Electrical Discharges: An Emerging Modality in Sterilization, Disinfection, and Therapeutics

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ABSTRACT:
Electrical discharges are the key mechanism to the generation of atmospheric pressure plasmas which are further classified as equilibrium and non-equilibrium plasmas, also referred to as thermal and non-thermal plasmas. The technological advancement of non-thermal plasma has extended its potential clinical non-invasive applications in a multitude of disciplines such as dermatology, ophthalmology and oncology, etc. to bolster tissue generation, refraction error correction and necrosis of the cancerous cells in the domain of plasma medicine, respectively. A fundamental on the various types of discharges and their mechanism is investigated. A perspective on the application of non-thermal plasmas in the domains such as sterilization and disinfection is presented in this review. We have focused on the plasma therapeutics and its significance as a clean and dry therapy to treat superficial skin diseases via the mechanism of proliferation of basal skin cells and prothrombin stimulation to cauterize the blood through Argon Plasma generated by Argon Plasma Coagulator. We propose to fabricate atmospheric pressure plasma devices and understanding of the associated plasma radicals that aids in the activation of biochemical and biomolecular reactions to treat the cutaneous and sub-cutaneous diseases.

KEYWORDS: Thermal and Non-Thermal Plasmas, Sterilization, Disinfection, Cell Proliferation, Dielectric Barrier Discharge, Argon Plasma Coagulator.

1. INTRODUCTION

Stars glowing brightly is an evident example of thermonuclear fusion reaction of hydrogen ions, which are also known as plasma, and hence these stars are nothing but balls of Hot Plasmas radiating EM waves of various wavelengths. So basically, Plasma is a Sea of ionized gases [1]. It is sometimes also known as the fourth state of matter. The logic behind this is like when we heat solid state, we get liquid state which in turn turns into gaseous state on heating. Then on further heating of gas leads to the formation of ionized gases i.e., plasma. But describing Plasma formation through heating is not correct. Plasmas are produced by making atoms collide with fast moving particles (photoionization [2]) or by electric breakdown by applying strong electric fields (When electric breakdown occurs electrons move with huge amount of energy between two electrodes). So, when these things occur the particles collide with the atoms making the electrons on the outer orbitals of the atoms leaves their place and become free. Due to this there is a creation of an ion and one free electron. When large number of atoms get converted to ion by leaving one or more electrons there is creation of Plasma. Thus, Plasma consists of charged particles but the total charge of it is zero i.e., its neutral. Plasma usually exists in vacuum because in presence of air the amount of heat gets dissipated thus the ions again turn into neutral atoms [1].

Plasma can`t be prepared at room condition because room temperature and conditions are not suitable for its creations. From Saha equation we know that $n_i/n_n \approx 2.4 \times 10^{21} (T^{3/2}/n_i)\, e^{(-U/RT)}$ [1], and if we put the value of the quantities for room condition, we get $n_i/n_n \approx 10^{-122}$ [1], which is very low to be recognized. As the temperature is raised, the degree of ionization remains low until U_i is only a few times KT. Then n_i/n_n rises abruptly, and the gas is in a plasma state [1].

Thus, to be now more precise we can say, that "Plasma is a quasineutral gas of charged and neutral particles which exhibits collective behavior." [1]. To understand the meaning of quasineutral and quasineutrality let us suppose that the density of the ionized ions is n_i, density of electrons is n_e. When $n_i \sim n_e \sim n$, where n is the common density, known as plasma density. This condition is known as quasineutrality and the medium is said to be in the state of quasineutral [1].

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The three conditions which plasma must satisfy are First, Debye Length: $\Lambda_D << L$, where Λ_D is the Debye length, L is the dimension of the system. The Debye length (the thickness of sheath) should be very very less than the dimensions of the system i.e., the density of particles in the Debye sphere should be high enough so that they can shield the effect of the charged balls keeping the thickness of the sphere much less than L [1]. Second, $N_D >>>1$, where N_D is the number of particles in Debye sphere. The number of particles in the Debye sphere should be very much larger than 1 so that they collectively can shield the effect of the charged balls [1], and third, $\omega_p\tau >1$, where, Ω is the frequency of plasma oscillation and τ is the mean time between two collisions. So as per the condition the product of the wavelength of the plasma particles and the time between two successive collisions should be greater than 1 [1].

