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Systematic Review on Sterilization Methods of Implants and Medical Devices

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Abstract: Sterile implants and devices should be introduced into any animal body, in order to avoid nosocomial infection which can subsequently cause implant failure and serious illness. Unsterile implants can become lethal to the host system. Hence, it is highly mandatory to achieve 'sterility', the absence of all living organisms such as virus, bacteria, yeasts and molds. There are numerous techniques to sterilize implants. Sterilization using Moist heat (autoclaving), Dry heat, Ethylene Oxide (EtO), Chlorine dioxide, Ozone (O_3), Vapor phase Hydrogen Peroxide (H_2O_2), Low temperature gas plasma, Glutaraldehyde solution, Formaldehyde, Peracetic acid and Radiation [Machine generated X rays, Gamma rays, Universal homogeneous ultraviolet (UHUV) rays, Accelerated electron beam] are some of the techniques frequently used. Each method has its own effect on the implant's characteristics. Since sterile conditions should be maintained till the time of implantation, it is wise to consider sterilization-related issues at the earliest, during the implant development process, so that more economic and readily sterilizable product is achieved. This review paper discusses some sterilization techniques and their effect on the implants sterilized, along with their advantages and disadvantages.
Keywords: Implants, Sterilization techniques, Medical devices, Radiation, Accelerated electron beam, Flash steam.

Introduction

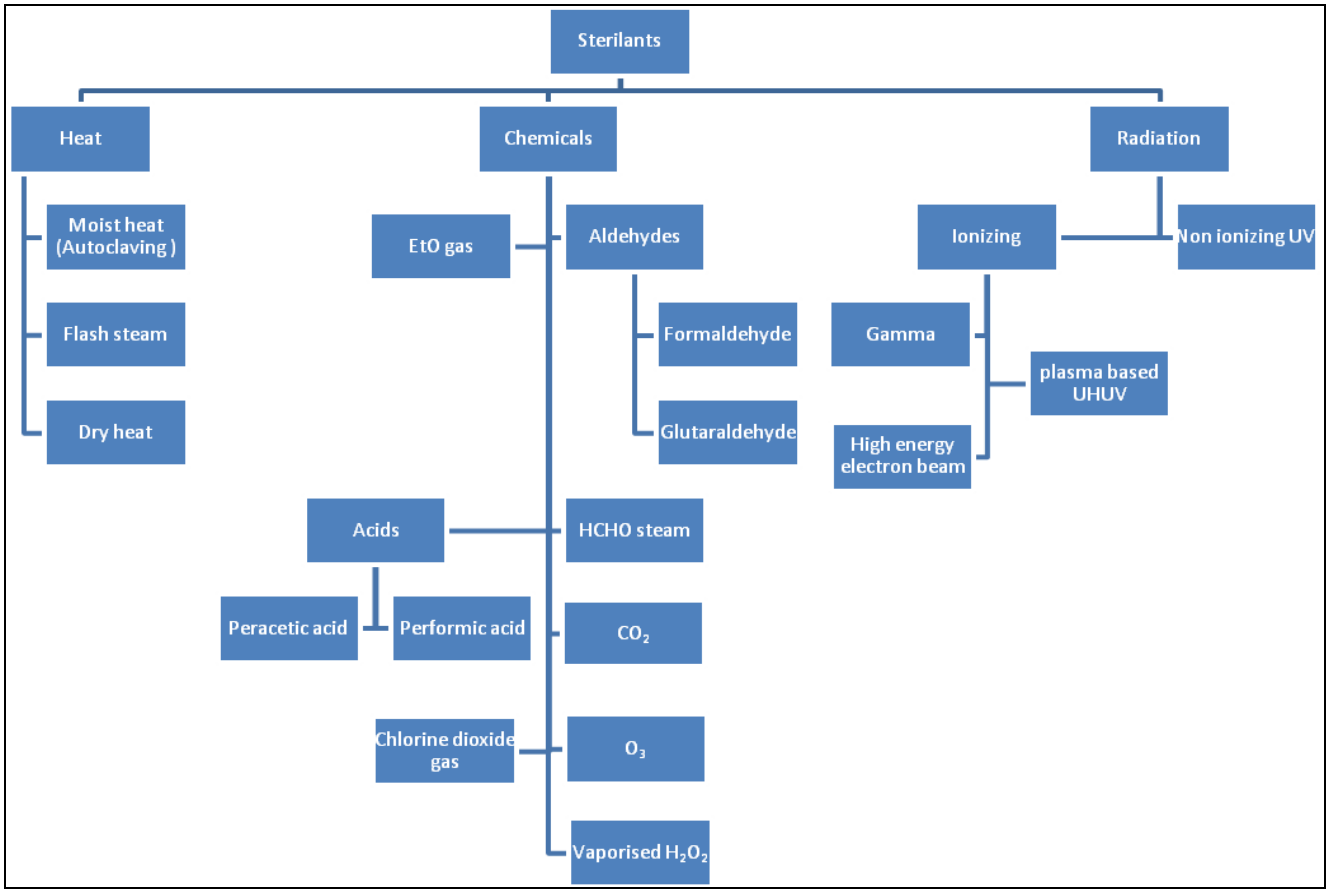
Medical devices can be classified based on the degree of risk of infection involved in their use as: *Critical, Semi-critical* and *Non-critical* [1,2]. *Critical* devices such as implants, cardiac & urinary catheters are those introduced to normally sterile area (e.g., blood stream) within patient's body, where contamination is highly risk. *Semi-critical* devices like flexible endoscopes & endotracheal tubes are those in contact with mucous membrane or non-intact (broken) skin, posing lower risk. *Non-critical* devices (e.g., stethoscopes) may contact only the intact skin and thus they present the lowest risk. As cleaning prior to disinfection and sterilization considerably reduces contamination and improves efficacy of further processes of disinfection or sterilization, it is highly recommended [3, 4, 5]. *Disinfection* can eliminate microbes, but not necessarily all microbial forms (e.g., bacterial spores) from the inanimate objects of interest. *Low-level disinfection* (e.g., Exposure to Quaternary ammonium germicidal detergent solution for maximum time of 10 min) can kill most vegetative bacteria, some (enveloped) viruses and some fungi. *Intermediate-level disinfection* can eliminate most bacteria (vegetative & mycobacteria including *M.tuberculosis*), most fungi and most (enveloped & non-enveloped) viruses [2]. Some semi-critical devices like thermometers can be sufficiently disinfected by their exposure to intermediate-level disinfectants (e.g., Ethanol (70% to 90%), chlorine, iodophor, phenolics) for maximum time of 10 min [4]. Disinfection of non-critical devices may be done in low-level or intermediate-level. *High-level disinfection* can destroy all microbes, with the exception of high number of bacterial spores. It is usually done for semi-critical devices by exposing them to disinfectant for minimum 20 min. Glutaraldehyde

