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Lipids - An Instrumental Excipient In Pharmaceutical Hot-Melt Coating

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Abstract: Coatings are widely used to provide drug protection, to increase aesthetic value of product (color, taste and texture), to reduces acidity if vitamins, to provide lubrication and modified drug release. Usually, coating agents are dissolved or dispersed in solvents (water or organic) prior to coating and glidants are commonly added to prevent particle agglomeration during coating. Lipids are the smart option to polymer coatings as they need melting before application directly on the substrate. As hot-melt coating (HMC) devoid of solvent use, solvent disposal, solvent evaporation and solvent treatment is not required; as a result powders with very high specific surface areas can be coated rapidly. Different lipids can be used in coating and selection of the right lipid for the application requires knowledge of their physico-chemical properties and its associated effect on drug release.
Keywords: Hot-melt coating, Lipid coating, Taste masking, Modified release, Fluid bed coater.

INTRODUCTION:

Coating is a vital stage in the design of pharmaceutical dosage form where ultimate objective is to modify drug release characteristics or to achieve superior aesthetic quality (i.e. color, texture, and taste) and superior physical and chemical protection.[1] Pharmaceutical coating maybe originated in the kitchens of confectioners during the early nineteenth century. The art of sugar coating was transferred to pharmacists around this time and used to improve the bitter taste of medicine. These coatings were freshly made in small batches and without specialized equipment. The 1950s marked the beginning of the modern pharmaceutical coating era with the emergence of a new film coating technique made possible through innovation in both coating equipment and polymer chemistry. With the dramatic rise in the number of drugs requiring coating, and the increased cost of process time and compounds used, technologist are now under growing pressure to increase yield, improve product quality and reduce process time. Two significant developments in this area were the invention of the perforated pan and fluid bed coater which enable precise, effective and elegant coating of many dosage forms and for a range of batch sizes.[2] Generally speaking, the coating material is dissolved in a solvent (water or organic) prior to spraying. During and after coating the solvent must be evaporated. The use of solvents nowadays is under constraint due to the problems of trace levels, while recovering a solvent often proves expensive. Due to its long evaporation time water could also be a problem.[3]

The use of organic solvent suffers from the toxicological, inflammable, explosive, environmental, cost and safety related issues. These disadvantages have been largely eliminated by the introduction of aqueous-based coating technology. However, aqueous film coating requires a slower drying process and high energy input because of the high heat of evaporating water (539.4cal/g). Aqueous film coating is lower solid content in the coating solution and risk of microbial contamination. The presence of water during the coating process and residual moisture in the film can affect stability of certain water sensitive drugs. But polymeric coating

associated with use of large amount of organic solvents, which are not environment friendly. Regulatory agencies such as the U. S. Food and Drug Administration (USFDA), Environmental Protection Agency (EPA), [4] Occupational Safety and Health Administration (OSHA) [5] too strongly restricted use of such solvent in this area. Looking at disadvantages of aqueous or organic solvent based coating it is necessary to develop novel coating process, which are simple, efficient, precise and cost effective and allow easy compliance with regulatory requirements.

HMC with materials such as thermoplastic resins, waxes, polyoxyethylene glycols or mixtures thereof began in the textile and paper industries in the 1940s[6]. However, the technique was used to coat large materials (paper, foil, textiles, etc.) and not discrete particles or dosage forms. During the 1980s the pharmaceutical industry was looking for new coating technologies that were simple, effective, and affordable and HMC appeared to be the answer.[7] Since the coating material is applied on the substrate in a molten state no solvent is required.[8] Despite HMC being adopted and used at an industrial scale in the pharmaceutical industry for the past 30 years today, the technique is not focused extensively in literature.

ADVANTAGES AND DISADVANTAGES OF HOT-MELT COATING:

Hot melt coating methods offer many advantages and disadvantages over current conventional coating techniques. As the coating material is in molten form the system is totally solvent free.

Advantages:

1. No need of use of costly organic solvents. Hence, the tedious process of solvent disposal, treatment or recovery associated with organic solvent is eliminated. Hence, the process is environment friendly.[9]
2. As the coating material used is in molten form. It is totally solvent free system, shorter time is requires for current practices and also have compliance from regulatory directives for the use of organic solvents is fully excluded, making HMC process efficient.
3. No risk of bacteriological contamination and hydrolysis of drug since no aqueous medium are used.[10]
4. Modified drug release pattern is possible by such coating.
5. Excising coating equipments such as pan coater or fluid bed coater can be easily modified to suit the requirement of HMC.
6. The lipids used for solvent free coating techniques are cost effective.

