REMOVAL OF MACROLYDES FROM WATER. ANALYTICAL REMOVAL TECHNIQUES. AN OVERVIEW

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ABSTRACT

Water is an essential substance to ensure the survival of human beings has been contaminated over the years, which has been reflected in the increase of contamination by substances from industry and domestic waste, deteriorating its quality and turning it into a risk for those who consume it or live in it. However, in recent years the interest of researchers to remedy this problem has led to the study of different techniques applied to remove these contaminants since the traditional methods used in water treatment plants do not satisfactorily fulfill this purpose. Among the contaminants of greatest interest and to which this review is directed are the emerging contaminants, substances at trace level of a large number of chemical compounds of different origin and nature, which accumulate in aquatic environments causing cardiac affections, psychiatric reactions, liver disorders, genetic mutation, ecotoxicological risks as well as bacterial resistance, such as macrolides. These compounds belong to the group of antibiotics used to treat mainly respiratory affections, but whose consumption has increased in the last couple of years due to their possible action for the prevention of contagion or reduction of symptoms in patients with the COVID-19 virus. Therefore, the objective of this review is to compile the techniques used for their removal, such as sonochemical treatment and continuous ozonation, from which removal percentages higher than 70% have been obtained for macrolides such as azithromycin, clarithromycin, and erythromycin, representative drugs of this type of antibiotics, this in order to conduct research and experimental work for the removal with techniques such as polymer-assisted liquid phase retention, ultranofiltration membranes, which have had high percentages of efficiency for different types of antibiotics and thus establish different ways of removal for these contaminants of interest.

Keywords: Macrolides, Removal, Contaminants, Aqueous Medium.

1. INTRODUCTION

Water is an essential substance for the survival of the human being, however only 1% of the planet's water is suitable for human consumption. That is why from the beginning civilizations have developed near water sources, these being considered an important element to take care of, however, this principle has been disappearing over the years, which has caused the increase in water pollution from agricultural activities by the use of pesticides and fertilizers, of industrial activities by plastic and the dumping of water contaminated with chemical substances or metals, of domestic activities by the discharge of wastewater with infectious agents. What has deteriorated the quality of the water to such an extent that it has become a risk to human health, precursor of the disappearance of marine life, destruction of aqueous systems and poisoning of species from other ecosystems by the consumption of contaminated water. (1) (2) (3) (4)

The increase in the need for water and the reduction of its availability due to pollution has increased the interest of authorities and scientists in search of alternatives to solve this growing need (2), it is in this way that the study to determine the effects produced in living beings and in aqueous systems different types of pollutants such as: pathogens, wastes that need oxygen to be biodegraded, chemical compounds, plant nutrients, sediments, etc. In addition to the implementation of new technologies useful to reduce these levels of pollution has been of great interest in recent decades. (5) (3).

The contamination of aqueous systems due to the presence at the trace level of a large number of chemical compounds of different origin and nature, in wastewater of industrial and domestic origin, which are not commonly monitored, since their low concentration has gone unnoticed so that conventional treatment plants do not have effective techniques to remove them, have now become a subject of scientific concern because of the toxicological and ecological impact they can cause. These types of contaminants can be pharmaceuticals, pesticides or pesticides, personal care products, industrial additives or by-products and are called Emerging Pollutants. (6) (7).

Pharmaceutical products especially (analgesics, antidepressants, antibiotics, and others) one of the classifications of emerging pollutants, enter an aquatic environment by urban wastewater, hospital, industrial and of agricultural or livestock origin are subjected to conventional treatment processes such as biological treatment where they cannot be eliminated, thus getting into the water cycle and therefore into the food web. This added to the lack of control for the normalization of permitted values in effluents and studies on the real magnitude of the environmental impact on aqueous systems of this type of pollutants has increased their accumulation and therefore the damage to ecosystems and humans (8).

Antibiotics are natural substances from microorganisms or synthetic and are used as bactericides (β-lactamicos, aminoglycosides, glycopeptides, quinolones, and phosphokine) or bacteriostatic (sulfonamides, clindamycin, macrolides, tetracyclines, chloramphenicol) of other microorganisms, that is, they attack bacteria but not their host, however, the persistence of these bacteria or their adaptation to the environment can cause greater problems. (9) (10).

