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Review Article

Thermo-Mechanical Dry Coating as Dry Coating Process is for Pharmaceuticals

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Abstract

The manuscript aims to provide glimpse on updated information relating thermo-mechanical dry coating processes (TMDCP) suiting in modifying surface attributes of fine and ultra-fine particle (FiUlFiP). FiUlFiPs are the integral component of pharmaceutical processes. They exhibit complex and queer properties, are conferred mostly from their surface attributes colligated with their higher surface area. Particle engineering technocrats extensively working for modifying surface & surface attributes of FiUlFiPs. These efforts are to find their worthy applications & new functionalities. Among available diverse particle engineering technologies/ process, TMDCP, a dry coating process (DCP), advocated being worthy and efficient. The TMDCP finds multidisciplinary applications, mostly in drug development & drug delivery. Said DCP involves fixing and/or attaching coating material (CoM) as particles herein synonym guest particle (GP) onto core/substrate particle (CSP) herein synonym host particle (HP). Attaching/ fixing the GPs onto HPs, in TMDCP, involve their mechanical and/or thermal interactions. Scientific literatures are evidencing diverse techniques and/or process, basing on discussed interactions. Amongst them novel techniques/ processes are Hybridization, Magnetically assisted impaction coating process (MAICP), Mechanofusion, Theta-composer, and high shear compaction. In this area diverse devices/ equipments are prevailing in market. Important are Hybridizer, Magnetically assisted impaction coater (MAIC), Theta-composer, Mechanofusion, Quadro Comil®, Cyclomix®, and many others. Attempt of this article is to discuss and present their method of working, working principle, applicability, limitations, and benefits. Contained information might be beneficial for professionals of pharmaceutical and allied field.

Keywords: dry coating, equipment, particles, processes, thermo-mechanical.

INTRODUCTION

Amongst the diverse pharmaceutical products solid dosage forms are the most popular one [1, 2]. In their manufacturing the most basic unit is FiUlFiPs whose handling is most inevitable [2, 3]. Further these possess extremely cohesive bulk flow and often tend to agglomerate [1-3].

High surface area of FiUlFiPs is reasoning for receiving interest [1, 2, 4]. Researchers (scientists and engineers) in pharmaceutical sectors working extensively in finding applications and taking advantage of many worthy properties and new functionalities attributed to FiUlFiPs, as drug delivery system/carriers [1, 2, 5]. They were exploiting numerous elegant strategies of particle engineering methods to modify density and/or shape of FiUlFiPs to resolve the problems caused by cohesion and find their worthy properties and new functionalities [1-3]. The surface modification strategy of FiUlFiPs is nowadays becoming vital in pharmaceutical sector for the active(s) that are difficult to formulate [1-3].

Modification of surface and surface attributes of FiUlFiPs can be achieved by coating/depositing an appropriate additive on their surfaces [1-3]. The processes of coating/ deposition, by method of either physical deposition or chemical deposition, is for modifying surface attributes of FiUlFiPs are complex one [4, 6-8]. Physical deposition method uses thermal, mechanical, thermo-mechanical, electro-mechanical, or thermodynamic means to produce a thin film of solid at surface of FiUlFiPs [1-3, 7, 8]. Chemical deposition methods involve occurring of chemical changes of a fluid precursor at surface of FiUlFiPs, leaving a solid-layer of coating [6, 7]. Examples are Photo curable coating or photo-curing, gas/vapour phase deposition (like chemical vapour deposition, Atomic/molecular layer deposition) [1, 2]. All these DCP basically comprises of layering/deposition of CoM particles, coalescence and sintering, and levelling [3, 7, 8]; refer Figure-1.

Most of techniques/ process for surface modifications of FiUlFiPs alter their innate properties either physically or chemically [1, 2]. Technologies of them involve use of high pressures, high shear, elevated temperatures, and/or solvents [2, 3]. Solvent based wet coating methods have become less preferable as can reduce stability, cause particle agglomeration, leave residual organic solvents, and environmental concerns, arousing from unwanted waste streams and possible emissions of volatile organic solvents [2, 4, 6-8]. The strategies involving chemical deposition inherit issues of relatively expensive, complex, and challenging scale up [1, 2]. This making most of the processes unsuitable for active(s) those are labile to such ambient conditions [1, 3].

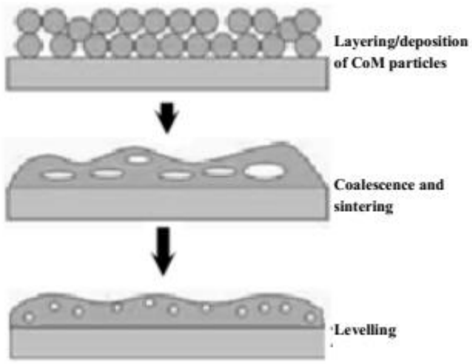


Figure 1: Stages of DCP, as adopted from references [1, 2]

Dry coating is a process to directly attach FiUlFiPs, or GPs, onto relatively larger (micron-sized) CSPs or HPs [1, 2]. Herein GPs are brought into close contact with HPs by application of the mechanical forces and does not call for any binder(s), solvent(s), or even water [1, 2, 4]. In general DCP involve use of higher temperature and/or impaction force or applying high shearing stress for resulting coating [1, 4, 9]. Strong mechanical/impaction force accompanied by generated heat causes embedding & layering of CoM particles or GPs onto the surface of CSPs or HPs [1, 10, 11].

Modifying surface attributes of FiUlFiPs via single-step, dry, thermo-mechanical method has been recognised as a potentially cheaper, simpler, safer, faster, and environment-friendly approach comparing other processes that are dry or based on solvent [1-3, 12].

TMDCP are relatively new with respect to dry and wet coating processes, are still in the R&D stage of development, and are rarely finds commercial applicability [1, 2, 4]. This manuscript is presented with hope to increase the visibility of TMDCP and inspiring other for working in this area [1, 2, 4]. These in turn will improve understanding of physico-chemical attributes/ principles influencing the TMDCP and to find novel/ improved industrial applications [1, 2, 13].

DRY COATING

Dry coating as a process directly attaches FiUlFiPs or the GPs onto the CSPs or the HPs by bringing them into close contact with use of mechanical forces [1, 2, 4]. As size of GPs is very small, the van der Waals interactions are sufficiently strong enough to keep GPs attached firmly to the HPs [1, 2, 4]. Thus the process makes achievable either a continuous or a discrete coating of GPs on the surfaces of the HPs. In both cases the coating can be of either a continuous film or a particle layer (monolayer or multilayer) [1, 2, 4], refer Figure-2.