based formulations (2%), Stabilized hydrogen peroxide (6%), Peracetic acid and Sodium hypochlorite solutions at suitable concentrations are some of high-level disinfectants required in case of most of the semi-critical devices (except dental items which should be heat sterilized) [4]. The *SAL* is the probability that a product will be non sterile after exposure to a specified sterilization process [6]. In general, the maximum acceptable SAL is 10^{-6}. Sterilants like steam, EtO and low temperature plasma are suggested in case of critical devices.

Implants & devices which are categorized *critical* should therefore be *sterilized* properly before their introduction into patient's body [6]. "Microbiologically clean" implant surfaces having "low bioburden", can be more readily disinfected and sterilized than those are highly contaminated. Small number of product samples can be checked for their sterility by simply dipping each of the samples in individual (sterile) containers having microbiological culture medium, at aseptic conditions. After incubation under proper conditions favorable for microbial growth without contamination, if any of the culture media becomes turbid, then the corresponding product sample is nonsterile. If the medium shows no microbial growth, then the sample kept in it is sterile. Sterility of large number of products from industrial scale sterilizer can be ensured by determination of SAL using sterilization product development and validation studies [6]. Recommended Standards of Practice for Monitoring Sterility in the preoperative setting were given by Association of Surgical Technologies (AST) in 2008.

Sterilization Processes

Sterilants used in the sterilization processes can be classified as:



Heat Sterilization

Autoclaving or Moist Heat Sterilization

This was the first method utilized for sterilization of medical products (ISO 11134, 1994) [6]. Autoclaves are mostly metallic vessels, which can withstand high temperatures and pressures. The sterility is achieved by direct exposure of the material to saturated steam at 121˚C or 132˚C in a pressure-rated sterilization chamber. The entire process lasts for 15 to 30 min after all surfaces of the product reach a temperature of at least 121˚C [5,6]. Gravity displacement autoclave and high-speed pre-vacuum sterilizer are the two fundamental

types of steam sterilizers. In case of gravity displacement autoclave, steam (121°C for 30 min) [5] enters near the top of the sterilization chamber displacing heavy air out the bottom of the chamber via drain vent. Here, incomplete air elimination would increase penetration time. The high-speed pre-vacuum sterilizers (Sterilization conditions: 132°C for minimum 4 minute) are similar to the former, except that a vacuum pump is attached to make sure that air is ejected from the sterilizer and load before steam is made to enter. In this case, nearly instantaneous steam penetration occurs even into porous loads. Steam flush pressure-pulsing process (Sterilization conditions: 132°C to 135°C for 3-4 min) is one another design which eliminates air rapidly by repeatedly alternating a steam flush and a pressure pulse above atmospheric pressure [5]. Due to elevated pressure, air leakage doesn't lower efficacy of the process. Sterilization time may vary depending upon nature (e.g., porosity) of the material, packaging material and the type of sterilizer used.

At given sterilization conditions, destruction of metabolic and structural components essential for replication of microorganisms occurs. The main lethal events are irreversible coagulation and denaturation of important enzymes and destruction of proteins & lipid complexes and bacterial endotoxins. Presence of moisture has considerable effects over protein coagulation temperatures and lethal temperatures of microbes.

Flash (Steam) Sterilization

Flash sterilization is a modification of conventional steam sterilization, in which the product to be sterilized is placed in an open tray or in a specially designed, rigid, covered container to allow rapid penetration of steam [5]. Gravity displacement cycle, Prevacuum cycle and Single-wrap cycle are some of the types of Flash sterilization cycles available.

The Centers for Disease Control and Prevention (CDC), The Association of Operating room nurses (AORN) and The Association of the Advancement of Medical Instrumentation (AAMI) all recommend not to flash sterilize implantable medical devices as they are *critical* [7].