Its mechanism of action is based on: inhibiting cell wall synthesis such as β-lactamics, inhibiting protein biosynthesis such as tetracyclines (30s) or macrolides (50s), inhibiting DNA replication such as quinolones, inhibiting folic acid metabolism such as sulfonamides or inhibiting RNA synthesis such as rifampicins. (see figure 1) (11) (12),

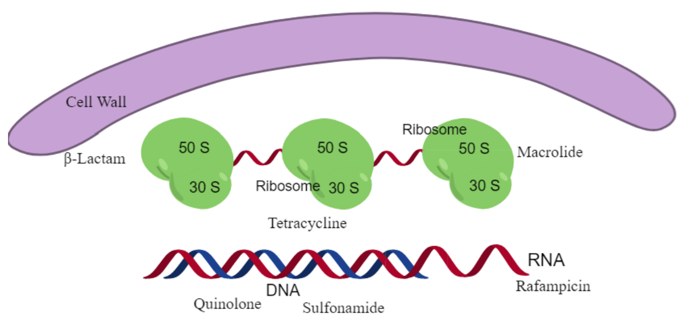

Figure 1. Scheme of bacterial structures including Cell Wall, Ribosome (30S, 50S) and Nucleic Acids; with examples of antibiotics that act on each structure. Source: (11) (12) ChemDraw Program.

The presence of this type of compounds in aqueous media due to its high solubility in water is a worrying issue since 1982 where a study was carried out to determine antibiotic residues in aqueous media in which traces of macrolides, tetracyclines and sulfonamides were detected with aqueous media with concentrations of 1 ug L^{-1} (13), and being present in wastewater where there is also no effective removal method implemented in treatment plants for this type of contaminants, over time it has come to contaminate surface water used for human consumption, groundwater and therefore soils, thus becoming a problem of great concern since although the adverse effects they have had until now antibiotics if they have been relevant some as cell damage, endocrine effects, teratogenic, modification of the bioavailability of other administered drugs, cardiovascular reactions, etc. (14)

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However, in the last decade a growing environmental concern about the presence of these pharmaceutical products disseminated in aqueous media has increased the interest of scientific research to know the possible effects of contamination of this type of ecosystems in particular, in addition to the interest in finding removal techniques different from those used in treatment plants since they have not been efficient in fulfilling the objective of their application in the process. However, in the last decade a growing environmental concern about the presence of these pharmaceutical products disseminated in aqueous media has increased the interest of scientific research to know the possible effects of contamination of this type of ecosystems in particular, in addition to the interest in finding removal techniques different from those used in treatment plants since they have not been efficient in fulfilling the objective of their application in the process. (7)

Research has focused in the last three years on determining what would be the effects that could originate or increase with the worldwide contagion of the SARS-CoV-2 coronavirus where although a decrease in pollution levels in water quality has been reported due to government restrictions imposed to try to control the spread of this virus (15) the increase in the indiscriminate use of high-end antibiotics especially macrolides such as clarithromycin and azithromycin as possible effective drugs to avoid contagion or counteract the respiratory symptoms that people present when infected, have also been reported. (16)

The result of different investigations show that contact over long periods of time in low concentrations of macrolide antibiotics have caused uncompensated cardiovascular reactions, hearing loss, liver disorders, alterations in the gastrointestinal flora, skin and soft tissue infections due to the potentiation of resistance to antibiotics, due to their presence in the environment, that is, the increase of bacterial resistance by adaptation, where bacteria subsist and reproduce especially in the aqueous media to which they can leach (17), since pharmaceutical products that do not have efficient removal techniques applied in wastewater treatment plants, also altering the biogeochemical cycle of the elements and environmental remediation, by causing the decrease of microbial diversity, the feminization of male fish, aquatic genotoxicity and immunity to pathogenic bacteria since bacteria like all living beings have undergone changes over time to adapt to the environment in which they are found, so the indiscriminate and unnecessary use in most cases of antibiotics has generated resistance to this type of pharmaceutical products due to prolonged contact. (14) (18) (19) (20) (21) (22)