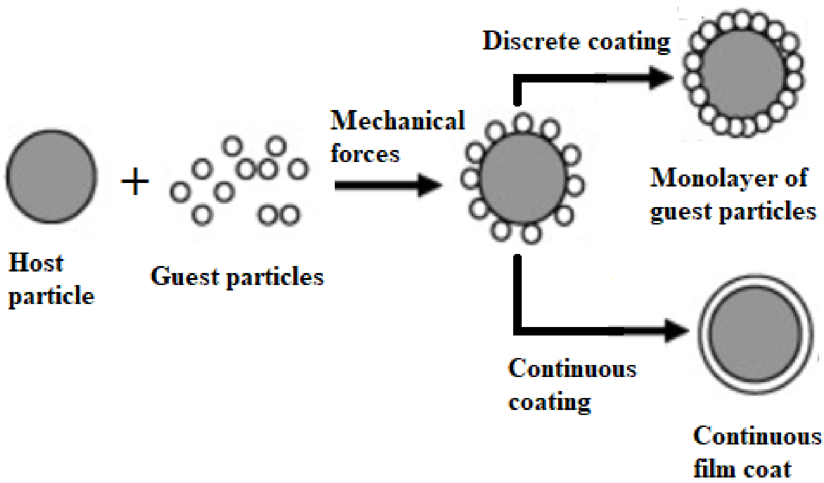


Figure 2: Types of coating resulting from DCP [1, 2]

Formation of either continuous or discrete coating depends on diverse operational conditions/parameters including process-time, weight fraction of GPs to HPs, curing step, and particle properties [1, 2, 13]. Usually, involvements of curing step results continuous coating [1, 2].

Dry coating of continuous type results a continuous film that is generally non-porous [1]. It completely shields surface of underlying CSP, are thus generally preferred [2, 4]. In other hand the film of discrete coating is porous. Porosity of discrete coating thus bears some unique pros [1, 2]. These are suitable in application calling for coating to have a change in specific surface property of CSP, but a complete shielding of underlying CSP is un-desirous [1, 2, 4, 13].

One approach of DCP is gas/vapour phase deposition method [1, 2]. This method involves physical/chemical vapour deposition and sputtering [2, 4]. Methods involving gas/vapour phase deposition of pharmaceutical importance are plasma-enhanced chemical vapour deposition, supercritical fluid technology, and aerosol flow reactor [3, 4]. All these methods call for generation of vacuum state [1, 4]. Thus these methods typically require huge capital investments & large overhead costs, in the process equipment [1, 2].

The DCP, in some instances, may either deform the GPs or cause the GPs to get embedded onto surface of HP, while bringing the GPs in close vicinity to the HP [1, 2]. Resultant embedding and/or deformation increase the contact area of GPs and HPs [1, 4]. This causes attraction amongst particles to become even stronger [1, 2, 4]. Thus result a much stronger coating is made obtainable side-by-side alters surface morphology and make feasible in reducing adhesive forces of HPs [1, 2].

By involving embedding and/or deformation approach the DCP creates engineered FiUlFiPs having tailored properties [1]. This value-addition process outcomes composite materials of

FiUlFiPs and makes possible the FiUlFiPs with new and/or exciting applications [2, 4]. From past few years, said approach had steadfastly established as a viable method in forming value-added composite particles [2, 13]. These approaches of DCP result dry coating by thermo-mechanical means [1, 13]. Besides producing value-added product, the TMDCP produces none of organic gas or aqueous or liquid waste streams [1, 4]. Thus, further to produce FiUlFiPs with complete different functionality, the TMDCP are cost effective and environmentally benign [2, 4].

With TMDCP highly expensive GPs can be coated onto cheaper HPs or carrier material [1, 2]. Thus TMDCP can reduce the use of high-priced or rare materials [2, 4]. Comparing wet coating method the TMDCP eliminates drying step thus can outcome in substantial energy savings [2, 13]. In this regards TMDCP are promising coating methods [1].

DRY COATING PROCESSES OR METHODS

The process basis followed to have dry coating of CSP may fall in any of follow categories [1, 2]:

a. Photo curable coating
b. Gas/vapour phase deposition or coating
c. Electrostatic dry coating
d. Plasticiser dry coating
e. Hot melt coating
f. Thermal dry coating
g. Mechanical dry coating
h. Thermo-mechanical dry coating

Photo Curable Coating

Photo curable coating or photo-curing is chemical approach designed to coat substrates at/or below room temperature, at very rapid rate [1, 2]. It is a process that rapidly converse specially formulated solventless compositions, usually in liquid state, into solid film by way of photo-curing [1, 2]. The photo-curing step involves irradiation of the product with ultraviolet or visible light [1, 2]. Comparing visible light, ultraviolet light curable coatings are strong and photo-stable [1, 2].

Gas/Vapour Phase Deposition or Coating

The technology of gas/vapour phase deposition method is recently up-roused DCP for solid substrates [14, 15]. It's a novel technique that enables synthesizing polymeric film-coat on the FiUlFiP surface [16, 17]. The technique results coating of FiUlFiPs with satisfactory uniformity [17, 18]. This is with orchestrated topography, surface, and functionalities [15, 16]. Vapour phase coating involves principle of vapour phase deposition/coating while gas phase coating uses supercritical fluids for realising coating of FiUlFiP [16, 18].

Vapour phase deposition involves 'electro-dispersion' process to disperse powdery or liquid coating materials [1]. Electro-dispersion is achieved by applying strong electrostatic field [2]. Employed intense electric field disperses a part of static-bed of powder/ liquid (GPs) into a stable cloud of fast moving HPs (dispersion medium) [1, 2]. Maintaining a dynamic equilibrium between the static phase and the dispersed phase realises coating [1, 2].

Supercritical fluids are the highly compressed gasses [1]. Near critical point, these possess several advantageous peculiar attributes of both gases and liquids [2]. Nearby critical point, minor changes in temperature and/or pressure induces significant changes in their density and rapid change in their solvent power [19, 20]. Rapid change in density and solvent power of supercritical fluids is underlying principle for realising coating of FiUlFiPs [21].

Electrostatic Dry Coating

Electrostatic dry coating, novel technique of DCP, is for coating of powders, tablets, capsules, and living cells [2, 9, 22]. The method realises electrostatic deposition of charged coating particles onto surface of CSPs [1, 9]. This in turn dramatically enhances uniformity of film coating [1, 2, 23]. DCP featured with combined usage of heat, plasticiser, and electrostatic field is termed plasticiser electrostatic heat-dry coating [1, 2]. The DCP involving coating with electrostatic field in fluidised-bed processor is termed electrostatic fluidised-bed coating [1, 22]. However an optimised electrostatic DCP for substrate coating in pan coater can produce coated substrate with excellent coating uniformity, continuous film-coat having smooth surface, and drug release significantly similar to that of substrate cores [1, 22, 23].

