Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense*)

Lat. Am. J. Pharm. **43** (4): (2024)

Hot Melt Coating: An Ecofriendly Technology In Pharmaceutical Product Development

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Abstract:
The objective of review is to explore various aspects hot melt coating (HMC) technology in the drug product manufacture. Global market drivers for oral solid dosage (OSDs) forms are generic market, newer indications of existing drugs, new combinations, life cycle extension of available drugs etc. To meet the needs of market and regulatory bodies, the melt coating technology can resolve the drug related issues of bioavailability, economy, formulation, stability and scalability. The HMC is rapid, reliable, cost-effective and environment friendly technique. Neither aqueous nor organic solvents are required for drug product design in this technique. The regulatory bodies are currently focusing on environment sustainability and safety issues which are strictly followed by this technology. The simple pan coaters or fluidized bed coaters with minor modification were deployed in this technology. It offers several applications in dosage form design. It is user friendly as most of lipid materials are used for coating which facilitate easy gliding of dosage form into gastrointestinal tract (GIT).

Key-words: Hot melt coating, Ecofriendly, Stability, Lipid, Solventless, Generic

Introduction

Majority of medicines and dietary supplements are orally administered. The OSD market is growing at higher pace due to several motives. Recently, the formulation and development scientists from pharmaceutical industries are manipulating available drugs into innovative delivery systems utilizing advanced technologies to provide better quality, safe, stable and efficient remedies than the currently available in the global market.[1] Many drugs are with several undesirable characteristics like-

1. Unacceptable color, odour and taste
2. Light, moisture or oxygen sensitive
3. Rapid dissolution causing irritation in GIT
4. Instability in stomach pH
5. Need tailored drug release profile from drug products
6. Poor bioavailability and flowing ability

Several techniques were reported to circumvent above issues. The coating of the OSDs is oldest practice to overcome all above problems. By choosing apt coat former the tailored drug release profile can be attained like the immediate release, delayed release, controlled release, regioselective release etc.[2] The coating can protect the GIT from hostile effects of active pharmaceutical ingredients (API) and vice- versa. It also shields medicament from light, heat, moisture and other environmental factors. The coated substrate has enhanced flowing ability that fascinates in accurate dosing of API.[3]

Need of Hot Melt Coating

The water based coating and organic solvent-based coating were most common. The coating agents are either dissolved or dispersed in aqueous or organic solvents with additives and sprayed or poured over the substrate or substrate sometimes dipped into coating solution for encapsulation of core. The residual moisture after aqueous coating may surge microbial burden over dosage form and residual organic solvent traces may cause solvent associated toxicity to patients. Leaving the organic solvents in environment leads to global warming

(greenhouse effect) and produce harm to industry workers. In contrast, the organic solvent recovery and treatment are inflated processes. The regulatory bodies like the United States Food and Drug Administration (US FDA), Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) are stalwartly confining the usage of organic solvents in pharmaceutical manufacture. Due to the several demerits of aqueous or organic solvent-based coating, researchers are in the need of simple, efficient, precise, scalable, economic and regulatory acceptable coating technology.[4,5]

Hence in 1940, the HMC was first employed in paper and textile industries and in 1980 onwards was continued in pharmaceuticals. The molten coating agents are either sprayed or poured over the substrate. The molten droplets are spread and solidify on the solid surface.[6] The beads, capsules, drops, granules, powders, pellets, spherules, tablets, etc. are usually used as substrate. Since last 60 years, HMC were utilized on industrial scale but at limited extent.[7,8]

Merits

1. Organic solvent free and environment friendly technique[9]
2. Bypasses steps like solvent disposal, treatment/ recovery associated with organic solvent[9]
3. Speedy process trails on regulatory directives for usage of organic solvents[9]
4. No or low risk of bacteriological contamination as water- free technique[10]
5. No chances of hydrolysis of drug or additives as no aqueous medium is used[10]
6. Tailored drug release profile can be attained using suitable coating composition
7. No need of costly equipments as pan/ fluid bed coater can be exploited
8. Regularity benefits like extension of patent life and product line
10. Opportunity of patenting and registration of invention to international marketplace

Demerits

1. Not suit for thermolabile therapeutic actives & additives and thus limits formulation development
2. Limited molten mass can be coated on substrate
3. Multilayer coating is difficult (superior layer coat former should have low MP than inferior)[11]
4.Thermal behaviour and compatibility of drug and excipients must be considered[12]
6. Polymorphic nature of HMC agents may alter dissolution profile among the batches[13]
7. Use of hygroscopic additive may affect thickness and moisture absorbed by coat. This is having direct influence on stability of drug[14]
7. The safety of operator is very critical since operation require higher temperature[5]
8. High energy is needed for melting of coat former
9. Complete toxicity study data of hot melt coating agent is necessary along with dosage form[4]
10. Suitable modification in coating machines is required

Applications

The substrates are coated to achieve several objectives (Table 1).