Disadvantages:

1. Temperature sensitive drugs may be degraded at a high temperature since HMC is carried at 40-200 ^{o}C.
2. A limited amount of coating agent can be deposited on the surface of the coating cores.
3. Multiple-layer coating can increase coating weight gain therefore it is limited process. In multiple-layer coating agents used in the outer coating layer must have a significantly lower melting point than inner coating agents.[11]
4. The thermal behavior such as for individual drug and excipients stability, drug-excipients interaction at high temperature, and stability of the dosage form need to be investigated carefully.[12]
5. The polymorphic characteristics of the coating material. The polymorphic behavior of the coating material may cause variability within batches of the dosage forms. Polymorphic forms have different physical properties such as transition temperature or melting point. It is reported that polymorphology can change intrinsic dissolution rates and other solid state properties of materials. Therefore, a full investigation of polymorphology of excipients is necessary.[13]
6. Moisture absorbed within the coating layer is one factor that may affect the drug stability. It was investigated the interaction of coating excipients (Polyvinyl alcohol and glyceryl behenate) with moisture absorbed inside the coating layers and the influence of temperature and film thickness on the percent of water.[14] As to safety conditions during the hot-melt coating process, it should not be neglected.
7. Safety for operators must be considered seriously because working with a coating pan at high temperature is risky.
8. Toxicology studies of commercial coating excipients are required with complete information of *in-vivo* results since the coating agents are consumed along with the dosage forms.
9. Requirement for complex equipment to maintain high temperature and the high cost to pay for high energy needed for heating.
10. Recommended properties for the coating excipients encompass a melt viscosity of less than 300 centipoises and a melting point below 80ºC for flow and spreadability of the coating material.[15]

APPLICATIONS OF LIPIDS IN HMC: Hot-melt coating with lipids offers a wide range of applications. Process involves coating the substrates like capsules, granules, pellets, particles, spherules and tablets of various drugs. This technique have shown promising for taste masking, gastric resistance, acid resistance, sustained release or bioavailability enhancement, based upon type of coating polymer.[3]

1. Taste improving and masking of drugs like aspirin,[16,17] paracetamol, [18,19] acetaminophen,[19] bromhexine hydrochloride,[20] salbutamol sulphate.[20]
2. Reduces acidity of vitamins.[21]
3. Protection of drug from environmental factors like light and/or humidity.[14, 22, 23]
4. Lipid melt onto solid particles provides lubrication of the material and thereby enhanced compressibility.[24]
5. Design of modified release dosage forms of wide variety of drugs like ambroxol,[25] cefuroxime Axetil,[1] chlorpheniramine maleate,[26,27] chloroquine, [28] diclofenac sodium, [29,30,31] metoprolol tartarate,[32] nifedipine,[33] paracetamol,[34] propranolol hydrochloride,[35] theophylline,[3,36,37] ranolazine,[38] ibuprofen,[39] chlorpheniramine maleate,[40] verapamil hydrochloride, [40] diltiazem hydrochloride. [40]

HOT-MELT COATING AGENTS:

The materials used for HMC technique are obtained from natural, synthetic and semi-synthetic sources. Modern technology today allows pharmaceutical companies to produce various types of fatty substances with a number of aliphatic carbon molecules bonded to the main chain as well as in the branches. Various types of substitution groups can be also added into the molecular structure. The molecular weight, hydrophobicity, melting point, rigidity, flexibility and rheological behavior are physicochemical parameters that can provide helpful information to correlate the ability of excipients to prolong drug release.[11] Lipids are a large class of materials that includes fatty acids, glycerides, phospholipids, sphingolipids, waxes and sterols. They are more or less digestible by lipases[41]. They may be insoluble in water, amphiphilic, and often identified by their fatty acid composition, melting point, Hydrophilic-Lipophilic Balance (HLB), and solubility in organic solvents. Vegetable oils and their derivatives are the primary source for the manufacture of hundreds of lipid-based excipients intended for the development of solid, semi-solid or liquid lipid-based formulations.[42] Gibson provides a list of the most commonly used excipients for oral administration.[43] A normal diet includes a daily intake of 60-80g of lipid mainly triglycerides. A normal adult's digestive system is powerful enough to hydrolyze around 100 -140g of lipid every day. Due to their resemblance to *in-vivo* components, lipids used in lipid based drug delivery systems are well tolerated in the organism, and less cytotoxic. Their presence in the gastrointestinal (GI) tract mimics the fed state, which in turn stimulates the secretion of bile salts.[44]

a. Waxes as a HMC agent: Waxes are obtained from animal, insect, vegetable, mineral, and synthetic sources.[45-51] They are plastic solid at room temperature and liquid of low viscosity above its melting point (>60^{o}C). They are chemically heterogeneous materials defined as esters of a monohydric long chain fatty alcohol and a long chain fatty acid. Waxes contain a wide variety of materials including glycerides, fatty alcohols, fatty acids, and their esters. In the literature, the terms waxes, fats, or lipids have often been used interchangeably and no consistent terminology has been established. They have in common their lipophilic character and their insolubility in water and solubility in non-polar solvents. Besides natural materials, many semisynthetic products such as fatty acids or alcohols or surfactants are derived from lipids. As they are hydrophobic materials generally with melting temperatures higher than 60◦C, hence their uses as prolonged release coating agents.

Lanolin is the most recognizable animal wax, which is obtained from sheep wool. It consists primarily of esters of C_{18}–C_{26} alcohols and fatty acids, sterols (cholesterol), and terpene alcohols. Spermaceti wax is obtained through the precipitation of the head oil from the sperm whale on cooling. It consists primarily of cetyl palmitate. Because of public concerns with animal-derived products, spermaceti has been replaced with other natural or synthetic products.

Bees wax is the most commonly used insect wax obtained from the honeycomb of the bees. White and yellow beeswax are GRAS-listed and consist of mixtures of various esters of straight chain monohydric alcohols with even number carbon chains (C_{24}–C_{36}) esterified with straight chain fatty acids. The major ester is myricyl palmitate. Beeswax also contains free acids and carbohydrates. White wax is obtained through bleaching of yellow wax with oxidizing agents or with sunlight. The National Formulary 18 (NF18)[52]specifications list a melting range of 62–65°C, an acid value of 17–24, and an ester value of 72–79. It is practically insoluble in water, sparingly soluble in ethanol, and soluble in chloroform and various oils.

