis* until 12 days after the start, for poly acid 2-acrylamide-2-methylpropane sulfonic modified lenses by plasma-assisted graft, without being cytotoxic (Pimenta et al. 2017).

6.2.5 Chemical Sensitive Polymers

Chemical sensitivity is a phenomenon in which a receptor recognizes and identifies a chemical species through a set of structurally well-defined molecular interactions

(Singh and Nath 2013; Jin et al. 2019). Bacterial infections exhibit overexpression of specific enzymes, including β-galactosidases, alkaline phosphatases, nitroreductases, proteinases, lipases, phospholipases, and hyaluronidases, which are determinants for the survival of infections (Su et al. 2019). This characteristic allows the localization of infectious focus, so they are used to trigger chemical sensitive drug carriers.

There are few studies about these systems but recent reports show them in a good choice (Pornpattananangkul et al. 2011; Xiong et al. 2012; Li et al. 2014). For example, a recent study shows a photosensitive metal-organic framework (MOF) system loaded with Ag ions and coated with hyaluronic acid (HA) as an antimicrobial alternative. The MOF was synthesized with 5,10,15,20-tetrakis (4-methoxycarbonylphenyl) porphyrin (TCPP) as ligands and Zr_6 groups as metal nodes, due to its high porosity, this structure allowed the load of an antimicrobial agent (Ag). Finally, the coating of HA gives high biocompatibility to the system, and in the presence of bacteria with high secretion of hyaluronidase, it is degraded and allows the release of Ag^+ ions that inactivate them in a more efficient and focused way (Zhang et al. 2019). Following the same path, Li et al. synthesized polymeric vesicles sensitive to β-lactamase and G amidase (important enzymes overproduced by different pathogens) from amphiphilic copolymers, consisting of a hydrophilic PEG block and a hydrophobic block, which contains a degradable backbone by the target enzyme, to be tested as carriers of various antibiotics, through an erosion controlled release (Li et al. 2016).

7 Targeted Drug Delivery System

As mentioned throughout the chapter, both localized delivery systems with the method of administration will depend on the target organ. To improve the treatment of infections in organs that are difficult to access by the systemic route, different alternatives have been studied, below are presented some specific delivery systems for treatments in the lungs, brain, and eyes.

7.1 Lung-Specific Antibiotic Delivery

Antibiotic administrated by inhalation allows a localized control increasing the bioavailability in the respiratory tract. This method has been used since the 1940s for the treatment of chronic infections with the use of aerosol formulations. Currently, some antibiotics are accepted by the FDA for use by this route, among which are amphotericin (liposomal form), colistin (solution and dry powder), and tobramycin (solution and dry powder) (Quon et al. 2014).

Additionally, inhalation treatments have been developed, for example, with levofloxacin for advanced cystic fibrosis, and liposomal amikacin for the treatment

of pulmonary disease of the *Mycobacterium avium* complex (Geller et al. 2011). These inhaled systems are under continuous improvement, for example, Reiter, et al. have studied the use of allicin, a natural antibiotic with a low bioavailability when is administrated via oral, for the treatment of lung infections, through an in vitro pulmonary platform, which allowed to accurately model the exposure to medications, they found that the model has the potential to determine the dosage regimes for bacteria that have different resistance to individual antibiotics, which would help in the development of better treatments (Reiter et al. 2020).

On the other hand, Falciani et al. manufactured a nanosystem consisting of the SET-M33 peptide captured in dextran nanoparticles, this peptide is a synthetic antimicrobial-resistant to degradation in biological fluids, the system proved to be effective against *Pseudomonas aeruginosa* with in vivo experiments with a mouse model of pneumonia, the system also showed a longer pulmonary residence time than the aerosolized peptide (Falciani et al. 2020).

7.2 Brain-Specific Antimicrobial Delivery

Infections of the brain are mainly from bacterial origin but also from viruses or fungi vectors of high risk, which treatment is especially tough. Many antimicrobials may target the brain tissue with a different degree of effectiveness, the main classes of anti-infectives with a certain degree of activity into the central nervous system are β-lactams, aminoglycosides, fluoroquinolones, macrolides, tetracyclines, oxazolidinones, metronidazole, rifamycins, sulfonamides, glycopeptides, peptides, antiretrovirals, antifungals, and anti-parasitic drugs (Nau et al. 2010).

One of the most relevant problems related to antimicrobial administration is the need to reach penetration in the nervous central system and keeping the integrity of the blood-brain barrier, which is an indispensable requirement for efficient delivery and to avoid possible side-effects. Intrinsically, some antibiotics may produce severe effects that trigger the development of neuropsychiatric disorders, particularly when administrated at an early age. For example, a study in mice during the perinatal period showed that small doses of penicillin provoke adverse effects of long-term in the progeny, said adverse effects are prolonged anxiety, aggression, and reduced social behavior (Leclercq et al. 2017).