Table 1: Application of Hot Melt Coating in Drug Product

Sr. No.	Utility	Active Pharmaceutical Ingredient
1	Taste masking[3]	Aspirin,[16] Paracetamol,[17-19] Bromhexine hydrochloride,[20] Salbutamol sulphate. [20]
2	Reduces acidity	Vitamins[21]
3	Improve stability	Hygroscopic or light sensitive or oxidizable drugs[14, 22, 23]
4	Improve flowability	Drug with poor flowability[24]
5	Modified release	Ambroxol, [25] Cefuroxime axetil, [1] Chlorpheniramine maleate, [26, 27] Chloroquine, [28] Diclofenac sodium, [29-31] Metoprolol tartrate,[32] Nifedipine, [33] Paracetamol, [16] Propranolol hydrochloride, [34] Theophylline, [3, 35, 36] Ranolazine, [37] Ibuprofen, [38] Chlorpheniramine maleate, [39] Verapamil hydrochloride, [39] Diltiazem hydrochloride[39]
6	Enhance shelf-life	Probiotics and herbal extracts[40]
7	Incompatible drugs	Multi-component drug delivery systems

Hot melt coating agents [41, 42]

All coating agents employed in conventional film coating or sugar coating are not apt for HMC. The ideal characteristics of coating agent for HMC are-

1) The required viscosity should be less than 300 millipoises at its melting point.
2) They should have spreadability over substrate.
3) They should have narrow and precise melting point range.
4) The melting point of HMC agent should be 60-80°C to facilitate ease in flow.
5) They should not show polymorphic transformation during product manufacture or storage.
6) The uniform substrate dimensions are prerequisite for batch-to-batch uniformity.

The lipids from natural origin (bees wax, cetyl alcohol, caurnava wax and spermaceti wax), hydrogenated oils (castor oil, sesame oil and arachis oil), polyoxy glycerides and partial glycerides/ surfactants are used in HMC. The summary of the HMC agents is given in Table 2.

Table 2: Hot Melt Coating Agents and their applications

Coating Agent and Meting Point	Chemical Nature	Application(s)	Example(s)
Animal fats ≈ 80 °C	Clarified butter	Sustained release	Cow ghee
Fatty acids ≈ 60-90 °C	Long chain unbranched saturated or unsaturated aliphatic fatty acids	Prolonged release and enteric coating	Behenic acid, Stearic acid, & Palmitic acid
Fatty alcohols ≈ 50-55 °C	Long chain fatty aliphatic alcohol containing 8 to 20 carbon atoms	Modified release, & Taste-masking	Cetyl alcohol, & Wool alcohol
Partial glycerides ≈ 55-75 °C	Mono-, di-, and triglycerides mixture. Based on physicochemical properties required substitutions were made	Modified release, Taste-masking, & Lubrication	Compritol® 888 ATO, Myvaplex™ 600, & Precirol® ATO 5
Polyoxy glycerides (Partially digestible) ≈ 50 °C	Mixture of glycerides and esters of fatty acid and PEG	Immediate release, & Modified release	Gelucire® 50/02, & Gelucire® 50/13
Vegetable oils (Generally digestible) ≈ 60-70 °C	Mixture of triglycerides, free fatty acids, phospholipids	Taste-masking, & Modified release	Hydrogenated cottonseed oil, Hydrogenated palm oil, & Hydrogenated soybean oil
Waxes (Lipophilic) ≈ 62–86 °C	Long chain alcohols and their esters with fatty acids	Modified release	White and yellow beeswax, Carnauba wax, Candelilla wax, paraffin wax, hydrogenated Jojoba oil, Rice bran wax
Polyethylene glycols (PEG), Propylene glycols and polyglycerol (Variable based on molecular weight)	Based on the average molecular weight, PEGs are available in various grades i.e., liquid, semisolid and solid. They are available in variety grades with vary in their physical properties.	Taste-masking, sealant & Modified release	PEG 1450 and 3350 molecular weights. Higher molecular weight PEG are not suitable since their melt have higher viscosity