Plasticiser Dry Coating

Techniques of DCP making usage of plasticisers are termed plasticiser dry coating [1, 2]. It is suitable for film-forming polymer with low glass transition temperature (*Tg*) [1, 2]. Spreading of powdery coating materials on surface of CSP and concomitant spraying of plasticiser followed by curing for pre-set time above *Tg* of coating polymer is the basis to form continuous film [1, 2].

Hot Melt Coating

This process involves applying (air-atomising and spraying) the meltable CoM, in molten state, onto CSPs [1, 2]. The product upon cooling realises solidification of meltable CoM results coating [24]. Usually lipid or waxes having low melting point are used as meltable CoMs [22, 26]. The process can be performed with spheronizer, conventional pan coater, fluid bed processors, and spouted bed processors [1, 2, 9]. It is suitable for moisture sensitive drugs and enhancing aqua solubility and dissolution rate of poorly water-soluble drug [27-29]. In this process solvent evaporation phase is absent thus results nonporous and strong particles [2, 24, 27-29].

Thermal Dry Coating

Inclusion of plasticiser in coating formulation is problematic for film-forming polymers with lower *Tg* and at high concentrations it cause pre-plasticisation [1, 2]. The heat-dry-coating combat said issues by abandoning plasticiser in the DCP, as it uses heat only as a binding force to realise coating [1, 2].

Mechanical Dry Coating

DCP involving high-shear and high-energy interactions amongst the particle-particle and/or particle-device wall to achieve coating are classed as mechanical DCP [1]. Said interactions are guided to form a coat of GPs on the surface of HPs [2].

Thermo-Mechanical Dry Coating

TMDCP is a recent strategy/ approach exploited for even distribution of GPs on HPs by high-shear mixing [1, 2, 30]. During processing in the thermo-mechanical reactor the sample gets subjected to mechanical compression & simultaneous thermal stress by intense shear [1, 2]. Inputted high mechanical energy in some instances effect coating through mechano-chemical reaction [1, 2, 4, 30]. The mechano-chemical reaction is effected at contact area of the HPs and GPs, thus resulting new composite [1, 2, 4].

MAICP

Ingredients that is thermo-labile, relatively soft, and easily deformable by intense mechanical and thermal stress call for soft coating processes/ methods having ability to attach GPs on HPs without their degradation and with minimal deformation of their shapes & sizes [1, 2, 9, 31].

The MAICP is devised to solve said issues [1]. Its design and operational mechanism is different to that of devices/equipments used in TMDCP [2]. Herein the principle involved in resulting coating is peening process [1, 2]. The process involves pouring powders of CoM or GPs and CSP or HPs into the processing vessel along with small oscillating magnetic-particles [1, 2]. Oscillating magnetic field is generated surrounding the processing vessel to oscillate magnetic-particles [1, 2]. Oscillation of magnetic-particles causes collisions between magnetic-particles and GPs/HPs, GPs and HPs, and vessel wall and GPs/HPs [1]. Thus achieving coating/fixing surface of HPs with GPs [2, 9], refer Figure-3.

The processing time with MAICP is short and the process demands lower energy [1, 9]. It possesses ability to coat CSP of nano size (up to 0.25 microns) [2]. Its batch processing limitation is overcome with patented continuous type MAIC [1]. The continuous one enables separation of coated CSP from magnetic-particles for facilitating continuous operation [2]. Some instances warrants for coating of the magnetic-particles, appropriately [1]. This is to overcome shedding of contaminants [9].

DEVICES AND EQUIPMENT OF TMDCP

Devices and equipment suiting TMDCP are basically high-shear mixers with approach of special type [1, 2]. The design approach of them aims to provide utmost surface interactions with minimal attrition effect [1, 2]. True mechanisms underlined in the TMDCP yet have to be amply understood, as involves complex physico-chemical interactions [1, 2]. Involved physico-chemical interactions are between guest-host particles, guest-guest particles, device wall-GPs, and device wall-HPs [1, 2]. Also it is postulated that chemical and/or physical binding might be contributing to adhesion/fixing of GPs onto surface of HPs [1, 2]. In some instance, a mechano-chemical reaction between HPs and GPs is devising coating [1, 2]. In totality, the binding/fixing mechanisms amongst the GPs and HPs are dependent on the TMDCP and the materials (powder mix of GPs and HPs) [1, 2].

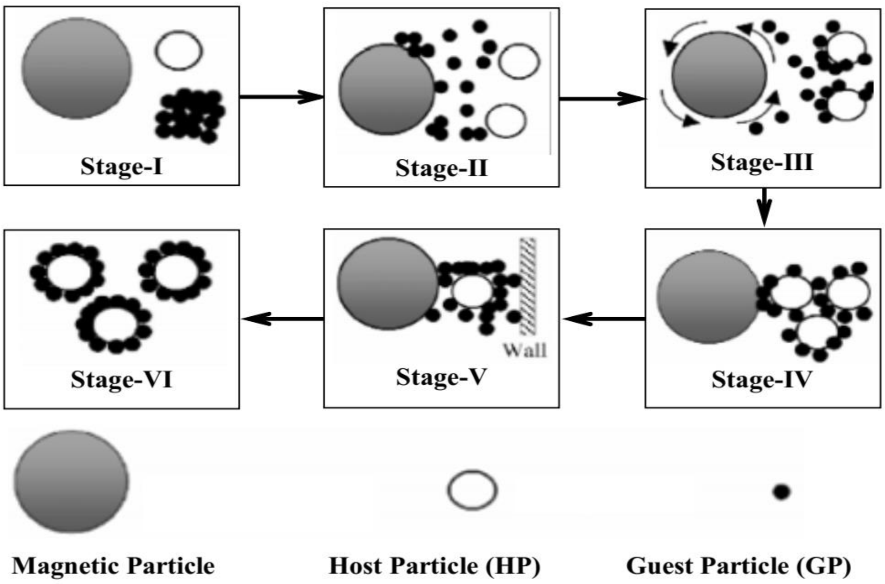


Figure 3: Schematic presentation on type and nature of collisions occurring in MAICP [1, 2].