Dry Heat Sterilization

The sterility is attained by exposure of the materials to extreme temperatures (>140°C). In general, temperature-time relationships for sterilization by hot air sterilizers are 170°C for 60 min, 160°C for 120 min, 150°C for 150 min. To monitor the dry heat sterilization process, spores of *B.subtilis* or *B.atrophaeus* must be used because; they are more resistant to dry heat than *B.stearothermophilus* [5]. Static-air type sterilizers are of oven-type in which heating coils at the bottom heat air and the heated air molecules rise within the chamber by gravity convection. Demerits of this type over mechanical convection sterilizers are: Low rate of heating, High time consumption, Less uniform temperature control. Forced-air type sterilizers or Mechanical convection sterilizers employs a motor-driven blower which circulates heated air with higher velocity throughout chamber [5]. This helps rapid energy transfer form air to the sterilized product. Surface characteristics like surface topography and energy of unalloyed Titanium implants, can change due to exposure to dry heat. Such alterations in implant surface characteristics have significant effects on biological responses [8].

Oxidation of cellular constituents is considered the primary lethal process, during dry heat sterilization [5,6]. Destruction of bacterial endotoxins is also told to be significant lethal factor.

Chemical Sterilization

Some of the chemical sterilants are discussed below. In order to protect tissues from damage, chemically sterilized devices or implants must be rinsed with sterile water or sterile saline before usage.

EtO Sterilization

This is a conventional chemical sterilization method. Below its boiling point of 11°C, EtO is a clear, colorless liquid. EtO is considered toxic and carcinogenic. Pure EtO and mixtures without proven inerting compound, are flammable and explosive. Hence, Pure EtO should be handled in explosion proof equipment. EtO (12%) mixed with Chlorofluorocarbon (CFC-12) becomes non-flammable sterilant. Due to the ozone-depleting effects of CFC on the earth's atmosphere, N_2, CO_2, HCFC (Hydrochlorofluorocarbon) or any other suitable non-ozone-depleting compound can be used as the inerting compound. HCFC is 50 fold less ozone-depleting than CFC. Hence, EtO(8.6%-10%)-HCFC(90%-91.4%) and EtO(8.5%)-CO_2(91.5%) form better alternatives to the EtO-CFC mixture [5]. 400 mg/l of EtO at 125°F to 130°F requires 30% relative humidity. H_2O molecules carry EtO to the sites of reaction on the material surface [5]. Materials or products packed into

gas permeable packaging are loaded into a sterilization vessel, usually made up of stainless steel. The process includes vacuum phase (pre-conditioning), humidification phase, gas introduction, exposure, evacuation (air removal) and air washes i.e. the vessel is evacuated to a final pressure compatible with product and packaging material and then moisture (from steam) is let in, so as to attain a relative humidity from 60% to 80%. The interdependent parameters like vacuum, pressure, temperature (of range 29°C-65°C), relative humidity, gas concentration (of range 450-1200 mg/l) and exposure time (2-5h in general) determine the sterilization efficacy. The sterilant (EtO gas or mixture) is then injected to a final gas concentration of ~600-800 mg/l typically at 40°C to 50°C. The sterilizer conditions are maintained at given conditions for sufficient time (2-16 hours typically) to obtain required SAL. To reduce EtO levels below acceptable limits, Reevacuation and air flushes are done. For effective removal of EtO residues on the materials after sterilization, further aeration (sometimes at elevated temperatures) will be needed [Andreas, 1999]. Efficacy of the method can be varied by length & diameter of lumen, inorganic salts and organic materials [5].

EtO being highly reactive epoxide is an alkylation agent. Hence, when radicals of carboxyl, amino, acidic, sulfhydryl, hydroxyl, phenolic groups (present in proteins and nucleic acids of microbes) come in contact with EtO, alteration in metabolism and reproduction of microbes take part, leading to death of microbes. The lethal effect is mainly due to alkylation of amine groups in nucleic acids of microbes [9].

Vaporized H_2O_2 (VHP)

H_2O_2, well known liquid chemical sterilant is used for sterilization in vapor state. Using deep vacuum, 30-35% liquid H_2O_2 is taken from a disposable cartridge through a heated vaporizer arrangement. After vaporization of the H_2O_2, the VHP enters the sterilization chamber. VHP can also be made to flow into sterilization chamber by a carrier gas at an appropriate pressure [5]. The cycle time is 2 hours when operated at 303K-403K.

Chlorine Dioxide (ClO_2):

The best operating conditions for the sterilant are 298K-303K for 6 hours while the concentration of ClO_2 is low. A compound of Dilute Cl_2 gas with Sodium chlorite is converted into ClO_2 which is then exposed to the equipment to be sterilized [10].

Ozone (O_3)

O_1 molecules when collide with energized O_2 molecules, O_3 is formed. The loosely bonded third oxygen atom readily oxidizes other molecules by attachment. Thus, O_3 is a powerful oxidant which is highly unstable (half-life is 22 min at room temperature). The O_3 sterilizer creates the sterilant O_3 from USP grade O_2, steam-quality H_2O and electricity [5]. Sterilization cycle lasts for 4 h 15 min (even upto 60 min depending on chamber size and load [10]) at 30-35°C. At the end of the process, the O_3 is converted back into H_2O and O_2 using a catalyst. Penetration of Ozone can be controlled by addition of humidity or by vacuum pressure.

