Low Temperature Plasma Pharmacy

A Study of the effect of Atmospheric pressure cold plasma processing on the physical and chemical properties of some pharmaceuticals

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CONTENTS

1. Introduction.
2. DBD Plasma and some configurations.
3. Processing of NIF & Poloxamer 188 with SDBD.
4. Discussion
5. Characterization & Results
6. Future Plan

1. Introduction

Plasma Medicine: a new independent field of medical research combining plasma physics, life science and clinical medicine to use physical plasma for mainly therapeutic applications .

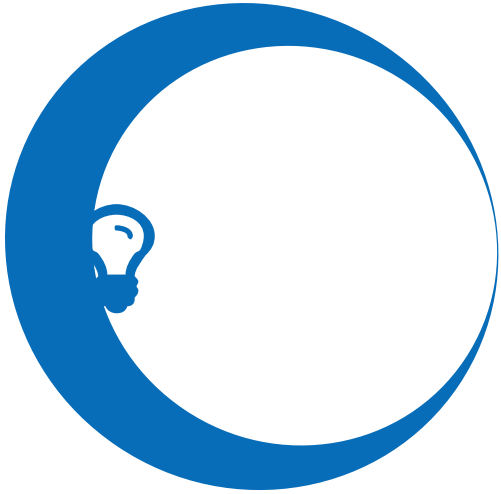
Plasma Pharmacy: A specific field within plasma medicine is which means the use of physical plasma for pharmaceutical purposes.

It uses of physical plasma to generate, modify and stabilize pharmaceutical preparations or to support its application.

Problem:

- Nearly half of the new active Ingredients are either insoluble or poorly water soluble.
- Size reduction to submicrometer range can lead to increase in the dissolution rate due to the increase in S/V ratio

Some Size reduction techniques:



Milling: changes to the crystal shape and may lead to formation of amorphous materials.

Electrospray crystallization: has low rate production.

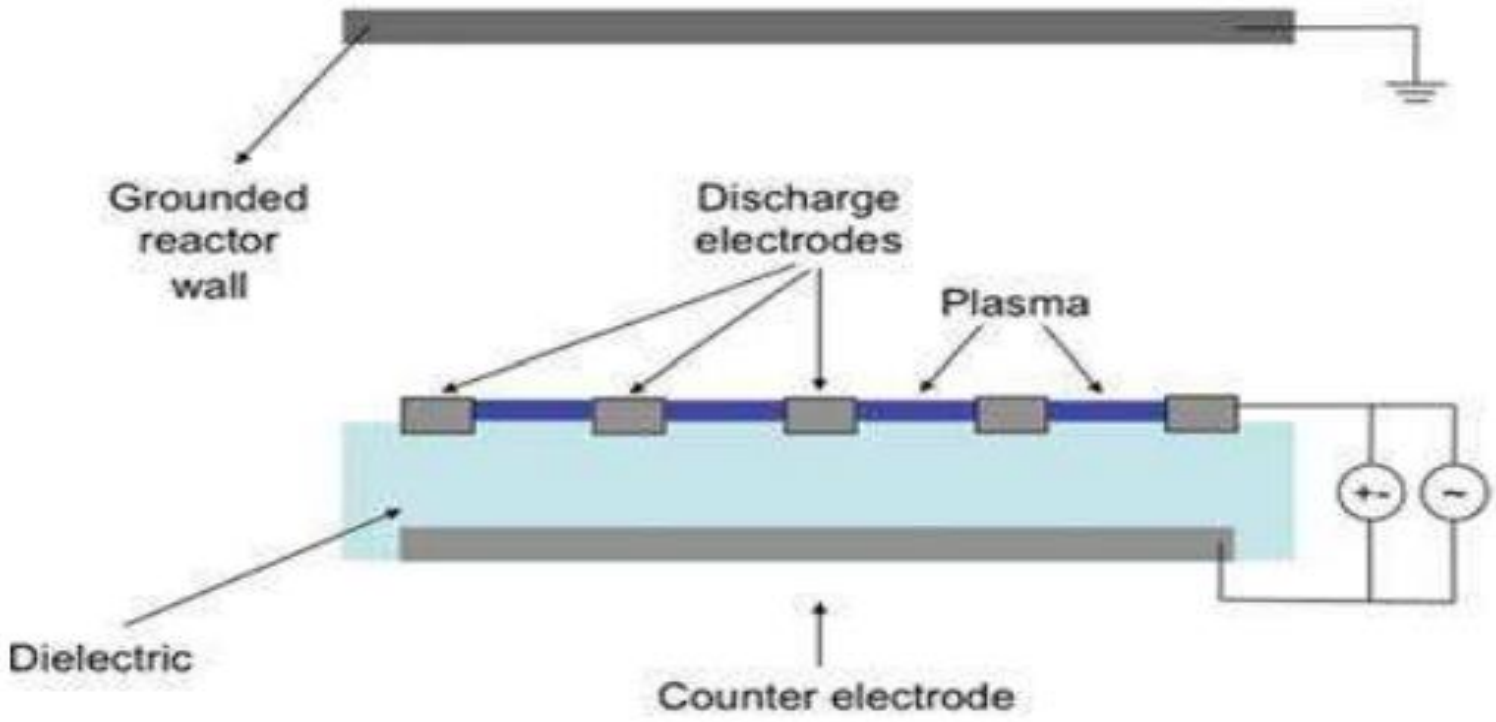
Cold plasma technology: inexpensive, easily scalable to industrial levels, environmentally benign.