Scientists and engineers configured and devised diverse devices and equipments suiting TMDCP [1]. Devised devices and equipments are available with various configurations but are based on similar operational principle [2]. Nowadays, amongst them some of these specialised devices are commercially available [1, 2]. These include Magnetically Assisted Impaction Coater®, Mechanofusion®, Hybridizer®, Theta-composer®, Quadro Comil®, Cyclomix® high shear mixer, and many more [1, 2]. Although Quadro Comil® and Cyclomix® are not for coating purpose but these finds applicability in coating of cohesive powders and FiUlFiPs [1, 2].

The operation of these devices and equipments is mostly a one-step straightforward process [1, 2]. Load the powder mixture (powders of GPs and HPs) in the processing bowel/vessel of them [1, 2]. Pre-set the operational time and/or speed and turn ON the device/machine [1, 2]. Then turn OFF device/machine and then unload the product [1, 2].

Some of the devices and equipments suiting TMDCP have ability for continuous processing, but with slight modifications [1, 2]. Upon optimisation and validation, the manufacturing process involving TMDCP will become robust [1]. These processes are with minimal concern of deviation, specifically to operator-skill [1, 2]. Thus have apparent to be scaled-up [1, 2]. However, their scalability potentialities for larger manufacturing-scale batches with pharmaceutical applications warrant more robust investigation [1, 2].

Mechanofusion

Mechanofusion, another strategy/ approach merges/fixes HPs on GPs particles by inputting high mechanical energy through mechano-chemical reaction [1, 2, 4, 30]. The mechano-chemical reaction takes place in contact area of the GPs and HPs resulting new composite [1, 2, 4]. During processing, the sample in mechanofusion reactor gets subjected to compression and simultaneous stress by intense shear [1, 2]. Both of the strategies are dependent on processing time and rotor speed [30],

Of the available dry coating technologies with pharmaceutical applications mechanofusion have arguably received utmost attention [1, 2]. Early version of the device based on mechanofusion concept has propeller processor having four blades, refer Figure-4(a) [1, 2]. The machine consists of processing vessel, round processor, blade scraper, and separate channels for powder inlet and outlet [1, 2]. Motor drives the vessel that rotates at a controlled speed of up to 2000 rpm [1, 2]. The processor and the scraper are stationary [1, 2]. The wall of processing chamber can be water jacketed so as to cool processing chamber, if warranted by process-induced heat [1, 2]. Its later version, a lab-scale one, is a simplified design has a rounded processor [1, 2]; refer Figure-4(b). Here the scraper and the processor are exchanged by a replaceable processor module [1, 2]; refer Figure-4(b). Herein processor rotates at a controlled speed of up to 6000 rpm while vessel is stationary [1, 2]. The coating quality of said two modules are apparently equivalent [1, 2], However, the earlier design comprises higher void space thus allows higher powder load [1, 2].

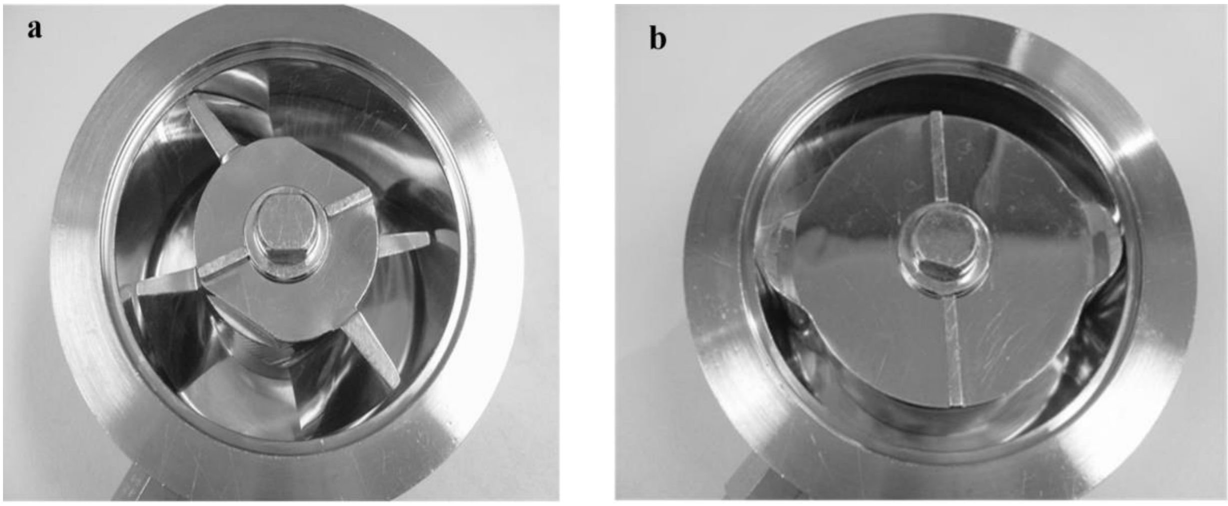


Figure 4: Type of Mechanofusion processors [1, 9].

Coating process in Mechanofusion involves placing of an aliquot quantity of power mixture, comprising HPs and GPs, into the rotating processing chamber/vessel [1, 2, 9]. The chamber rotates at a controlled speed that is set between 200 to 1600 rpm [30, 32]. Rotation of chamber pushes powders outwardly towards chamber wall [33-35]. Gap between rotating chamber & inner stationary piece is regulated/controlled [1, 2]. As a result, powder particles while passing through the gap are subjected for intense forces of compression and shearing [30, 32-35]. Intense shearing force may alter physico-chemical attributes of powders which are consociated with size reduction to some extent [1, 2, 35]. Joint action of shearing and compression forces acting on particles build-up localised heat [1, 2, 35]. The generated heat is ample for fusing the GPs onto the surface of HPs [30, 32-34].

The size of gap between chamber wall and inner piece plays crucial role [30, 32]. This controls thickness of the coating [33, 34]. Further the gap between the chamber wall and the scraper requires controlling [1, 2, 9].

Mechanofusion holds follow advantages [30, 32-34].

- Results composite particles possessing controlled particle shapes [1, 2].
- Eliminates necessity for pre-mixing of powder particles during particle performance improvement processes [1, 9].
- Process temperature can be monitored and controlled [1]. This is by jacketing the processing vessel [2].
- Design of device is compact [1]. Thus eases processing and enhances performance [9].