To understand the above-mentioned terms let us assume a setup where two oppositely charges balls are kept in a medium of air [1]. The balls are covered by dielectric materials so that the gas molecules don't get in touch with those balls. As soon as these balls are kept in the air, opposite charges from the air medium will get attracted towards those balls, thus forming a layer of opposite charges around those balls. Such layers are known as a Sheath. So, here the thickness of the sheath is denoted by Λ_D. This quantity is known as Debye length [1]. Due to this phenomenon a sphere of molecules is formed around the ball. This sphere is known as Debye sphere [1] and the number of particles in this sphere is denoted by N_D. Rapid oscillation of electron density can be found in plasmas [3]. Let us suppose a plasma in equilibrium i.e., none of the ions or electrons are moving. So, at this time if somehow one of the ions or electrons get displaced from their initial position then there will be a restoring force which will act on that particle leading to oscillation of that particle and when this thing occurs in mass number this will alter the electron and ion density, which will seem like in oscillation. The frequency of such oscillation is known as plasma frequency [1] and denoted by ω_p. In plasma no particle is stationary. Every particle is continuously moving and hence collision is inevitable. So, the mean time between such collisions is denoted by τ. Plasma exist in various forms where temperature ranges from 2×10^3 eV to 10^{-2} eV (1eV = 11600 K) and electron density ranges from 10^{26} electron per cm^3 to 1 electron per cm^3.

2. DISCHARGE MECHANISMS

Electric discharge is basically the process of generation and transmission of electrons across an electric field. When two electrodes are inserted into a glass tube that can either be evacuated or filled with gases is connected to a power supply, electrons are generated. The primary electrons provide the initial current. As the voltage applied between the two electrodes increase, the current suddenly increases sharply at a certain voltage. At this voltage intensive electron avalanche occurs. If the pressure is kept low, the large resistance of the external circuit prohibits the development of large current thereby producing a glow discharge.

2.1. Townsend Mechanism

Considering a simple electrode arrangement with a gap of width d immersed in a gas at pressure p. If uniform electric field E is applied between the electrodes, the electrons are liberated at cathode. When this electron is placed in electric field, it will be accelerated towards anode. While travelling towards anode, these electrons collide with other gas molecules. If the energy is sufficiently large, on collision it will cause a breakup of atoms or molecules into ions and electron [2]. The created electrons form an avalanche and reaches the anode and current is generated. When the current is large enough, it results in formation of conducting path between the electrodes in the breakdown of the gap [2].

If n_0 is the number of electrons emitted from cathode and α is the Townsend's ionization coefficient which means average number of collisions made by an electron per centimeter in the direction of electric field.

$$\frac{\mathrm{dn_e}}{\mathrm{dx}} = \alpha n_e \tag{1}$$

$$n_e = n_{0e} e^{\alpha x} \tag{2}$$

Positive ions generated near the cathode by each electron is $e^{\alpha x} - 1$ which leads to extraction of $\gamma * [e^{\alpha x} - 1\,]$ electrons from cathode due to secondary electron emission γ (Townsend's coefficient). Current at cathode is given by $i_{cath} = i_0 + \gamma i_{cath}[e^{\alpha x} - 1\,]$. The total current can be written as i= $i_{cath}e^{\alpha x}$ which leads us to the average current in gap before the breakdown

$$i = \frac{i_0 e^{\alpha x}}{1-\gamma[e^{\alpha x}-1]} \tag{3}$$

The current in the gap is not self-sustained as long as the denominator in the above equation is positive. If the distance d or electric field is increased, α increases and the denominator tends to zero and the current is then self-sustained. This is called Townsend's breakdown mechanism.

$$\gamma[e^{\alpha x} - 1] = 1 \tag{4}$$

Townsend's mechanism explains the breakdown only at low pressure and small gaps [2].

2.2. Streamer Mechanism

The streamer mechanism can be applied for high pressure and larger gaps. This theory suggests the development of spark discharge directly from a single avalanche. The charge developed by the avalanche transforms the avalanche into plasma streamer. The primary electrons generated at cathode by ionizations causes avalanche that crosses the gap. The electrons are directed towards the anode. A positive charged space is formed at anode by the time electron reaches. This positively charged space enhances the field and secondary avalanches are formed. The positive space charged formed at anode extends rapidly to cathode forming a streamer. When the streamer tip reaches cathode, a stream of electrons moves from cathode to neutralize the positive charged space created. This causes spark and spark breakdown occurs [2]. Formation of avalanche is shown in Fig. 1.

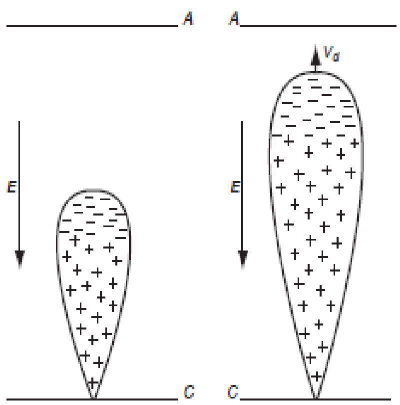

Fig. 1. Formation of avalanche in spark gap. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2].