Carnauba wax is obtained from the carnauba palm tree dried leaves, indigenous to Brazil. It is a complex mixture of high-molecular-weight esters of acids and hydroxyacids. Carnauba wax is very hard and brittle with a high melting point. The NF18 specifications list a melting range of 81–86°C, an acid value of 2–7, and a saponification value of 78–95. It is insoluble in water, slightly soluble in boiling ethanol, and soluble in warm chloroform. Besides the sustained-release applications described later, it is used as a polishing agent in sugar coating because of its high gloss, and in topical preparations. Other, less used vegetable-derived waxes include candelilla wax and castor wax. Together with candelilla wax, hydrogenated jojoba oil, rice wax and paraffin wax it is used between 10 and 30 wt% in sustained release or taste-masked formulations.

Microcrystalline waxes are mineral-derived waxes are obtained from petroleum, which is microcrystalline in nature. They are both obtained from petroleum: the quality and quantity of the wax depends on the source of the crude oil and the refining process. Microcrystalline wax (petroleum ceresin or wax) consists of straight chain and branched saturated alkanes with a chain length range C_{41}–C_{57}. The NF18 specifications list a melting range of 54–102°C; it comes in plastic and hard grades. It is insoluble in water, slightly soluble in ethanol, and soluble in chloroform. It is used as a sustained release carrier. In addition of these waxes to EVA based coatings improves resistance to animal and vegetable fats, improves adhesion to various substrates, and increases resistance to low temperature cracking. High and low melting microcrystalline waxes used alone or in combination provide various desired physical properties including gloss retention and sealing strength improvement.

Carbowaxes are water soluble and often used for taste masking or seal coating.[53] Carbowaxes are waxy material composed of polyethylene glycols (PEGs); but chemically it is not a wax. PEGs with a molecular weight (MW) ranging from 1450 to 3350 are suitable for the HMC process, whereas higher MW PEGs cannot be used due to their high viscosity.

b. **Vegetable oils and their derivatives:** Vegetable oils consist of not only triglycerides (90–95%), but also fatty acids, phospholipids and unsaponifiable compounds (pigments, sterols and fat soluble vitamins). These oils and their derivatives are used as coating agents with a wide scope of applications due to the range of physicochemical properties (melting point, hydrophilic lipophilic balance (HLB) [42] and digestibility. In general for both taste masking and prolonged release applications a lipid with medium to high melting temperature, 55–80^{o}C. In fact, the lipids must not melt too early to avoid a premature release of the drug. Excipient digestibility also determines its functionality. Digestible lipids are suitable taste masking agents since the first human lipase (inducing lipid hydrolysis) is located in the stomach.[41] Upon contact with the tongue the protective lipophilic coating remains intact however once exposed to the gastro-intestinal fluid the coating is rapidly digested, drug dissolution is accelerated, resulting in immediate drug release. Lipid coatings can also comprise surfactants to facilitate immediate release. Alternatively, if non-digestible lipids are used for coating, drug release occurs most of the time via diffusion through the coating barrier; as such drug release is both retarded and prolonged over several hours. Therefore it is important to understand the nature and degree of digestion of the lipid coating agent in order to achieve the desired effect on drug release. For sustained release applications lipids with a high melting point are generally used in sustained release dosage forms. Hydrogenated vegetable oils are obtained by catalytic hydrogenation of the double bonds of vegetable oils. The hydrogenated cottonseed oil (Lubritab® from JRS) and other hydrogenated vegetable oils like Durkee Stearine™ are hydrophobic waxy solids used as sustained release coating agents or for taste masking.[19, 54-57.]

Hydrogenated vegetable oils are prepared by hydrogenation of refined vegetable oils. Hydrogenated vegetable oil consists of mixtures of triglycerides, with two types being defined in the USP23. Type II includes partially hydrogenated vegetable oils and has a lower melting range and a higher iodine value than Type I. Type I melts in the range of 57–70°C and has iodine value of 0–5, while Type II has a melting range of 20–50°C and an iodine value of 55–80. They are used as lubricants, taste masking agent and sustained-release coating materials.

Saturated polyoxylglycerides are waxy solids dispersible in water, obtained by alcoholysis of hydrogenated vegetable oils using polyoxyethylene glycols of molecular weights between 200 and 2000. These products are marketed under the trade name Gelucire® (by Gattefosse). [35, 58] Gelucires® (Gelucires) are a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their Hydrophilic Lipophilic Balance (HLB 1-14) and melting points (33^{o}C-65^{o}C) range. Depending on their melting point and HLB value, these products can be used to slow down (Gelucire® 50/02) or to accelerate the release of active substances by creating hydrophilic pores (Gelucire® 50/13). Fatty acids with a melting point between 60 and 90◦C including stearic and behenic acid are also used as coating agents.[1,23,59] The esterification of glycerol with these fatty acids produces glycerides comprising mono-, di- and tri-esters with excellent coating properties. For example, two glycerides obtained by

direct esterification of glycerol with either palmitic and stearic acids (glyceryl palmitostearate, Precirol® ATO 5 by Gattefossé) or behenic acid (glyceryl behenate, Compritol® 888 ATO by Gattefossé) are used as coating agents for sustained release applications.[3,16,26,28,35,36] The Gelucires containing only PEG esters (Gelucire 55/18) are generally used in preparation of fast release formulations, while Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations.[60] Gelucire 50/13 contains a large proportion of PEG mono- and di-esters with palmitic (C_{16}) and stearic (C_{18}) acid, with 20% glycerides and 80% PEG esters. [61] Gelucire 50/13 has a nominal melting point of 50^{o}C and an HLB value of 13.