Hybridizer

The approach of achieving coating with Hybridizer comprises of subjecting powder blend of HPs and GPs to high shear impaction and dispersion, as in mechanofusion [1, 2]. Here rotational speed is employed to disperses powder blend and impart them thermo-mechanical energy [1, 2]. Imparted high impaction force induces the powder particles to undergo numerous collisions and builds-up temperature [1, 2]. Said collisions cause breaking-up of fine agglomerates and coating of FiUlFiP [2]. Thus occurrence is the embedding or filming of GPs onto the surface of HPs [1]. Built-up temperature assists embedding or filming [1, 2]. This batch operated device is very fast to embed and/or coat the GPs onto the HPs surfaces, within 1-5 minutes [1, 2].

Hybridizer has similar design approach as of mechanofusion [1, 2]. Its design basically comprises of follow components [1, 9], refer Figure-5.

- a processing vessel/chamber,
- a six bladed rotor assembly fitted in the vessel,
- a stator,
- a re-circulation unit/device for powder re-circulation. It is built up of stainless steel or ceramic,
- an unit for powder inlet, and
- an unit for powder outlet.

During operation, rotator assembly revolves at very high speed, up to 16,000 rpm [1, 2]. The processing chamber is jacketed [1, 2]. This is for maintaining temperature and to control local built-up temperature [1, 2]. During processing the re-circulation unit/device move the powder particles continuously in & out of the processing chamber [1, 2]. The movement of powder particles is against the rotor blades [1, 2].

The coating operation is performed in two steps namely pre-mixing and hybridization [1, 2]. Pre-mixing steps involves placing of GPs and HPs in a high shear for mixing and dispersing them to get an ordered mixture [1, 2].

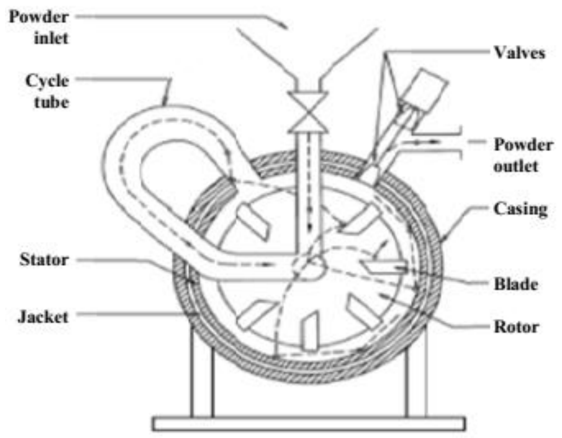


Figure 5: Schematic diagram of Hybridizer [1, 9].

The hybridization step is to subject the ordered mixture for high shear impaction and dispersion [1]. For this, ordered mixture of HPs and GPs are poured into processing portion of the hybridizer vessel [2]. During operation the blade assembly of hybridizer gets high rotational speed [1]. As a result the rotating blade assembly disperses ordered mixture and impart HPs and GPs thermo-mechanical energy [2]. Imparted mechanical energy induces the particles to undergo numerous collisions [1, 2]. Said collisions result breaking-up of fine agglomerates and embedding or filming of of HPs surfaces with the GPs [1, 2]. In other hand the high impaction forces builds-up temperature [1]. This assists embedding or filming [2].

Theta-composer

The design of Theta-composer device is presented with Figure-6(a) & 6(b). The basic design of the device comprises of outer elliptical-vessel and inner elliptical rotor [1, 2], refer Figure-6(a) & 6(b). The vessel and the rotor rotate in opposite direction to each other [1, 9], refer Figure-6(a), 6(b) & 6(c). Vessel rotates slowly at a fixed speed between 30-40 rpm [2, 9]. The rotor rotates very fast at a fixed speed between 900-1200 rpm [1, 9]. Rotor rotates anticlockwise inside the clockwise rotating vessel [1]. Result is changes in clearance width between rotor and vessel wall from smallest to larger [1], refer Figure-6(c), 6(d) & 6(e). Due to change in clearance width the particles are subjected to simultaneous lifting and compression [9]. In one stage, the particles are lifted up by the vessel thus mixing occurs [1], refer Figure-6(d). In other stage the particles pass through a very narrow clearance between the vessel wall and the rotor [1], refer Figure-6(e). At this stage they receive strong compaction forces and shear stress [1, 2]. Concomitant application of strong shear stress and compaction force on the FiUlFiP results their strong coating [1]. This results the formation of composite particles [9].

The powder blend comprising HPs and GPs are fed into the device [1]. The rotor and vessel continued to rotate [9]. Peculiar rotation of rotor and vessel changes the clearance width between rotor and vessel wall [1]. Thus in one stage, forces powder mixture of thru small clearance between the rotor and the vessel [1, 2], refer Figure-6(e). In this stage powder blend is subjected for shearing and compressive stresses [1, 9], refer Figure-6(e). Continued rotation of rotor and vessel, in another stage, said clearance width becomes large [1, 2], refer Figure-6(d). In this stage there will be bulk mixing of powder mix [2, 9], refer Figure-6(d). Thorough blending of powder be doing at a condition comprising of vessel speed at low and rotor speed at high [1, 9]. Higher rotor speed applies strong shearing and compression forces that accelerate precise blending & composite fabrication [1, 9]. Thus it is desirous to set the operational speed of the vessel and rotor considering the critical revolution speed [1, 2].

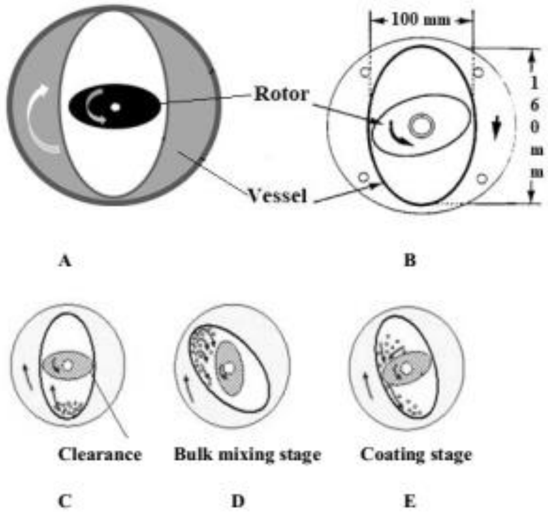


Figure 6: Schematic diagram on operation of Theta-composer [1, 9].

The critical revolution speed (N_c) of the particles can obtained by follow mathematical relation [36].

$$N_c = \frac{60}{\pi}\sqrt{\frac{g}{2D}}$$

Where, 'D' is the inner diameter of the vessel and 'g' is the acceleration due to gravity.

The revolution speed of outer vessel must be much smaller than N_c [1]. Otherwise centrifugal force acting on FiUlFiPs will cause their adherence to vessel wall [1].