2. ANTIBIOTICS IN AQUEOUS MEDIA

The contamination of aqueous media by antibiotics can affect the biological balance of aquatic and subsequently terrestrial organisms that are not their objective of action. This contamination occurs mainly since by their nature antibiotics do not undergo a complete metabolization in the human body, being excreted unchanged or as active metabolites through urine and feces to wastewater and due to their low concentration have gone unnoticed that conventional treatment plants do not have effective techniques to remove them being released into the environment accumulating in this type of ecosystems in addition to persisting intrinsically as tetracyclines and macrolides, thus affecting humans and animals that make use of these bodies of water for their different daily activities, since they cause bacterial resistance making them inefficient for the treatment of the diseases for which they are commonly used, being necessary the use of more aggressive drugs that in turn will lead to greater problems. However, the ecotoxicological data and the contribution of risk to health for most of these pollutants, more specifically has little literary contribution. (23) (24) (25) (26) (27)

Recently, results were reported from monitoring 1052 sampling sites in 104 countries on all continents of pharmaceuticals by New York University where concentrations of sulfonamides reaching 181 ng L^{-1}, β-lactamics up to 40.6 ng L^{-1}, macrolides of 32.4 ng L^{-1} and tetracyclines of 18.1 ng L^{-1} were found at least one of the sampling sites. (28)

Although we cannot attribute all the alterations of the aqueous environment to contamination by antibiotics, we can say that the significant and in some cases unnecessary increase in the use of some classes of antibiotics such as macrolides in the eradication of COVID-19, a virus that has affected the whole world since 2019, could cause or increase the harmful effects in this type of media, as can be seen in studies carried out in the Region of Murcia, Spain where when performing the control of wastewater and treated were found the highest values of persistence after biological treatment macrolides such as clarithromycin with 400 ng L^{-1} and azithromycin of 930 ng L^{-1}, being evident the need for effective techniques for the removal of these compounds, and in the same way in studies carried out in rivers of the city Wuhan, China where the increase in concentrations of macrolides is evidenced with respect to studies carried out before the bread. (15) (20) (29)

3. MACROLIDES

They are a type of polar antibiotic, non-volatile, poorly soluble in water were discovered in 1952 from metabolic products of Streptomyces spp., such as erythromycin from which semisynthetic compounds were obtained to improve their properties. The lipophilic structure of macrolides is constituted by a laconic ring composed of carbons and joined by glycosidic bonds to amino deoxysugars without nitrogen atom and with low number or absence of double bonds, are classified by the number of atoms that make up the ring can be 14, 15 or 16 carbons (see figure 2) and also by its natural or semi-synthetic nature such as the most representative of this group erythromycin a natural weak base of 14 carbon atoms semi-synthetic clarithromycin of 14 atoms synthesized from the need to improve the stability of erythromycin, obtained by methylation to obtain spirochetal bonds and azithromycin an azalide, that is, a semi-synthetic compound of 15 atoms obtained from erythromycin where a nitrogen atom is added within the cycle providing that they have greater activity against large negative microorganisms and better stability in acidic pH . (30) (31)

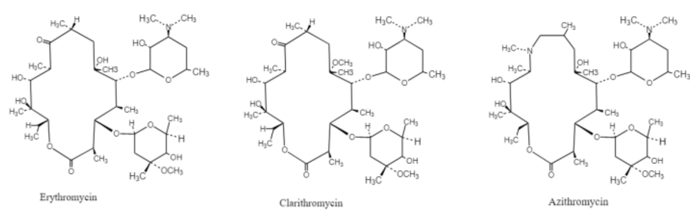

Figure 2. Natural macrolide chemical structure of 14C-Erythromycin (a.), semisynthetic 14C-Clarithromycin (b.), semisynthetic-15C-azithromycin azalide (c.) Source: (30) Programa ChemDraw.

The mechanism of action of these antibiotics is by inhibition of protein synthesis, where for a bacterium to begin to synthesize proteins the DNA molecule is twisted and separated in the section in which a specific protein can be made, only one of the DNA strips serves for this transcription, which results in messenger RNA that will subsequently bind to the ribosome which is made up of 30S and 50S units (larger size); before these units gather around the messenger RNA chain, the synthesis of the polypeptide chain involving the transfer RNA begins, which follow the sequence along the messenger RNA, carrying with it only one amino acid which passes in line along the messenger RNA, causing the ribosome to bind to these amino acids forming a polypeptide chain until the messenger RNA section ends (these signals how far the passage of amino acids should stop), to finally release the protein molecule (see figure 3).

