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Sterilization of implantable polymer-based medical devices: A review

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ABSTRACT

This review article is focused on the sterilization techniques used for polymer-based implantable medical devices as well as the regulatory aspects governing sterile medical devices. Polymeric materials are increasingly used in implantable devices due to their biodegradable and biocompatible nature. Patients and medical staff often prefer long-term implantable devices and these can be achieved using high molecular weight polymers. Sterilization of polymer-based implantable devices is critical. Since all implantable devices must be sterile, the effect of the sterilization method on the different device components (such as, the polymer, the drug, the electronics, *etc.*) has to be considered. A comprehensive summary of the established sterilization methods is provided along with the possible effects on polymers. In addition, novel sterilization methods are also discussed.

1. Introduction

As per the definition stated by the Food and Drug Administration (FDA), a medical device (MD) is “an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is: (*i*) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; (*ii*) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or (*iii*) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" (FDA, 2017a).

Medical devices (MD) are regulated in the US by the FDA under the Medical Device Regulation Act of 1976 and by the subsequent amendments made to the Federal Food, Drug and Cosmetics Act of 1938. The MD’s have been organized into three classes by the FDA, namely Class I, II and III based on the risks involved, and the degree of regulatory control necessary to ensure a device’s safety and effectiveness (FDA, 2017b). Class I devices such as bandages, gloves and hand-held surgical tools are considered low-risk, and are subjected to the lowest level of regulatory control. Class II devices such as condoms, pregnancy test-kits and powered wheelchairs are considered higher-risk compared to Class I devices and thus require special controls for labeling, guidance, tracking, design, performance standards, and post-market monitoring. Many Class II devices require premarket notification 510 (k) to demonstrate substantial equivalence (*i.e.* that they have the same intended use and technological characteristics) to a legally marketed device. Class III devices such as implantable glucose sensors, pacemakers and breast implants are considered the highest risk and require stringent regulations. Most Class III devices require pre-market approval (PMA). PMA examines a variety of factors in weighing the probable health benefits from the intended use of a device versus the probable risks. Fig. 1 shows a flowchart of the classification of MD’s and steps involved in the approval process (US FDA, 2017).

Implantable MD’s fall under Class II/III devices and are defined as devices placed inside the body for a short or long-term period in order to serve their intended purpose. Based on their application, implantable MD’s are divided into three groups: Orthopedic implants, Cardiovascular implants and implants for other use (Khan et al., 2014). The US implantable device market is expected to be worth $73.9 billion by 2018 (Top 5, 2017). Orthopedic implants are the most commonly used medical implants and have the largest market share.

Currently, polymeric materials are rapidly replacing or are used in conjunction with other materials such as metals, alloys and ceramics in device preparation (Teo et al., 2016; Lyu and Untereker, 2009). Table 1 provides a list of polymers used in implantable devices along with their preferred sterilization methods and applications. Biodegradable polymers such as polyesters, polycarbonates, polysaccharides, *etc.* are preferred over non-biodegradable polymers as they are cleared from the body over time thus allowing the neighboring tissues to restore their functionality following treatment with the implantable device.

Infection is a major problem associated with implantable devices and involves bacterial, device and host related factors (Matthews et al., 1994).

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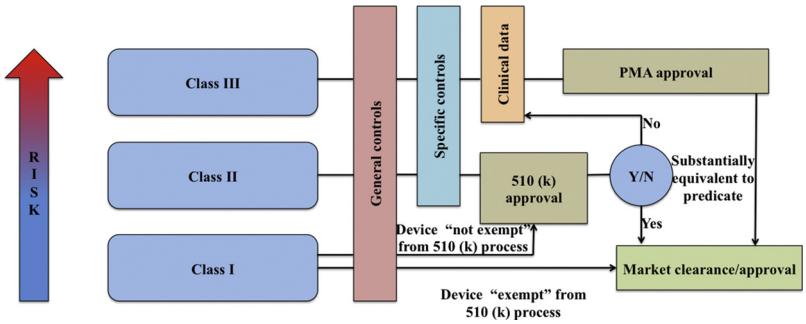

Fig. 1. Classification of Medical Devices according to FDA and steps involved in the approval process.

