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Sustainable antibiofilm self-assembled colloidal systems

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Biofilms find a favorable environment in industrial processes such as food, cosmetic, or medical prosthesis and devices, being responsible of approximately 80% of human bacterial infections. Prevention and/or eradication of microorganism' films is a worldwide need. There is an increasing interest on the finding and use of novel antimicrobial compounds without side effects. An additional challenge is to fight the antimicrobial resistance that some bacteria and microorganisms develop with traditional antibiotics. Also, in recent years, sustainability and natural source of the antibiofilm chemical principles are also a priority demand. Colloidal systems such as vesicles, particle suspensions, or emulsions are becoming increasingly useful tools for biocompound delivery due to their ability to protect the compound encapsulated against external factors and their possibility to be used as target delivery systems. During the last decade, these types of systems have been widely used for the encapsulation of traditional and novel compounds with antimicrobial properties. The present study summarizes different types of natural compounds tested against several types of bacteria and their feasibility to be encapsulated in different types of colloidal systems.

KEYWORDS
biofilms, colloids, antimicrobial activity, encapsulation, nanocarriers, antibacterial

1 Introduction

Microorganisms can form very complex ecosystems, called biofilms, which are able to colonize in all kind of environments. Approximately 40%–80% of bacterial cells reside on biofilms (Flemming and Wuertz, 2019). Formation of biofilms and their persistence may have a harmful effect on public health and its corresponding economic impact.

Biofilms find a favorable environment in industrial settings involving food processing: dairy products, meat, and seafood, etc. These facilities often provide suitable conditions for bacteria, such as source of nutrients, temperature, or humidity, thus enabling them to grow on food contact surfaces, processing machinery, and other equipment. Therefore, biofilms constitute the main cause of food spoilage and complicate their complete

FIGURE 1
Types of commonly colloids used as antimicrobial carriers. Created with *BioRender.com*.
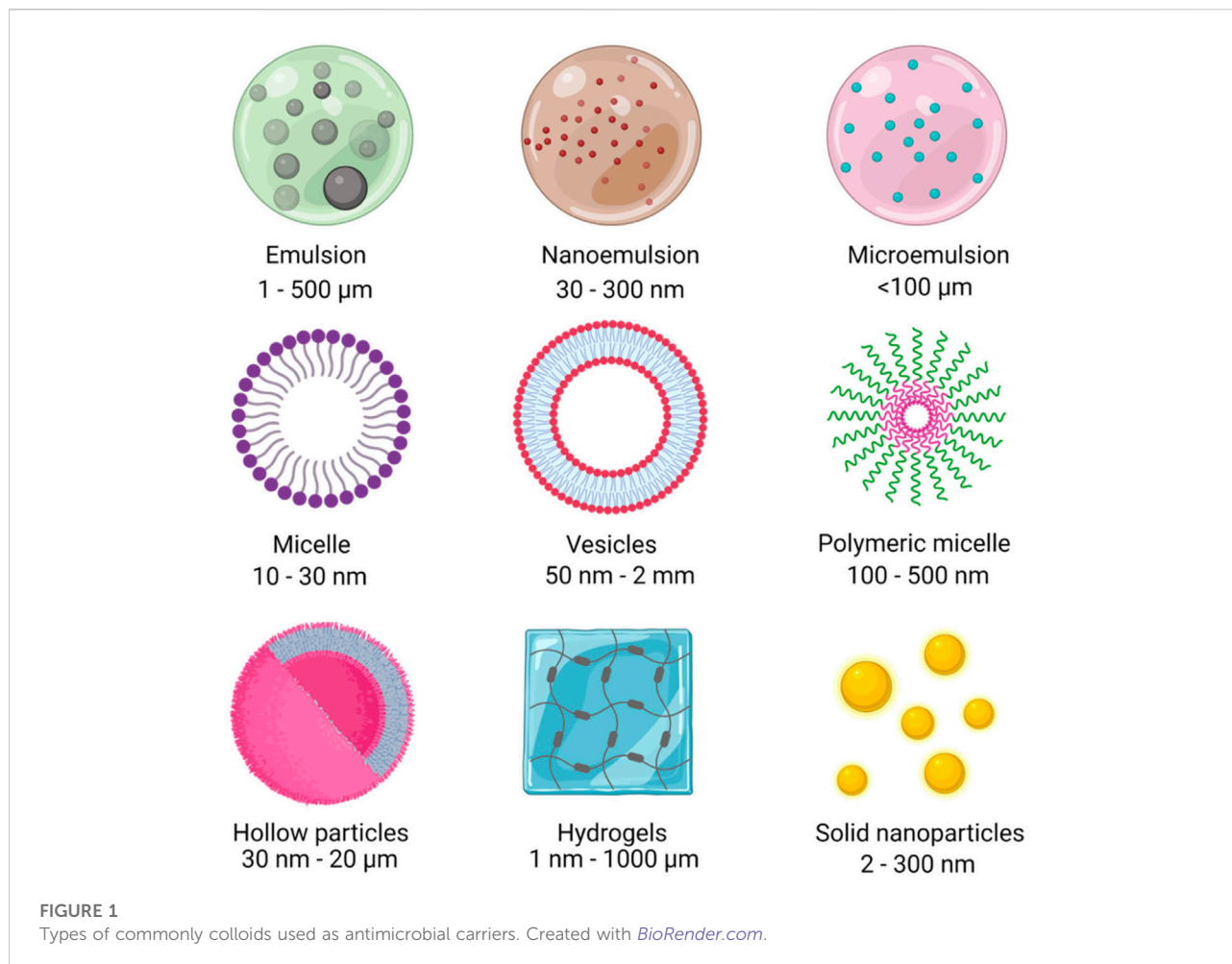
eradication in the industry. For a detailed review on the impact of biofilms on the food industry, see Galié et al. (2018) and the references therein.

In the clinical field, biofilms are estimated to be responsible for approximately 80% of human bacterial infections, including persistent chronic infections (Attinger and Wolcott, 2012; Römling and Balsalobre, 2012). They can develop on the surface of medical devices: catheters, pacemakers, implants, and ventilators. Furthermore, the formation of biofilms provides greater protection against chemical agents, such as disinfectants, biocides, or antimicrobials. In this sense, antimicrobial resistance is considered one of the major medical threats (and up to date, uncontrollable).

The prevention and eradication of biofilms is critical in both food industry and medical sectors. Current antimicrobial disinfectants (e.g., alcohols, aldehydes, and strong oxidants, etc.) have residual effects and produce harmful by-products. In addition, bacteria develop resistance to biocides (Abdallah et al., 2014). As a result, there is an increasing need for new,

green, and sustainable technologies to counteract the antimicrobial resistance.

Colloidal drug delivery systems have been developed as alternative mechanisms for administration with a controlled release of biocompounds, which increase film eradication and enhance antibacterial compound effects on time compared to the effect produced by the non-encapsulated biocompounds. Different types of colloidal systems can be found in the literature, emulsions being one of the most frequently found systems. However, other types of colloids and nanocolloids can be found in the literature, as is the case of vesicles, that have been already clinically tested (Huang et al., 2022).

