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RECENT TECHNIQUES OF PHARMACEUTICAL SOLVENTLESS COATING: A REVIEW

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ABSTRACT

The coating of solid pharmaceutical dosage forms began in the 9th century B. C., with the Egyptians. Conventional coating techniques are based on solvents or water. Solventless coatings are alternative technique of coating. In solventless coating, the coating material is directly spread on the core and then it is cured by special method to form coat. Solventless coating avoids the use of water or it reduces to very small amounts with respect to the coating material hence it overcomes the limitations of conventional coating such as need for time, energy consuming, drying steps and the most important drug stability issues. A variety of solventless coating approaches are described in this review as powder coating, hot melt coating, supercritical fluid coating, magnetically assisted impaction coating, Plasma enhanced chemical vapor deposition. This review summarizes basic principle and process of the coating techniques.

INTRODUCTION: Pharmaceutical solid dosage forms such as tablet, pellets, pills, beads, spherules are coated for different reasons such as aesthetic property, to enhance drug stability (from light, moisture, oxygen), to separate reactive components in formula, modified drug release, identification, prevention from gastric acid and enzyme, improved mechanical strength [1]. Film coating can be carried out using either an organic solvent or water [2]. The liquid coating technology can obtain extremely uniform smooth, gleaming coating surface [3, 4].

Organic solvents are toxic, flammable, vapor of organic solvent causes environmental pollution and hazard to coating equipment operator, long processing time due to evaporation of solvent, vaporization of organic solvents is energy consumptive, high cost of solvent, strict environmental regulation placed on use of organic solvent [5,6].

USFDA, Environmental Protection Agency and Occupational Safety and Health administration (OSHA) have strict requirement regarding use of solvent in pharmaceutical industry [7, 8]. Thus, aqueous based coating is increasingly used compared to organic based coating. However aqueous based coating also having following drawbacks:

- Degradation of certain drugs due to use of heat and water.
- Validation of coating dispersion for controlling microbial presence.
- High energy consumption and long processing time [6].

In order to overcome the drawbacks of liquid coating technology, solventless coating has emerged. Solventless coating eliminates many problems associated with the use of solvent i.e., residual solvent,

solvent exposure, solvent disposal in coating. As there is no use of solvent, it eliminates the solvent evaporation step and thus reduces the processing time also solventless coating reduces overall cost because it eliminates the tedious and costly process of solvent disposal and treatment. Solventless coating can be applied to thermosensitive drugs except hot melt coating [5, 9, 10].

It can obtain much thicker coat than conventional liquid coating and Process can be recycled. The main aim of this review is to discuss mechanism, current status and future development of the solventless coating techniques such as powder coating, hot melt coating, photocurable coating, magnetically assisted impaction coating, supercritical fluid coating, Plasma enhanced chemical vapor deposition [12].

Techniques of Solventless Coating:

Powder/dry coating: The concept of powder coating originated in the USA in 1950s [11]. The principle of powder coating involves spraying of mixture of powdered coating material along with polymer and then heated in curing oven to form a coat. Application of the powder coating technology has been booming in metal and wood coating, which has a new application in the pharmaceutical industry to coat solid dosage forms. Several dry coating has developed depending on the method of particle adhesion on solid dosage forms such as Plasticizer-dry-coating, Heat Dry Coating, Plasticizer-electrostatic-heat dry coating, and Electrostatic coating. Dry coating, a novel coating technology for solid pharmaceutical dosage forms [12].