c. Animal fats: Animal fats are not commonly used as pharmaceutical excipients; however cow ghee is a clarified butter with a high melting point and has been described as a sustained release agent.[29] HMC employed waxes such as cetyl alcohol, beeswax, lanolin, etc. which have definite disadvantages such as ability to demonstrate hypersensitivity or immunogenic responses in certain individuals. It is an important component of our daily diet and absolutely free from the hypersensitivity skin and other reactions.

CHALLENGES IN USE OF LIPIDS AS HMC AGENT:

Lipids are sensitive to oxidation, especially for unsaturated triglycerides and fatty acids. It occurs during storage or processing, and leads to a loss in product quality. When lipids are exposed to environmental factors such as light, air or temperature, auto-oxidation may occur, and can produce change of texture, color, rancid flavor or loss of quality and even the generation of toxic compounds with health risks for patients. Other degradation pathways are catalyzed by lipoxygenases enzymes. Trace of metals like iron, copper, and cobalt can have a significant impact in promoting oxidation. Auto-oxidation seems to be a key and complex mechanism in lipid oxidation. It mainly generates hydro-peroxides and volatile compounds, generally through a three-phase process (initiation, propagation and termination).[62]

Nitrogen flushing can prevent oxidation in closed systems such as capsules.[63] To avoid metal-based catalysis, the use of chelating agents (EDTA or citric acid) is an alternative. The use of antioxidants can prevent oxidation reaction by different mechanisms that have been described by several authors and reported by Karabulut.[64] Alpha-tocopherol is a primary antioxidant responsible of terminating free-radical chain reactions by donating hydrogen or electrons to free radicals, and converting them to more stable products. The pathways mainly used to inhibit oxidation with antioxidants are singlet oxygen deactivation (ascorbic acid), free radical scavenging (ascorbyl palmitate) and chain-breaking reactions (β-Carotene). Blends of antioxidants can be used to combine the effects. To assess the effects of antioxidants on oxidative stability, several analytical methods can be used, such as peroxide value for primary oxidation value and p-anisidine value for secondary oxidation products, scanning calorimetry, [65] and thermogravimetry.[66] Cyclic voltammetry is a rapid method used for identifying excipients in which the drug is more sensitive to oxidation, and for screening antioxidants.[67]

REGULATORY ISSUES IN USE OF LIPIDS AS COATING AGENT:

From a regulatory point of view, quality and safety issues related to preclinical and clinical studies are the main difficulties likely to be encountered in launching a lipid-based dosage form on the market, and above all the demonstration of the therapeutic efficacy. The overall drug stability and absence of immunological reactions to the oils or lipids has to be demonstrated. Sufficient details explaining the use of lipids and the types of dosage form, the drug release mechanism and their manufacture should be provided to convince the regulatory authorities of their acceptability.[68] Safety assessment and the potential influence of biopharmaceutical factors on the drug or lipid excipients need to be explored. It may be difficult to predict *in-vivo* performances of a lipid dosage form based on *in-vitro* results obtained with conventional dissolution methods in view of the convoluted gastrointestinal processing of lipid formulations. More mechanistic studies should be conducted to facilitate a better understanding of the pharmaceutical characteristics of lipid formulations and interactions between lipid excipients, drug and physiological environment. The lack of predictability for product quality and performance may be due to the nature of empirical and iterative processes traditionally employed.[69]

With the aim of rationalizing the design of HMC lipid formulation, and to better understand the fate of a drug after oral administration in a HMC lipid formulation, a Consortium, composed of academics and industrial scientists, has been created (www.lfcsconsortium.org). The Consortium sponsors and conducts research to develop *in-vitro* methods to assess the performance of lipid based drug delivery system during dispersion and digestion, which are critical parameters. The primary objective is to develop guidelines that rationalize and

accelerate the development of drug candidates through the identification of key performance criteria, and the validation and eventual publication of universal standard tests and operating procedures. In order to establish approved guidelines, appropriate dialogue with pharmaceutical regulatory bodies (FDA, EMEA) is also foreseen.

EVALUATION OF PHYSICO-CHEMICAL PROPERTIES OF LIPIDS:

Since the harvesting of vegetable or insect waxes is often from wild, non-cultivated sources and because of their complex composition, it is important to characterize the chemical and physical properties of the waxes.[45-50] The composition of natural materials often varies with location, weather, season of harvesting, and age. A good quality control of the raw materials is of upmost importance in order to obtain pharmaceutical products of high quality. The chemical methods to characterize waxes include the determination of the acid, saponification, iodine, hydroxyl, and peroxide values.

(i) Color: The color of the wax will affect the color of the finished product. A Lovibond tintometer is often used for color measurements, whereby the color of the raw material is compared against a series of colored standard glasses, under a standard light source. The color of the solidified wax of the same sample may be different depending on the amount of occluded air, the rate of cooling, or surface finish. Therefore, the color of many waxes is best measured in the molten state. Two ASTM color standards are used to measure dark-brown to off-white color and off-white to pure white. The refractive index and the specific gravity are other parameters often determined.