Most types of colloidal systems used are surfactants based, such as niosomes that are a type of vesicles mainly formed by non-ionic surfactants (Marchianò et al., 2020). Moreover, it is also possible to find some other types such as surfactant micelles or surfactant-stabilized emulsions, nanoemulsions, and microemulsions.

There are other types of colloidal systems that are based on other types of compounds, for example, polymers or other inorganic materials, as is the case of hydrogels of different nature or emulsions, micelles, and vesicles stabilized by the presence of these compounds (Ahmadian et al., 2022).

However, other sustainable systems can also be found such as natural biodegradable polymers used to prepare nanoparticles (NPs). These natural polymers could be from different natural sources of such proteins or starch (Li et al., 2018).

The present study summarizes the recent works regarding antimicrobial activity biocompound encapsulation using different types of colloidal carriers. The types of biocompounds encapsulated in several types of colloidal systems are described, followed by the description and preparation commonly used for colloidal system preparation. Figure 1 presents a schematic diagram of the most commonly found colloids used as antimicrobial carriers.

2 Natural antimicrobial compounds

The encapsulation process of one substance, in this case the antimicrobial compound, consists of trapping into another one, giving rise to soft particles with dimensions lying in the nano-, micro-, or millimeter scale (Zanetti et al., 2018).

The main antimicrobial natural compound that has been encapsulated in recent years is curcumin, a natural dye that is obtained from plants of Curcuma longa species. Curcumin has shown to be antioxidant, anti-inflammatory, anticancer, antimicrobial, and useful in photodynamic therapy. However, curcumin has a low solubility in water and low bioavailability, and it is barely absorbed and even when it does, it is eliminated quickly from the body. Being only soluble in certain organic solvents makes it difficult to use curcumin as a therapeutic drug (Trigo-Gutierrez et al., 2021).

Another natural compound with antimicrobial, antimutagenic, anticancer, and antioxidant properties is vanillin, which is extracted from the pods of the vanilla flower. However, most vanillin is produced synthetically. Only 1% of vanillin is naturally derived from vanilla, and the rest is synthesized by chemical processes because it is more economically profitable. The main problem with vanillin is its short shelf life (Calva-Estrada et al., 2018).

Other natural compounds that have been proven to inhibit the growth of bacteria (both Gram-negative and Gram-positive) [1], fungi, and yeast are essential oils (EOs) of different plants. The International Organization for Standardization (ISO) defines an EO as a "product obtained from a natural raw material of plant origin, by steam distillation, by mechanical processes from the epicarp of citrus fruits, or by dry distillation, after separation of the aqueous phase—if any—by physical processes" (International Organization for Standardization,

2014). The main limitation to these types of compounds is volatility and hydrophobicity (Ríos, 2016; Maes et al., 2019).

Another alternative to antibiotics is the use of metallic microparticles or nanoparticles. They inhibit the proliferation of the most resistant strains by targeting multiple biomolecules (Slavin et al., 2017). The four main mechanisms for this antibacterial activity are: 1) direct contact with microbes, 2) formation of an ionic state, 3) production of reactive species (ROS), and 4) penetration into the inner environment of the bacteria (Zhai et al., 2022). This kind of nanoparticles rapidly agglomerates in a biological medium, affecting their antimicrobial activity (Sharma et al., 2020).

These common problems for these antimicrobial agents can be solved by using encapsulation techniques, which improve their handling, physicochemical and microbiological stability, and release (Hemmati et al., 2021). Table 1 shows some recent antimicrobial studies, which discuss about encapsulating the aforementioned main antimicrobial compounds.

In relation with the encapsulation of curcumin, Rahbar Takrami et al. studied the inhibition of resistant *P. aeruginosa* strains by combining curcumin-loaded micelles with ciprofloxacin treatment at a lower concentration than the minimum inhibitory concentration (MIC). One half of MIC of ciprofloxacin together with encapsulated curcumin at a concentration of 400 µg/ml induced bacterial death up to 50% in the isolated strains. This is due to the downregulation of *mexX* and *oprM* genes, which are involved in efflux pump systems, one of the main mechanisms responsible for bacterial resistance in Gram-negative biofilm structures. This allowed the microbe to regulate their inner environment by removing toxic agents (including antibacterial drugs) (Soto, 2013). By inhibiting this mechanism, less ciprofloxacin is withdrawn, and hence the treatment is more effective. This proves a synergic effect of curcumin on antibiotics and suggests their combined use against resistant bacterial strains (Rahbar Takrami et al., 2019). Rupel et al. (2021) also achieved a lower antimicrobial concentration of curcumin for *P. aeruginosa*. This was accomplished using antimicrobial photodynamic therapy (APDT) in which a visible light (in this case a blue laser light) activates the photosensitizer non-toxic molecule (curcumin) generating ROS that kill any microbe through an oxidative burst (Cieplik et al., 2018). For this, curcumin was encapsulated in different nanomicelles. The best results were obtained when encapsulating with spermine, as higher formal charge interacts better with the outer membrane of the studied bacteria. Curcumin has also shown to be effective on Gram-positive bacteria (Rupel et al., 2021). Pourhajibagher et al. used APDT against *S. mutans* combined with ultrasonication. This combination increased the inactivation from 90.8% (just APDT) to 99.9% (APDT + ultrasonication). This was because more ROS were produced (10.8-fold), as ultrasound waves form microbubbles that implode catastrophically, exciting curcumin

TABLE 1 Antibacterial compounds typically encapsulated.

Encapsulated compound	Tested on	Antimicrobial concentration	Reference
Curcumin	*P. aeruginosa*	400 µg/ml	Rahbar Takrami et al. (2019)
Curcumin	*P. aeruginosa*	50 nM–1 µM	Rupel et al. (2021)
Curcumin	*S. mutans*	50 mM	Pourhajibagher et al. (2020)
Rosemary EO	*S. aureus*, *L. monocytogenes*, *S. flexneri*, and *E. coli*	2.5 mg/ml	Amani et al. (2021)
Mānuka EO	*B. cereus*	0.15% w/v	Liu et al. (2021)
Clove EO	*L. monocytogenes*, *S. aureus*, *S. typhi*, and *E. coli*	Minimum inhibitory volume: 2 µL	Hadidi et al. (2020)
Lemongrass EO	*C. albicans*, *S. aureus*, *L. monocytogenes*, and *E. coli*	0.19—6.25 mg/ml	Soltanzadeh et al. (2021)
Peppermint EO (PO) and green tea EO (GTO)	*S. aureus and E. coli*	0.57(PO) and 1.11 (GTO) mg/mL for *S. aureus* and 1.15 (PO) and > 2.72 (GTO) mg/mL for *E. coli*	Shetta et al. (2019)
ZnFe$_2$O$_4$ NPs	*P. aeruginosa*, *E. coli*, *S. epidermidis*, and *S. aureus*	64 and 128 µg/ml for Gram-negative and Gram-positive bacteria, respectively	Sharma et al. (2020)
Cu NPs	*E. coli*, *S. aureus*, and *P. aeruginosa*	7.5—11.25 µg/ml	Chen et al. (2019)
Ag NPs	*E. coli* and *S. aureus*	6.4 and 8.2 µg/ml for *E. coli* and *S. aureus*, respectively	Khan and Al-Thabaiti (2019)

and producing ROS, as described previously (Pourhajibagher et al., 2020).