Table 1
Polymers used in implantable medical devices with their preferred sterilization methods and applications (Magnan et al., 2013; Anagnostakos et al., 2006; Faris et al., 2006; Sharkey et al., 2002; Edwards et al., 2001; Jaganathan et al., 2014; Mahyudin et al., 2016; Maitz, 2015; Cao et al., 2012; Gentile et al., 2011; Ghanbari et al., 2009; Yee Han et al., 2011; Bezuidenhout et al., 2015; Ormiston and Serruys, 2009; Baino, 2010; Gaviria et al., 2014).

Type of Implant	Polymers used	Polymer-based preferred sterilization method(s)	Specific application(s)
Orthopedic	Polymethyl methacrylic acid (PMMA)	EO, H_2O_2	acrylic bone cements anchoring of hip prostheses vertebroplasties and kyphoplasties
	Polyethylene (PE)	EO, radiation	liner of acetabular cups in hip arthroplasties tibial insert and patellar components in total knee arthoplasties
	Polydimethyl siloxane (PDMS)		replacement for small joints in hand and foot
	Polypropylene (PP)	steam, EO	bone fixation devices
	Polysulfone (PS)	steam, dry heat, EO, radiation	bone fixation devices, total joint arthoplasties
	Polycarbonate (PC), Poly glycolic acid (PGA),	**PC**- EO, radiation; **PGA**- steam, dry heat, EO, radiation;	bioabsorbable fixation devices, bone regeneration and
	Polylactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA),	**PLA**- EO, radiation; **PLGA-** EO, gamma;	drug delivery
	Polydioxanone (PDS), Polycaprolactone (PCL),	**PCL**- dry heat, EO, radiation	
Cardiovascular	Polyamides (PA)	EO, radiation	transparent tubing's hemodialysis membranes percutaneous transluminal coronary angioplasty (PTCA) catheters
	Polyolefins- PP and PE		tubing's and housing for blood supply PP: heart valves structure
	Polyesters- PGA, PLA and PLGA		bioabsorbable stents
	Polytetrafluoroethylene (PTFE) or Teflon	EO	vascular grafts sutures heart valves
Other implants			
Ophthalmic	Hydrogels of cross-linked polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyacryl amide (PAA)	**PEG**-EO; **PVP**- steam; **PVA**-EO	retinal detachment treatment
Gastroenterological	Nylon, polyvinyl chloride (PVC), silicones	**Nylon, PVC**- EO; **silicones-** steam, dry heat, EO, radiation	
Dental	Polyurethane (PU), polyamide, PMMA, PTFE	**PU**- EO, radiation	
Gynaecological	Polypropylene		scaffold for growth of fibro-collagenous tissue

Commonly found bacteria include Staphylococcus *aureus*, Staphylococcus *epidermidis, Eschericia coli, etc*. (Darouiche, 2001). Several device factors such as shape, size, and location can also facilitate virulence. To prevent infection, sterilization is a critical step in the manufacturing of MD's and also in the preparation for reuse of MD's (such as suction tubes, endoscopes, *etc.*). Failure in sterilization for a MD can leave the patient exposed to various nosocomial infections, which could in turn be life threatening. It is important to consider sterilization and related issues early on in the development of the MD as opposed to the final stages to ensure the safety and effectiveness of the device. This review article focuses on established as well as novel sterilization techniques for polymer-based implantable MD's providing an emphasis on the impact of these techniques on polymer stability and degradation.

2. Sterilization

Sterilization is defined as the process by which all-living cells, viable spores, viri and viriods are either destroyed or removed from an object. Sterilization can be achieved through the use of a passive process (aseptic processing) or through an aggressive process (terminal sterilization). As aseptic processing is expensive, terminal sterilization is the most commonly used method. Sterilization of implantable MD's is performed to eliminate pathogenic organisms and thus minimize the risk of infection.

Sterilization efficiency or sterility is measured in terms of the Sterility Assurance Level (SAL). A SAL limit of 10^{-6} is generally acceptable for pharmacopoeial sterilization procedures and is defined as

'the probability of finding not more than one viable microorganism in one million sterilized materials' (von Woedtke and Kramer, 2008). Upon optimizing an existing sterilization technique or developing a novel technique, method validation studies have to be performed. The validation studies should document that the product can achieve the required SAL post sterilization by the proposed method. In the industrial setup, sterilization validation is generally evaluated by: (*i)* determining the qualitative and quantitative bioburden after product manufacture; (*ii)* determining the rate of killing using fractional-run sterilization; and (*iii)* determining the duration required to achieve 10^{-6} SAL. In fractional-run sterilization, the product is exposed to a fixed dose of sterilant, following which the number of resistant microorganisms is reported graphically on a semi-logarithmic plot and by extrapolation, the dose and time required to achieve 10^{-6} SAL is estimated (Katoh and Yoshida, 2009).