O_3 oxidizes organic & inorganic materials exposed to it and thus sterilizes it. O_3 penetrates cellular membranes of microbes causing their rupture.

Formaldehyde Steam (HCHO-Steam)

Formalin is vaporized into formaldehyde gas and then allowed to enter the sterilization chamber which is pre-evacuated & steamed with heated load (i.e. Evacuation preceding Steam admission and heating of the load followed by HCHO gas pulses) After the formaldehyde gas pulses are entered, steam is flushed inside. Eventually, HCHO is eliminated from the chamber and the load by repeating alternate evacuations and steam & air admissions. Operating temperature is of range: 70-75°C and optimal concentration of gas is 8-16 mg/l. Reliability of sterilization is attained at high concentrations of gas at 60°C-80°C with 75-100% relative humidity [4].

Aqueous Glutaraldehyde Solution

This technique is used when aeration time after EtO sterilization is not acceptable or the product is heat-sensitive. FDA approved 2.4% Glutaraldehyde solution which requires 45 min immersion at 25°C to support high level disinfection. It has been reported that Treatment of endoscopes with 2% Glutaraldehyde used in automated sterilizing equipment would be the efficient sterilization method to remove biofilms from endoscopes [11].

Peracetic Acid Solutions

Peracetic acid can maintain its efficacy even in the presence of organic soil. This low temperature sterilization process is microprocessor controlled and being widely used. Along with an anticorrosive agent, 35% Peracetic acid (PA) enters the container, which is said to be punctured, immediately prior to the closure of lid and process initiation. The PA is diluted to 0.2% with filtered (.2 μm) water at 50°C. This diluted PA is allowed to circulate within the chamber of the sterilizer and pumped into the channels of the load say, endoscope for 12 min. Channels connectors available for almost all types of flexible endoscopes & similar semi-critical devices are used to ensure direct contact of sterilant with the contaminated sites. Sewer disposes spent PA and the load is repeatedly rinsed with filtered water.

PA, a highly biocidal oxidizer is thought to act as an oxidizing agent as it denatures proteins, disrupts cell wall and oxidizes sulfhydryl & sulphur bonds in enzymes, proteins & other metabolites [4].

Low Temperature Gas Plama Sterilization

Gas molecules can be excited by radio frequency or microwave energy under deep vacuum in an enclosed vessel, so that gas plasma (ionized gas) is formed. When gas plasma is subjected to an electric field, it gets ionized into ions, electrons, UV photons and radicals. Of these, UV photons and radicals carry out UV irradiation, photo-desorption and chemical etching (triphasic behavior). Cells and spores contain atoms of C, N, O, H which are attacked by the free radicals formed from plasma. Eventually, simple compounds like CO_2 are generated and flushed out. Devoid of C, H, N, O atoms, the spores or microbes will die. Low risks, Non toxicity, High rate of treatment, Efficacy, Versatility are the advantages of the technique.

Hydrogen Peroxide Gas Plasma

According to the first design of H_2O_2 sterilizer, H_2O_2 solution is injected into pre-evacuated sterilization chamber, where the solution is vaporized to a final concentration of 6 mg/l. This H_2O_2 vapor, the sterilant then diffuses through the chamber (50 min) and starts inactivating microbes on exposed surfaces of the load. On application of radio frequency, an electric field is generated which is applied to the chamber to form gas plasma. Microbicidal free (hydroxyl and hydroperoxyl) radicals are them formed in the plasma. The excess air is eliminated. By introduction of high-efficiency filtered air, the pressure of the chamber is brought back to that of atmosphere. Process operating conditions: 37°C-44°C for 75 min. If moisture exists, evacuation can't be achieved and the process ceases [5]. The efficacy of the sterilizer was then improved by having two sterilization cycles with 2 stages (a H_2O_2 diffusion stage and a plasma stage) per cycle. The time required for the entire process decreased. A relatively low process time of 28-38 min was then achieved by using new vaporizing system which can remove water from H_2O_2 [5].

Radiation Sterilization

By this method, sterility of the implants is achieved by their exposure to ionizing radiation which is often High energy electrons beam (a variant of Beta radiation), Gamma radiation from ^{60}Co or ^{137}Cs, Universal homogeneous ultraviolet (UHUV) radiation and High energy X radiation (bremsstrahlung). International Atomic Energy Agency (Vienna) provides detailed procedures for validation, selection of dosage and routine control for the sterilization of Tissue allografts by radiation.

Electron Beam (EB) Sterilization

Machine-generated, highly accelerated electron beam can be used to sterilize medical products. The accelerator is located within a concrete room, to contain *stray electrons.* When the accelerator is turned off, no radiation is possible. The sterility is achieved by passing the articles under electron beam for time sufficient for accumulation of desired dose (25 kGy). Surface sterilization is effectively achieved.

Lethality of microbes is due to the ionization of key cellular components.

It has been reported that crystallinity of copolymers of 1,5-dioxepan-2-one (DXO) and L,L-lactide (LLA) increased, at minimal sterilization dose [12]. Caprolactone (CL)- and LLA-containing copolymers also showed increase in crystallinity on exposure to EB.