Regarding EOs, an improvement on their stability and solubility, by means of encapsulation, enhances their antimicrobial activity. This was demonstrated in Amani et al. (2021). Rosemary essential oil (REO) encapsulated into starch nanoparticles with a high amylose content showed that these nanocarriers protect the EO from the environment, enhancing their antibacterial properties. This is observed considering that the minimum bactericidal concentration (MBC) was higher than that of the others for *L. monocytogenes* (7.05 against 3.52 mg/ml) when free REO was employed. However, when it was encapsulated, the MBC not only was the same for all the bacteria tested but also decreased down to 2.5 mg/ml in all the cases (Amani et al., 2021). Advantages of encapsulation were proven in Liu et al. (2021); antimicrobial activity of Mānuka EO (MEO) was improved encapsulating it into yeast cells by reducing three times the bacterial population during the same time (1 hour). An interesting conclusion of this study is that encapsulation boosted MEO antibacterial properties in an organic-rich environment. This shows that a controlled release prevents non-specific reactions of the bioactive compound that would be consumed by organic matter in the surroundings undesirably, worsening its antimicrobial activity (Liu et al., 2021).

One common encapsulating compound is chitosan nanoparticle (CNP). These nanoparticles have antimicrobial activity themselves. These were tested in several studies giving different results depending on the EO encapsulated (Shetta et al., 2019; Hadidi et al., 2020; Soltanzadeh et al., 2021). Free CNPs show antibacterial properties because of their positively charged

amino groups that bind to the bacterial wall destroying their membrane. However, in all the reviewed studies, it can be seen to possess limited antimicrobial activity. This can be explained taking into account the crosslinking of the chitosan polymer with tripolyphosphate (TPP), which is anionic, in the preparation of the CNPs, limiting the availability of cationic CNPs that would penetrate the negatively charged biofilm matrix damaging the bacteria (Soltanzadeh et al., 2021). Hadidi et al. tested clove EO-loaded CNPs, and the highest inhibitory effect was always achieved with the clove EO encapsulated into the CNP for both Gram-negative and Gram-positive bacteria (Hadidi et al., 2020). Shetta et al. (2019) also achieved very low bactericidal concentrations of green tea oil by encapsulating it with CNP against both kinds of bacteria. Although this is the general trend, encapsulation is not always the best way to achieve the highest antimicrobial activity (Shetta et al., 2019). In Soltanzadeh et al. (2021), Gram-positive and Gram-negative bacteria inhibition was studied by encapsulating lemongrass EO into chitosan. However, in this case, free EO had more antimicrobial activity than that of the EO encapsulated in CNP against Gram-negative bacteria. Same results were obtained by Shetta et al. (2019) when encapsulating peppermint EO in CNP. They explained it considering the chemical interactions and the good loading of the antimicrobial agent inside the CNPs as well as the slow release of the bioactive compound that produce more hydrophilic particles that resist to the penetration of the encapsulated molecules through the lipophilic bacterial wall of this kind of microbes. Hence, encapsulation of these types of EO would be recommended only against Gram-positive bacteria.

Also, several kinds of metallic NPs were tested for their antimicrobial activity. Sharma et al. demonstrated that $ZnFe_2O_4$-loaded chitosan not only avoids biofilm formation but also helps with the inhibition of already formed biofilms. They attribute this to the generation of ROS. $ZnFe_2O_4$ is a semiconductor that has a narrow band gap and hence presents photocatalytic activity. With the presence of electrons in its conduction band and holes in the valence one, redox reactions take place producing a huge number of electron–hole pair systems, generating free radicals. Water reacts with holes producing OH, and the lone electrons from the conduction band react with the dissolved O_2 giving a superoxide ion that possesses antibacterial activity. It is also important to consider that by coating the $ZnFe_2O_4$ NPs with chitosan, the band gap is reduced, so the movement of electrons is enhanced, boosting the production of ROS and then increasing the antimicrobial activity (Sharma et al., 2020). A different mechanism of bactericidal activity is proposed by Chen et al. (2019), where they encapsulated Cu NPs into graphene sheets. Cu^{2+} leakage from the encapsulated NPs was very limited, so the mechanism depends on the ability to capture the microbes and release copper cations that would kill the bacteria. The synthetized NPs encapsulated with carbon had a very large specific surface, increasing the contact area for the bacteria and improving the adsorption into them. The antimicrobial activity was especially remarkable in the case of Gram-negative bacteria, as the copper cations interacted with the cell membrane, and the graphene sheets captured the microbes (Chen et al., 2019). Same happened when Khan and Al-Thabaiti, (2019) encapsulated biogenic silver particles into starch: silver cations would form complex with the amino acids present in the cell membrane and associate with the cytoplasm and penetrate the bacteria. The incorporation of the metal would again affect the DNA ability to replicate, also inhibit the breathing process, and produce structural changes in the microbe, finally killing it.

3 Different types of colloids used for encapsulation

In this section, the different types of colloids that can be used as carriers for antimicrobial activity compounds as well as their preparation method are described. Table 2 summarizes all the parameters discussed in this section for different types of colloids.

3.1 Vesicles

Vesicles are colloidal systems plenty used in pharmaceutical, cosmetic, and food industries as carriers for drugs or biocompounds. They are essentially formed by an aqueous core surrounded by a membrane in which the components can be phospholipids, non-ionic surfactants, or polymers (Tibbitt et al., 2016). For their nature, hydrophobic and hydrophilic compounds can be encapsulated based on their affinity for the aqueous core or organic layer. According to the size and different numbers of lamellas in their layer, they can be classified into small unilamellar vesicles (SUVs) with a size in the range of 20–100 nm, large unilamellar vesicles (LUVs) with a larger size greater than 100 nm, and multilamellar vesicles (MLVs) with a minimum size of 500 nm (Gonçalves et al., 2018).

These types of nanomaterials have many advantages for overcoming antibiotic resistance. One of them is the possibility to get the antimicrobial or antibiotic to the specific target with the right concentration to obtain the desired therapeutic effect because one of the mechanisms of bacterial defense is to degrade the antibiotic in an enzymatic way before reaching the site of action (Kelly et al., 2020). Moreover, vesicles can interact with the bacterial membrane, thanks to the ability to merge and fuse with the membrane (Ma et al., 2013), and can enter into the complex structure of the biofilm through their water channel, thanks to their size (Galié et al., 2018). In terms of production, the advantages are low-cost manufacturing and reagents and ease of scale-up. However, there are some disadvantages that must be considered such as the possibility of loss of the drug during the production phase and a relative shelf life and stability based on the type of vesicles (Ghafelehbashi et al., 2019).