(ii) Dilatometry: The expansion or contraction of waxes is also important during the processing of wax melts, for example, during the preparation of microparticles by spray congealing, hot-melt coating, or hot-melt filling of hard gelatin capsules. The dilatation of waxes or thermal expansion during the transition from the solid to the liquid state can be measured with a dilatometer.

(iii) Goniometry: Goniometry is measure of the contact angle between the lipid coating surface and a droplet of water. It is usually used to evaluate the hydrophobicity of the coating agent. This straightforward technique enables a rudimentary prediction of the effect of the coating on drug release: drug release rate decreasing with increasing hydrophobicity of the lipid coating.

(iv) Hardness: The hardness of a wax is measured with a penetration test, whereby the depth of penetration of a needle under a given weight is measured, preferably at different temperatures.

(v) Melting Point and Polymorphism: Various tests to measure the melting point of waxes often yielding different values. Since waxes are non-homogeneous in chemical composition, a melting range rather than a clear melting point is most observed. The melting point of glycerides generally increases with increasing hydroxyl number, decreasing degree of unsaturation, and increasing molecular weight of the fatty acid. The melting point of many waxes can be determined with capillary tubes. It is important to understand the thermal behavior of a lipid excipient when used for coating since the process engenders melting and, in some cases, exposure to temperatures close to 150^{o}C. Therefore, ideally the lipid should possess the following thermal properties: (i) physico-chemical stability at temperatures up to 150^{o}C; (ii) a melting point no higher than 85^{o}C since the product is maintained 40-60^{o}C above during the coating process; (iii) a narrow melting range to prevent sticking, a consequence of low melting point fractions agglomerating the coating substrates; (iv) a stable fusion/crystallization profile, i.e. not affected by the storage conditions and thermal history. It is widely known that lipids are chemically complex, typically exhibiting a wide melting range. The melting point generally increases with the hydroxyl value and/or the molar mass and decreases with the degree of unsaturation. Differential scanning calorimetry (DSC) is a fundamental technique for the characterization of the thermal behavior of lipid excipients including their melting and solidification point, their phase transition temperature and the solid/liquid ratio. DSC can be coupled with X-ray diffraction (XRD) to gain a deeper insight into the polymorphic behavior of lipid excipients. This combination enables elucidation of the morphological and structural changes throughout these thermal events. The thermal history of a glyceride determines its composition in terms of crystal structures including (i) hexagonal (α), (ii) orthorhombic (β') and/or (iii) triclinic (β), which show different polymorphic transition temperatures and melting points. By tempering the lipid around its melting point for a given time, or by controlling the rate of crystallization, the polymorphism of glycerides can usually be controlled[12]. Indeed, crystallization toward the thermodynamically most stable form can be achieved by seeding hydrogenated vegetable oils with triclinic crystals (0.1–30.0 wt%).[57] It should be pointed out that polyethylene-glycols used as coating agents either alone or in combination with lipids (e.g.

polyoxylglycerides) also exhibit polymorphism. Again, this can be controlled by an appropriate thermal treatment. [13]

The slip point is defined as the temperature at which a column of the testing material starts raising in an open-ended capillary tube, which is dipped in water, filled in a beaker and heated under specific conditions. The drop-point test can be used; however, it is not reliable for more viscous waxes. The congealing point of a wax is the temperature at which the molten wax stops to flow upon cooling. Thermal methods such as differential scanning calorimetery (DSC) are widely used to characterize the heating and cooling profiles of waxes in a qualitative and quantitative manner. Potential polymorphic transitions and recrystallization during processing can be simulated by running different temperature profiles. The smoke point is the temperature at which the sample begins to smoke when tested under specified conditions. Temperature at which a thin continuous stream of bluish smoke is first observed. The flash point is the temperature at which a flash appears at any point on the surface of the sample due to the ignition of volatile gaseous products. The fire point is the temperature at which evolution of volatiles due to the thermal decomposition of the lipids proceed so quickly that continuous combustion occur. Wiley melting point is the temperature at which the disc changes shape to a sphere. Cloud point is a measure of the temperature at which crystallization begins in liquid oil. It is often of practical importance to have oil which does not crystallize when stored at 0^oC for prolonged periods. A simple test to determine the ability of lipids to withstand cold temperatures without forming crystals.

(vi)Viscosity: The viscosity of the molten wax is an important parameter, especially for processes such as hot-melt coating or spray congealing, where wax melts are processed. In an ASTM monograph (D 88), the time that a certain quantity of molten wax requires to flow through an orifice of specified dimensions is measured. The viscosity of the lipid as a function of temperature must be evaluated to ensure that the viscosity of the molten lipid is sufficiently low to provide continuous flow through the peristaltic pump and the nozzle during substrate coating. Generally, the viscosity of the molten lipid excipient is less than 300 cPs at 80^oC.[15]

(vii) Water sorption: Water sorption/desorption isotherms determined by Dynamic Vapor Sorption (DVS) illustrate the behavior of lipid excipients in controlled relative humidity. This information is useful when a lipid coating is being considered to provide protection of a water sensitive ingredient against the effects of relative humidity. For instance, lipophilic films composed of Compritol® 888 ATO form a very effective barrier against water vapor protecting substrates from relative humidity and degradation.[14, 22]