Gamma Radiation Sterilization

The devices to be sterilized are kept in the vicinity of the radioactive source until they receive the required dosage of radiation. For immediate use of the sterilized implant, it must not have absorbed radiation. Due to leakage problems and heat transfer problems associated with ^{137}Cs, ^{60}Co is preferred. The ^{60}Co isotope is sealed within stainless steel pencils (~1 × 45 cm) which are held within a metal source rack. The radioactive source is usually encapsulated by a double layered stainless steel to protect environment from irradiation. Else, when irradiator is not in use, the source rack is kept in a water-filled pool(~25 ft deep). For Radiation shielding, the surrounding walls (including ceiling) are constructed using thick, reinforced concrete. During sterilization, the materials to be sterilized are moved around the source by a conveyor system, ensuring uniform delivery of required dose. Dosimeters (Radiation measuring devices) are kept along with the materials to be sterilized, in order to monitor and control the dose for sterilization. The most commonly validated dose used to sterilize medical products is 25kGy. Irradiators and product loading patterns are constructed to minimize the overdose ratio (The ratio of maximum dose to the minimum dose) [6].

The radioactive isotope ^{60}Co decays into ^{60}Ni and an electron, along with the emission of gamma rays. The Gamma rays ionize key cellular components (especially nucleic acids) which lead to death of microbes. As the ejected electron has no sufficient energy to penetrate the wall of the pencil, it has no role in sterilization by this method.

B_2O_3 and TiO_2 based bioactive glass and Hydroxyapatite micro & nano-crystalline particles(HAp)-bioactive glass composite coating on Titanium based alloys were studied by Bharati S et al (2009) [30]. When the coated samples were subjected to 25kGy Gamma irradiation, scratch resistance of both composite coating and the bioactive glass coating improved surprisingly. The bioactive glass coating showed improved mechanical properties after irradiation. It has been reported that crystallinity of copolymers of 1,5-dioxepan-2-one(DXO) and L,L-lactide(LLA) increased, at minimal sterilization dose[12]. But, CL- and LLA-containing copolymers showed decreased crystallinity on exposure to gamma radiation. Due to occurrence of simultaneous increase in chain length (by cross-linking reactions) and decrease in chain length (by chain scissions) throughout the molecule, new groups with high thermal stability are formed at ends. Induced oxidation of PE (Polyethylene), delamination and cracking in PE knee bearings [5]. Irradiation brings free radicals into UHMWPE (Ultra High Molecular Weight PE) [13, 14] & Polyolefins [13]. This results in recurring chain scissions & induced oxidation reactions leading to embrittlement of the polymer. To avoid oxidations that cause deterioration of UHMWPE, Premnath et al (1996) suggested irradiation in inert atmosphere or vacuum. It has been shown that irradiation in gamma inert atmosphere (N_2, argon) followed by treatment at elevated temperatures will crosslink all reactive free radicals by stabilization. Then, Oxidation is prevented in the compound on re-exposure to O_2 and other oxidative agents. The compound shows improved resistances to wear and creep along with enhanced mechanical properties [15].

Plasma Based UHUV Irradiation Sterilization

A low pressure discharge device consists of a cylindrical inner quartz glass tube (diameter 35 mm, length 100 mm) surrounded by a glass vessel. The glass vessel is filled with argon at 3 torr along with a small amount of mercury while the inner tube provides place for the materials to be sterilized. Opposing a single cathode, three one-pin anodes are mounted at an angular distance of 120^o. Passage of electric discharge through low-pressure mercury vapor generates UV-emitting plasma. Inherent anode oscillation makes the plasma to circulate around the inner tube, at several kilohertz frequency. This general construction principle makes the system adaptable to various shapes and geometries, thereby expanding the range of sterilizable implants. Measurement of the irradiation energy, E254 nm (mW/cm^2), for the resonance wavelength 254 nm, which is dependent on the angular position and electrode current, showed an irradiation field in the inner tube which was spatially nearly homogeneous. Therefore, this has been named universal homogeneous ultraviolet (UHUV) irradiation [16]. For *Bacillus subtilis* spores, lethal dosage ranges from 10 to 60 mW/cm^2 where the radiation sterilization is by conventional means. As reported by Von Woedtke et al (2003), In case of non turbid spore suspensions of *B.subtilis*, UHUV irradiation dose of 9 mW/cm^2 is enough to bring down the viable count of 105-106 folds. Wiping of infected Dental hand pieces and Orthodontic forceps using disinfection cloths (Meliseptol), followed by UHUV irradiation effectively reduced viable counts, even in the presence of organic matter. By using UV transparent wrapping (e.g.: Polyethylene foil) UHUV irradiation of ready-for-use products is feasible. In combination with one or more sterilization procedures, this method may greatly decrease the viable cell count. Due to High biocidal activity, Low potential for damaging materials and Manageability of the technique, it can be considered for optimization for specific practical applications.

X Radiation

When atomic nuclei (of target material) deflect high energy electrons, they emit X rays. This ionizing radiation with maximum energies of 5 MeV to 7MeV has permeability greater than that of large, uncollimated Gamma rays. For the sake of high dose uniformity and maximum utilization of X radiation, the load must be treated from opposite sides by passing at least twice by the X ray target material [17]. Cleland M R (1993) provides further information on X-ray processing rates and dose distributions. Monte Carlo methods can be applied to simulate the X-ray conversion process [18, 19]. For products of high density, 'palletron', a concept of X-ray irradiator was proposed [19].