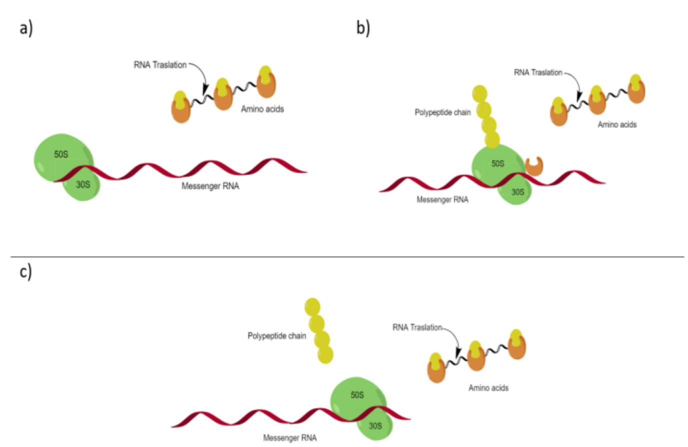

Figure 3. Protein synthesis of a Bacterium Source: Author-Program ChemDraw.

The macrolides when binding to the 50s ribosome block the sequence of translational RNA along the messenger RNA thus blocking the passage of the amino acid thus inhibiting its function to synthesize the polypeptide chain being considered bacteriostatic (see figure 4), although sometimes depending on the concentration (high concentrations), the growth phase of the bacterium and its susceptibility can lower the density of the bacterium or the rapid bacterial growth, being able to have a slow bactericidal behavior. (30) (32) (33)

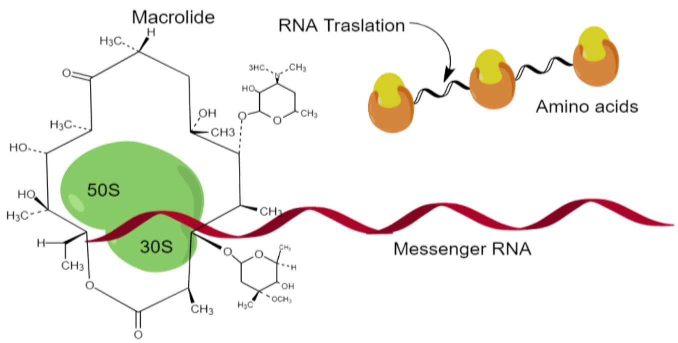

Figure 4. Representation of a membrane bioreactor assembled at laboratory scale. Source: (52).

These antibiotics can be concentrated at the intramolecular level, especially within bacteria, being active mainly against large positive cocci and aerobic bacilli such as Staphylococcus spp. and Bacillus spp., against gram-negative aerobic bacteria such as Actinobacillus, cocci and anaerobic bacilli such as Clostridium spp., (34) semi-synthetic macrolides such as azithromycin in particular that decreases the viscoelasticity of secretion respiratory, acting against bacteria producing an inflammatory and immunoaccumulating effect has an activity against Chlamydia. (35) (36)

3.1 Macrolide Uses and Related Adverse Effects

Macrolides are mainly used as drugs for the treatment of chronic inflammatory respiratory diseases such as cystic fibrosis, asthma, in addition to sexually transmitted diseases, gastrointestinal conditions, skin hypersensitivity, infectious diseases, growth promoters, reproduction control, elimination of gram-positive cocci on farms, however, the prolonged and indiscriminate use of these compounds in the treatment of diseases of humans and animals produce side effects such as uncompensated cardiovascular reactions, hearing loss, psychiatric reactions, liver disorders, alterations in gastrointestinal flora, skin and soft tissue infections, in addition to their constant incorporation into the environment, which have produced their bioaccumulation and persistence, causing the imbalance of ecosystems, in humans and animals difficulty in the treatment of diseases by generating bacterial resistance by the alteration of the ribosomal receptor hindering the entry of antibiotics into the bacterial cell. (7) (30) (31) (33) (37)

Some adverse effects from contact for long periods of time with macrolides has been studied and reported for example the cardiovascular effects that trigger the consumption of Azithromycin are the prolongation of the QT interval and rhythm disorders that could become lethal, so it is recommended the intake of this macrolide for no more than 5 days, (38). Similarly, studies conducted in Copenhagen hospitals have reported that the use of clarithromycin increases cardiovascular and total mortality in patients with ischemic heart disease. (39) (40)

A study also reports psychiatric reactions by use of clarithromycin or azithromycin in infants due to its inhibition of glutaminergic neurotransmission in the brain thus producing manic pictures, irritability, even when these adverse effects are reported with low frequency is important to know. (41)

These investigations were reported by the intake of this type of antibiotics by medical prescription, however, the bioaccumulation of macrolides in the aqueous systems as mentioned above can reach the organism in one way or another, increasing the probability of occurrence of these dangerous effects in humans.