EQUIPMENTS USED FOR HOT-MELT COATING:

The process conditions and equipment for HMC has been published by Jones and Percel.[70] Various types of equipment can be used for the HMC process: a fluid bed coater equipped for top, bottom, tangential spray, the turbo jet, and the modified conventional pan coater. The latter requires dissolution of the lipid (triglycerides) in a solvent (dichloromethane), which makes this technique less attractive than the others.[71]

1 Hot-melt coating in pan: HMC can be possible using conventional pan coater with slight modification by pan-spray or pan pour technique (figure 1). The pan spray coating technique is the best technique to control the release due to uniform film formation, while pan pour technique shows variation in the release of drug from the same batch this was due to non- uniform coating and very low coating efficiency. The HMC is carried out to coat capsules, granules, pellets, spherules and tablets by simple modification. The substrate to be coat with molten blend coating agent in a coating pan equipped with 4 radially arranged baffles and system to heat the pan. The process consisted of first melting the coating agent, raising the temperature of molten mass to slightly above melting point of coating agent with stirring at the same temperature. Substrates were then rolled in the coating pan which was heated from outside by convection using room heaters until a bed temperature of 60^oC was attained. The molten coating mass was then loaded onto the hot rolling substrates in a slow stream or sprayed with controlled rate with insulated spray nozzle. After the completion of application of coating solution, the substrates were allowed to roll further for 10 minutes during which the bed temperature was allowed to gradually come down. The substrates were then removed and cured in a dryer for few hours to days.[29]

A B

Figure 1: Hot-melt coating using modified conventional pan showing (A) Pan spray and (B) Pan pour method.

2 Hot-melt coating in spouted bed: Basic fluid dynamic characteristics for the spouting of the tablets were determined according to well known procedures.[72] A prismatic spouted bed apparatus which consists of transparent acryl-glass with two horizontal and adjustable gas inlets. The coating is carried out under the maximum spoutable bed height and with an air flow rate 40 % above the minimum spouting velocity. Substrate such as tablets were weighed and loaded into the column, the desired air flow rate was adjusted and then the temperature was set up. After the bed temperature was stable, wax beads were loaded in the equipment by simple dropping from the column top at once. The solids suspension was spouted for 5 minutes and then the heating was shut down. Temperature drop was monitored until it reached room temperature and then allowed to spout for additional 5 minutes. The coated tablets were collected and weighed. The process efficiencies were calculated using the initial and final substrates weight and coating material load, according to the definition in Equation (1)

$$\% \text{ Coating efficiency} = \frac{\text{Initial weighhhhhht of substrate} - \text{Final weight of substrate}}{\text{Coating material load}} \quad (1)$$

3 Hot-melt coating in fluidized bed coater: Any fluidized-bed coating equipment can be modified for hot-melt coating process. There are five well known hot-melt coating techniques which have been applied in the pharmaceutical industry: top spray, bottom spray, tangential spray, turbo jet and solid dispersion. Top spray coating or standardized fluidized bed is the most common for hot-melt coating. The core can be small pellets, granules or particles. The top spray mode, in which the wax melt is sprayed downward on upward moving particles, is the system of choice for HMC (Figure 2).

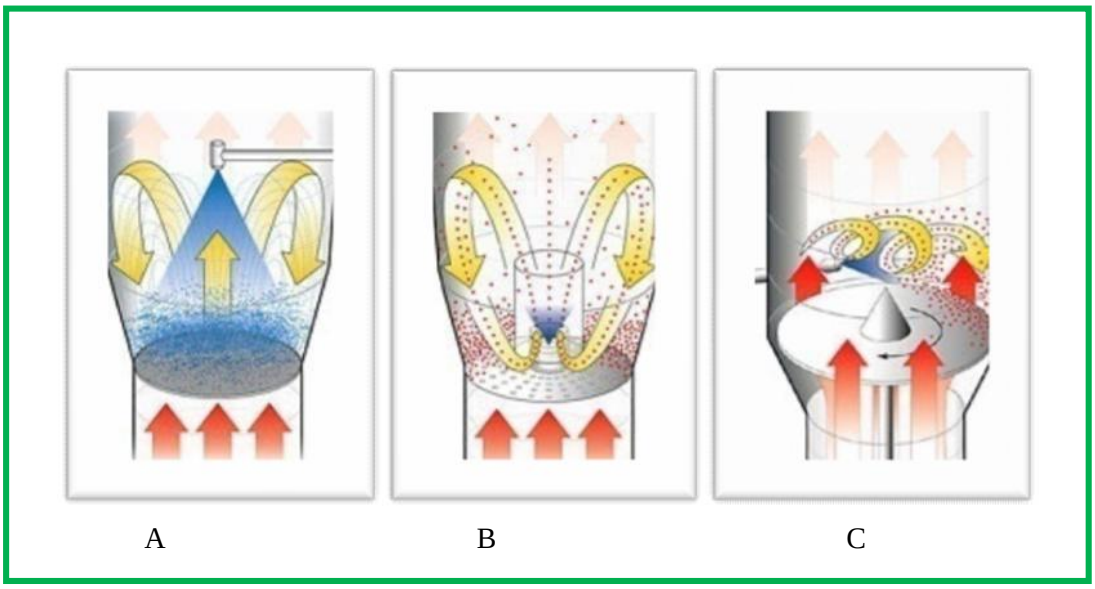

Figure 2: Hot- melt coating in fluidized bed coater showing (A) Top spray, (B) Bottom spray and (C) Tangential Spray.