3. Regulatory aspects governing sterilization

FDA has categorized sterilization methods for MD's in the manufacturing setup as established and novel methods (FDA, 2016). Established methods are further divided into Categories A and B. Category A methods include dry heat, ethylene oxide (EO), steam and radiation sterilization. These methods have a long history of safety and efficacy demonstrated through the large number of marketed products as well as multiple sources of information such as clearances of 510 (k)'s and approval of PMA applications. There exists consensus standards for development, validation and process control for these methods that are recognized by FDA. Category B methods include hydrogen peroxide and ozone. These methods have no dedicated FDA-recognized consensus standards. However, there is published literature on the development, validation and process control for these methods. Novel sterilization methods such as vaporized peracetic acid (VPA), high intensity or pulse light and microwave radiation are newly developed methods where little or no information is available and no FDA-recognized consensus standards exist.

Implantable devices are always labeled 'sterile' and the sponsor has to submit all documents as listed in the guidance of 'Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile' (FDA, 2016).

4. Polymers used in implantable medical devices

A wide range of polymers is used in implantable MD's (refer to Table 1). Polymers can serve as a protective coating (*i.e.*, a layer separating two materials) or as a substrate for the device (Teo et al., 2016). Although the use of polymers in implantable MD's has increased, they can be very sensitive towards different sterilization techniques such as steam, dry heat and ethylene oxide sterilization. This can limit the use of these techniques for sterilization of implantable MD's. Therefore, polymer selection for MD's requires serious consideration regarding the design, processing and performance of the device as well as the biocompatibility, functionality and the effect of sterilization on the polymer.

5. Established sterilization methods for implantable devices

5.1. Dry heat sterilization

Dry heat sterilization is a simple sterilization technique typically performed using an oven at high temperature (approximately 160 °C) for 2 h (Rogers, 2012a; Darmady et al., 1961). The duration and temperature can be controlled depending on the targeted microorganisms. The microorganisms are eliminated by coagulation of proteins.

Heat-resistant polymers such as polyether ether ketone (PEEK), silicone, acetal, polypropylene (PP), Teflon®, polyurethane (PU) can be sterilized using the dry heat technique Heat-sensitive polymers such as poly lactic acid and poly glycolic acid cannot be sterilized using dry heat and accordingly, other methods must be used The high temperature used in dry heat may result in thermal transitions such as melting, softening or expansion of polymers Therefore, the temperature selected for this technique should be under the melting and degradation temperature of the polymer (Rogers, 2012b).

5.2. Steam sterilization

Steam sterilization uses an autoclave, which combines heat and moisture with elevated pressure to achieve sterilization (Dion and Parker, 2013). The presence of moisture significantly speeds up heat penetration and therefore lower temperatures and shorter times can be used compared to dry heat sterilization. High temperature steam (generally 121 °C) is forced under high pressure, thereby displacing air. Steam destroys microorganisms by the irreversible coagulation and denaturation of enzymes and structural proteins. The critical parameters of the autoclaving cycle are the temperature and duration, which are dependent on pressure and the type of microorganism to be targeted. Following sterilization, steam is released and the sterilized objects are removed. The entire cycle takes between approximately 20–60 min.

Steam sterilization is suitable only for polymers that are heat and moisture resistant (such as PEEK, polysulfones, *etc.*). Thermal degradation and decomposition as well as hydrolysis can occur for heat and moisture sensitive polymers (such as PLGA, nylon, polystyrene, *etc.*).

5.3. Ethylene oxide (EO) sterilization

Many implantable MD's, especially drug/polymer-coated implants cannot withstand the high temperature used during dry heat sterilization and are sensitive to moisture used in steam sterilization. Such devices may be sterilized at low temperatures using EO gas. EO is a colorless gas with a boiling point of 10.4 °C at 760 mm of mercury. The biocidal activity of EO is dependent upon its alkylating power and in turn on the unstable three-membered ring structure shown in Fig. 2a. Alkylation involves the addition of certain saturated hydrocarbon groups to reactive amino (NH_2), sulfydryl (SH), hydroxyl (OH) or carboxyl (COOH) groups on protein molecules and to amino (NH_2) groups, which are part of the ring structure of nucleic acid bases. The efficiency of EO sterilization depends upon the concentration of the gas, temperature, relative humidity and gas exposure duration. The typical steps involved in an EO sterilization cycle are shown in Fig. 2b.