Hot Melt Coating Method

The HMC is usually performed using conventional coating pan or fluidized bed coater with slight augmentations. The pan coating is executed by pan pour or pan spray method. The fluidized bed coater can be achieved by top spray, bottom spray, tangential spray method, turbo- jet coating or solid dispersion technique. The direct blending and spouted bed techniques are least common methods employed in HMC.[43]

1. Pan Coating: The modified conventional pan coater is employed for pan spray or pan pour HMC technique. The substrate is coated either by pouring or spraying the molten coat former in a coating pan equipped with baffles or other augmentations and temperature regulating systems. The coating agent is heated slightly above

its' melting point (5-10°C) and other excipients are mixed in the melt with stirring. The substrates are rolled in the coating pan and heated until substrate temperature reach to 10°C below melting point of coat former. The molten mass is loaded onto the hot rolling substrates in as a slow stream or sprayed with controlled rate with insulated spray nozzle from optimized distance using appropriate spray pattern. The substrates are allowed to roll for 10-20 min during which the bed temperature bring gradually down. The coated substrates are removed and cured in a dryer for few hours. The pan spray coating is more efficient and that provides controlled release of medicament due to uniform film formation, while pan pour method demonstration variation in the drug release profile with in same batch of product because of uneven coating. Therefore, pan pour technique is used in modifying organoleptic drug products, improving flowability, and reducing acidity of drugs.[29]

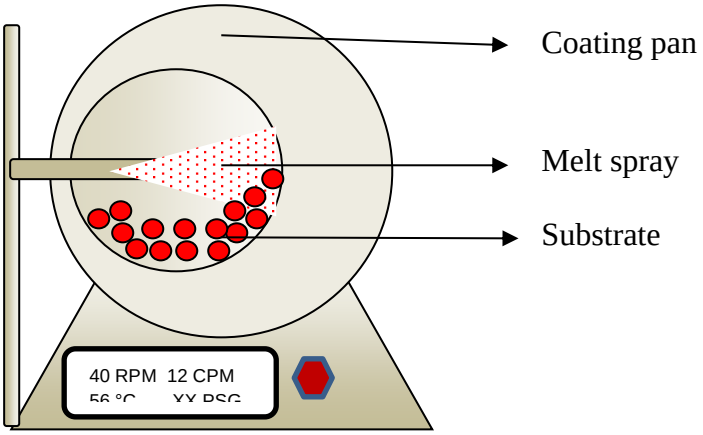

Fig.1 Pan coating.

2. Spouted Bed Coating: The well-defined fluid dynamics was reported to coat tablets in a prism shaped spouted bed made up of transparent stainless steel and borosilicate glass with adjustable horizontal air vents. Generally, the coating is performed at maximum height maintain air flow above 40% as minimum air velocity in spouted bed using air compressor provided with orifice meter. The weighed substrate is placed in spouted bed and the temperature and air flow rate are adjusted. Once the temperature of substrate become steady, the coating agents are added from the top at one time in column of equipment. The content is spouted for optimized period. The heating is stopped and coated substrate is allowed to cool to room temperature. Further spouting of coated substrate is continued to avoid aggregation of substrate. The coated substrate was collected and weighed to estimate coating efficiency using initial weight and final weight of substrate along with coating material added for coating.[44]

$$Coating\ efficiency\ (\%) = \frac{Final\ weight\ of\ coated\ core - Initial\ weight\ of\ core}{Coating\ material\ loaded} \times 100$$