The substrate temperature should be kept closest to the congealing temperature of the wax when compared to the other two spray modes. The wax has to be kept in a molten state in order to be atomized into the fluidized bed. A special nozzle had to be developed. The nozzle wand had a triaxial structure with a center tube for the molten liquid, which is surrounded by a small air space for the delivery of high-pressure, low-volume air to control the valve in the nozzle, which opens when the pump was running. Both of these tubes were surrounded by a larger air space through which the heated atomization air was supplied (Figure 3). The nozzle should be placed as closely as possible to the substrate bed in order to minimize the distance that the molten droplets had to travel prior to contacting the substrate surface.

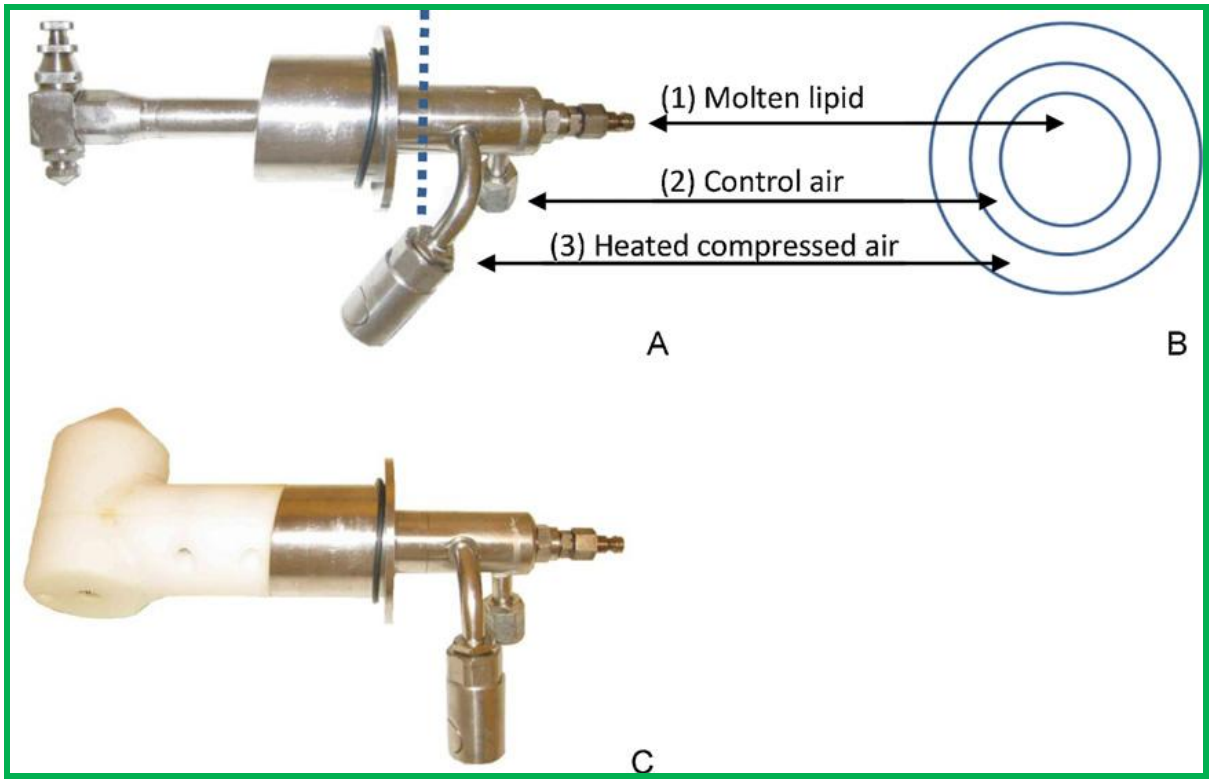

Figure 3: Nozzle for HMC with a top-spray fluid bed coater. (A) Nozzle without the insulation; (1) molten lipid, (2) control air, (3) heated compressed air; (B) Nozzle cross-section; (C) Nozzle covered with the Teflon insulation.

3.1 Top-spray fluid bed coater: The top spray is restricted in application due to product fluidization and flow. The top spray fluidized-bed coater was the most suitable for hot-melt coating due to its ability to operate with product temperatures closest to the congealing temperatures of the molten excipients.[71] In other words; top spray coating can reach minimum product temperature over the melting point (PT/MP ratio). The process is composed of three sequential steps. (i) HMC materials are melt; (ii) The molten material is sprayed onto substrate surface then it spreads around the substrates, and (iii) Coated substrates are congealed. The molten coating agent is maintained typically at 40- 60°C above melting point. The substrates are kept at 10-20°C below the melting point of the coating agents.