Plasticizer- Dry Coating:

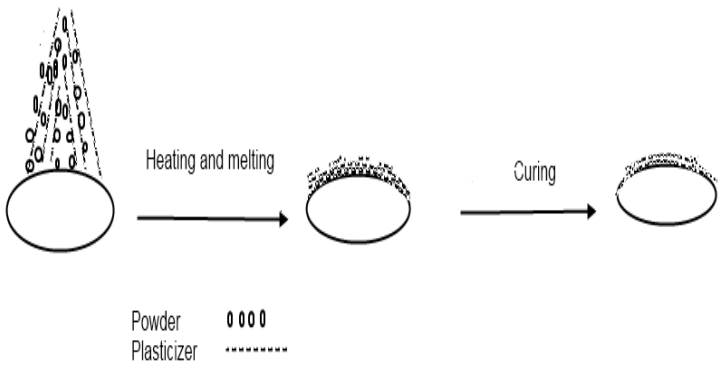

FIGURE 1: PLASTICIZER COATING

The first dry coating technology is mainly based on the usage of plasticizers. Here, this technology is referred to as "plasticizer-dry-coating. In this technology, powdered materials and plasticizer are injected onto dosage surface simultaneously from separate spraying nozzle. The sprayed liquid plasticizer would wet the powder particles and the dosage surface promoting the adhesion of particles to dosage surface. The coated dosage forms are then cured for predetermined time above the glass transition temperature (Tg) of the polymer, forming a continuous film [13-16].

By means of the plasticizer-dry-coating technology both tablets and pellets could be coated. The former were generally coated in a pan coater. However, for the latter a fluidized bed coater is required in order to avoid formation of agglomerates caused by the smaller size and higher specific surface area of pellets and thus strong interactions [15-17]. The adhesion of particles to dosage surface is primarily by wetting of particles and dosage surfaces by plasticizers and the film formation is the collective response of improved viscous flow and particle deformation resulted from plasticizer and heat [13]. Moisture would significantly accelerate the film formation and optimize the film smoothness and integrity of ethylcellulose-coated pellets during the heat curing phase [15].

These phenomena are similar to those observations for film formation of aqueous dispersions [18, 19]. The application of liquid plasticizer has to be considered influencing the film formation by temporarily building capillary forces between the polymer particles before the plasticizer will have been taken up by the polymer [13]. The heat-humidity curing condition suppresses the evaporation of the plasticizer, resulting in higher plasticizer levels remaining in the films, as compared to the heat-only curing condition. The heat humidity curing also significantly increased the mechanical strength and decreased the water vapor permeability of the films [20]. Plasticizer dry coating is the technique that looks promising, from all points of view, for coating food ingredients (time, energy savings and high productivity) [21]. This technique has a low moisture level compared with aqueous coating systems.

However, quite a small level of water was detected in the granules [2%], and this is not acceptable for applications to some sensitive products such as probiotics [22]. Coat thickness increases with increasing plasticizer concentration. Adversely, additional plasticizer leads to very soft or sticky films. It is difficult to balance the plasticizer concentration for a sufficient coat thickness and that for a flexible and dry coat [21].

Heat Dry Coating: This method is named as Heat dry coating by Y Luo *et al* (2008) [23]. In this technique heat was used as a binding force to realize the dry coating of tablets. Heat dry coating was developed by Cerea *et al* (2004). In this coating technology, Eudragit EPO (a copolymer based on dimethylaminoethylmethacrylate and methacrylates) particles were constantly spread onto the tablets contained in a lab-scale spheronizer by means of a motorized single screw powder feeder, with an infrared lamp positioned on the top of the spheronizer as a heating source, without using any solvent and plasticizer.

Recently, tablets were pre-plasticized before the coating process by mixing polymer powder with plasticizer and then sieving [24]. Powder adhesion onto the tablet surface is enhanced only by the partially melted polymer that generates binding forces between the particles and between the tablet surfaces [25].

Bodmeier R *et al* (2005) showed that spray-dried surelease as a pre-plasticized ethylcellulose powder required only mild curing conditions to achieve extended drug release from dry polymer powder coated pellets [26].

The heat dry coating process occurs in the three stages:

1. Pre-heating: In this stage the uncoated tablets are heated to the predetermined temperature.
2. Powdering: In this stage the powder is transferred into the coating equipment and distributed onto the cores.
3. Curing: Here polymeric particles adhere to the surface of the substrate to form a Polymeric film coating [27].