In addition, studies of moderate ecotoxicological risk have been reported in green algae and daphnias, a low risk in fish due to the presence of macrolides, azithromycin and clarithromycin specifically in the effluents of the Wastewater Treatment Plants in the Region of Murcia. (20) In the same way, research has been reported on the genetically toxic effects of macrolides due to their accumulation in tissues producing cardiovascular damage in zebrafish, developmental delay, metabolic changes and induction of oxidative stress at concentrations less than 1ug L^{-1} in fish such as rainbow trout. (42) (43).

4. ANTIBIOTIC REMOVAL TECHNIQUES IN AQUEOUS MEDIA

Although antibiotics eventually degrade in aqueous ecosystems, the time in which this occurs depends on different variables such as temperature, composition and frequency of release of these pollutants into the environment, such as antibiotics that have a constant release due to their wide use in medicine and veterinary medicine, being important to determine efficient techniques for its removal and avoid or reduce its bioaccumulation and therefore harmful action in this type of ecosystems. (26)

Most conventional water treatment plants are not designed to remove such contaminants due to their polarity, contaminant diffusion ratio, medium temperature, retention times and plant design characteristics, so it is of great importance to determine economically affordable removal methods, efficient and environmentally friendly that solve this problem. (44) (45)

Conventional methods such as biological treatment, fluid extraction, adsorption have been used, however, the desired results have not been obtained, for this reason in recent years research has been carried out for the removal of antibiotics with alternative, non-destructive and innovative methods. (46)

4.1 Biodegradation

Biodegradation is a removal process where strains of white rot fungi are used in which the problem of activated sludge is eliminated as it is an environmentally friendly process as well as being low cost in its application, when performing this biotransformation (47) in addition to obtaining high removal results as in those reported in the study for the removal of isoxazolil-penicillins when using Leptosphaerulina sp. a fungus native to Colombia, after 8 days has attracted the attention of researchers for the high efficiency of the process, with non-toxic transformation products and no antibiotic activity and a removal percentage of approximately 100%. (48) similarly the use of microalgae S. capricornutum and C. vulgaris for the removal of macrolides such as clarithromycin and azithromycin, was greater than for other classes of antibiotics with an approximate removal percentage of 78% due to their ability to fix carbon in aqueous solutions, this technique being an efficient technique for antibiotic removal. (49) (50)

4.2 Biorreactor of membranes

The use of membrane Bio reactors a biological removal process combined with a membrane removal process whose operation is based on the passage of wastewater through a membrane filter due to a pressure produced by a pump this avoids the need for secondary clarification and sedimentation problems since the sludge is retained in this membrane, (51) therefore, the effectiveness of removing contaminants such as antibiotics is significantly increased. Thus, the study on the removal of quinolone in activated sludge reactors, indicating the improvement in the removal efficiency to certain conditions, being necessary techniques for removal of these antibiotics in the sludge (see figure 5) (52), while the use of an electrochemical membrane biofilm reactor achieved an elimination of 94.9% of this antibiotic. Therefore, the application of an electric field could improve the efficiency of the process, however the problem of tertiary treatment in terms of sludge obtained after the process is still present in this type of removal technique. (53)

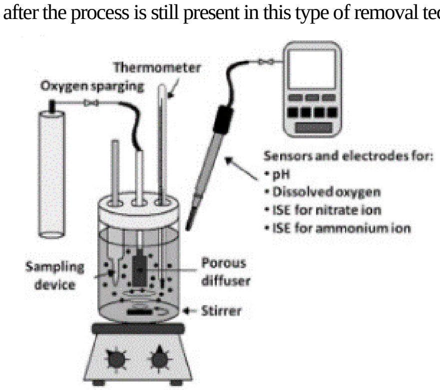

Figure 5. Representation of a membrane bioreactor assembled at laboratory scale. Source: (52)