Advantages: Follows are the advantages of Theta-composer [1, 2]:

a. Simple structure [1].

b. Operation and maintenance is easier [9].

c. Improved handling of the product [1].

d. Processing time is very short [9].

e. Optimum rotational conditions can be set, suiting the material(s) [1, 9].

f. Suppress hygroscopicity and increases flowability of material [1, 9].

Features: Follows are the features of Theta-composer.

a) Inside rotor rotates at high speed [1]. Thus impart high shear stress needed for coating [9].

b) Outside vessel rotates slowly [1]. This promotes and favours bulk mixing [9].

c) Elliptical shape of outside vessel and inside rotor lends stress and relaxation [1, 9].

d) Instant compression and shearing of particles is during stress state [1]. This minimises rise in the temperature of materials and prevents thermal deterioration [9].

e) Rotational motion of the vessel assists for getting extremely homogenous powder composite [1, 9].

Conical Mills

Conical mills are high speed and high shear batch mixer commonly used for de-agglomeration/ de-lumping. The basic design of mills comprises a conical vessel & a rotating paddle [2, 37]; refer Figure-7(a). The rotating paddle applies strong impact & shear forces onto powder [1]. Thus resulting dispersion and mixing is of high degree [1, 38]. Their design feature and operational & working principle suits them for finding their applicability in dry coating of powders [1, 2, 38]. Basing on said feature and principle Quadro Comil® and Cyclomix® are the available marketed products [37, 38]. These machines are having similar working & operational principle, but have differing design features [38].

Quadro Comil®

Capability of conventional Quadro Comil® for de-agglomeration with intensified mixing is the basis to exploit its applicability in DCP [2, 38]. The schematic diagram of the Quadro Comil® is shown in Figure-7(a); which comprises screen, spacer, and impeller as key components [1, 38]. These mills combine sieving and milling operation into a single unit-operation and are available in diverse design [2, 37]. Diversity of design is based on ranges of screen sizes, screen types and impeller types [1]. Available screen types are round hole and rasping while impeller types are like square edge & round edge [1, 37]. The impeller is operated with a variable speed motor [1]. The typical rotation of impeller allows a range of tip speeds to be made achievable [2, 38]. The spacer is to adjust distance between impeller and screen [38].

The design of Quadro Comil® gets it amenable for both batch and continuous operations [1, 38]. Quadro Comil® is either over-driven or under-driven [38]. Both the design approach uses cone shaped mill screen but the impeller is driven and rotated from the top or bottom [1]. Over-driven has vertically mounted impeller is driven from top by direct drive belt [37]; refer Figure-7(b). In the case of under-driven one impeller is driven and rotated from bottom using sealed gearbox [38]; refer Figure-7(c). Under-driven one is more compact design and suited ideally for integration with downstream and upstream equipment [37]. These are ideal one in the situations calls mills needed to be put in on height adjustable columns or lifts, or inside an isolator [38].

A
Basic design of conical mills

B
Over-driven Quadro Comil®

C
Under-driven Quadro Comil®

Figure 7: Schematic diagram of Quadro Comil® [38].

Availability of options for largest selection of screens, impellers, and widest impeller speed range of any Quadro Comil®, enable it to achieve wished particle size distributions and improve capacity without making changes in base model [1, 37]. Further refinements of said basic configuration may also be adopted on case-to-case basis [2].

Upon charging the powder mix of GPs and HPs, into mill, they are in-feed into the conical screen chamber [1]. During operation, vortex flow pattern is imparted to powder mix by rotating impeller to incoming material [38]. Thus the powder mix is retained and blended in the middle of conical vessel [2, 37]. Conical design of vessel along with imparted centrifugal force by the impeller propel particles of powder mix outward and up towards impeller tip and screen [1, 38]. By this powdery material is forced to surface of screen by centrifugal acceleration [2]. All these mechanistic feature ensuring a continuous delivery of feed into an action zone [1]. The action zone exists between impeller and screen [38]. Instances when the particles get trapped between screen & impeller edge, at the action zone, the imparted shear stresses de-agglomerate the GPs [2, 37]. Its postulation that, during said residence phases larger agglomerates of nano-sized GPs are breaking-down into smaller sub-agglomerates [1, 38]. Resulted sub-agglomerates then preferentially attaches to considerably larger HPs through van der Waals attractions [2, 37]. In subsequent further residence state, expect is encouragement of repeated collisions between larger HPs (that attached with some sub-agglomerates) and sub-agglomerated GPs [1, 37]. This would lead to transfer/ redistribution of nano sized GPs [38]. Ultimate is resulting of a uniform coating [2, 38]. After completion of shearing process, under sized coated particles passes through screen while the oversized are moved back into central mixing zone [1, 38]. Likewise particles pass through screen until entire charged volume is processed and subsequently emptied [2, 37]. The coated product is emptied and collected at bottom of the device [1].

The process of DCP calls for proper selection of Quadro Comil® accessories (impeller & screen) and operating it with suitable operational parameters (operating speed & powder feeding rate) [2]. These settings are for maximising dispersion and enable high throughput without blinding of screen [38]. Said all settings are product specific that to candidate powder [1, 37].

Cyclomix®

The Cyclomix® is multi-purpose, high-shear impact mixers [38]. These are the conical mills designed with a unique mixing principle to suit varieties of application [39]. The machine possesses ability to combine different processes [40]. It is chosen ideally for intensive thermal processing with high energy input, high degree of homogeneity and dispersion, and ultra-short cycle times [41]. It finds applications in processes involving [42]:

- Intensive mixing of slurries, liquids, and cohesive powders [39].
- Low-speed blending of slurries, liquids, and cohesive powders [40].
- Agglomeration by moisture addition and/or using temperature [41].
- Coating of powdery materials with liquid(s) or powder(s) [42].
- Grinding and de-agglomeration.
- Densification of powder.
- Spheronization.
- Chemical reactions.
- Dispersion of pigment(s).
- Vacuum drying and also liquid recovery, at lower temperature [40].

Features: The Cyclomix® bears with follow features [39].

- Unique mixing action: Achieves fast mixing (ultra-short cycle time) with high degrees of homogeneity & material dispersion [40, 41].
- Jacket for highly efficient heat transfer: The machine designed with jacket makes an efficient use of surface for heat transfer [39]. This is for allowing more efficient cooling to be occurring while processing thermo-labile materials [40].
- Monitoring jacket temperature: This makes possible in controlling material temperatures accurately [41]. Thus allowing coating or mixing of materials at specified temperature [42].
- Easy discharge: Conical casing design along with full bore ball-segment valve assembly enables easy discharge of materials with no holdup [39, 42].
- Easy to clean: Top cover-lifting device, optional design, makes simpler the interior cleaning. Changes of product can be done easily [39, 41].