And distortion of electric field in an avalanche is shown in Fig. 2.

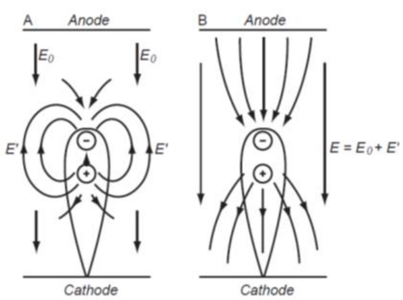

Fig. 2. Distortion of electric field in an avalanche: a) external electric field and space charge electric field shown separately, b) combination of external electric field and space charge electric field. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2].

3. TYPES OF ELECTRICAL DISCHARGES

3.1. Glow Discharge

Glow discharge is defined as self-sustained continuous DC discharge with cold cathode that emits electrons as a result of secondary emission induced by positive ions. The discharge occurs at low pressure and high temperature. This is characterized by a diffused luminous glow which depends on the cathode and the gas used. The space between the cathode and anode has intermediate dark and bright regions. The voltage drops between the electrodes remain constant (100-500 V). this configuration is primarily used in fluorescent lamps that we use at our home. It is also used in voltage regulation tubes for rectification or as an amplifier [2].

3.2. Arc Discharge

Arc discharges are self-sustaining DC discharges characterized by low cathode fall voltage and high current density. The electrons are emitted thermionic or field emissions. Due to Joule heating, the cathodes reach a very high temperature which can cause evaporation and erosion of electrodes [2]. The discharge is luminous and is accompanied by a specific hissing noise. This type of discharge is used in cutting and welding metals or as light source in carbon arc lamps [2].

3.3. Radiofrequency and Microwave Discharge

A high frequency current is passed through a solenoid coil. A dielectric tube is inserted in the solenoid to provide the plasma in the gas of our own choice. The axial magnetic field produced by the solenoid induces the vortex electric field sustaining the radio frequency inductively coupled plasma. The electric field is proportional to the frequency and current passed in the solenoid determines the magnetic field. There is no direct contact between the plasma and the electrodes [27]. The schematic of generation of ICP is given in Fig. 3.

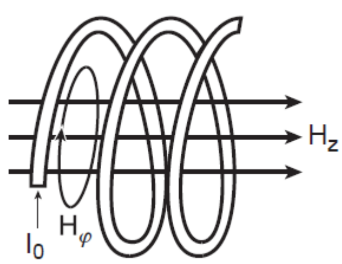

Fig. 3. Physical schematic of generation of ICP. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2].

3.4. Corona Discharge

Corona discharge is a non-thermal, atmospheric pressure, week luminous discharge that occur in a non-uniform geometry in presence of non-uniform electric field [2]. A hissing sound is produced in the regions of high electric field. They are most commonly found in transmission lines, masts of ships or lightning rods. Power is lost in corona discharge which means there is current passing through the wire.

3.5. Dielectric Barrier Discharge

Dielectric Barrier discharge is also a type of non-thermal atmospheric discharge. A dielectric material is inserted in the gap between the two electrodes such that it stops the current and prevent spark formation. This discharge produced by this process is called dielectric barrier discharge (DBD) [2]. DBD is also referred to as silent discharge because there is no formation of spark in it. DBD is widely used in large plasma display panel, generation of ozone and also in pollution control. It has various biomedical applications as well [2]. The common configurations are shown in Fig. 4.

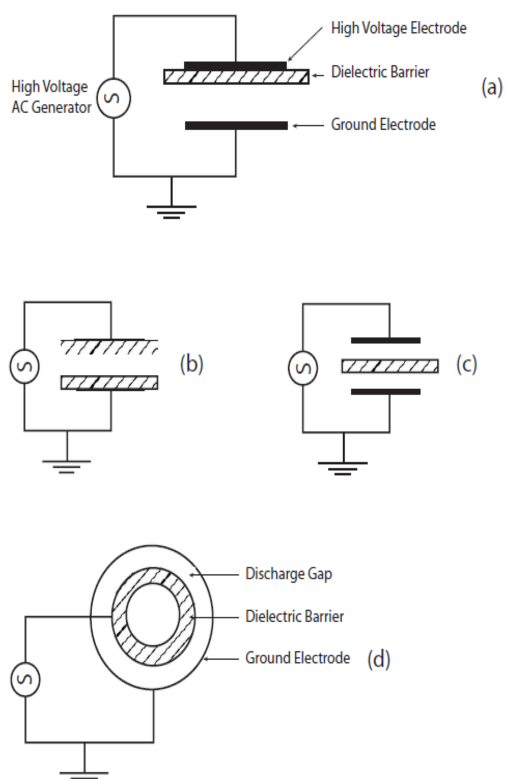

Fig. 4. Common configuration of DBD discharges. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2].