A different classification can be considered referring to the membrane components that influence not only the chemical and physical properties and stability but also the pharmacokinetics and pharmacodynamics of the drug encapsulated. The common vesicles used in antimicrobial and antibiotic encapsulation are described in the following paragraphs.

Liposomes are vesicles with a size less than 200 nm in which the main components are phospholipids that form a lipid bilayer. The surface can be conjugated with positively or negatively charged molecules that give charge to the liposome and make them applicable in different routes of administration in the human body, prolong the release of the drug, or interact with the cellular membrane of bacteria through adsorption, endocytosis, exchange, or transfer of lipids (Dimov et al., 2017). Usually, cholesterol is added as a component in order to stabilize not only the lipid structure and fluidity but also a possible drug leakage. Lipids have a fluid state ($T > T_M$, T_M being the melting temperature) and a gel state; the fluid one is exploited to load the liposome because the lipids are more permeable to water ($T > T_M$).

Niosomes are characterized by non-ionic surfactants as membrane components, amphiphilic molecules with a hydrophilic head and a hydrophobic tail. They are more stable than phospholipids. The selection of surfactants is made considering hydrophilic–lipophilic balance (HLB) and critical packing parameter (CPP) values (Mahale et al., 2012). The HLB value indicates the balance between the hydrophilic and lipophilic part of the surfactant. The range is from 0 to 20;

TABLE 2 Examples of recent studies on different colloids used for the encapsulation of compounds with antimicrobial activity and against what they have been tested.

Type of colloid	Preparation method	Colloid size	Encapsulated compound	Tested on	Reference
SNPs	Nanoprecipitation	135–190 nm	Curcumin	*In vitro* digestion	Acevedo-Guevara et al. (2018)
SNPs	Nanoprecipitation	323–615 nm	Catechin	*In vitro* digestion	Ahmad et al. (2019)
SNPs	Nanoprecipitation	84 nm	EOs	*S. aureus and E. coli*	Qiu et al. (2017)
SNPs	Microemulsion	76 nm	Vancomycin	*S. aureus*	Einipour et al. (2022)
SNPs	Nanoprecipitation	283 nm	Triphala Churna	*S. dysenteriae, S. aureus, and S. typhi*	Nallasamy et al. (2020)
SNPs	Nanoprecipitation	141–198 nm	Curcumin	Food simulants	Nieto-Suaza et al. (2019)
SNPs	Microemulsion	40 nm	Penicillin/streptomycin	*S. pyogenes and E. coli*	Ismail and Gopinath (2017)
PLGA NPs	Physicochemical solvent/ nonsolvent	63 nm	ZnO/PLGA	Bacterial strains	Stanković et al. (2016)
PLGA NPs	Single emulsion–solvent evaporation method	162–205 nm	TMZ and O6-BG/PLGA	GBM treatment	Ramalho et al. (2019)
PLGA NPs	Nanoprecipitation	170 nm	EtNBS/PLGA	Cancer cells	Hung et al. (2016)
PLGA NPs	Single solvent evaporation	0.84–1.23 μm	Drug/PLGA	Triple-negative breast cancer (TNBC)	Jusu et al. (2020)
PLGA NPs	Emulsion solvent evaporation	114–128 nm	Hydrophilic drugs/PLGA	Enhancing encapsulation efficiency and controlling the release of hydrophilic drugs	Ryu et al. (2021)
Liposomes	Thin-film hydration	179 nm	Bateriocin and garlic extract	*S. aureus* and *E. coli*	Pinilla and Brandelli (2016)
Polymersomes	Ethanol injection method	300–400 nm	Cationic peptides	*E. coli*	Cantor et al. (2019)
Liposomes	Reverse-phase evaporation	100 nm	Rifamicin	*M. tuberculosis* and *S. aureus*	Gonzalez Gomez et al. (2019)
Liposomes	Thin-film hydration	200 nm	Endolysin	*E. coli*	Bai et al. (2019)
Niosomes	Reverse-phase evaporation	814.2 nm	Rosemarinic acid	*S. aureus*	Budhiraja and Dhingra (2015)
Liposomes	Ethanol injection method	270 nm	Levoflaxacin	Acute otitis media	Abdelbary et al. (2019)
Niosomes	Thin-film hydration	6 μm	Myrtle oil	*S. aureus* and *E. coli*	Raeiszadeh et al. (2018)
Hollow particles	Hydrothermal method	200 nm	Cu-phthalocyanine/ZnO*	*B. cereus* and *P. aeruginosa*	Mohamed et al. (2019)
Hollow particles	Hydrothermal method	25 nm	Graphene oxide–gadolinium oxide*	*E. coli*	Lingamdinne et al. (2021)
Hydrogel particles	Crosslinking	~50 μm**	Urea	*B. cereus, A. tumefaciens, A. flavus, F. avenaceum,* and *F. solani*	Arafa et al. (2022)
Hydrogel particles	Crosslinking	~3 mm**	Grapefruit seeds and citrus peel extracts	*L. monocytogenes*	Oh et al. (2021)
Hydrogel particles	Polymerization	-	Vancomycin and tobramycin	*E. coli*	Heffernan et al. (2022)
Nanoemulsion	High-pressure homogenization	~300 nm	Resveratrol and oregano EO	*S. aureus*	Ai et al. (2022)
Nanoemulsion	PIT method	~200 nm	Neem oil and ampicillin	*E. coli, S. aureus,* and *S. pyogenes*	Safaya and Rotliwala (2022)
Pickering emulsions	High-pressure homogenization	~20 μm	Oregano essential oil and ZnO nanoparticles	*S. epidermidis* and *E. coli*	Wu et al. (2021)
Pickering nanoemulsions	High-pressure homogenization	~200 nm	Resveratrol–zein–pectin complex particles and peppermint oil	*S. typhimurium*	Cheng et al. (2020)
Pickering nanoemulsions	Ultrasound	~100 nm	Coumarin and curcumin	*S. aureus, S. Epidermidis, S. faecalis,* and *E. coli*	Asabuwa Ngwabebhoh et al. (2018)
Pickering nanoemulsions	Ultrasound	~200 nm	Oregano oil	*S. aureus, B. subtilis,* and *E. coli*	Zhou et al. (2018)
Nanoemulsions	High-pressure homogenization	~20 nm	Lemongrass or clove EOs	*E. coli*	Salvia-Trujillo et al. (2015)
Pickering emulsions	Mechanical agitation	~600 nm	Cinnamon EOs	*A. alternata* and *B. cinerea*	Jiang et al. (2020)

the low values are referred to more lipophilic surfactant and the higher to more hydrophilic surfactant. The values between 4 and 8 indicate good surfactants for the preparation of vesicles (Varun et al., 2012). The CPP predicts the self-assembled structure and consequently the geometry of vesicles. The values $1/2 \leq CPP \leq 1$ suggest the formations of the bilayer vesicles (Ge et al., 2019).