Principle and operation: The machine comprises of a conical shaped mixing vessel, a top driven central rotor assembly, a domed cover at the top of vessel, and a knife blade [40], refer Figure-8. The rotor assembly has numerous paddles and is cantilevered with drive at the top to drive the paddles [41]. The paddles are placed in an order so as to create an upward flow and downward flow, in sequences [42]. The paddle at topmost position can attain tip speed up-to 30 m/s [40]. Said rotor assembly rotates along the inner surface of mixing vessel [39]. The rotor assembly is to fed the material into the Cyclomix® and move them along the vessel wall [40].

The rotation of central rotor, at a speed up to 30 m/s, within the conical shaped mixing vessel creates centrifugal forces [39]. Generated strong centrifugal forces push the product towards vessel wall while shape of vessel results a spiral upward movement [40]. As material move upwardly, increased diameter of the rotor accelerates the material, thus causing generation of strong frictional forces [41]. Said force induces shearing stress on the materials [42]. The domed cover at the top decelerates material and guides them towards centre of mixer and at top [40]. Knife blade or impact blade imparts further impact & shear forces [38]. This is for efficient dispersal of the liquids and cohesive powders [41].

This results high-shear field comprising upward and downward circulation of material in accelerated and decelerated state, shear forces from the paddles, shear forces between particles, and impact force from impact blade [40, 41]. Created high-shear field along the vessel wall leads to quick mixing and speedy build-up of agglomerates, whilst impact blade control maximum agglomerate size [42].

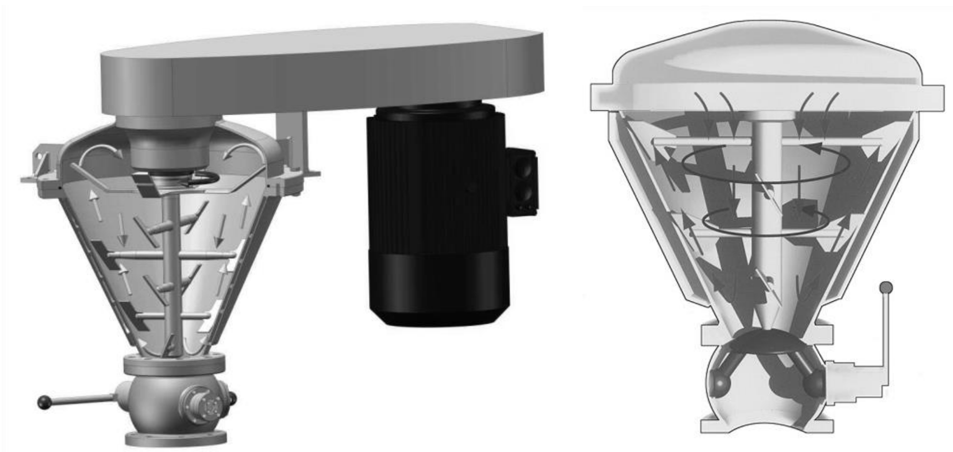


Figure 8: Figure of Cyclomix® [38].

The mill uses ball segment valve, unique discharging feature, allows discharge of product without any holdup [39]. There also jacket for cooling/heating [40]. All these features are contributes working the mill with very high efficiency/ performance during operations like coating, mixing, spheronization and particle composing [41]. Further the mills suits for mixing of cohesive and/or wet powders, thermo-labile materials, materials with low melting point (like meltable binders), and powders with liquids [42].

Intensive mixing taking place close to vessel wall allows effectual heat transfer amongst the product and the jacketed vessel wall [40]. This feature allows optimal temperature control during the processing [41]. Result is very accurate agglomeration while using meltable binders and rapid drying of wet agglomerates [42]. Its high speed paddles applies high shear force and achieves faster mixing thus reduces mixing time [39].

By adjusting mixing time and speed Cyclomix® can be versatile device to perform processes like mixing, bonding, coating, spheronization, densification, etc [41, 42].

Fluid Energy Mill

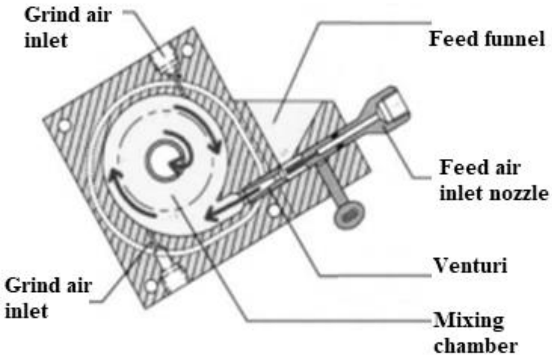


Figure 9: Cross-section of the milling chamber of the fluid energy mill [43, 44].

The fluid energy mill is primarily used for size reduction of FiUlFiPs find applicability in their coating with some modification [43, 44]. The modified device includes three air-inlets [44, 45], refer Figure-9. Amongst them two are air-inlets for grinding air and one air-inlet is for feeding FiUlFiPs [1, 2]. The FiUlFiPs are fed into the feed funnel attached to feed air-inlet [2]. During operation venturi region is made by the feed air [1]. Through the venturi region the feed is then sucked into the milling chamber [43]. Some instances warrant a volumetric feeder to control the feed rate [43]. Grinding-air pressure, feed rate of FiUlFiPs, and feeding-air pressure are the operational parameters requiring control [1]. All these define performance and operation the machine [2]. The use of fluid energy mill for DCP and simultaneous micronising was pioneered by several research groups [43].

Resodyn Acoustic Mixer

It's a sophisticated bench top high shear mixer [46]. Here mixing operation is founded on resonant acoustic technology [47]. Said technology creates a low frequency and high intensity shear field [48]. Generated shear field helps in uniform & thorough mixing of material within very short time [46]. In this system the primary parameter exploited for promoting coating is impact due to acceleration [49, 50]. Refer Figure-10 for its principle and operation [50].

Here use of acoustic energy is in the form of intense vibrations [46]. Said vibrations are to create high shearing zones, within the mixing vessel of the device [47]. Said state along with high energy creates a virtually fluidised state for powder of FiUlFiPs, comprising GPs and HPs [48]. Due to fluidisation process submicron sized GPs collide with HPs. in the fluidised state of FiUlFiPs [49]. The frequency of vibration is usually between 50-65 Hz [47]. Associated intense vibration disperses GPs and adhere/fixes them to surface of HPs [50]. Thereby resulting is in dry-coated HPs with uniform coating layer [46]. To control intensity of vibration and mixing time there is external digital control system [48].