Non-Ionizing UV Radiation

Intensive sporicidal and virucidal activity of ultraviolet (UV) irradiation, make it applicable for sterilization. Since UV irradiation is non-ionizing, products of unstable composition can be sterilized by this method. Nucleic acids present in the microbes absorb UV radiation. This causes formation of cyclobutane type dimers between Thymine residues of DNA and similar dimers between Cytosines and Thymine-cytosine residues. These irreversibly bound, stable dimers prevent replication and transcription processes, thereby leading to death.

Table 1: Comparison of sterilants' advantages, disadvantages and applications.

Sterilant	Advantages	Disadvantages	Major Applications
Moist heat	• Efficacy, • Speed, • Process simplicity, • Reliability, • Non-toxicity, • Rapidity, • Ideal nature for metal instruments, • Ability to penetrate fabrics • Low D-values (time to achieve 90% reduction in the surviving population). $D121^{\circ}C$ – values for *Geobacillus stearothermophilus* range from 1 to 2 min [4]. D-values of other heat resistant non-spore forming bacteria, viruses and fungi are undeterminably small. • Portability. Table-top sterilizers are available. • Mechanical properties like osteoconductivity, stiffness etc. are retained by bone grafts even after steam sterilization.	• Temperature sensitive, unstable products can't be sterilized by this method. Thus, high operating temperature and pressure limit sterilizable (or compatible) materials of fabrication and packaging. • Steam may hydrolyze or degrade certain plastics. e.g.: Many grades of polyethylene (PE) whose melting points or glass transition temperatures are below the operating temperature of the sterilization process. Such polymers can't be steam sterilized. • Autoclaving increased cytotoxicity of orthodontic elastics in chain form [21]. • Lubricants associated with dental hand-pieces get corroded and combusted [4] • In laryngoscopes transmission of light is reduced [4] • Corrosion is possible.	Sterilization of heat resistant and moisture resistant materials like • laboratory media and water, • pharmaceutical products (like Surgical and diagnostic devices, Ophthalmic preparations, Containers, Aqueous injections and Irrigation fluids [20] • regulated medical wastes, • non-porous articles [4]. • Metallic surgical instruments, • Surgical supplies (e.g., linen drapes and dressings), • Stainless steel sutures, • Intravenous solutions.
Flash steam	It is an effective sterilization process for critical devices, if	• All process parameters (temperature, time, pressure) are minimal. Hence, to ensure	• It is an acceptable sterilization method only for the cleaned objects which can't be

	rightly done.	sterility of the product, exposure time should be extended. • Lack of biological monitors those can monitor efficacy in time. To overcome this demerit, biological monitors which produce result in 1 hour time can be used. • No protective packaging is done after sterilization process. Therefore, to avoid contamination during transportation to operation theatres and to facilitate aseptic delivery of implants, either the flash sterilization must be performed in closer proximity to the point of use or protective packing material that allows steam to pass through should be used. • Flash sterilized product is potentially hot and can cause burns in staff during transportation as well as patient during implantation. Usage of heat resistant gloves by staff is therefore recommended. Air cooling the devices or their immersion in sterile liquids (e.g., saline) can prevent patient burns [4].	pre-sterilized and stored. • Orthopaedic screws, plates etc, are unavoidably sterilized by this method, though it is not recommended for implantable devices.
Dry heat	• High penetration power, • Metals and sharp instruments do not get corroded. • Kilpadi *et al* (1998) studied effect of nitric acid passivation and dry heat sterilization on the surface topography & energy of the unalloyed titanium and reported that together, the techniques increased the surface energy of the unalloyed titanium. • Non toxic and eco-friendly. • Easy installation • Economic	• Temperature sensitive, unstable products can't be sterilized by this method, • Low rate of penetration, • Time consuming method.	Sterilization of heat resistant products including • Medical materials, • Powdered compounds, • Sharp instruments, • Petroleum products, • Drug Suspensions in non aqueous solvents, • Oils and Oily injections, • Ophthalmic preparations [20]
EtO gas	• This is a low temperature sterilization process. Therefore, it has wide range of compatible products and	• Pure EtO is toxic, carcinogenic, flammable. Thus, it is potentially hazardous to patients and workers. According to Occupational	• A wide range of medical products including therapeutic materials, micro surgical equipments [Szycher, 1991], surgical sutures,

	packaging materials including heat and moisture sensitive materials. • Efficacy even at low temperatures, • High penetration ability, • Compatibility with wide range of materials, • High microbicidal activity [4]. • EtO-CO_2 gas mixture, an eco-friendly sterilant is more economic than EtO-HCFC.	Health and Safety (OSHA) regulations, no worker may be exposed to more than 1ppm of EtO during 8-hour time-weighted average work day. • Costly explosion-proof equipment demands utilization of inerting compound. • Usage of ozone-depleting CFC must be avoided. • Complex process. • EtO is a surface sterilant. It can't reach blocked-off sites. • Formation of toxic residues. EtO in presence of moisture and chloride ions, form Ethylene glycol and 2-chloroethanol, a non-volatile toxic residue. Residual EtO, Ethylene chlorohydrin are some of the undesired, toxic by-products sometimes formed during sterilization. • For certain applications, aeration time after the sterilization process is not desirable. It has been reported that EtO residual level of 66.2 ppm was observed even after standard time of degassing.	• neurosurgery devices, absorbable bone-repair devices, ligament and tendon repair devices, • intraocular lenses, • absorbable and nonabsorbable meshes, • heart valves, • vascular grafts, • stents coated with bioactive compounds • Flexible and Rigid endoscopes, • Heat and moisture sensitive electronic goods and other long term implants[22]. are usually sterilized using EtO. Moisture and heat sensitive critical & some semi-critical items can be sterilized by EtO. EtO(66 mm Hg for 3 hours) is suitable for sterilization of orthodontic elastic chain(packed in sealed wrappings) since no increase in cytotoxicity is observed [21].
Glutaraldehyde		• It has been reported that Immersion in Glutaraldehyde(2%) solution for 10 hours increased cytotoxicity of orthodontic elastics in chain [21]. • It reduces bone-inductive capacity of demineralised bone implants to a greater extent, when treated [23]. • Time-consuming process. • Glutaraldehyde is highly irritating and sensitizing.	High level disinfection of Arthroscopes, Hysteroscopes, Cystoscopes, Endoscopes, Laparoscopes etc. is achieved by immersion in Glutaraldehyde solutions for several hours.