In these processes, dry coating technique was proved to provide both bead and tablet products having sufficient gastric resistance, with a substantial reduction of processing time [1]. The advantage of heat dry coating includes abandoning plasticizers for lower Tg film forming polymers, or avoiding high concentrations of plasticizers because of pre-plasticization. However, it is a challenge for heat dry coating to get a smooth, uniform and thick coating only by the help of heat based adhesion [28].

Electrostatic Coating: Electrostatic coating is extensively used in the painting industry and the snack food industry, metal coatings, finishing industry and coating of living cells as an alternative to traditional powder coating [29-33].

The principle of electrostatic powder coating involves spraying of finely grounded particles and polymers simultaneously onto a substrate surface without using any solvent and then heating the substrate for curing on oven until the powder mixture is fused into film. There are two types of spraying units, generally in the form of powder coating guns, as per their charging mechanism(corona charging and Tribo charging) [11, 34].

Electrostatic coating promotes an even dispersion of the powder over all the surfaces of the products [29]. Coating efficiency during electrostatic coating is enhanced by a large charge to mass ratio. The larger the charge during electrostatic coating, the greater the improvement seen with the process [34]. Phoqus Pharmaceuticals Limited, an oral drug delivery and development company has invented both apparatus and formulations of powdered coating materials based on electrostatic coating of solid dosage forms [35].

Corona Charging Mechanism: The corona spray gun has an electrode located near the tip of the gun, which emits a field charge that imparts a negative charge onto the particles of powder as they penetrate this field that results in the powder being attracted to the grounded work piece [34].

This leads to more consistent film thickness control and makes it easier to powder coat complex shapes. The movement of particles between the charging gun and the substrate is derived by the combination of electrical and mechanical forces. The mechanical forces produced by the air blows the powder towards the substrate from spray gun and electrical forces are produced from the electrical field between the charging tip of spray gun and earthen substance and from the repulsive forces between the charged particles [23, 34, 36, 37].

Tribo- Charging Mechanism: Tribo- charging use frictional charging techniques to charge the powder particles Tribo-charging guns create a charge on the powder particles via intimate contact with the gun walls. Principle of friction charging associated with the dielectric properties of solid materials and therefore no free ions and electrical field will be present between spray gun and substance [34, 36].

For tribo charging guns, the electrical forces are only regarded to the repulsive forces between the charged particles.

Steps in the deposition of charged particles onto the substrate are;

Charged particles are uniformly sprayed onto the earthen substrate in virtue of mechanical forces and electrostatic attraction,

Particles accumulate on the substrate before the repulsion force of the deposited particles against the coming particles exceeds and increases the electrostatic attraction,

Finally, once the said repulsion becomes equivalent to the said attraction, particles cannot adhere to the substrate any more, and the coating thickness does not increase any more.

After spraying charged particles move into the space adjacent to the substrate, the particle to deposit on the substrate due to the attraction forces between the charged particles and the grounded substrate. Charged particles are homogeneously sprayed onto the earthen substrate in virtue of mechanical forces and electrostatic attraction.

Once the said repulsion becomes equivalent to the said attraction, particles cannot adhere to the substrate any more, and the coating thickness does not increase to any further extent [23].

Measurement of the electrostatic powder coating properties for corona and triboelectric coating guns can be done by using the Electrostatic Powder Coating Diagnostic Instrument (EPCDI). EPCDI analyses the electrostatic powder coating deposition efficiency by measuring the powder adhesion properties in the pre-cured state and it also measures the uniformity of the powder coating by moving the powder sample and measuring the infrared light transmission through it [38].

Further methods of adhesion measurements are drop test rig and virtual oscilloscope [39].

Plasticizer-Electrostatic-Heat Dry Coating (PEH): Plasticizer-electrostatic-heat dry coating is named here primarily because this technology is combined practice of plasticizer, electrostatic attraction and heat. In this technology, the steps of coating process consists of, [40]

- Positioning preheated solid dosage form in a chamber of the rotatable, electrically grounded pan coater,
- Spraying powdered coating materials and plasticizer simultaneously on the solid dosage forms in the pan coater, during rotation using an electrostatic sprayer,
- Curing the coated solid dosage forms to form continuous, uniform and flexible coats.