Table 1. Various types of discharges.

Discharge Type	Conditions	Pressure	Gas Temperature
Direct current corona discharge	5-30 kV, direct current, 10-20µA, dry or wet, O2, N2, Ar, He at 10 L/min	1 atm	Room Temperature
Atmospheric plasma jet microwave	2.45GHz, He/O2/N2 at 2.0/1.2/1/5 L/min	1 atm	Max. 50.8^0 C on surface, 20^0 C on agar surface
Dielectric barrier discharge	±2.5kV, 5kHz, air, humidity 64.4%	1 atm	Approximately 50^0 C
Micro-hollow cathode discharge	1.5-2.5 kV, DC 20mA, air (0.1-8 L/min)	> 1 atm	Room Temperature (220 mL/ min), >55^0 C (5mm from nozzle, 220 mL/min)
Pin- to- hole discharge	4kV DC, approx. 1.8 J/pulse	1 atm	9030 ± 320 K (by Boltzmann calculation)

The above table summarizes the various types of discharges and the conditions required for their production [2,14].

4. DIELECTRIC BARRIER DISCHARGE IN BIOMEDICAL APPLICATIONS

Dielectric-barrier discharge (DBD) is the electrical discharge between two electrodes separated by an insulating dielectric barrier. It is also known as silent discharge, ozone production discharge [6] or partial discharge [7].

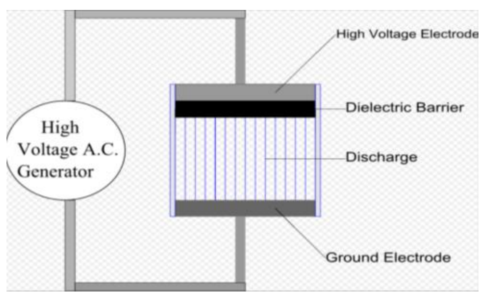

Fig. 5. This is a planer configuration of DBD devices. Own work Francis E Williams. 10 Dec 2010, https://upload.wikimedia.org/wikipedia/commons/e/e6/DBD.png [9].

The above Fig. 5 is the typical construction of a DBD (Dielectric Barrier Discharge) device which has a planer configuration [9]. The thin lines represent the discharge filaments between the plates. Between the plates a rare gas or a halide mix rare gas is filled at various pressure. When the pressure of the gas is almost equal to 1 atm the high voltage source is required so generally AC source is used. Some of the common dielectric materials are glass, quartz, ceramics and polymers. These dielectric materials cover the electrodes. The distance between the two electrodes or plates varies from 0.1 mm in plasma displays, several millimeters in O_3 generators and several centimeters in CO_2 lasers. DBD devices also come in other configurations like cylindrical, using coaxial plates with a dielectric tube between them.

This process normally uses AC current with frequency starting from RF to microwave. But other methods were developed to bring the operational frequency range down to DC. One of the methods was to use a high resistivity layer to cover one of the electrodes. This is known as the resistive barrier discharge [8]. And the other way is using a semiconductor layer of gallium arsenide (GaAs) to replace the dielectric layer. This enables these devices to work on DC voltage between 580 V and 740 V [5].

The working of the DBD can be explained in following steps:

STEP 1: When voltage is applied across the electrodes then there is accumulation of charge on the surface of the dielectric.

STEP 2: When the amount of charge accumulated increases then they discharge within seconds leading to re-accumulation elsewhere [10].

STEP 3: The contained plasma is sustained if the continuous energy source is provided to overcome the recombination process which otherwise leads to the extinction of the discharge plasma.

STEP 4: The discharge process causes the emission of energetic photons whose frequency and energy are same as that of the gas used to fill the discharge gap [10].

This is the basic working of the DBD devices. Since we are working on the topic of sterilization, disinfection and therapeutics we should go a deep into the device used to sterilize and disinfect medical appliances.

DBD are used in various parts of medicine. The cascaded DBD, the in-package surface DBD and the contacted plasma device are used to sterilize liquid transfer devices like pipette tips, cannula and pin tools. To decontaminate rotating cutting tools, the tool is used as a grounded electrode and two equal dielectric isolated electrodes release the plasma from both sides. The gap is almost 4 cm so high voltage is used in such cases. [11, 12]

For therapeutics such devices are used which are safe for people and are handy to use for the doctors. Floating electrode DBD are used for such purposes. The discharge device consists of a dielectric-protected powered electrode and is operated by high voltage pulses. The material itself acts as the electrode hence the plasma is in direct contact with the plasma. By changing the voltage to high low current is made to flow hence electric shock is eliminated. Such devices are used to coagulate blood, decontamination of skin cuts, etc. [11, 13].