4.3 Vertical flow wetlands

Vertical flow wetlands are treatment systems that use filter beds where aquatic vegetation is planted where wastewater is dosed vertically to later be collected in a drainage pipe This process is carried out in aerobic conditions, it has been used for the removal of contaminants, as in reported studies in which they help reduce the total nitrogen characterized with zeolite for the removal of sulfametazine in wastewater pigs, where an elimination percentage of 73% have been obtained, being therefore a viable alternative for the elimination of these contaminants. (54) (55)

4.4 Foto-Fenton

The use of photo-Fenton processes an advanced oxidation technique in which hydrogen peroxide reacts with Fe^{2+} where the latter is catalytically regenerated by UV-Visible radiation up to 50 nm like the Sun being an alternative of low cost and environmental interest, (56) so it has been used to reduce the chemical demand of oxygen used for degradation of (a) amoxicillin, (b) ampicillin and (c) cloxacillin in aqueous solution where a complete degradation was obtained in two minutes at a pH of 3 resulting in the mineralization of organic carbon of the antibiotic molecule (see figure 6) (57).

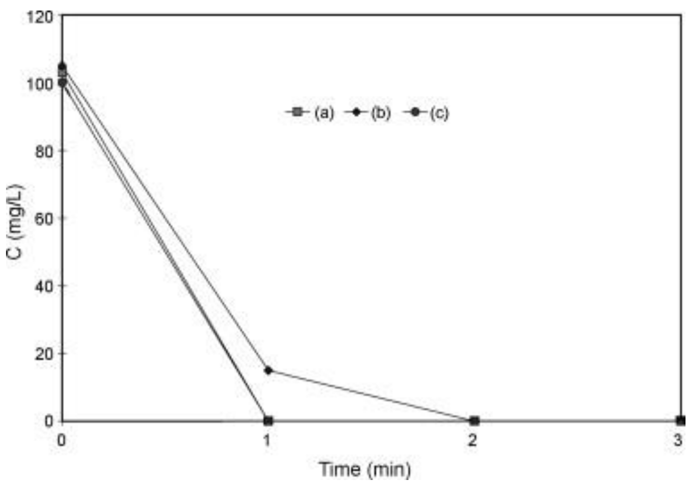

Figure 6. Degradation in optimal conditions by process Photo Fenton. Source: (57).

4.5 Sonochemical treatment

The sonochemical treatment is a technique where a large amount of energy released under ultrasonic irradiation is needed, causing thermal decomposition with low interference of the matrix, has been used for the treatment of water contaminated with pharmaceuticals and has shown good results in studies carried out in recent years such as in the removal of oxacillin where favorable results were obtained in the selective degradation of this contaminant and the elimination of its microbial activity by transforming the study solution to compounds more susceptible to subsequent biological treatments of elimination as for the elimination of azithromycin that when applied to the sonochemical treatment the photo-Fenton process was obtained with 5 ppm of Fe^{2+}, a removal of 87.36% was reached (58), in the same way it was applied in the removal at 375 kHz of ampicillin with an elimination percentage of 82%, however this process is carried out over long periods of time (elimination of total organic carbon of 9% in 18 min) so the combination of this technique with advanced oxidation or application of a sono-photo-Fenton system can have high percentages of removal and short periods of time in a way that efficiency at the male level is considered applicable. (59)

However, the combination of the sonochemical technique when using semiconductor materials as catalysts manages to increase the efficiency of the removal processes since it increases the formation of reactive radicals, being immobilized by nanoparticles as reported in the study of TiO_2 immobilized in montmorillonite for the removal of ciprofloxacin, achieved low removal results (>10%), So it should be taken into account that for the application of this type of technique S must contemplate the role of hydroxyl radicals in the decomposition or removal of the substance of interest. (60)

4.6 Ozonization

Continuous ozonation is a little-known process with great oxidation potential for antibiotics depending on the amount of ozone supplied that spontaneously transforms into oxygen and the contact time (see figure 7), as obtained in the study of urban wastewater at a concentration of 0.125 g of O_3 / g DOC with 20 min of contact removal percentages were obtained for azithromycin, clarithromycin, erythromycin 73%, 98%, 70% respectively, however, at a longer contact time of 40 min they degrade completely. (61) (62)