During the whole coating process, the solid dosage forms and the chamber are always kept in hot state by heating the air in the coater or directly heating in the coater. According to the coating process, PEH-dry-coating is characteristics of integration of five kinds of forces, softening or melting effects of particles by heat, wetting of dosage surface by a plasticizer, electrostatic attraction forces, hydrodynamic force due to spraying and mechanical force due to rotation of pan coater. They are combined to develop the adhesion of powdered coating materials to solid dosage surface.

Firstly, the movement of the powdered particles from the charged gun to the dosage surface is promoted by the combination of electrical and hydrodynamic forces. The adhesion of the powder particles on to the dosage surface is by means of electrostatic attraction between the charged powder particles and earthed dosages. Softening effect of the powder is due to heat from preheating and heating during coating. Wetting effect is due to plasticizers.

Secondly, the hydrodynamic forces from compressed air and mechanical forces from the tumbling effects of the pan coater are both helpful to the adhesion of powders on the earthed surface due to the combination of electrostatic attraction and heat. Finally, the repulsion between the same charged particles on the dosage surface support the even distribution of the particles on the dosage surface and prevent the coalescence between solid dosage [23].

Hot Melt Coating: The hot-melt coating techniques have been shown to avoid the use of solvents and show promising for taste masking, gastric resistance, acid resistance, sustained release or bioavailability enhancement, based upon type of coating polymer [41]. It has been adopted because it is faster and cheaper than the conventional coating techniques where evaporation and/or recovery of solvent can be expensive, tedious and time consuming [42].

In this method, the coating material is applied in its molten state on the substrate. Thermostable materials with a relatively low melting point (<80°C) such as lipid, waxes and fatty bases high molecular-weight polyethylene glycols are the most suitable coating material in hot melt coating. Examples of some marketed hot melt coating excipients are Gelucires, Precirol, Stearines, Myvaplex, and Compritol 888ATO [41, 46, 48].

It offers several benefits and potential for a wide variety of application in pharmaceutical formulation [43-46]. The most common applications of this technique consist of the coating of pellets, granules and powder particles, particularly to obtain moisture-protected or modified-release dosage forms [47]. The various technologies of hot melt coatings are fluidized bed coating (top spray and bottom spray), spray congealing/coating, and pan coating (pan spray and pan pour) [46].

Jannin V *et al* (2003) carried out the comparative study of the lubricant performance of Compritol®888 ATO on Lactose either used by blending or by hot melt coating and found that the hot melt coating process induces a homogenous repartition of the lubricant on the lactose surface in a lower concentration as compare to classical blending procedure [46,50,51].

TABLE1: LIST OF HYDROPHOBIC SUBSTANCES USED AS COMPONENTS OF EDIBLE FILMS AND COATINGS, BASED ON RESEARCH AND PATENTS PUBLISHED IN THE LAST 15 YEARS [49]

Hydrophobic substances	Sources
Oils, fats, shortening, margarine	Animal and vegetable native oils and fats (peanut, coconut, palm, palm kernel oils, cocoa, milk butters, lard, tallow, etc.) Fractionated, concentrated and/or reconstituted oils and fats (fatty acids, mono-, di-, and triglycerides, cocoa butter substitutes, etc.) Hydrogenated and/or transesterified oil (margarine shortenings, etc.)
Waxes	Natural vegetable and animal waxes: candelilla, carnauba, jojoba bees, whales Non-natural waxes : paraffins, mineral, microcrystalline, oxidized or non-oxidized polyethylene
Natural resins	Asafoetida, Benzoin , Chicle, Guarana, Myrrh, Olibanum (incense), Opoponax, Styrax
Essential oils and liquorices	Camphor, mint, and citrus fruit essential oils Liquorices and pure glycyrrhizin
Emulsifiers	Lecithins, mono- and diglycerides