New devices are being made using flexible materials which will help us to sanitize materials of some weird size or shape. Such devices use high voltage AC current and the dielectric film is made of polymer equipped with a thin, uniform powered electrode on one side and a thin, meshed grounded electrode on the other side which enables the construction of formats as much large as required by the wound or skin area to be treated. In this way there is no electricity flow through the subject body leading to more safety of the subject`s skin or body. The flexible surface DBD plasma strip also helps to reduce the number of bacteria on the skin thus making it very much effective for sterilization [11, 17].

DBD are also use to sterilize or disinfect complex parts of medical equipments like the tubes of equipments. The bifilar helix electrode configuration helps to do plasma operations in tubes having diameter ranging from meters to 2mm [18]. The powered and grounded wire electrodes are equidistantly twisted around the tube and are embedded with an additional dielectric layer helping to prevent discharge outside the tube [11].

4.1. Sterilization and Disinfection

Plasma is also applied in biomedical applications such as sterilization and disinfection.

Disinfection is a couple of order decrease in microorganism population [2]. The disinfectants are categorized into the following categories such as *High Level Disinfectants*: High level disinfectants (HDL) are mostly used in critical medical equipment, *Intermediate Level Disinfectants*: Intermediate level disinfectants are used in disinfection of environmental and non-critical medical devices [15], and *New Disinfectant Formulations*: There are certain new disinfectant formulations which have the potential to be used in medical facilities. An example of this kind is Akwaton (poly hexamethylene-guanidine hydrochloride) which is a biocide of guanidine family. Its sporicidal activity can be seen at low concentrations against *Bacillus sutillis*. [15]. Sterilization usually implies 10^4-10^5 fold reduction in population of microorganisms [2]. Sterilization methods using high temperature and pressure and ethylene oxide gas have some restrictions for utilization.

The sterilization factors of low temperature plasma have a short lifetime (less than ms) [16].

Non thermal plasma is an excellent source of active species. These active species are capable of deactivating, killing or even disintegrating the bacteria and viruses without any significant effect on temperature [2]. Gases with no germicidal properties become biocidal when the plasma is ignited [2]. The medical instruments can be sterilized or disinfected without the use of aggressive chemicals or high temperature [2, 16]

As we know that the atmospheric pressure non thermal discharge plasma has a relatively high density of active species, it is able to kill the microorganisms without any significant heating of the substrate [2]. Dielectric barrier discharges are quite effective in killing the self- resistive microorganisms such as *Bacillus anthracis*, *Bacillus subtilis* and *Deinococcus radiodurans* [2, 15]

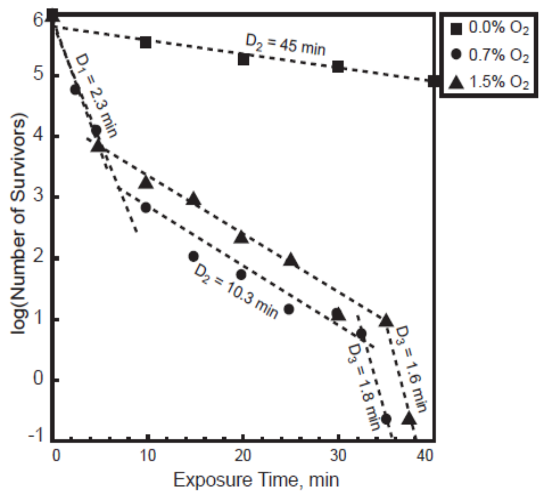

Fig. 6. Survival curves for *B. subtilis* spores exposed to N_2/O_2 discharge afterglow. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2]

As illustrated in the above Fig. 6, the death phase of a bacteria is subdivided into three inactivation phases. The first phase has the shortest D value (D value refers to the time required to reduce an original concentration of microorganisms). The second phase has the slowest kinetics. It involves erosion by active species. In the third phase, the UV hits the genetic material of the spores that are still alive [2,14-16]. *subtilis* before and after treatment with DBD plasma is shown in Fig. 7 and Single phased surviving curve for *E. coli* exposed to He- air DBD is shown in Fig. 8.

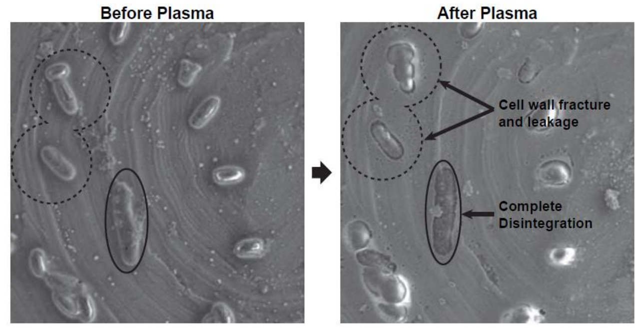

Fig. 7. *subtilis* before and after treatment with DBD plasma. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2].