2. DBD Plasma and some configurations

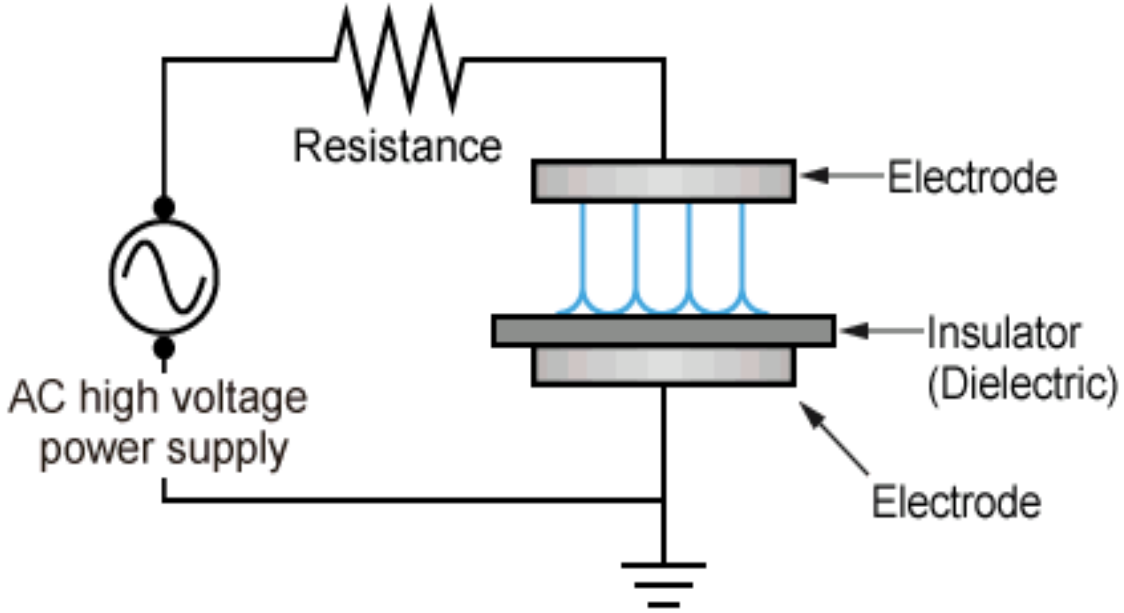
- A discharge that occurs when AC voltage is applied to one or both electrodes made of 2 metal plates and one is covered with an insulator.
- In DBD, excessive and rapid discharge is suppressed by the insulator, resulting in a discharge that doesn't produce a spark, during it: a purplish like light plasma is observed in the discharge area.