Polymersomes are composed by synthetic amphiphilic block copolymers with high molecular weight, for example, poly (ethylene glycol) (PEG) blocks. The compound is released thanks to the response of polymers to external stimuli such as pH, radiation, and temperature. Advantages of this type of vesicles are the possibility to better control the release and direct the drug on a specific target, higher stability than liposomes, and biodegradability (Lee and Feijen, 2012).

Proniosomes are dry formulations that include water-soluble carriers such as mannitol and surfactants. Niosomes are produced through hydration with an aqueous solution that contains the drug. Unlike conventional niosomes, physical stability is higher with a longer storage, and it reduces aggregation problems and leakage of the drug (Blazek-Welsh and Rhodes, 2001).

Vesicles for antimicrobial compound encapsulation can be prepared by several methods.

Thin-film hydration is one of the main synthesis methods. Surfactants and cholesterol are dissolved in the organic phase in a flask, and then the organic solvent is evaporated using a rotary evaporator considering the temperature of the bath being above the transition temperature of the lipids or surfactants used for the membrane bilayer. In this way, a film on the wall of the flask is formed, and then an aqueous solution is added into the flask to hydrate the film with a constant rotation in the bath. The interested compound is dissolved in the organic phase or in the aqueous phase, according to its nature. Afterward, the suspension is homogenized by sonication. Multilamellar vesicles are obtained using this method (Thabet et al., 2022).

When using the ethanol injection method, the membrane components are always dissolved in an organic solvent (ethanol) and injected through a needle in an aqueous solution while stirring under a constant temperature, above the boiling point of the organic solvent. The solvent is then evaporated using a rotary evaporator; thus, unilamellar vesicles are formed (Mozafari, 2005).

In the reverse-phase evaporation method, the ingredients of the vesicle's membrane are dissolved in a mixture of chloroform and ethanol that is added to the aqueous phase. This mixture is sonicated forming an emulsion, and organic solvents are evaporated. During the evaporation, large unilamellar vesicles are obtained (Kaddah et al., 2018). Figure 2 illustrates, briefly, the three methods described previously.

3.2 Emulsions

Emulsions are compounds formed by at least two immiscible liquid phases in which one is dispersed when dropped in the other. Simple and multiple emulsions can be found, and their main difference is based on the number of droplets that are located inside the drop, as schematically described in Figure 3.
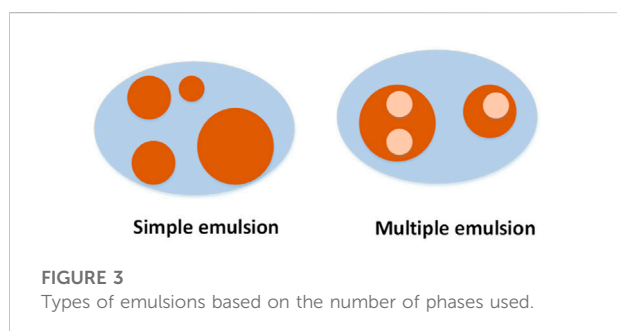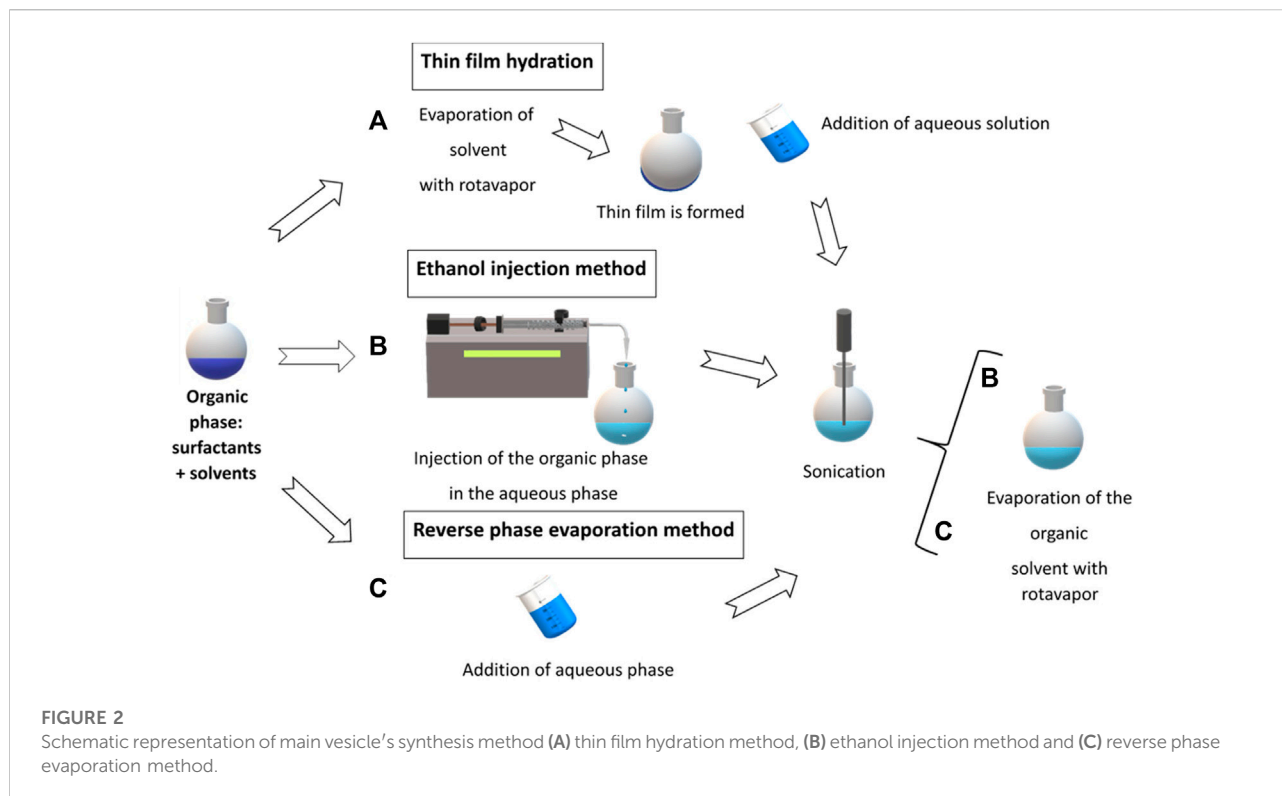
Based on the droplet size and their thermodynamic stability, three main types of emulsions can be found: macroemulsions, commonly named emulsions, nanoemulsions, and microemulsions (Figure 1). Macro- and nanoemulsions are thermodynamically unstable, and energy is required for its formation; the difference between both types is the size of the droplet size. Macroemulsions contain droplet sizes around several microns, whereas nanoemulsions contain a droplet size of lower than 200 nm (frequently extended up to 500 nm) (McClements and Jafari, 2018). However, microemulsions are thermodynamically stable and are spontaneously formed when one phase is continually added to the other one.

In any case, all types of emulsions require at least the presence of a third compound acting as stabilizer, of one phase into the other. The stabilizer can be located at the interphase surrounding the drops of the dispersed phase. Several types of stabilizers can be found, such as proteins, polymers, or particles; when particles are used as stabilizers, emulsions are named Pickering emulsions (Binks and Lumsdon, 2000).