Peracetic acid	• Low temperature process • High efficacy (than EtO).Exposure to 0.05%-1% PA for 15 s to 30 min is lethal to bacterial spore suspensions [4]. • PA can completely kill 6-log10 of Mycobacterium chelonae, Enterococcus faecalis, and B. atrophaeus spores with both an organic and inorganic challenge [4]. • Structural integrity and bioremodelable properties of the collagenous tissue are found to be conserved • Safety. • Non-toxicity. • Short cycle time(30 min) [10].	• Choice of channel connector should be done with care because wrong choice can lead to inadequate sterilization [4]. • Sterility of filtered water used at various stages of sterilization, must be ensured & maintained.	• Gastro intestinal endoscopes, • Flexible endoscopes, • Bronchoscopes, • Arthroscopes, • Rigid lumen devices, • Dental and surgical instruments can all be sterilized. Sterility of collagen and collagenous tissue can achieved by low concentration Peracetic acid solutions as sterilants. Kemp PD (1995) got patented his invention that Peracetic acid can be used for sterilization of collagen and collagenous tissues [29].
Chlorine dioxide gas	• Efficacy, • Rapidity (Duration of 1.5 to 3 hours), • No need for post-sterilization aeration as only low amount of sterilant residuals form with the most materials. Thus, it is advantageous over EtO sterilization, • Concentration of the green colored gas within the sterilization chamber can be efficiently measured using spectrophotometer, • Easy regulation of the gas concentration	• Prehumidification of ClO_2 is mandatory. • Corrosive.	• Pharmaceutical components, • Medical products and • Barrier isolation systems can be effectively sterilized.
VHP	• Rapidity or shorter cycle time (30-45 min). • Eco-friendly as by-products (H_2O, O_2) are safe. • Good material compatibility [4]. • Easy operation, installation and monitoring.	• Cellulose can't be subjected to VHP. • Nylon becomes brittle. • Less ability to penetrate than EtO	
Ozone	• High efficacy. • High material compatibility. • No toxic residues or	• A gaseous O_3 generator is not sufficient to decontaminate an MRSA infected hospital room [4].	• Reusable medical devices, • Rigid lumen devices, Implants and • Devices made of materials

	emissions. • No manual handling of the sterilant. • Low temperature process. • Self-contained monitoring. • Compact chamber size (4 ft3).	• Corrosive nature of ozone gas.	like stainless steel, titanium, anodized aluminum, ceramic, glass, silica, PVC, Teflon, silicone, polypropylene, polyethylene and acrylics [4]. It can effectively sterilize synthetic Isoprene and similar grades of rubber[23]
Formaldehyde-steam	• Low temperature process (but not lesser temperature than that of EtO). • Rapidity (greater than that of EtO) • Lower cost per cycle when compared to EtO.	• HCHO is mutagenic and potentially carcinogenic to humans. The permissible exposure limit for workers is .75 ppm HCHO or 8 hour TWA. • Less power of penetration than EtO. • Lack of control of temperature and humidity. • The sterilant is not properly circulated throughout the sterilization chamber. • *Low* partial pressure of *slowly* released gas produced from paraformaldehyde tablets.	
H_2O_2 gas plasma	• Less process temperature(<50°C), • Rapidity (Total process time doesn't exceed 75 min), • No need for post-sterilization aeration as the by-products (e.g., H_2O, O_2) are non-toxic. • Availability of the material for use, immediately after sterilization. • High microbicidal and sporicidal activity [4]. • High compatibility. • Safety, • High efficiency, • Low moisture environment.	• If moisture exists, evacuation can't be achieved and the process ceases [4]. • Eqipments like flexible endoscopes can't be sterilized by H_2O_2 gas plasma as long narrow lumens are open only at one end. • Process compatible packaging is mandatory. • Time consuming process. • Suitable biological indicators must be employed. • Expensive. • Damages Nylon based substances[10].	More than 95% of medical devices can be sterilized by this method. E.g., Rigid endoscopes.
Electron beam	• No need of water pools as the electron beam generation is completely controllable, • Easy storage, • No risks or safety issues.	• Due to the less penetrating power than Gamma rays, thick and densely packed materials can't be sterilized. • Attenuation diminishes sterilization power.	• In-line sterilization of thin products immediately following primary packaging is the unique application for this method. • This method has same potential range of applications as that of gamma radiation.e.g.,Sterilization of Tissue allografts.
Gamma	• High Penetrating power ensures complete sterilization of all parts	• Molecular-chain scission and/or cross-linking may result in undesirable effects of	• ^{60}Co radiation sterilization is widely used for medical products, such as surgical sutures and