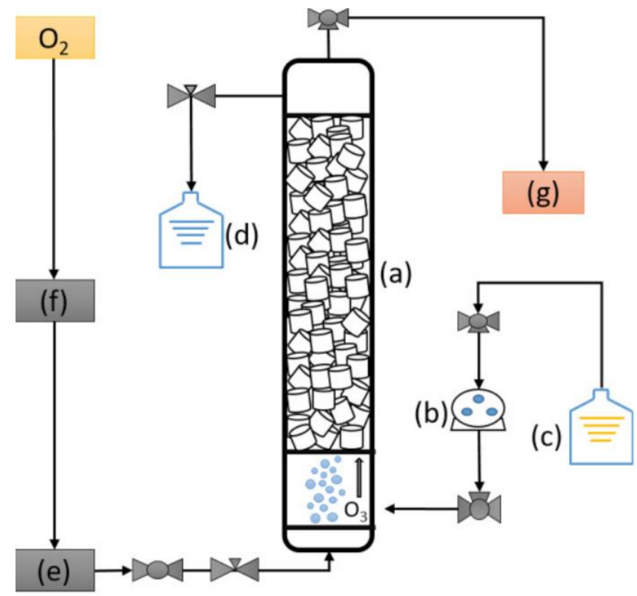

Figure 7. Experimental configuration of the ozonation reactor Source: (61).

4.7 Adsorption

Adsorption technologies for the removal of contaminants from aqueous systems have had good results and are considered highly efficient methods due to the low cost and ease of application (63), as in the results for the removal of sulfamethoxazole in magnetic nanoparticles of Ni encapsulated in carbon nanofibers with high percentages of removal in aqueous solution at pH 7, (64) however, the use of advanced oxidation processes using a floating photocatalyst composed of TiO_2 for this antibiotic in aqueous solution, allowing a photo-induced charge separation of electrons that can react with water to form reactive oxygen species, allowing mineralize this molecule, at a wide pH range in irradiation with energy in the nearby UV region (see figure 8). (65)

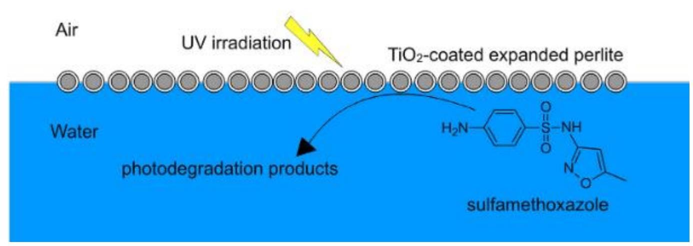

Figure 8. Advanced oxidation process using a floating photocatalyst composed of TiO2 Source: (65).

4.8 Adsorption by Aerogels

An aerogel is a very light and porous colloidal or polymeric network material with a high absorption by the volume of the pores that constitute it, obtained from replacing by air the liquid of the pores of the network of a wet gel (66). Recent study has shown that the removal of antibiotics such as chlortetracycline from wastewater by using organic aerogels of resorcinol formaldehyde modified with 1% by weight graphene oxide fucionalized to an amino group by a pore filling mechanism has an efficiency of 94.37% and an absorption capacity of 472 mg g^{-1} at pH of 4 (see table 1). (67)

Table 1. Adsorption removal of chlortetracycline (R (%) at different pH values**.**

Sample	pH	Chlortetracycline		
		Final concentration (after the adsorption)	***Removal (%)***	***Qe* (mg g^{-1})**
RF-GOA1	2	3.49 ± 0.2	91.27	456
	4	2.25 ± 0.1	94.37	472
	6	4.41 ± 0.2	88.97	445
	8	5.82 ± 0.3	85.45	427
	10	5.82 ± 0.2	85.45	427
	12	7.70 ± 0.5	80.75	404

***Source**: (Behzadi, Hashemi Motlagh, Raef, & Motahari, 2022)* (67)

Similarly in the use of 3D porous bio-carbon aerogel from lyophilized chitosan a biodegradable natural product with high resistance in alkaline medium, which in the application for the Adsorption of this aerogel obtained removal for broad-spectrum pheniclo antibiotics of 90% (68).