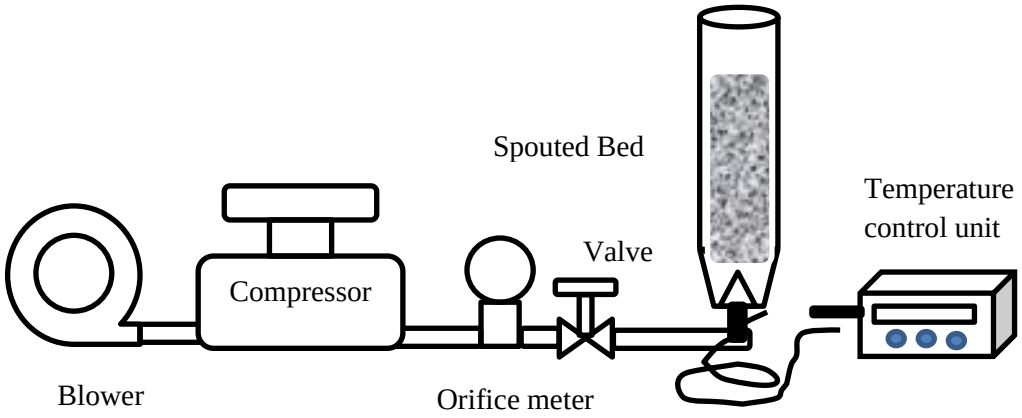

Figure 2. Spouted bed coating

3. Fluidized Bed Coating (FBC): The various types of substrates can be coated with top spray, bottom spray and tangential spray using fluidized bed coater provided with specially designed triaxial nozzles. The molten coat former is passed through central tube of nozzle edged by high pressure and low volume air valve. The both coaxial tubes are covered with large air space through heated automized air. The nozzle is normally fixed closed to the surface of substrate bed to reduce the distance so as to prevent congealing of molten mass before touching the substrate surface. The spray nozzle and tank with hot melt coating material is insulated to maintain uniform temperature throughout coating.

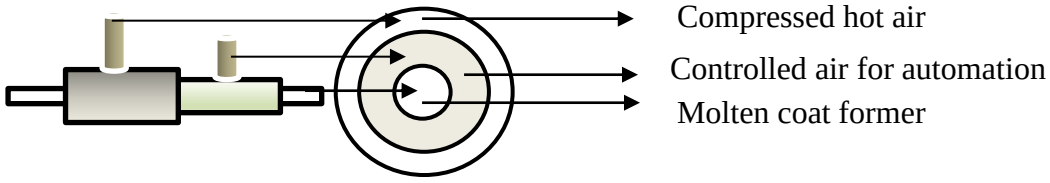

Figure 3. Modified nozzle for HMC for fluidized bed coating coater

Types of Fluidized Bed Coating:

3A. Top spray Fluidized Bed Coating

It is common, efficient and standard technique used for HMC of pellets, particles and granules. During the coating operation, upward moving substrates are coated with downward moving molten coating mass. The substrate temperature is kept below 10-20°C than the melting point of melting agent of coat former. It has limitation of fluidity and flow. The top spray coating involves three steps: i) melting of coat former, ii) spraying of melt over substrate and iii) congealing of coated substrate.

3B. Bottom Spray Fluidized Bed Coating: An alternate technique to top spray fluid bed coating that is employed for coating of small substrates like beads, granules, larger particles, pellets and spherules. This technique provides well-organized air and coating mass flow. It is effective for hot melt coating on small scale. The coating on large scale can be possible at the disbursement of PT/MP ratio.

Bottom spray coating instrument comprise of an air handling unit, distribution plate and spray nozzle at the bottom. The distribution plate is perforated plate that facilitates the uniform distribution of fluidizing substrate in the coating region by the virtue of large volume of air. When substrate is suspended in coating zone, the molten hot melt mass is sprayed over substrate and the coated substrate fall on peripheral part of coating zone on distribution disc. The disc used for HMC are more perforated and with higher hole diameter than the conventional solvent-based coating for providing more efficient air distribution. This will avoid agglomeration of substrate during coating. It the height of coating zone is doubled; the substrate coating will be reduced coating thickness.

The substrates with poor flowability such as larger particles and/or particles of higher density that are difficult to coat with the top spray technique, and hence, the bottom spray method should be preferred in that case. The add-on critical parameters associated with equipment includes the height of the partition area (determined by the size, density and the desired substrate speed), and the type of distribution disc, which is chosen according to the substrate nature (particles of 50 µm, pellets or tablets).[46]