1 Initial evacuation and nitrogen dilution- This step removes almost 97% of oxygen from the sterilization chamber by pulling either a deep vacuum or prolonged series of shallow vacuums followed by nitrogen injections.
2 Conditioning – The sterilization chamber is heated and humidified to regain the moisture lost during evacuation.
3 EO injection and dwell time- EO gas is introduced in the chamber at a pre-determined pressure. The gas is kept in contact with the materials to be sterilized for a specified amount of time (approximately 3 h).
4 EO removal and nitrogen washes- EO gas is removed from the chamber by a series of vacuum pulls followed by nitrogen injections.
5 Air in-bleed- The sterilization chamber is brought to atmospheric pressure by bleeding in filtered air.

A typical EO sterilization cycle takes about 2.5 h excluding the EO removal step. The air-bleeding step may take approximately 8 h. The usual temperature range is 30–60 °C (Matthews et al., 1994; Rogers, 2012a). The EO sterilization process is well suited for MD's with embedded electronics such as glucose sensors (Mendes et al., 2007). However, the vacuum involved during the sterilization process may not

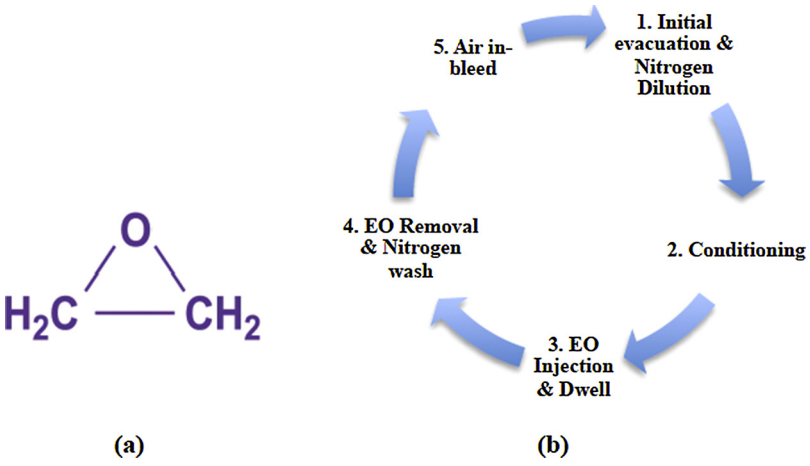

Fig. 2. (a) Ethylene oxide structure; (b) A typical ethylene oxide sterilization cycle.

be suitable for embedded batteries (Linke, 2011). As EO is a highly flammable gas and a carcinogen, proper precaution must be taken while handling. Heat-sensitive polymer-based implantable MD's can be sterilized using EO sterilization. As low temperatures can be maintained during processing, the polymer can remain below its glass transition temperature and thus can retain its physical form and properties without undergoing thermal transitions. EO sterilization is compatible with almost every polymer used in implantable MD's (Steripro and Emeaa, 2017). One of the limitations of EO gas sterilization is that toxic residues such as ethylene chlorohydrin may remain post sterilization. The amount of residues can vary with EO gas concentration, duration and the absorptivity power of the polymers (Matthews et al., 1994). EO sterilization is a gentle sterilization process compared to radiation, steam and dry heat, therefore, typically no polymer degradation is observed.

5.4. Radiation sterilization

Radiation sterilization can be of two types depending on the source of radiation: Gamma sterilization and Electron beam sterilization Gamma radiation utilizes high-energy gamma rays, which have excellent penetration powers Electron beam sterilization employs a constant stream of high-energy electrons Radiation sterilization is a fast process, requiring only one dose between 15–45 kGy, thus resulting in ease of application 25 kGy is a typical dose commonly employed to destroy the microbial load Although radiation is an effective sterilization technique, the initial capital costs for setting up a radiation facility is very high Radiation kills bacteria by breaking down the bacterial DNA thus inhibiting bacterial division Radiation can also kill bacteria by formation of free radicals (Aquino, 2012).

A typical radiation sterilization cycle consists of: (*i*) loading the product to be sterilized into the processing container as per its size; (*ii*) dosimeters are placed in the sterilization chamber and the product is exposed to the radiation field, typically a Cobalt 60 source (gamma radiation) or fast accelerating electrons (electron beam radiation); and, (*iii*) following exposure to the radiation for the optimized duration, the dosimeters are analyzed to confirm that the required dose has been delivered. Radiation dose, temperature and duration are critical parameters that have to be controlled during sterilization.