SDBD :

- The plasma is a result of discharges caused by a pulsed high voltage between the discharge electrode and counter electrode.
- The plasma is generated on top of SDBD plate, the plate is made of a dielectric material in which an electrode system is embedded, the discharge electrodes are on one side that consists of line shaped conductors that are deposited on or partially embedded in the dielectric material.
- on opposite side of the plate, a plate-shaped counter electrode is coated on the dielectric.
- This configuration results in a strong electric field close to the discharge electrodes.



VDBD: Plasma is generated between the electrodes such as two parallel plates with a dielectric in between



SDBD Vs. VDBD:

In SDBD, generated plasma is more homogeneous, microdischarges are limited to the surface, their density is higher than that in VDBD, in the other hand, VDBD is less complicated than SDBD.

3. Processing of NIF & Poloxamer 188 with SDBD:

Aim of the study:

- To prepare submicrometer sized crystals of NIF and it's excipient Poloxamer 188 to achieve fast dissolution and rapid onset of the drug effect using atmospheric pressure cold plasma crystallization.

- Niflumic acid (NIF) : pale yellow, crystalline powder, important anti-inflammatory with weak analgesic effect, used to treat rheumatoid arthritis, has poor aqueous solubility and dissolution rate.

- Poloxamer 188 : white, solid, faintly perceptible, water soluble powder.

- D- Mannitol : White, solid, odorless,water soluble powder.

Experimental :

- Niflumic acid: particle size of about 80 micrometer.
- Poloxamer 188 : particle size of about 122 micrometer.
- D- Mannitol: particle size of about 86 micrometer.
- Different solution concentrations were prepared with 99.8 % acetone, using a mixer for 10 minutes.

- Plasma is generated on the top of the surface of SDBD plate , made of alumina ceramics Al2O3 and 1 mm thickness.
- Plasma is a result of discharges caused by a pulsed high voltage between the discharge and counter-electrodes.
- AR gas at 2 bar pressure was transported through a collision nebulizer and carried the solution an an aerosol spray into the Plasma chamber.
- A stainless steel nozzle was used an 8 mm slit with 70 mm length to direct the entire solution above the plasma.
- DC bias voltage added to the setup,connected between SDBD plate electrodes with 5 Mohm resistor, superposed on the AC voltage, So that plasma can be used as charger for solution drops , and charged particles can be collected on the grounded plasma reactor chamber wall.

Discussion :

- Poloxamer 188: helps as a stabilizer by wetting the particles to minimize the aggregation of the drug.
- D- Mannitol: acts as a carrier that provides the homogeneous distribution of NIF crystals.

Plasma crystallization:

- SDBD micro discharges ionize the aerosol droplet that are sprayed into the Plasma.
- Plasma has 2 functions :

1- acts as a heat source and thus enhances the evaporation rate of the solvent drops.

2- Plasma electrically charges the solution droplets, as the surface charge reaches a critical value (Rayleigh limit) , electrostatic force overcome the surface tension and the droplets disrupt into a myriad of smaller droplets to reduce the surface charge density, this disruption process is called Coulomb fission and results in micrometer sized droplets

- At some point, this force becomes sufficiently large for crystal nucleation and growth to occur.

5. Characterization & Results

Particle size:

- NIF crystals are somewhat spherical with mean size of 700 nm, aggregated into 5-6 micrometer clusters.
- Poloxamer 188 of particle size 1-3 micrometer.

FT - IR Spectroscopy: IR Spectra showed no chemical change in the process , no physical decomposition was observed.

Dissolution rate measurement:

- The measurement was performed in gastric ph 1.2

- For conventional NIF : LOW dissolution rate ,31% of the drug dissolves in the first hour.

- Conventional NIF with Conventional excipients: 40% of the drug dissolves in the first hour.

- Plasma processed NIF: has high dissolution rate, 50% of the drug dissolves in the first hour .

- Conventional NIF with plasma processed Poloxamer 188 and conventional D- mannitol: Significant increase in the dissolution rate ; 81 % of the drug dissolves in the first hour.

- Plasma processed NIF with plasma processed Poloxamer 188 and conventional D- Mannitol : 76% of the drug dissolves after 15 minutes,96% in the first hour and complete dissolution after 90 minutes.

Future Work:


Thank you