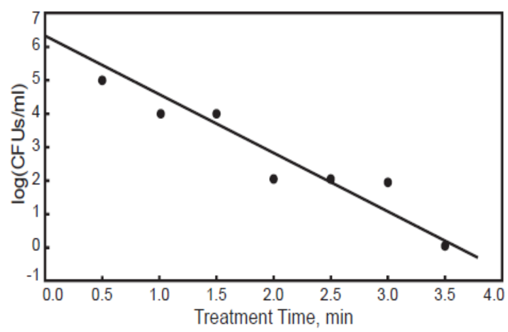

Fig. 8. Single phased surviving curve for *E. coli* exposed to He- air DBD. The D values ranges between 4s to 5 min. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2].

4.1.1. Factors affecting Sterilization and Disinfection

Due to collision at higher pressure, the active species of different variety is involved in the sterilization process. Type of bacteria, type of medium in which the cell is cultured, number of cell layers, type of exposure, contribution of UV and operating gas mixtures are some of the factors which impact the killing process. The sterilization also depends on plasma species and the biological pathway [2].

The externally applied electric field has no direct effect on the sterilization and disinfection process but it plays an important role in rupture of the outer membrane of the particle. The deposition of the charged particles on the outer membrane causes an electrostatic force. When this force exceeds the tensile strength of the membrane, it ruptures [2].

Neutral species also play an important role in disinfection and sterilization especially at high pressures. Some very reactive oxygen and nitrogen-based species such as O, O_2, ($^1\Delta_g$), O_3, OH, NO, NO_2, etc., are obtained from strongly non equilibrium air plasma [2]. The strong oxidative nature of oxygen and nitrogen-based plasma has an impact on outer structures of the cell. The germicidal effect of ozone can be attributed to its long lifetime and interference with cellular respiration system. The concentration of NO_2

and O_3 are given as a function of discharge power and air flow rate below [2] in Fig. 9 and Fig. 10 respectively.

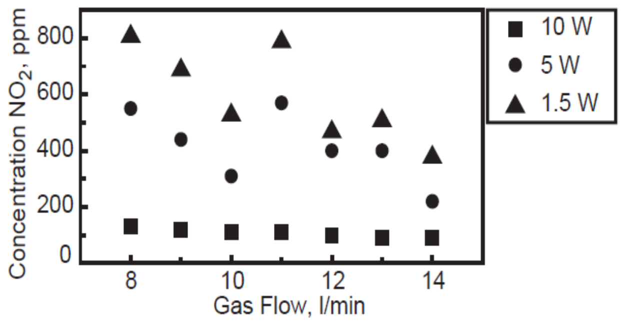

Fig. 9. NO_2 concentration generated in air DBD as a function of flow rate at three power levels. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2]

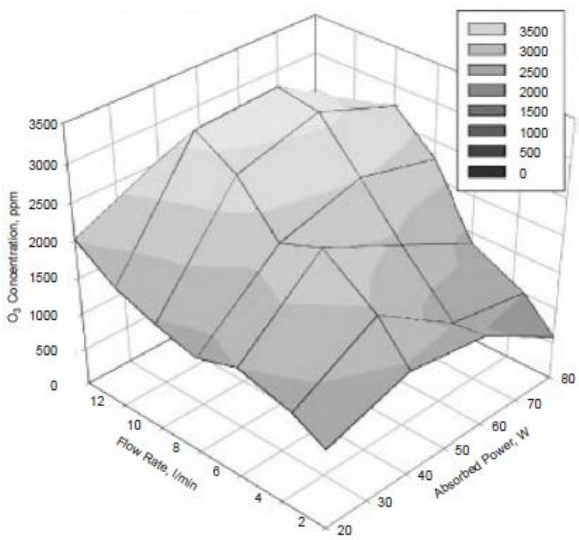

Fig. 10. Ozone concentration generated in air DBD as a function of flow rate and dissipated charge power. Fridman, A. (2008). **Plasma chemistry**. Cambridge University Press [2]

4.2. Therapeutics

Usage of plasma in the field of medicine is an emerging topic. The usage of plasma in medicine can be divided into two parts, namely, Indirect: This approach is used to treat surfaces, materials or devices to realize specific qualities for subsequent special medical applications [19], and Direct: Here the plasma is directly applied on living tissues or cells to know the therapeutic effects.

The field of plasma applications for the treatment of medical materials or devices is intensively researched and is getting better and better with each year passing. Being in the starting stage of the research it is being used in various parts of medicine.