Supercritical Fluid Coating: A new method for coating polymeric thin films on particles has been achieved by simultaneous nucleation of polymeric material out of a supercritical fluid, encapsulating the particles fluidized in the supercritical fluid, and further curing and binding the material coated on the particles [52]. Microencapsulation using supercritical fluid technology combines a liquid- like density and solvating power with gas-like transport properties (like viscosity, diffusivity). Carbon dioxide is the most widely used supercritical fluid because of its relatively low critical temperature (31°C) and

pressure (74 bars). The use of supercritical fluid technology, especially CO_2 for encapsulation purposes is mainly due to the mild processing condition, allowing microencapsulation of sensitive ingredients for cosmetics, pharmaceuticals [53].

The coating method involves an enclosed system that provides;

- For suspension of the solid particles to be coated,
- For dissolution of the coating material in the supercritical fluid solvent,
- For temperature or pressure swing operations causing film deposition/coating of the suspended solid particles and,
- Additional chemical addition and/or thermal cycles providing for any additional reactions required (such as polymerization) [54].

There has been a continuing growth of interest in replacing conventional organic solvents with environmentally friendly supercritical fluids in chemical processes. Among them, supercritical carbon dioxide emerged as an excellent candidate due to its superb characteristics and properties: it is inexpensive, nontoxic, nonflammable, readily available, easily recycled, and as a solvent, it possesses both gas-like diffusivities and liquid-like densities and solvencies [55, 56].

A number of approaches to the use of supercritical technologies for the deposition of modifying coatings on solid substrates are described in the literature such as Rapid expansion of supercritical fluid (RESS), supercritical antisolvent (SAS), Aerosol solvent extraction system (ASES), solution enhanced dispersion by supercritical fluid (SEDS), Gas Antisolvent (GAS) etc [57].

The two methods that are most widely used for applying SC Co_2 to the formation of thin layer coatings are the rapid expansion of supercritical solutions or suspensions (RESS) [58-64] and the method involving supercritical antisolvent (SAS) [65-70]. In RESS method polymer is dissolved in supercritical carbon dioxide with or without cosolvent.

Then, it is injected through nozzle (depressured), generating microparticles with a polymer coating on the surface. Due to rapid de-pressurization of the supercritical solution polymer looses it's solubility and is deposited on substrate surface [71, 72]. However, the application of the RESS process is severely limited by the fact that polymers because they have very limited solubility in SC CO_2 at temperatures below 80°C [72].

Kim *et al.,* reported the microencapsulation of naproxen using rapid expansion of supercritical solutions (RESS) [60].

In the SAS method, a homogeneous solution of various solutes and polymer is injected into the SC CO_2, which in this case acts as an antisolvent. Co-precipitation of the solutes and polymer occurred and composite microspheres or microcapsules were formed [73]. An important feature of the SAS process is that the organic solvent can be almost completely removed by simply flushing with pure CO_2.

Thus, dry particles are produced after a CO_2 extraction step (flushing) following feeding of the organic solution [73, 76]. SAS provides wide range of solvent choice [73, 77]. Ribeiro D *et al* (2002) performed the encapsulation of the bovine serum albumin with lipidic compound (Dynasan 114 or Gelucire 50-02) using supercritical process and determined the release kinetic and found that smooth and uniform coating can be obtained by this method [79].

Photocurable Coating: This is a chemical advance anticipated to rapidly coat tablets at or below room temperature [80, 81]. Photocuring as a process of rapid conversion of especially formulated (usually liquid) solventless compositions into solid films by irradiation with ultraviolet or visible light [82-85]. Photocuring has wide commercial application in dental and medical fields. It is also used to form films of varnishes, paints, and coatings for paper, plastic, wood, metal surfaces, Composite dental fillings, preventive treatment for caries, assembly of medical devices, and wound dressing [87]. The UV-curable coating is strong and photostable. By changing the pore-forming agent and with choice of material, number of layers and thickness of the coating it was reasonable to produce immediate as well as sustained release [84].