Nevertheless, due to the low permeability of some hydro soluble antibiotics in the blood–brain barrier (Neuwelt et al. 1984), the treatment of infections in the central nervous system requires an administration of drugs locally (Slavc et al. 2018); otherwise, a non-local administration may yield to an ineffective therapy due a low bioavailability (Xie et al. 2015). These issues may be treated using intracerebroventricular devices that allow a direct administration, the use of these devices may help to control the dosage of antimicrobial by slow bolus injection in an isovolumetric delivery. For example, an implanted intracerebroventricular device eases the therapy, making it convenient for the healthcare of patients with chronic treatments (Slavc et al. 2018).

Additional menaces after infection in brain tissue may arise, for example, in neurocysticercosis (NCC) that is originated by a parasite with a heteroxenous life cycle, it causes the most damage in the human brain tissue by the formation of larval cysts, the vector is the pork tapeworm (*Taenia solium*). Being the risk of death is latent, no matter if the cysticidal is administrated in time, because during the posttreatment phase, an inflammatory response may occur. Therefore, the combination of drugs such as anti-inflammatory, anti-tumor necrosis agents, and/or corticosteroids work better throughout the therapy (Mahanty et al. 2017).

Overcoming the concerns associated with drug delivery to the brain may be solved by developing materials, such as lipid nanoparticles, liposomes, dendrimers, poly dendrimers, or polymeric nanoparticles; in which stimuli-responsive properties are exploited (Bors and Erdő 2019). A concrete example is the nanomaterial of PEG/cholesterol micelles of average diameter smaller than 180 nm and loaded with ciprofloxacin, which was specifically designed to penetrate the blood–brain barrier under simulated physiological conditions (pH 7.4 at 37 °C) (Liu et al. 2008).

7.3 Ophthalmic-Specific Antimicrobial Delivery

The eye is an organ which function is vital to perceive the environment, but due to its partial exposure to the outside, it becomes susceptible to form microbial biofilms, this is particularly true during surgery processes. In this section are revised some aspects related to bacterial infections and local antimicrobial therapy in ophthalmic treatments.

Antibiotics are widely used during ophthalmic surgery in both pre-operative and post-operative because the organ is prone to infection as a result of its exposure. A common post-operatory issue associated with the optic organ is endophthalmitis. This inflammatory response to ocular surgery may produce irritation, hyperemia, chemosis, lid edema, and/or blurred vision.

The most severe cases are also complicated with hypopyon or vitritis because of an unfavorable recovery. Exposure to bacteria is the main responsible for these complications, among the more pathogenic there are *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Bacillus sp*., and Coliforms (Starr 1983). Specifically, due to the low penetration of antimicrobials administered via topical, systemically, or by periocular injections, an alternative as the intravitreal injection is indicated to avoid endophthalmitis.

Although intravitreal injection has inherent disadvantages as an invasive maneuver, being the cause of retinal toxicity, the balance ratio, among pros and cons, favors the administration of antimicrobials via intravitreal injection (Baum et al. 1982). Medical studies have proved that the administration of antibiotics during the pre-operative stage reduces significantly the probability of infection (Allen and Mangiaracine 1974). Even with the adverse effects of antibiotics during local administration, therapeutic prophylaxis is highly recommended over a post-

operatory systemic administration. Despite some examples of ophthalmic antibiotics as chloramphenicol, which causing aplastic anemia (Fahmy 1980).

The degree of success for containing bacterial proliferation and complications derived will depend on the correct choice of antibiotic. Local administration of wide-spectrum antibiotics as trimethoprim and polymyxin B (a natural macrolide) may help to treat the most bacterial infections associated. Also, penicillin antibiotics as ampicillin, amoxicillin, cloxacillin, dicloxacillin, and penicillin G may be applied via subconjunctival or topical (Lesar and Fiscella 1985). Nonetheless, it is more extended the use of fluoroquinolones like ciprofloxacin, norfloxacin, and ofloxacin, also these options are available of local administrations and helpful of intraocular infections, these antibiotics act by inhibition of bacterial enzyme DNA gyrase as well as by other intracellular mechanisms.

8 Conclusion

The next generation of antimicrobial materials are double-purpose, the first is to satisfy the function for which they were designed and the second is to achieve a local antimicrobial delivery. Therefore, these systems provide better opportunities to carry and release the antimicrobial in the target organ, either during intensive or prophylactic infections treatment. Besides, they are designed to overcome the inherent limitations of pharmacokinetics and pharmacodynamics of systemic administration. Strategies for achieving antimicrobial materials include modifying the shape and size of metallic or lipid nanoparticles, finding the right balance of solubility between liposoluble and hydrosoluble, and endowing the material with stimuli-responsive features (pH, temperature, magnetic or photo responsiveness). Antimicrobial materials aim to improve pharmacological parameters of selectivity and efficacy, while are minimized side effects. Local delivery systems are especially useful for manufacturing biomedical devices, sanitary materials, anti-biofilms, and antibiotic systems.

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