Polymer compatibility is a challenge for radiation sterilization. Radiation can cause degradation of polymers by cross-linking, chain scission or a combination of both (Hasanain et al., 2014; Montanari et al., 2001; Sterilization and Sciences, 2012). Upon exposure to gamma radiation, molecular bonds may be broken. A polymer may regain its original configuration following gamma sterilization if the polymer bond strength is strong. However, if the polymer bond strength is weak, chain scission may happen, resulting in the formation of shorter chains, which can further undergo degradation, effectively weakening the polymer. Radiation affected bond strength can cause changes over the life of the polymer implant. Therefore, polymers with high bond energies (consisting of benzene rings) are more stable towards radiation sterilization. In radiation sterilization, free radicals are produced, which can initiate a chain reaction that propagates and causes cross-linking.

The effects of radiation on polymers can be influenced by several polymer properties such as chemical composition, crystallinity, molecular weight and density along with radiation dose, dose rate and temperature Some of the commonly used polymers sensitive to radiation include poly glycolic acid (PGA), polymethyl methacrylate (PMMA) and polyvinylidene fluoride (PVF) (Rogers, 2012b).

5.5. Hydrogen peroxide (H_2O_2) sterilization

H_2O_2 is known to have microbicidal effects. It can be used in two ways to sterilize MD's: (*1*) vaporized hydrogen peroxide and (*2*) hydrogen peroxide plasma. H_2O_2 kills microorganisms by generating oxidative stress by producing reactive oxygen species (*e.g.* hydroxyl radicals) that attack multiple molecular targets, including nucleic acids, enzymes, cell wall proteins, and lipids. H_2O_2 is used predominantly in hospitals and less so in MD manufacturing. It is most often used as a surface sterilization technique for implantable devices (Rogers, 2012b; Oshiro et al., 2012).

5.5.1. Vaporized hydrogen peroxide (VHP) sterilization

A typical VHP sterilization cycle consists of three stages: (*i*) vacuum generation; (*ii*) H_2O_2 injection; and (*iii*) aeration. The temperature range used for sterilization is 25–50 °C and the total duration takes approximately 1.5 h. VHP sterilization is suitable for implantable medical devices that cannot sustain the high temperature and moisture necessary for steam sterilization. Due to its low temperature of operation, the VHP sterilization process is appropriate for medical devices with embedded electronics. The penetration capabilities of VHP are lower than that of EO gas.

5.5.2. Hydrogen peroxide plasma (HPP) sterilization

The HPP sterilizer is first filled with the objects to be sterilized. A typical HPP sterilization cycle consists of four stages: (*i*) vacuum generation; (*ii*) H_2O_2 injection; (*iii*) diffusion; and (*iv*) plasma discharge. The temperature range used for sterilization is 40–65 °C and the total duration takes approximately 1–3 h. HPP sterilization inactivates microorganisms by the combined use of H_2O_2 and the generation of free radicals (*e.g.* hydroxyl and hydroperoxyl free radicals) during the plasma phase of the cycle. The required vacuum is not as deep as with VHP sterilization. Although HPP sterilization utilizes low processing temperatures, high radiofrequency energy (RF) of 13.56 MHz in the

range of 200–400 W is produced during the plasma discharge phase, which can pose problems for the embedded electronics in the devices to be sterilized.

H_2O_2 can be utilized for sterilization of several different polymers. The number is still limited when compared to EO sterilization because of the severe oxidizing effects of H_2O_2. However, this technique has advantages over EO with regards to the shorter processing times and no toxic residue accumulation on or in the sterilized product. Some polymers such as PU, nylon, and cellulose are H_2O_2 absorbers and therefore, it is best to avoid H_2O_2 sterilization. HPP sterilization at low temperature has less effect on polymers compared to VHP as the plasma destroys more peroxide residues compared to the aeration used in VHP.