- Photocuring systems have four major components:
- UV-visible light source,
- Liquid prepolymers or monomers,
- Pore forming agent,
- An initiator [88].

UV-visible Light Source: An often-used lamp type is the 80 W/cm medium-pressure mercury lamps, which emits a broad spectrum in the short wavelength range from 200 to 320 nm but also at discrete wavelength numbers of 360, 410, and 430 nm [89].

Liquid Prepolymers or Monomers: Primary component in a photocuring system is the photocurable film-former a polymer or monomer [90]. It includes a meth acryloyl monomer, a meth acryloyl oligomer, an organic solvent, epoxy acrylate, polyester acrylate, polyurethane acrylate, hexanediol diacrylate, unsaturated polyester, trimethylolpropane triacrylate, tripropyleneglycol diacrylate, which provides heat resistance, storage stability and high light transmission while having a low viscosity sufficient to avoid discoloration of the optical product.

Tetraethyleneglycol dimethacrylate (TEGDMA) and bisphenol A-glycidyl methacrylate (Bis-GMA) are two photocurable monomers that are comprehensively used in dental composites [89, 91-95]. Polydimethylsiloxane is extensively used as a photocuring material because of its good thermal stability and extraordinary flexibility additionally it is used in transdermal drug delivery systems, composite dental fillings and other medical products [93].

Pore Forming Agent: Ratio of solid pore forming agent(S) to liquid pre-polymer (L) is the most important parameter which determines the coating efficiency and uniformity of coating. When wider range of S/L ratio was investigated, good coating efficiency was favored by the lower particle size, and in case of larger particle sizes there is sharp decline in the coating efficiency at low S/L ratios [5]. The initial study performed by Wang and Bonger, where UV light was used to cure derivatized silicon polymer films on non-pareil beads but film formed by this method is complete and almost perfect barrier to drug diffuse, such drug release depend on defects or weak points in the coating. Hence, they realized to incorporate pore forming agents in the polymeric film to prepare functional coatings. Pore forming agents are Lactose, sodium chloride, Explotab, Ac- Di-Sol, PEG 800, etc [92, 96].

Photoinitiator: The Photoinitiator is an important ingredient of UV-curable coatings and has to have sufficient absorption in the 250~400 nm range, high reactivity, and high thermal stability, in addition to being nonyellowing, and nonodorous [99]. The photo initiator absorbs the UV-radiation and generates free radicals. The free radicals start and propagate chemical reactions that convert the reactive compounds into a cured film [97, 98]. Ciba spatiality chemicals provide Photoinitiator under various brand names such as IRGACURE184, IRGACURE500. Monomolecular-type photoinitiators are Benzoin ether, Diethoxy aceto phenone, Hydroxyketones, Aminoketones, Bisacyl phosphine oxides, etc [89, 101].

Magnetic Assisted Impaction Coating (MAIC): Many food and pharmaceutical ingredients, being organic and moderately soft, are very sensitive to heat and can easily deform by severe mechanical forces. Magnetic Assisted Impaction Coating method can attach the guest (coating material) particles onto the host (material to be coat) particles with a least degradation of particle size, shape and composition caused by heat and mechanical forces. The rise in temperature is negligible; this is an additional benefit with thermosensitive powders such as pharmaceuticals [102].

The following steps involved in the mechanism of coating in the MAIC process:

1. Excitation of magnetic particle
2. De-agglomeration of guest particles
3. Shearing and spreading of guest particles on the surface of the host particles
4. Magnetic-host-host particle interaction
5. Magnetic–host–wall interaction and;
6. Formation of coated products [102]

The surrounding electromagnetic coil creates a magnetic field. It is used to accelerate and spin the large magnetic particles mixed with the host and guest particles promoting collisions between the particles and with the walls of the vessel, creating a fluidized state. During collision there is de-agglomeration of guest particles since the magnetic particles ''fluidize'' the host and guest powders, ''soft'' coating occurs by powder impaction [103, 104]. There are several unique features of MAIC that make it advantageous as a dry particle coating device. Firstly, the MAIC can coat soft organic host and guest particles without causing major changes in the material shape and size [103].