Regarding the preparation methods used, several methods can be found; mechanical agitation is the most frequently used method in which both phases are mixed at high speed in the presence of the stabilizer. In order to produce emulsions with a low drop size (as it is the case of nanoemulsions), a second step is frequently required for which sonication or high-pressure homogenization is employed.

However, other low-energy methods based on spontaneous changes of concentration (phase inversion composition or PIC) or temperature (phase inversion temperature or PIT) can be found, which are frequently used for the formation of microemulsions and nanoemulsions (Mei et al., 2011; Solans and Solé, 2012).

Emulsions are used for several purposes, such as drug delivery, reaction matrix, preparation of novel materials, or lubricants, with several applications in clinical, pharmaceutical, food, and cosmetic industries. During the last 30 years, their potential application as antimicrobial agents was explored (Floyd, 1999), and special attention has been focused in the last 10 years on the antimicrobial activity that essential oils had demonstrated. This could exert synergic effect using other antimicrobial agents encapsulated producing a green safe material for several pharmaceutical and food applications (Pandey et al., 2022).

FIGURE 2
Schematic representation of main vesicle's synthesis method **(A)** thin film hydration method, **(B)** ethanol injection method and **(C)** reverse phase evaporation method.

FIGURE 3
Types of emulsions based on the number of phases used.

3.3 Hydrogels

Hydrogels are a polymeric matrix with a principal structure, hydrophilic in nature, and a 3D structure bestowed with the potential use of storing liquids or solids. Hydrogels are composed of hydrophilic natural or synthetic polymer chains, which can be produced into different types based on its shape, size, and form (Mirzaei et al., 2021). Hydrogels of natural sources, such as proteins and carbohydrates like starch or alginate, offer a large advantageous in terms of biocompatibility and biodegradability.

Hydrogels have gained attention due to their unique qualities, like low cost, water-based components, and biocompatibility (Manzoor et al., 2022).

For hydrogel preparation, chemical, physical, or physicochemical methods can be used. The chemical method based on polymerization–crosslinking method is the most frequently used method. First, polymerization under controlled temperature and atmosphere forms a water-soluble gel, which is suitable for the transportation and delivery of soluble biocompounds (Heffernan et al., 2022).

The use of a crosslinker allows getting a gel-based matrix with hollow internal cavitation. The internal cavitation is suitable for transport of active compounds in either a solid or liquid phase (Oh et al., 2021; Arafa et al., 2022; Manzoor et al., 2022). The crosslinker used could be physical or chemical. Physical crosslinking is based on the blending of the polymer solution with other inorganic material such as metal particles or organic materials such as other polymers. However, chemical crosslinking is based on the grafting of other compounds on the polymeric matrix in order to modify its hydrophobicity (Manzoor et al., 2022). Figure 4 shows a schematic diagram of the hydrogel formation process.

During the last decade, several works have been reported in which hydrogels were used as antimicrobial agent either by its encapsulation of antimicrobial compound or by the use of a

FIGURE 4
Hydrogels by crosslinking formation.
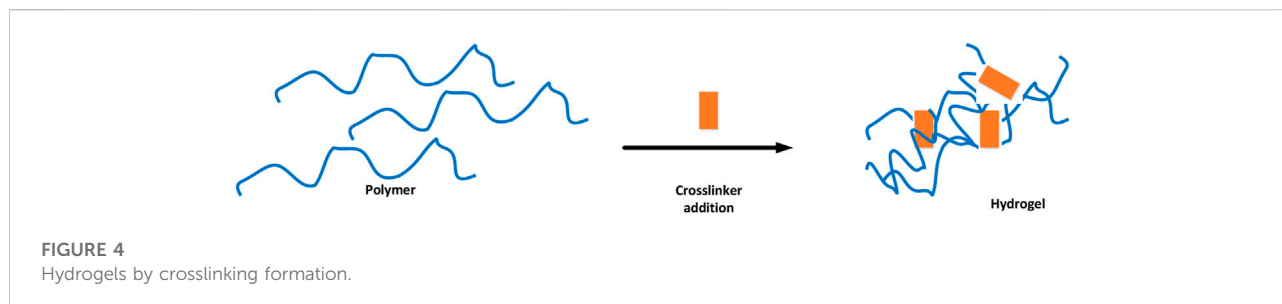
polymeric matrix testing the antimicrobial activity (Oh et al., 2021; Arafa et al., 2022; Heffernan et al., 2022; Manzoor et al., 2022).

3.4 Particles

3.4.1 Hollow particles

Hollow particles are typically spherical particles with an empty capacity in its inner part with application in coatings, microreactors, and drug delivery for several purposes (Sharifzadeh and Parsnasab, 2021; Kitayama et al., 2022).

Different methods can be found for hollow particle preparation, such as Pickering emulsion and hydrothermal method.

The Pickering emulsion-based method is focused on the preparation of an O/W emulsion using particles as stabilizers and a solvent as an oily phase with high vapor pressure, such as an alcohol or other organic solvents. The Pickering emulsion prepared is then placed in a rotavapor, where under vacuum conditions the solvent used as the oil phase is evaporated creating a hollow particle also named in the literature as colloidosomes (Ao et al., 2011; Sharifzadeh and Parsnasab, 2021).

The hydrothermal method is a commonly used method in which nanomaterials can be synthetized with a high control of the final size and shape with low loss of the raw material used. Due to high control on operating conditions such as pressure and temperature, a reactor is used for this synthesis (Mohamed et al., 2019; Gan et al., 2020).

Recently, the use of metallic hollow particles and composites are being synthetized and tested for antimicrobial applications with promising results for final industrial applications (Mohamed et al., 2019; Lingamdinne et al., 2021).