3.2 Bottom-spray fluid bed coater: An alternative for top spray fluid bed is bottom spray[47]which is useful for small substrates like granules, pellets, spherules and larger particles. It creates more ordered flow and it is appropriate for small coating levels. Large coating levels are also possible at the expense of PT/MP ratio. Bottom spray is characterized by an air distribution plate at the bottom of the tank and the Wurster inset. The distribution plate facilitates the distribution of fluidizing particles in the expansion zone. The center of the distribution plate is pierced with holes larger and thicker than the peripheral areas and the largest volume of air passes through these holes pulling particles from the periphery to the center of the coating zone. The substrate enters the coating zone via the Wurster, a cylindrical tube with a diameter half the expansion chamber (partition area). Once the substrate leaves the Wurster it expands and falls down in the peripheral zone of the tank. Distribution plates used for hot-melt coating possess generally more holes with bigger diameters, which allow the air flow to be more efficient than in standard coating processes. As a result it reduces the agglomeration of particles. Moreover, the Wurster position is raised (two-fold) to enable vigorous substrate fluidization in the beginning, which reduces with increasing coating thickness. The spray nozzle, which should be insulated without impacting particle fluidization, is located at the bottom of the tank at the center of the partition area and disperses the lipid with the particle flow (as opposed to top-spray). Substrates with poor fluidization characteristics such as larger particles and/or particles of higher density are difficult to coat with the top spray mode, and the bottom spray mode should be preferred. Additional critical parameters for this type of equipment include the height of the partition area (determined by the size, density and the desired substrate speed), and the type of the distribution plate, which is chosen according to the substrate nature (particles of 50 µm, pellets or mini tablets).

3.3 Tangential-spray fluid bed coater: Tangential spray system is novel fluid bed system in which the energy from disk aids spreading and smoothing of the coat is a modification of the equipment used for fluid bed method. Large 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 movement, 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. Relative to the other two fluid bed techniques, particles are exposed to higher mechanical stress therefore substrate that are highly resistant to these forces are well-suited for this process. Similarly 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. Demerit of this device is its limited capacity.

3.4. Solid dispersion coating technique: The solid dispersion coating technique was introduced by Kennedy et al, [53] which does not require the spraying process. The Wurster column in the fluid-bed coater devoid of the nozzle spray system, hence this technique is not as complicated. The substrate is combined with a coating agent in the fluid bed chamber due to the temperature inside the chamber by following four simple steps: (i) Chamber warming up, (ii) Preheating, (iii) Melting and (iv) Spreading and cooling-congealing. Unlike conventional method, a series of weak-points can be found in this process. The cores and the coating excipients are put into a chamber at a high temperature which is not very feasible. It was discovered that the porosity and density values of substrates affected the method's reproducibility. The nonpareil-sugar beads tend to agglomerate if the particle size is smaller than 40 mesh for coating agents PEG 1450-8000 and MPEG 2000 and 5000. For homogeneous spreading, the optimal viscosity of the coating agent is less than 300 cPs. Also this method allows only a low percentage of hot-melt coating 2.5-5%. In fact, in real cases a higher percentage of coating is required to be deposited. Kennedy et al.[27] applied this improved technique for preparing chlorphenaramine maleate coated beads and its dissolution profiles were also tested. The Kennedy et al.[53] reported that the gap needed between melting points for two coating agents to be applied using the hot-melt fluid bed method for dual coating was 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. The quality of the fluidized bed coating processes can be evaluated in both macroscopic and microscopic levels. In the former level, the production time, yield, energy and materials are considered based on the coater performance. In the latter level, the coating quality is characterized mainly as a function of two factors, coating mass uniformity and coating morphology and measured by both the standard achieved and its repeatability for properties or specifications of it, e.g., assay of the active ingredient, dissolution characteristics, appearance, 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 introduced to the process. The difference represents the product losses that occur during coating. In the fluidized bed coating process, product losses, occurring generally due to imprecise design of the process, 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. Improper design of the coating process affects also the quality of the coating. Therefore, the correct design 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 product and process variables are involved in the fluidized bed coating. These variables can be classified as apparatus variables, product variables and process variables. Apparatus 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. As pointed out by Schinzinger and Schmidt,[73] 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.

3.5 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.[74] An advantage 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: Hot-melt coating by direct blending is the simplest way to make coat particles. Although the 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 consists of the following five steps: (i) Melting coating agent, (ii) Drug dissolution or dispersion in the molten coating material, (iii) Good 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.[75] These sugar beads are homogenous in size and shape and easily adhere to waxes. Customers can select an appropriate size of sugar beads for a reasonable price. The smaller the size the substrate is, the larger surface there is for coating agent to deposit onto. In this technique very small modification is done that is molten coating material contains less than 10% solvent.[76] 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 a laboratory scale research project it has been found that size range of sugar beads is 30-60 mesh work nicely as demonstrated herein. 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. It is reasonable that 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. It is well-known that 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 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]

CONCLUSION:

Now a day more attention is given operator safety and protection of the environment by reducing the use of solvents in pharmaceutical processes and production. Hot-melt coating with lipids offers a smart option for pharmaceutical manufacturers since from a processing aspect the lipid coating agent is simply melted and directly applied onto the substrate. Indeed, even if the spraying rate of lipid is slow, the lipid is not diluted with solvents, which results in higher and uniform application rates when compared to other techniques. Furthermore, lipids are functional, safe and have well-established history of use in oral dosage forms. The equipment of choice for hot-melt coating with lipids are fluid bed coater and modified conventional coating pan, since the product temperature is close to the solidification temperature of the recommended excipients. With HMC, lipids provide numerous functions including modification of drug release, reduces acidity of vitamins and few drugs, taste masking (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, in particular due to the as yet limited toxicological data – even if some lipid excipient suppliers have taken on the task of generating such data , and the lack of widespread awareness at the regulatory level even if, again, collective efforts progressively address the issue.

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