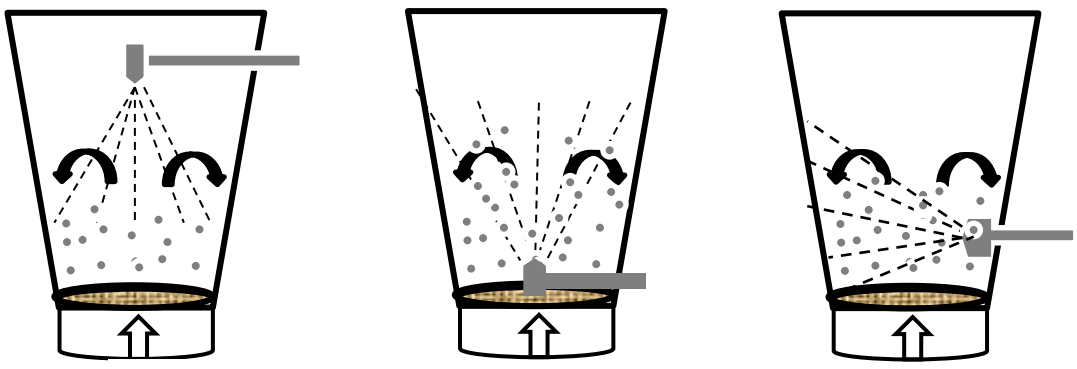

Figure 3: Types of (A) Top spray, (B) Bottom spray and (C)Tangential spray

3C. Tangential-spray fluid bed coating: It is an innovative fluid bed coating technique where the rotating dispersion disc is employed for spraying and smoothing of the coat. The higher coating levels are possible at expense of PT/MP ratio. It is mainly used to produce pellets by powder layering (alone, in suspension or in solution). The rotor system features the spray nozzle, which is located laterally to the substrate, and the rotating disk (rotor) based at the bottom of the tank. Three mechanical forces cause particle motion, mixing and granulation. The centrifugal force developed by the rotating disk projects the substrate to the periphery where the fluidization air suspends and particles gravimetrically fall back on the disk. The substrate is exposed to higher mechanical stress than former two fluidized bed coating techniques. Hence, the substrate that are highly resistant to these forces are well suited for this process. Similar to the top or bottom fluid bed systems, the spray nozzle is heated through compressed air and insulated to prevent re-melting of the lipid coat. However, as particle adhesion to the tank is likely the product temperature is kept lower compared to the top-spray system. This technique has limited coating capacity.

3D. Solid dispersion: The solid dispersion technique was acquainted by Kennedy et al which devoid of spraying process and hence nozzle spray system. Hence, method is least complicated. In this method, the substrate is combined with coating agent in the fluid bed chamber undergo four simple steps: (i) warming up of chamber, (ii) preheating core, (iii) coating agent melting & mixing other additives and (iv) spreading and congealing. But, the series of weak-points may be found in this process like conventional method. The cores and coating melt are kept into a chamber at high temperature is not feasible. It was reported that, the porosity and density of substrate affected reproducibility of the technique. When the nonpareil-sugar beads are used for coating tend to agglomerate, if the particle size is smaller than 40 mesh for coating agents PEG 1450-8000 and MPEG 2000 and 5000. For the uniform spreading of hot melt coating, the optimal viscosity of the coating agent is less than 300 centipoises. This technique allows coating up to 2.5-5% w/w. In fact, in real cases a higher percentage of coating is required to be deposited.

Kennedy et al., improved technique by coating the drug beads with two different coating agents by one by another. But he specified that the difference between melting points of two coating agents should be at least 15°C. In this respect, fluidized bed coaters are preferred for coating due to the inherent advantages of the technology such as high flowability of particulate materials, temperature homogeneity, more uniform coating due to very good solids mixing and lower process time due to high heat transfer.[27]

The quality of the fluidized bed coating can be assessed in both macroscopic and microscopic levels. In the former case, the production time, practical yield, energy consumption and material required are considered based on the coating performance. In the later case, the coating quality is characterized mainly as a function of two factors, coat uniformity, coat morphology and measured by both the standard achieved and its repeatability for properties or specifications of it, like appearance, assay of the active ingredient, dissolution profile, particle size distribution and shelf-life. The product yield is simply the ratio of the mass of the product which meets the required specifications to the total material mass used in the process. The difference represents the product losses that occur during coating. In the fluidized bed coating process, product losses, occurring generally due to improper process planning, are mainly composed of raw materials entraining out of the system before being coated and agglomerated particles whose particle size and specifications are not within the acceptable particle size range. It affects also the quality of the coating. Therefore, the correct planning and precise control of the process parameters is of paramount importance. However, this indeed is not an easy task as the fluidized bed coating process is a complex process with many interrelated process variables. As stated by Jones nearly 20 products and process variables are involved in the fluidized bed coating. These variables can be classified as apparatus variables, product variables and process variables. The instrument variables, such as geometry of the unit, distribution grid, spray nozzle characteristics, filter mechanism etc. are determined by the equipment used. Product variables depend on the formulation used.[47]