Secondly, although there is some heat generated on a microscopic level due to the collisions of particles, there is negligible heat generation on a macroscopic level and hence no increase in temperature of the material during processing by MAIC. This is desirable when processing temperature sensitive powders such as pharmaceuticals. Lastly, the device can be operated both as a batch and continuous system making it versatile in the amount of material it can process [105].

According to Singh P *et al* (2001) model, the coating time in the MAIC device depends on the number density of host particles, the diameters of the host and guest particles, the initial and final bed heights, and the material properties of the host and guest particles [106]. Yang J *et al* (2005) observed that the reduction in the cohesion force for the coated particles is inversely proportional to the size ratio of the guest and the host particles, indicating that smaller guest particles provide a larger reduction in the cohesive force [104].

Plasma enhanced Chemical Vapor Deposition (PECVD):

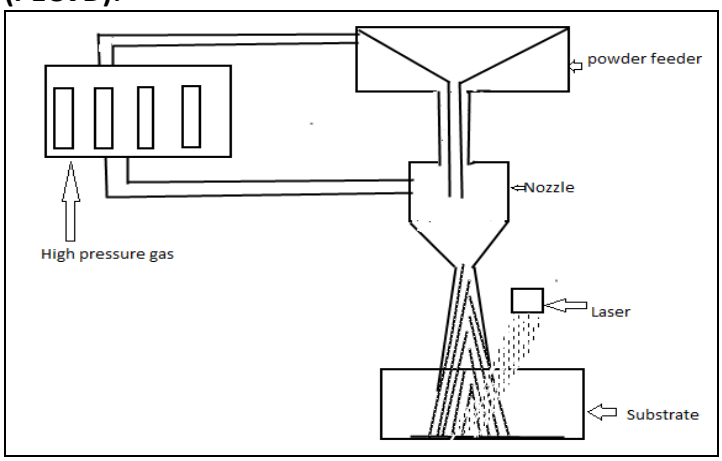

FIGURE 2: PLASMA ENHANCED CHEMICAL VAPOR DEPOSITION

Plasma polymerization is also known as plasma-enhanced chemical vapor deposition (PECVD) [10]. It involves the fragmentation of gaseous monomers into activated species, generally free radicals and ions, which then recombine and condense on the surface of the substrate as a solid polymer film (i.e. in situ polymerization). The plasma energy is provided for monomer activation, which can be induced by a range of sources including radiofrequency and microwave radiation [108]. These techniques originally from semiconductor industry, such as chemical vapor deposition (CVD), atomic layer deposition (ALD) used to coat particle. Use of non-thermal plasma creates the possibility to treat heat sensitive material with combination of charged particles, which preventing agglomeration before and during the coating process [109, 110].

Specifically, PECVD allows deposition of thin films on a wide variety of substrates, including sub-micron particles [19]. PECVD has become an attractive tool in the food, biomedical and pharmaceutical fields and has been used for a wide variety of applications from increasing biocompatibility and cell adhesion to controlling drug release [109, 112-114].

Plasma polymerization, also known as plasma-enhanced chemical vapor deposition (PECVD), a dry coating method, was chosen to deposit thin hydrophobic polymer films on the surface of amorphous ketoprofen (KET)/ Methocel™ E5 aggregate particles [107].

CONCLUSION: Solventless coating technologies are having many advantages over conventional liquid coating such as solventless coating does not emits volatile organic compounds, it can achieve much thicker coat, produce less hazardous waste, having less operating coat, less recovery time, less processing time. The equipment is needed for pan coater, fluidized bed coater, spray coater with slight modification. However, for magnetically assisted impaction coating, electrostatic coating special equipments are required. Solventless coatings produce uniform thick coating. Electrostatic coating is able to apply different color coating on tablet. But before commercialization of these techniques, additional research is to be made on scale up test evaluation for drug release profile, clinical test.

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