4.2.1. Cancer

Initiation of apoptosis, or programmed cell death, is very important issue in cancer treatment as cancer cells frequently have acquired the ability to block proptosis and thus are more resistant to chemotherapeutic drugs [20]. Selective destruction of cancerous tissue is very important. It is needed for the enhancement of current methods to problems currently lacking a solution such as lung cancer. Floating Electrode Dielectric Barrier Discharge (FE-DBD) plasma when applied not only these cells die immediately by high doses of plasma treatment, but with low doses apoptotic behavior can be detected by TUNEL staining and subsequent flow cytometry. Thus, it can be said that when plasma acts on the cells directly but doesn't hamper the surroundings of the defective cell even through a layer of such solution [20].

4.2.1.1 Skin Cancer

Cold Atmospheric Pressure (CAP) plasma when applied on the diseased tissues reduces cell proliferation, adhesion, and migration, and induce selective apoptosis of neoplastic cells without damaging normal cells. The treatment is controlled by varying the time of treatment, gas source composition, gas flow rate, voltage applied, etc. [20, 21].

4.2.1.2 Gastric Cancer

Nonequilibrium atmospheric pressure plasma (NEAPP) when used as a medium of treatment it becomes NEAPP Applied Medium (PAM). PAM treatment for 24 h affected cell morphology, suggestive of induction of apoptosis. PAM cytotoxicity was influenced by the time of exposure to PAM, the type of cell line, and the number of cells seeded [20, 22].

4.2.1.3 Breast Cancer

Cold Atmospheric Plasma (CAP) when applied on BrCa cells lead to the reduction of breast cancerous cells, resulting in tumor remediation with near complete ablation while maintaining healthy cells and tissue intact. [20, 23].

4.2.1.4 Pancreatic Cancer

Non-Thermal Plasma (NTP) when applied on cancerous cells yields a positive result by reducing them, more especially when used in combination with antitumor drugs. The excellent tolerability and the effectiveness of NTP towards MIA PaCa2-luc cells *in vivo*, together with the ability to deliver NTP via a small capillary open new interesting perspective for loco-regional or *in situ* applications [20, 16]. So, such method can be used to cure pancreatic cancer.

4.2.1.5 Lungs Cancer

Atmospheric pressure plasmas have been used as a therapy for cancer. Precise treatment of tumors is difficult but is very effective. The lung carcinoma cells were found to be more sensitive to plasma treatment than the fibroblast cells based on the overall plasma dose conditions [20,25].

4.2.1.6 Cervical Cancer

The atmospheric pressure dielectric barrier discharge (DBD) plasma can be used to treat cancerous cells. With the increase of exposure time (60 or 80 s), the cell viability decreased. Similarly, Non-Thermal plasma (NPT) exposures for 40 destroy significant number of cancerous cells without damaging the healthy tissue cells [20,26].

4.2.1.7 Head and Neck Cancer

The treatment of locoregional recurrence (LRR) of head and neck squamous cell carcinoma (HNSCC) requires surgery. Small malignant growth can be eradicated by using Cold Plasma Treatment (CPT) prior to surgery while having a minimal effect on the normal adjacent tissue. It becomes more effective when coupled with endoscopic technology. [20,27]

4.2.1.8 Blood Cancer

Low Temperature Plasma (LTP) was used to counter the growth of leukemia cell. The effect of plasma exposure was not immediate, but had a delayed effect and increasing the time of plasma exposure resulted in increased leukemia cell death. [20,28]

4.2.2 Glioblastoma

Cold plasma is generally used for glioblastoma treatment which mainly focused on the apoptotic and survival signal pathways mediated by the reactive species from the plasma emissions or the plasma-mediated medium. The first-line glioblastoma chemotherapeutic drug is temozolomide (TMZ). Recent studies have shown that the plasma can induce an independent mechanism of death in the glioblastoma affected cells. The combined treatment of TMZ and plasma resulted in cell cycle arrest and the inhibition of cell growth [20, 29].

4.2.3 Corneocyte desquamation

The skin, our body`s first line of defense against pathogens, had to go through various diseases such as soap-induced xerosis, sunburn to skin cancer, as well as skin wrinkling and thickening, etc.