3.4.2 Starch nanoparticles

The considerable versatility of starch makes it a potential candidate to the development of high-efficiency and additional-value biomaterials for many fields, among which the drug delivery would stand out in the biomedical field. This is because starch-based materials can be easily adapted to many applications due to thei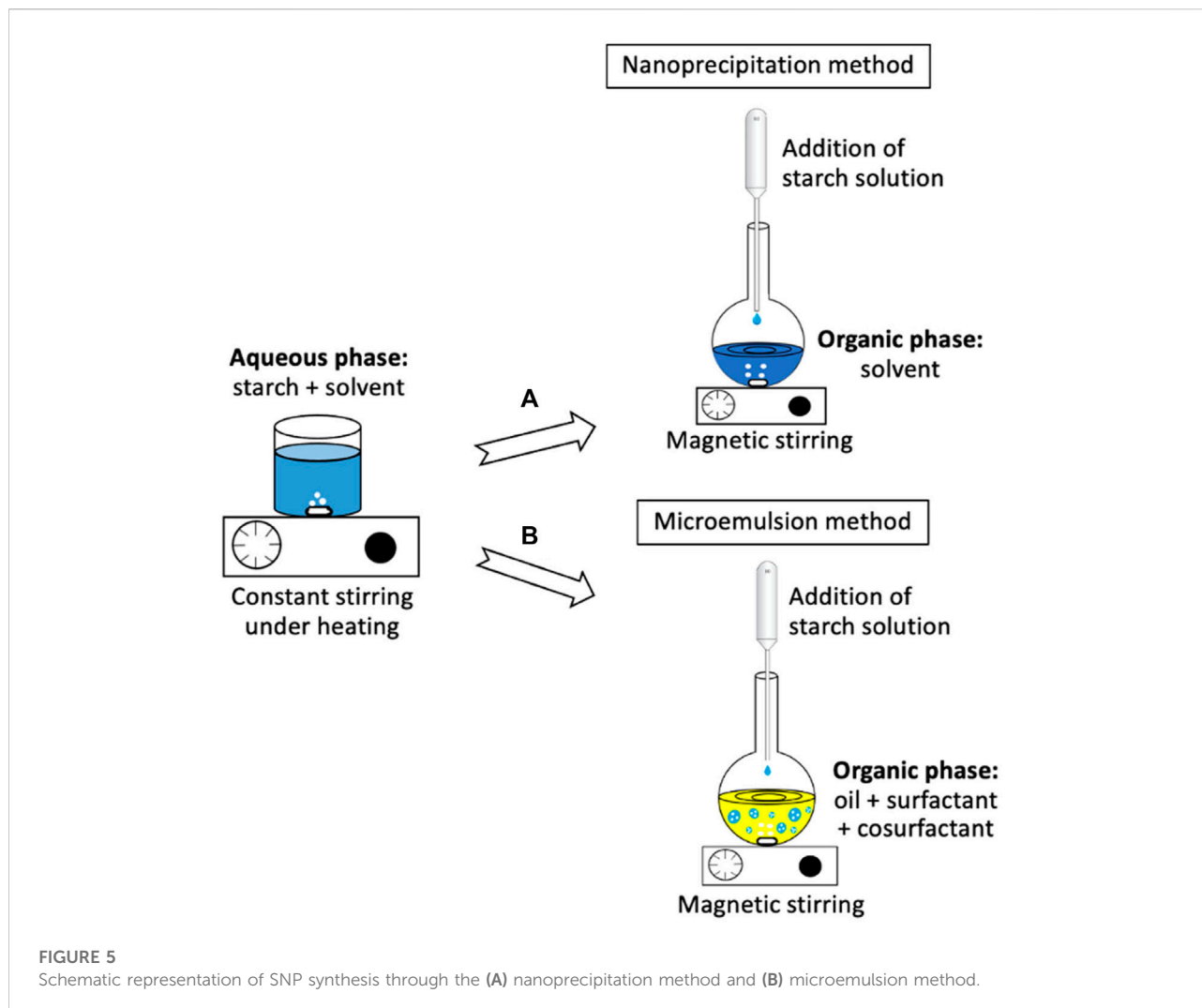r use as templates into which specific compounds are introduced (Sarder et al., 2022). For this reason, starch nanoparticles (SNPs) are considered new and promising sustainable biomaterials for their use in such different bioapplications (Kim et al., 2015).

SNPs can be obtained from the breakdown of starch granules through different synthesis methods that involve both physical and chemical processes, as a combination of both. Both synthesis method and operation conditions will influence their final properties for the different further applications.

Several methods have been known to produce SNPs (Morán et al., 2021), but two soft chemistry techniques with a growing interest to synthesize SNPs are nanoprecipitation and microemulsion methods, since these methods do not require sophisticated equipment, hazardous reagents, or extreme conditions, and efficient control of the size, shape, monodispersity, and composition of the final nanoparticles can be achieved (Gutiérrez et al., 2020).

Both methods involve the successive addition of a dilute aqueous polymer solution to an organic phase that leads to precipitation of the polymer in the form of SNPs. For the nanoprecipitation method, the organic phase consists simply of a solvent such as acetone or absolute ethanol. On the other hand, for the microemulsion method, the aqueous phase containing the starch is added to an oil, surfactant, and co-surfactant mixture. These two phases are intensively stirred to form an emulsion, and the droplets formed produce the precipitation of the polymer into nanoparticles. A schematic representation of the nanoprecipitation and microemulsion methods is represented in Figures 5A) and b, respectively.

As mentioned previously, curcumin is one of the most typically encapsulated antimicrobial compounds. In recent years, Acevedo Guevara et al. studied the curcumin encapsulation and delivery when it is loaded into native and acetylated banana starch nanoparticles carrying out *in vitro* gastrointestinal release studies. In both cases, satisfactory results were achieved. However, the release of curcumin was not complete as some of the curcumin was trapped inside the particles (Acevedo-Guevara et al., 2018). Continuing with simulated *in vitro* digestion studies, in 2019, Ahmad et al. studied the release behavior of catechin encapsulated into starch-based nanoparticles from three different sources (horse

FIGURE 5
Schematic representation of SNP synthesis through the **(A)** nanoprecipitation method and **(B)** microemulsion method.

chestnut, water chestnut, and lotus stem). They concluded that nanoparticles could offer protection against the environmental agents. Moreover, it was found that SNPs help to retain bioactive properties of encapsulated compounds (Ahmad et al., 2019).

In addition, EOs also show antimicrobial and antioxidant activities. However, their applications are negatively influenced due to their low water solubility and easy degradation by heat. For this, Qiu et al. (2017) carried out a study to evaluate the enhancement in antioxidative and antimicrobial activities of EOs encapsulated in starch nanoparticles prepared by short glucan chains successfully achieving the extension on the properties by their encapsulation into these. The encapsulated oils' antimicrobial activity was tested against *S. aureus* and *E. coli*, and the authors concluded that the EOs studied showed better antimicrobial activity against Gram-positive (*S. aureus*) than against Gram-negative (*E. coli*) bacteria (Qiu et al., 2017). Following the line, Einipour et al. tested

against *S. aureus* as well to evaluate the antimicrobial activity of a wound dressing containing vancomycin-loaded dialdehyde SNPs. Despite having antimicrobial activity in the tests using SNPs, the results concluded a higher release of vancomycin in the absence of SNPs (Einipour et al., 2022). In 2020, Nallasamy et al. also tested against *S. aureus*, *S. dysenteriae*, *and S. typhi* using SNPs loaded with a polyherbal formulation known as Triphala Churna. The results concluded that Triphala Churna encapsulated in SNPs retained its antimicrobial and antibiofilm activities, which would make the starch a suitable drug delivery system (Nallasamy et al., 2020).

Also, Nor Syahida et al. carried out a study based on the enhancement of the antibacterial effect by antibiotic-loaded SNPs testing on *S. pyogenes and E. coli*, as they found that the introduction of multiple antibiotics into SNPs increased the diameter of the inhibition zone compared to the condition not using the loaded SNPs. The results were satisfactory

and concluded that multiple antibiotics can be encapsulated in SNPs to increase the inhibition properties without complication of resistivity (Ismail and Gopinath, 2017).