4.9 Membrane of nanofibres

A method of removal of antibiotics that has given good results in aqueous media is the use of nanofiber membranes a separation process by which a fluid passes through a semipermeable membrane under certain pressure conditions, can be seen in the results in the study on the degradation of chlortetracycline when using Lacase, a type of fungal ligninolytic enzyme immobilized in a nano fibrous membrane composed of polyacrylonitrile-biochar by obtaining removal efficiencies for a flow rate of 1 mL/hcm^2 of 58.3% and an 80% removal in tetracycline removal in the first 12 h when Cerrena Laccase was immobilized in ceramic membranes. (69) (70)

4.10 Ultrafiltration

As in studies on the removal of ciprofloxacin from aqueous media when using ultrafiltration membranes with water-soluble polyelectrolytes a technique in which toxic and inorganic species are separated, without diffusion problems, that is, a type of filtration improved by the use of polymers where the order of the solute is 100 nm being able to retain macromolecules as evidenced in the results obtained sen the removal of 80% with poly[3-(acryloylamino)) propyl] trimethylammonium-*co*-sodium chloride 4-styrenesulfonate] in a ratio of 20:1 at pH 5. (71)

4.11 Liquid-phase-polymer based retention, LPR

The technique of retention in liquid phase assisted by polymers is a combined method of separation by ultrafiltration and membrane with water-soluble polymers, where it is possible to separate substances of low molecular weight that are dissolved in an aqueous medium, since the polymers coupled to these membranes trap the species of interest and retain them (see figure 9). This technique has been applied in the removal of antibiotics such as amoxicillin, tetracycline, and ciprofloxacin, obtaining removal percentages greater than that 70% due to adsorbent-adsorbate homogeneity and affinity. (23) (72) (73) (74) (75) (76) (77) (78)

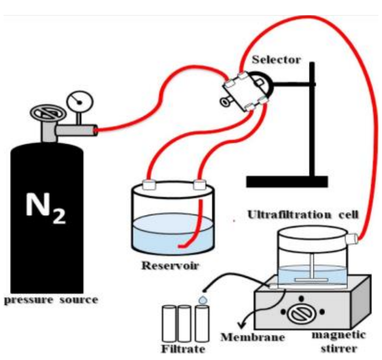

Figure 9. Representation of the technique based on polymers in liquid phase. Source: (71)

Despite the numerous antibiotic removal techniques reported above, only three macrolide removal techniques have been reported, with high removal rates, however, more information is needed (see table 2).

Table 2. Techniques reported for macrolide removal

Macrolide	Analytical Technique	Removal (%)	Reference
Azithromicin **Clarithromicine**	Biodegradation by microalgae S. capricornutum and C. vulgaris	78%	(50)
Azithromicin	Sonochemical	87.36%	(79)
Azithromicin **Clarithromicine** **Erithromicine**	Continue ozonation	73% 98% 70%	(61)

5. PROJECTION

As mentioned above, the importance of this type of antibiotics is high due to the increase in their consumption in recent years and the inefficient removal techniques reported and studied, in addition to the scarce information in the literature about their harmful effects; so this research is projected to the study and development of new sustainable techniques to be applied in the removal of macrolides such as azithromycin, such as the use of water-soluble biopolymers combined with membrane ultrafiltration membranes a technique that has been studied and has obtained good removal percentages for antibiotics such as ciprofloxacin and tetracycline.

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CONCLUSIONS

This review presents an overview of antibiotics as emerging contaminants in aqueous media, specifically macrolides since, due to the increase in their consumption in the last couple of years to avoid contagion or reduce the symptoms of COVID-19, their presence in this type of medium has been reported in increase, which would subsequently mean an increase in the harmful effects they can cause, to humans and animals, due to their bioaccumulation due to inefficient removal techniques existing in conventional treatment plants.

The development of this review allowed us to know that the presence of antibiotics such as macrolides is potentially harmful, however, in the literature the data reported for effective removal are scarce, which makes future research work for its detection, quantification, determination of specific harmful effects for this type of antibiotics, in addition to new and efficient techniques for its removal are necessary.

Despite the significant increase in the consumption of antibiotics, also macrolides, and their harmful impact on the environment, there is no research and development of techniques for its removal from aqueous medium. This review is an effort to present and analyze the few analytical techniques investigated to remove this type of antibiotics. That is why there is a great challenge for the scientific community for the near future.

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