	of the product exposed, • Process simplicity: No need of specialized packing and no need for maintenance of specialized conditions of temperature, pressure, etc., • Efficacy, • Rapidity, • Simplicity, • Measurability and controllability (by straightforward dosimetry methods) • Reliability due to control of single variable-time of exposure to radiation. • Suitability for large-scale sterilization.	radiation sterilization on certain materials. • Rays are emitted in all directions from the radioactive source and hence large amount of energy is likely to be wasted. • Radiation sensitive materials like PTFE (Polytetrafluoroethylene) can't be sterilized by this method. Some plastics and polymers cannot withstand required levels of ionizing radiation. e.g.: Polypropylene based dialysis membranes, PGA sutures. On exposure to radiation, many therapeutic formulations are found to be degraded. Blood fraction components produce hydroxyl radicals that can cause damaging reactions. Hence, containers with pre filled therapeutic products cannot be subjected to radiation sterilization. FDA recognizes irradiated therapeutic products as new drugs and demands new approval for the product. [9] • The sterilization process should be carried out with high safety concerns as ionizing radiation is harmful to human workers in the environment. The spent radioactive nucleotides are still potentially harmful demanding careful disposal. • Continual decay of the isotope (even when the irradiator is not working). • It is suspected that radiation may decrease life-time of implants of long term usage. e.g.: Pacemakers and Pacemaker accessories. • Induced oxidation of PE (Polyethylene), delamination and cracking in PE knee bearings [4]. • The radiation brings free radicals into UHMWPE (Ultra High Molecular Weight PE) & Polyolefins[Goldman et al, 1996]. This results in recurring chain scissions & induced oxidation reactions leading to embrittlement of the polymer. Hence the loads should be irradiated in inert atmosphere.	drapes, metallic bone implants, knee and hip prostheses, Unit dose ointments, syringes, Pharmaceutical containers, Protective clothing, Hand wear, Baby bottle nipples, Sanitary napkins and neurosurgery devices. • A wide range of materials are compatible with radiation sterilization, including polyethylene, polyesters, polystyrene, polysulfones, and polycarbonate. • Tissues (Allografts) for transplantation are said to be sterilized by this method [4]. • Gamma rays (of dosage: 2.55 mrad from 60Co; 333 K; 30 min) are suitable for sterilization of orthodontic elastic chain (packed in sealed wrappings) since no increase in cytotoxicity is observed [21]. • Gamma rays reduce bone-inductive capacity of demineralised bone implants only by half,when irradiated and hence they can be promising sterilants [22].

		• PVC and Acetal are incompatible.	
X rays	• High penetrating power similar to gamma rays, • Non isotopic source of irradiation: Machine generation. • At usual dosage range, there exists low temperature elevation causing no damage to plastic materials, • No toxic residue is formed. • Uniform dosage is possible when compared to Gamma, • Less costly, • Smaller irradiation chamber is sufficient, • High efficiency: Their angular dispersion drops as the energy of incident electron increases. The efficiency is directly proportional to atomic number of the target material.		• Sterilization of Tissue allografts, • Sterilization of food at 7.5 MeV. [18]
UV Rays	• Intensive sporicidal and virucidal activity, • Since UV irradiation is non-ionizing, products of unstable composition can be sterilized by this method [16].	• UV rays have less energy and lower penetrating power than Gamma rays. • Distance of the material (to be sterilized) from the UV source determines homogeneity of the sterilization or that of the microbial inactivation. • Antimicrobial efficacy varies from material to material. Some materials like glasses and plastics absorb UV irradiation. Poly ethylene foil is found to be effectively sterilized by this method, due to its UV transparency. But, materials like aluminium foil, polystyrol, polypropylene etc. are impervious to UV irradiation. In general, UV rays can be used for surface sterilization. • Organic matter such as blood and saliva can prevent UV irradiation from inactivating the microbes.	• UV rays(254 nm) are suitable for sterilization(for 1 h i.e., 30 min on each side) of orthodontic elastic chain since no increase in cytotoxicity is observed [21]. • Dynamic sterilization of Titanium implants using UV rays for 20 seconds was found to be effective by Singh et al. 1989 [25].

UHUV	• Ionizing radiation. Hence more efficient than UV radiation in sterilization.		• UHUV irradiation over 300 s and hydrogen peroxide(0.15%) treatment for 3 days proved to be efficient combination of sterilants for the glucose biosensors in in-vitro studies[26].

Conclusion

Choice of method of sterilization of implants or medical devices must be carefully made at the earliest, because effects of sterilization processes on the devices greatly depend on material of construction of the medical devices. Based on intended use of the object and properties (e.g. Heat resistance, Moisture resistance, Shape, Porosity, etc.) of the object, the sterilization method has to be chosen, in order to attain higher efficiency in the process of sterilization. Combination of different sterilization techniques can also be helpful in attaining sterile conditions of interest. Altering sterilization environment is another useful strategy which may enhance properties of device subjected to sterilization as well as overcome disadvantages of the sterilant. Besides, Packing, Dose of sterilant and time of exposure to the sterilant can significantly affect extent of sterilization.

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