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Low-temperature atmospheric-pressure plasma sources for plasma medicine☆

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ABSTRACT

In this review paper, fundamental overviews of low-temperature atmospheric-pressure plasma generation are provided and various sources for plasma medicine are described in terms of operating conditions and plasma properties.

Plasma-processing technologies have been intensively developed for more than three decades and have made remarkable and successful progress as key manufacturing technologies for a variety of industrial applications [1–11] ranging from surface modification of materials to advanced device-manufacturing technologies and biomaterial processes. These plasma-processing technologies have been based on generation and control of reactive species (radials and ions) in low-pressure plasmas sustained in vacuum [1,10]. Due to insufficient collisions between electrons and gas molecules in these low-pressure plasmas, the gas temperature is maintained usually at temperatures much less than the electron temperature of a few electron volts. In spite of the successful development of the low-pressure plasmas as key manufacturing technologies, the low-pressure plasmas have several drawbacks; vacuum systems are required for plasma generation at reduced gas pressure and thus the low-pressure plasmas cannot be directly applied for processing or treatments of biomedical tissues with liquid phase.

Plasma generation at atmospheric pressure can overcome the drawbacks of the low-pressure plasmas. Sustaining atmospheric-pressure plasmas, however, requires high voltage for gas breakdown and tends to exhibit arcing and gas heating due to enhanced collisions between electrons and gas molecules [12]. For avoiding arcing and lowering gas temperatures in atmospheric-pressure plasmas to attain low-temperature sources, several schemes have been developed via properly designing electrode configurations and discharge-excitation voltage waveforms for limiting discharge duration [13].

Major methodologies for avoiding arching and gas heating include dielectric barrier discharge (DBD) [14,15] and use of pulsed voltage or high frequency (HF) voltage [16] for discharge excitation rather than direct current (DC) voltage. In the DBD configuration, discharge current enhancement causing considerable electrode heating (one of the major causes for arching generation) can be avoided by covering one or both of electrodes with dielectric materials, which can automatically stop discharge current enhancement via discharge-voltage reduction due to charge accumulation on the dielectric surface before transition to arching every time the discharge is ignited. Because of this operation regime, the DBD is considered as self-pulsing discharge.

For the sources with bare metal electrodes, pulsed voltage or high frequency (HF) voltage can be used for discharge excitation, in which discharge duration can be controlled via temporal waveforms and the electrode temperatures can be controlled below the levels for causing arcs.

With inclusion of methodologies mentioned above, a variety of plasma sources have been developed and characterized in recent years for generation of stable plasmas at atmospheric pressure with gas temperature maintained at as low as the level acceptable for processing of organic materials and biomedical applications. Excellent reviews of these sources can be found elsewhere [12–14,17–23].

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The low-temperature atmospheric-pressure plasma (LT-APP) sources are attractive in that the LT-APP can provide enhanced gas chemistry via production of high density reactive species (radicals and ions) while the gas temperature is maintained at as low as the level acceptable for processing of organic materials and biomedical applications. The attractive features of the LT-APP have led to open intensive research activities that require low-temperature processes in materials processing [23] and in biological and/or biomedical applications [18–23].

Especially, biomedical treatments with the LT-APP have attracted great interests due to significant medical effects and have been extensively investigated worldwide as an emerging scientific field referred to as "plasma medicine" [24–26]. Extensive research activities with the LT-APP have shown remarkable effects in wide rage of biomedical applications including sterilization and bacterial inactivation [27–30], treatment of skin diseases and wound healing [24,31–33], cancer therapies [34–40], LT-APP interactions with DNA [41–43], blood coagulation during surgical procedures [44–46], and gene transfection [47] as an emerging field of application. Furthermore, cell culture medium treated with atmospheric-pressure plasma, which has been referred to as "plasma -activated medium" (PAM), has been shown to exhibit remarkable effects as anti-tumor fluid in recent years [48] and has been expected to lead new trends in cancer therapies. Behaviors of reactive species including reactive oxygen species (ROS) and reactive nitrogen species (RNS) in liquid through plasma-liquid interface have been elucidated in the excellent review paper [49]. Following the review paper [49], the ROS and RNS components and relative concentrations in the plasma irradiated water depend on the type of plasma (e.g., DBD, plasma jets, microwave torch, etc.), the nature of the mass transfer and mixing between the gas and liquid phase, the presence of other components in the water and so forth.

In this review article, fundamental overview of low-temperature atmospheric-pressure plasma generation will be provided and the various sources for plasma medicine will be described.