Scherzinger and Schmidt pointed that, the process parameters are the most important and easily variable parameters and knowledge and determination of these parameters is essential for achieving a controllable and successful process. Although, the fluidized bed coating process has been investigated and used in different industries for years, trial and error together with experience is still the most preferred method for determining the optimum values of these parameters in the pharmaceutical industry. Therefore, there is still limited number of studies in the literature on the investigation of the effect of the process variables on the performance of different fluidized bed systems. [48]

3E. Turbo Jet Coating: This process is adapted to coat solid particles by suspending them in a spiral of ascending air that provides the homogeneous distribution of individual particles. The molten lipid is dispersed from the bottom of the tank and tangential to the particle flow. Here, lipid crystallization within the nozzle expansion is prevented by a micro-environment surrounding the nozzle out-let.[49] The merit of this technique is its ability to suspend particles within the ascending air stream, allowing the coating of very fine particles.

4. Hot-melt coating by direct blending: It is the one of the simplest ways to make coat particles. This technique does not require complicated equipment, the obtained results are quite surprising and it can be applied for a wide range of different size substrates as well as multiple coated layers. The method comprises of five steps: (i) melting of coating agent, (ii) drug dissolution or dispersion of other excipients into molten coating, (iii) mixing of the substrate and molten coating agent, (iv) cooling with continued stirring of the mixture, and (v) congealing the coated particles. The active ingredient can be deposited in the core by a granulating method, and then coated out-side by a coating layer. The drug also can be dispersed into the coating agent and then the mixture is coated outside the coating core. Ready-made sugar beads of various sizes are commercially available.

Wax formulations for coating drug-loaded sugar beads have been investigated by Bhagwatwar and Bodmeier.[50] The sugar beads are homogenous in size and shape and easily adhere to waxes. The smaller the size of substrate, the larger is the surface area available for coating agent to deposit onto. In this technique, very small modification is done that is molten coating material contains less than 10% solvent.[51] Weight gain during coating can reach a high value. However, extremely tiny particles are likely to agglomerate which increases the variability of the coated beads mixing and coating must be appropriately controlled to avoid variability. To obtain high weight gains with readymade substrates, the process is most simple if the core has a large enough surface area but is not too small in size (so as to avoid agglomeration).

In other words, it is desirable that the coated beads contain a large amount of drug but the variability is reduced to a minimum value. For laboratory scale research projects, it was found that the size range of sugar beads 30-60 mesh work excellently. The coated beads then are loaded into hard gelatin capsules which are the final and complete dosage form. Coated beads may be used to compress into tablets, too. There are no documents that list waxes that should be applied in the coating process to obtain slow drug release. The reason behind that is the waxes with high molecular weight and hydrophobicity are likely to reduce the drug dissolution rate in water. Conversely, substances which are hydrophilic or increase the wetting characteristics of the drug are likely to increase the rate of drug dissolution like PEG. All the waxes need to be hard enough to congeal at room temperature.

Nifedipine is sensitive to light, yet there are no reports on the behavior of nifedipine at high temperature. Thus, it is obligatory to investigate carefully the stability of the active substance to heat. Moreover, sugar beads are made of sucrose which is easily burned at high temperature. So that, the limiting temperature is 100°C. Hot melt direct blending coating, involves application of a molten coating material onto beads or capsules in a heated tablet coating pan. In the hot-melt pan coating cetyl alcohol and Gelucire® (Gelucire) 50/13 were used as coating agents.[33]

Conclusions

In pharmaceutical industries, the safety and protection of the workers and environment are considered at highest priority along with drug product safety and efficacy. Therefore, now a day, industries are in the search of solvent free processes and production. HMC offers a novel and smart option to pharmaceutical manufacturers. HMC technique presents economic, easy, efficient, ecofriendly, and rapid technique in comparison to conventional coating methods where solvent evaporation, recovery and treatment can become very expensive, time consuming and may harm operators of industry and environment. Definitely, even if the spraying rate of coating agent is slower than conventional coating, but the HMC agents are not diluted with solvents, which results in higher and uniform application rates when compared to other techniques.

Furthermore, the equipments of choice for HMC are fluid bed coater and modified conventional coating pan. HMC provides several utility including modifications of drug release, reduces acidity of vitamins and few drugs, masking objectionable drug characteristics, (with immediate release obtained by the addition of surfactants to the lipid coating agent), drug protection and the lubrication of particles exhibiting a large specific surface area. However, the progress of these innovative systems remains more challenging than that of traditional methods and hence collective efforts progressively address the issue.

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