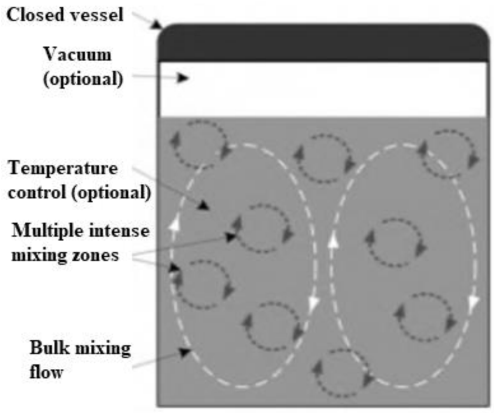


Figure 10: Principle and operation of Resodyn Acoustic Mixer [46-48].

MAIC

Apparatus/Device: The device of MAIC comprises processing vessel [1]. The vessel is surrounded with series of electromagnets. Said electromagnets are connected to alternating current [2, 9], refer Figure-11. Herein the coating is resulted with the assistance of oscillating magnetic particles [2]. The magnetic particles usually are of barium ferrite [2]. These may be coated with polyurethane [1]. The coating is for preventing contamination of coated particles [9].

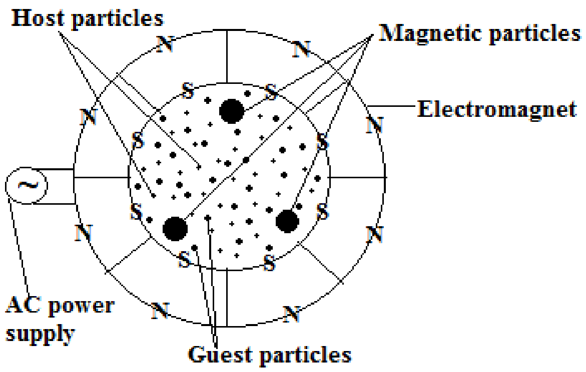
Upon coating of FiUlFiP following DCP using MAIC, the process can modify surface property of HPs while keep-up their size and shape almost original [9, 51].

Coating process: During processing the powders of GPs and HPs are poured into the vessel [1]. This is followed by pouring measured mass of magnetic particles [9]. As the apparatus is turned ON magnetic field is generated [1]. Said magnetic field agitates magnetic particles thus they oscillates (move frequently) inside vessel [2]. This fluidises the powder particles [2, 52]. Agitated magnetic particle imparts energy to GPs and HPs and cause their collisions [9]. Said collisions are between GPs and GPs, HPs and HPs, HPs and GPs, HPs/GPs-vessel wall [1, 9]. The collisions out comes impaction and/or peening of GPs onto HPs, thus coating of HPs with GPs [2, 9].

At the initial phase, due to magnetic field, primary motion associated magnetic particles are spinning type [1, 2]. This promotes de-agglomeration of GPs along with their shearing and spreading of them onto surface of HPs [9, 52]. During latter stage the translational speed allows impaction of one particle onto some other [9, 51]. This stage has significant effect in promoting and achieving coating [1, 2].

Performance of MAIC depends on several parameters [9]. Follows important parameters must be considered while processing with the MAIC [1, 52].

- Particle size of GPs and HPs [1],
- Particle size ratio of GP-to-HP [2],
- Particle size ratio of magnetic particle-to-HP [1],
- Ratio of magnetic particles-to-powder mass (mass of the CoM and the CSP) [9, 52],
- Speed of magnetic particle [2],
- Voltage or current and frequency of alternating current [1], and
- Processing time.



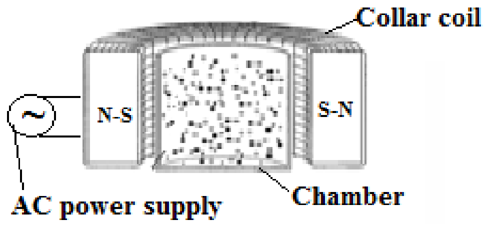


Figure 11: Basic design of MAIC [1, 2, 9].

The coating time depends on diverse parameters including follow [1, 51, 52]:

- number density of HPs [9],
- diameter ratio of HPs-to-GPs [1],
- initial & final bed height of fluidised particle bed [2], and
- material properties of GPs and HPs [9].

There an optimum value of these parameters for which coating time is minimal [9, 52]. Coating time sharply increases as [9, 51],

- bed-height is lower or higher than optimal value [1], and/or
- diameter of the HPs increases [2], and/or
- diameter ratio of HPs-to-GPs are increased [9].

CONCLUSION

Handling of FiUlFiPs is a generic problem in pharmaceutical industrial field. Further these particles inherit complex and queer properties. Discussed issues are associated primarily with their size and surface attributes. Their shape and density are also contributors. To overcome their discussed inherited problems and/or to confer them with worthy applications & new functionalities, calls for modifying and/or engineering their surface and surface attributes. Nowadays among the available diverse process and/or techniques of DCP the TMDCP had received much more attentions.

The sequential steps involved in TMDCP, application and fixing of GPs on HPs followed by coalescence/ sintering of GPs, are influenced by coating formulation and employed process. GPs and HPs with appropriate particle size ensure coating, and coating with uniformity and wished & reproducible thickness.

A recommendation, in general, is diameter of the GPs be less than 1 % that of the HPs. This permits application of CoM onto surface of CSPs with degree of uniformity to an acceptable level. Further, this improves coating's adhesion and appearance, and lowers processing time.

The TMDCP relies basically on mechanical compaction, occurs naturally during the process, as this facilitates adhesion and coalescence. Herein, the stresses on coating layer particles results consolidation of CSPs bed and spreading of CoM layer across interface that is driven by deformation. In case of elastic CoMs the deformation is reversible. This is bearing for their poor contacts across the interface of CSPs. In cases where coatings are exhibiting plastic behaviour the deformation is permanent (irreversible). Herein the conferred mechanical compaction contributes to greater adhesion of surface layer. The stated improved adhesion is attributed from larger surface area available for contact between CSP surface and coating, as well as from possible mechanical interlocking of the CoM and CSPs. During coating process the *Tg* of the CoM(s), causing its softening and facilitate its adherence to substrate, plays crucial role. Thus while following TMDCP, process temperature should be maintained above the *Tg* of the CoM(s).

Technologies of TMDCP possess enormous advantages. But result coating film with inferior coating uniformity. This is biggest challenge that hinders their application & commercialisation, the main issue requires addressing.

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