5.6. Ozone sterilization

Ozone is a strong oxidative gas, which can chemically alter and inactivate numerous chemical contaminants and pathogens. Ozone is produced when O_2 is energized in an electric field. O_2 splits into two monoatomic molecules. The monoatomic oxygen molecule then collides with an O_2 molecule to form ozone (O_3). The sterilization cycle usually lasts about 4.5 h. The first step involves vacuum creation, followed by humidification of devices and generation of ozone. An in-line monitor measures the produced ozone gas. After exposure to two ozone cycles, ventilation is carried out to remove ozone from the chamber. The medical devices to be sterilized should be resistant to oxidation owing to the highly oxidizing nature of ozone. Certain polymers can react with ozone and hence, cannot be sterilized by this technique. However, there are no toxic residues left behind on the product as observed in EO sterilization. Ozone has a greater penetration power compared to H_2O_2 vapor and plasma sterilization but a lesser penetration power compared to EO gas. Several commonly used polymers such as polyacetals, polyethylene, polyesters, polycarbonate and polyvinyl chloride can be sterilized using ozone sterilization (Rogers, 2012b; Rediguieri et al., 2016).

6. Novel sterilization techniques for implantable devices

6.1. Vaporized peracetic acid (VPA) sterilization

VPA is recognized as a sporicidal. Limited information is available in the literature regarding the mechanism of action of peracetic acid (PAA) but it is thought to function as other oxidizing agents, *i.e.*, it denatures proteins, disrupts cell wall permeability, and oxidizes sulfydryl and sulfur bonds in proteins, enzymes, and other metabolites (Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008). VPA delivery at room temperature is compatible with most materials and therefore can be ubiquitously utilized. A typical VPA sterilization cycle consists of the following stages: *(i)* chamber evacuation; (*ii)* chemical injection *via* vaporization; (*iii)* chamber dehumidification; and (*iv)* chamber ventilation. Depending on the complexity of the device, several injection blocks can be used to achieve complete sterilization. The entire cycle takes place at room temperature and is complete in 2–4 h. Post sterilization, VPA is broken down into relatively harmless, naturally occurring substances such as water, oxygen and carbon dioxide compared to the toxic residues left behind during EO sterilization.

6.2. Ultraviolet light (UV) sterilization

UV light sterilization utilizes UV rays that have a wavelength ranging from 328 to 210 nm to kill microorganisms. The maximum bactericidal effect is obtained between 240–280 nm. Mercury lamps are the commonly used light source. UV light has a very low penetration power compared to other radiation based sterilization techniques. Therefore, this technique is limited to treatment of water and surfaces. UV sterilization is being explored for use in sterilization of implantable devices (Rogers, 2012b; Iwaguch et al., 2002).

6.3. High intensity light or pulse light (PL) sterilization

Pulsed light also known as white light sterilization is an emerging technique and has been the subject of a number of patents. The complete mechanism of this technique is unclear as yet, but ultraviolet radiation plays an important role in it. Short duration pulses of intense, broad-spectrum light are utilized for the sterilization of surfaces. This technique, like UV sterilization, has the limitation of poor penetration. Therefore, PL sterilization is considered as a surface decontamination technique (Chen et al., 2015).

6.4. Microwave radiation

The nonionizing radiation of microwaves produces hyperthermic conditions that disrupt life processes. This heating action affects water molecules and interferes with cell membranes of microorganisms. Microwave sterilization uses low-pressure steam with the nonionizing radiation to produce localized heat that kills microorganisms. The temperature is lower than the conventional steam sterilization method. It has been suggested as a practical physical sterilization method considering its low cost, speed and simplicity. However, there are few publications on this sterilization technique and limited information is available on the applicability of this technique to sterilize polymer-based implantable devices (Iwaguch et al., 2002; Chau et al., 1996).

6.5. Sound waves

Sound waves, with frequencies beyond the human hearing range (*i.e.,* beyond 20 kHz) are used to form oscillating bubbles by a process called cavitation These bubbles act on debris to remove it from the instruments This also is a surface de-contamination technique and is being investigated for potential use in sterilization of implantable devices (Dai et al., 2016).

7. Conclusions

There has been a tremendous increase in the number of polymer-based implantable medical devices over the last decade. Polymer-based implantable devices are preferred over non-polymer based implants due to their biocompatibility and long-term efficacy. There is no one standard method with standard parameters recommended by the FDA for sterilization of polymer-based implantable medical devices. Manufacturers must optimize the method and its critical parameters depending on the device components, size, type, *etc*. Currently, ethylene oxide sterilization is the most widely used method for sterilization of polymer-based and electronic implantable devices. However, the residues that are left behind by this process are toxic and carcinogenic. A novel method such as vaporized peracetic acid has potential for use as a safer alternative to ethylene oxide sterilization. Other novel sterilization methods are being investigated for their use in sterilization of polymer-based implantable devices and presently remain as surface decontamination techniques.

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