The drugs present currently need to be taken orally which is constrain due to high metabolic activity in the gastro-intestinal tract and in the liver. So, to counter such problems we have another type of drug known as gaseous plasma that can even invade the protective barrier and could bestow therapeutic effect to the mammalian cells. The meaning of the title can be explained as

Corneocyte: Corneocyte are terminally differentiated keratinocytes which form the outer layer of epidermis. They are regularly replaced through desquamation. They are biologically dead but remain active, being filled with keratin, lipids, fatty acids, etc, thus acts as the first line of defense. *Desquamation*: it is the process of regular shedding of outer layers of tissue or membrane, such as of skin. The current study aims to investigate the mechanism of corneocytes desquamation by numerical simulation of shining a non-thermal plasma beam, to treat thickened and rough skin without causing any damage to the healthy skin nearby. The mechanism is still in the preliminary stage and researchers are trying hard to get a proper explanation of the mechanism. When this way of treatment of skin diseases will be on its final stages then it would be a major breakthrough in skin treatment in the domain of plasma medicine [22]. A device working on the principle of DBD is currently being utilized in the hospitals and clinics with the name Argon Plasma Coagulator [31], the image of which is shown in the Fig. 11 below.

[1] **Fig. 11.** An Argon Plasma Coagulator (APC) device. https://de.erbe-med.com/de-en/ [31].

4.2.4 Reactive Oxygen Species and Reactive Nitrogen Species in Plasma Chemistry

The Reactive Nitrogen Species (RNS) and Reactive oxygen Species (ROS) generated by Atmospheric Pressure Plasma Jet (APPJ) treatment are some of the important outcomes of plasma in medical field [32]. Usage of RNS and ROS play a positive role in physiological treatment like in maintaining homeostasis, initiating immune responses, and regulating cell differentiation and proliferation [20]. NO which is also a product of plasma plays an important role Central

Nervous System (CNS). It has been found that various drugs which had NO and gaseous NO has been used for treatment of CNS disorders and brin injuries [33, 34]. So now researchers are making efforts to treat Central Nervous System disorders using plasma.

5. CONCLUSION AND FUTURE WORK

Plasma, sometimes also known as the fourth state of matter, is made of large number of charged particles consisting of electrons and ions but the total charge remains zero, i.e., neutral. Plasma can be produced through discharge mechanisms. There are two discharge mechanisms Townsend mechanism and steamer mechanism. Townsend mechanism is for low pressure of the gas used and small gaps between the electrodes for the production of plasma and steamer mechanism is for large gaps between the electrodes and large pressure of the gas used to produce the discharge. The types of discharges are of five types glow discharge, arc discharge, radiofrequency and microwave discharge, corona discharge and dielectric discharge.

Dielectric Barrier Discharge or DBD or silent discharge is a type of discharge where a dielectric material is inserted between the two electrodes to prevent the charged particles from directly getting in touch with the electrodes. It generally works at 1 atm pressure on AC current but now some changes are being made so that it can be made to work on DC current. The discharge from DBD devices can be used in various fields of Medicine like sterilization, disinfection, therapeutics, etc.

The main difference between sterilization and disinfection is that in sterilization is about a 10^4-10^5 times reduction of population of microorganism whereas disinfection as a couple order reduction in population of microorganism. Non thermal plasma is an excellent source of active species which can kill or destroy the microorganisms. Non-lethal gases become germicidal when plasma is ignited in them. The DBD is also capable of killing some self-resistive bacteria. Non-reactive gases with high oxidative properties also play an important role in germicidal works. They have the capability to destroy the outer cell membrane of cells thus help in disinfection and sterilization.

Plasma discharges directly or indirectly, are also used in therapeutics. For the treatment of various types of cancer like skin cancer, leukemia, head and neck cancer, breast cancer, lung cancer and even for glioblastoma and corneocyte desquamation where the upper outer layer of the epidermis is made to shed the dead tissues, treat the rough part and prevent the thickening of skin without harming the healthy cells thus help to prevent misfunctioning and help the skin to remain healthy for a long period of time.Even Plasma have the potential to treat Central Nervous System Disorders. Currently it is in the research phase.

The biomedical application plasma device which could especially be Argon Plasma Coagulator (APC) works on the principle of dielectric barrier discharge mechanism excited by the frequencies of 0.05-500 kHz at atmospheric pressure. The planar or cylindrical electrodes with a gap of about 0.1 mm to a few centimeters can be utilized to generate the plasma plume at room temperature. The plasma plume is embedded with the generation of plasma radicals which stimulates the biological phenomenon of skin cell proliferation and blood cauterization to name a few of them. Argon Plasma Coagulator has also been used to ablate dysplastic heterotopic mucosa, to recanalize occluded or overgrown metal stents or cut displaced metal stents. Besides, the APC is currently being used in small series to treat tumors of the ampulla of Vater, and nonsuperficial colonic tumors. Moreover, APC was also tested for nonoperative candidates with endosonographic and histologic T1 tumors of the esophagus, stomach, and rectum. Conclusively, the five major areas in which the APC might have potential applications are in the domain of surgery, gynecology, gastroenterology, interventional bronchology, and ENT giving special attention in the area of abdominal surgery, breast surgery, tumor reductions, tumor bleeding, and rhinology, respectively.

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