3.5 Polymeric micelles

Poly (lactic-co-glycolic acid) (PLGA) is a hydrophobic polymer which has attracted much attention due to their biodegradability, low systemic toxicity, functionality, and biocompatibility. They have application in different industries, such as food, pharmaceutical, and biomedical (Danhier et al., 2012; Liu et al., 2019). PLGA copolymers are normally synthesized by ring-opening copolymerization of lactic acid (LA) and glycolic acid (GA) cyclic dimers, and the degree of crystallinity, LA:GA ratio, and molecular weight porosity of the polymeric network has effects on their characteristics (Zare et al., 2020; Shariati et al., 2022). They offer the possibility of the encapsulation of the nanoparticles to make a complex for increasing their stability in colloidal systems and possibility for interaction with biomolecules by modifying the surface properties. Also, they improve the biocompatibility of metal NPs and decrease their toxicity (Zare et al., 2020). For example, Stanković et al. (2016) investigated antimicrobial inhibition activity of PLGA/ZnO against bacterial strains. Their results showed that after immobilizing ZnO with the PLGA matrix, cytotoxicity was significantly lower than ZnO NPs alone. Moreover, they were not toxic against host cells but had antimicrobial activity against bacterial strains (Stanković et al., 2016). In the other work, Hung et al. successfully encapsulated EtNBS in PLGA. EtNBS is a cationic molecule EtNBS (5-ethylamino-9-diethyl-aminobenzo [a] phenothiazinium chloride), which has been proven to have potential to kill cancer cells; however, it is a toxic compound. Their results showed that after encapsulation with PLGA nanoparticles, the toxicity of EtNBS was significantly reduced. Also, they found that EtNBS encapsulated in PLGA was able to penetrate deeply into the hypoxic and acidic cores of 3D spheroid cultures (Hung et al., 2016). In the last years, PLGA nanoparticles also have gained increasing interest as drug delivery systems. Encapsulation of drugs in PLGA nanoparticles increases the therapeutic effects of drugs and minimizes the toxicity of the drug. Also, PLGA nanoparticles enable the drugs to release in a controlled way and sustain for long periods. Additionally, they can be absorbed by the endocytic mechanism and enable the accumulation of the drug in the target cells (Ramalho et al., 2019). For example, Ramalho et al. used PLGA nanoparticles for entrapping both TMZ and O6-BG for better GBM treatment. TMZ is the drug for GBM chemotherapy;

FIGURE 6
Influencing factors of the drug release mechanisms. Created with BioRender.com.
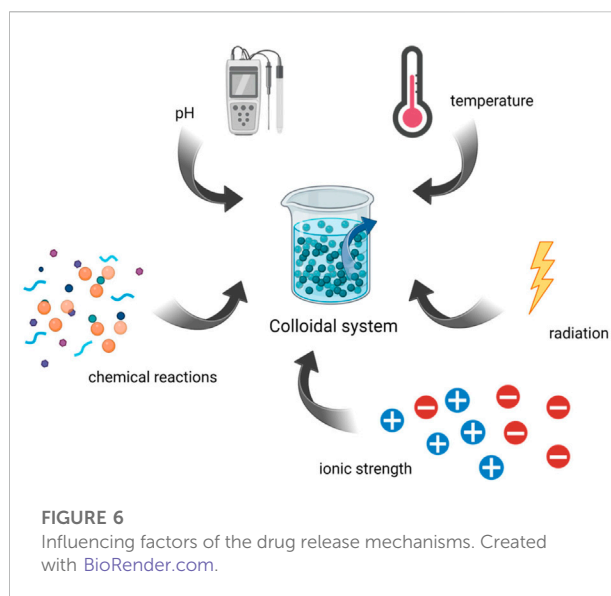
however, it is not able to effectively cure GBM patients. Their results showed that PLGA NPs created an efficient approach for the co-administration of TMZ and O6-BG for the intrinsic resistance mechanisms to TMZ (Ramalho et al., 2019).

4 Antibiofilm drug-controlled release

As explained previously, the colloidal systems are widely used in the encapsulation and control release of bioactive compounds for many applications due to their unique properties. Regarding the controlled release, two mechanisms can be distinguished: targeted and triggered. The targeted mechanism takes place when there is a reaction with a compound present in the environment. The colloidal systems are modified by incorporating antigens, antibodies, enzymes, proteins, and vitamins, etc., and when the targeted colloidal system reaches its absolute complementary affinity, it accumulates in the affected area and releases the encapsulated compound. On the other hand, the triggered mechanism happens when a chemical substance is incorporated into the colloidal system, which promotes changes in its structure because of external influences, that is, variations in pH, ion concentration, temperature, and light irradiation. The influencing factors of these release mechanisms are depicted in Figure 6. Once the colloidal system reaches the biofilm surface, release can be achieved through five different methods, as described by Ringe et al. (2004): 1) desorption of the drug bound to the surface, 2) diffusion through the nanoparticle matrix, 3) diffusion through the polymer wall of nanocapsules,

4) nanoparticle matrix erosion, and 5) a combined erosion–diffusion process (Ringe et al., 2004).

Regarding this, Einipour et al., who evaluated the use of antibacterial wound dressings based on starch nanoparticles, conducted the controlled release by immersion in a phosphate-buffered saline (PBS) solution and a subsequent incubation at 37°C. Similar studies were carried out by Nallasamy et al. who obtained results with a quick release of the drug at a physiological pH of 7.4. In 2021, Hoang et al. studied the compound release under different pH environments and temperatures showing an almost complete release of 92% at pH 7.4 and 37°C (Huong et al., 2021). Although this is one of the most common release mechanisms used, drug release can be carried out also with external light irradiation, as in the case of the study performed by Hung et al. (2016) in which the compound remains inside the nanocarrier until it is irradiated, stimulating a radical-mediated process that degrades PLGA nanoparticles and releases the active compound. At the same time, Zhao et al. (2018) proposed that thermosensitive liposomes with a positive charge and small size could enter the microchannels of the biofilms and trigger thermally activated drug release, leading to the biofilm dispersion and the death of residual bacteria. The authors concluded that the near-infrared-activated carriers can enhance the antimicrobial efficiency (Zhao et al., 2018).

5 Conclusion

The use of natural compounds with an antimicrobial activity could be a promising alternative to the conventional antibiotics used, which could have non-beneficial residual effects; moreover, during the last decade, bacteria have developed some resistance against them.

Colloidal systems such as particles, vesicles, or emulsions are a promising tool for natural compound encapsulation with antimicrobial activity.

Natural compound encapsulation could avoid compound oxidation or inactivation due to external factors such as light, temperature, or pH. Moreover, their encapsulation could be an advantage since the target delivery would elude side effects

produced by some of the biocompounds used. Also, the use of specific material for the colloidal particle formation could produce a synergic effect against microorganisms like bacteria.

Author contributions

MCB, ES, GG, and MM: conception of the study. DM, CS, VM, SB, and GG: first draft of the manuscript. MCB and MM: revision of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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