1. Fundamentals for low-temperature atmospheric-pressure plasma generation

When a DC voltage applied to the gas medium via electrodes exceeds the breakdown voltage for the gas, a discharge can be ignited and plasma can be sustained. This breakdown voltage depends on *pd* product, where *p* is the gas pressure and *d* is the distance between the electrodes, and the dependence of this breakdown voltage on the *pd* product is known as Paschen's law [9,50]. The breakdown voltage expected from the Paschen's law shows minimum value at around $pd = 1$–10 Torr cm for a variety of gas molecules. This implies that with increasing gas pressure a narrower electrode-gap distance is favored to attain a practical breakdown voltage for ignition of the gas discharge. At atmospheric pressure, the Paschen-minimum condition can be attained at a gap distance much less than a millimeter, at which the DC voltage required for the gas breakdown is expected to be a few 100 V. Nevertheless, with a gap distance of 5 mm the breakdown DC voltage for argon gas at the atmospheric pressure is estimated to hike to a few kV [12].

From the viewpoint of plasma source design, lowering of the breakdown voltage is favored for easy operation of the source and for flexibility of the source configuration and/or handling. One of the methodologies for lowering of the breakdown voltage is the usage of HF voltages at higher frequency. Discharge voltage dependence of emission signal intensity of He 706 nm from the atmospheric-pressure He discharge for 0.6 mm gap distance, as schematically shown in Fig. 1, is summarized in Fig. 2 with discharge-voltage frequency as a parameter [51]. Recalling that the DC voltage required for the breakdown for this configuration as schematically shown in Fig. 1 was 600 V, considerable decrease of the gas-breakdown voltage was attained with increasing driving frequency, and low voltage operation of the atmospheric-pressure He plasma is realized by applying less than 150 V via application of HF voltage at 60 MHz. At HF frequency of 100 MHz, the atmospheric-pressure He plasma can be sustained with HF voltage less than 100 V. In terms of the frequency dependence of the atmospheric plasma sources, the readers may also refer to the excellent review paper [13] for characteristics of the atmospheric plasma sources sustained with excitation power source from DC to microwave.

In a glow discharge sustained at low pressures, the discharge is sustained by ionization of gas molecules via collision with accelerated electrons. Typical electron density (or plasma density) of the glow discharge at low pressure is in the range of 10^8–10^{13} cm^{-3} [9] and the electron-molecule collision is not sufficiently enough to attain thermal equilibrium. Thus the electron temperature T_e is higher than the gas temperature T_g and the ion temperature T_i by one or two orders of magnitude as schematically illustrated in Fig. 3 for a discharge with a mercury and rare gas mixture [12,52]. This feature of the glow discharge is referred to as "non-equilibrium plasma" or "cold plasma".

With increasing pressure, enhancement of energy exchange from electrons to gas molecules and ions via collisions leads to thermal equilibrium of electrons, gas molecules and ions to attain a condition of $T_e \sim T_i \sim T_g$ as illustrated in Fig. 3. This condition of the discharge is designated as "thermal plasma" and the attained electron density (or plasma density) is in the range of 10^{16}–10^{19} cm^{-3} [12]. Thermal plasma processing has been originally developed as an effective coating technology primarily due to its highly collisional characteristics (i.e., its extremely high temperature reaction environment), and thus high processing rates are attained in general [53], however, application to biological and/or biomedical treatments is considerably difficult without cooling the gas at extremely high gas temperature.

As described above, the discharge sustained at an atmospheric pressure tends to be in thermal equilibrium state, in which the electron temperature tends to decrease and the gas temperature tends to increase due to enhancement of energy exchange via electron collisions with gas molecules and ions. When the discharge duration τ_d and/or the residence time of the source gas τ_{res} are considerably shorter than the electron energy relaxation time τ_{relax} ($\tau_d \ll \tau_{relax}$ and/or $\tau_{res} \ll \tau_{relax}$), however, suppression of the energy exchange of the electrons with the gas molecules and ions can be possible. Consequently, low-temperature plasmas in non-equilibrium state ($T_e \gg T_g$) can be achieved even in the discharges sustained at the atmospheric pressure [54], as shown in Fig. 3.

Major methodologies for achievement of low-temperature plasmas in non-equilibrium state ($T_e \gg T_g$) via avoiding gas heating include dielectric barrier discharge (DBD) [14,15] and use of pulsed voltage or high frequency (HF) voltage [16] for discharge excitation.

Discharge conditions to maintain the non-equilibrium state ($T_e \gg T_g$) as mentioned above can be attained with DBD regimes [14,15]. The source configuration for this discharge regime consists of two parallel metal electrodes, on which at least one electrode is covered with a dielectric material, as schematically shown in Fig. 4. In the DBD regime, due to the charge accumulation on the surface of the dielectric material, the discharge duration τ_d can be effectively suppressed so as to be considerably shorter than the electron energy relaxation time τ_{relax}, as $\tau_d \ll \tau_{relax}$. Furthermore, in this discharge regime, plasma is generated through a number of