International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.5, No.3, pp 879-893, July-Sept 2013

An Extensive Insight On Physico-Chemical Characterization Of Hot-Melt Coating Excipients

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Abstract : Hot-melt coatings (HMC) are widely used to provide drug protection, to increase aesthetic value of products, to reduce acidity if vitamins, to provide lubrication and modified drug release. In hot-melt coating the substrates are coated with molten form of coating materials. Substrates used for coating are beads, capsules, granules, pellets, pills, spherules and tablets. Hot-melt coating 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. HMC technique not only protects the operators from solvent but also protect the environment. Hot-melt coating materials are mostly hydrophilic as well as hydrophobic in nature. Majority of hot-melt coating materials are obtained from natural, semi-synthetic and synthetic sources. Generally, lipids are the smart option to polymer coatings as they need melting before application directly on the substrate and make the technique cost effective. Depending upon sources of the lipids, the physico-chemical properties of them may change. 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 processes utilizing coating pan and fluid bed have been widely employed for the formulation and development of many pharmaceutical dosage forms. Historically, solutions of polymers and organic solvents have been used to produce the desired coatings.[1-3] The coating solution has been commonly applied onto the substrate with the aid of a high-pressure, pneumatic, or ultrasonic nozzle. Several factors have contributed to the search for alternatives to organic solvent systems. In 1970 the U.S. Environmental Protection Agency (EPA) introduced the Clean Air Act reducing the amount of atmospheric solvent emissions, thereby dictating the use of expensive recovery systems.[4] The Occupational Safety and Health Administration (OSHA) in 1976 implemented new worker restrictions on the amount and du- ration of worker exposure to many organic solvents.[5] Finally, the corresponding increase in the cost of these solvents encouraged the pharmaceutical industry to seek alternative systems.[1-2]

Many alternatives have been evaluated in the literature eliminating or reducing the use of organic solvents.[1] These systems have included aqueous solutions, mixed organic/aqueous systems, alkali salts, emulsions, hot-melts, and latex or pseudolatex dispersions. Pseudolatex dispersions offer a promising range of pharmaceutical applications including sustained and enteric release.[6,7] Potential problematic attributes of aqueous polymeric dispersions well noted in the literature include the penetration of substrate core,[8] microbial contamination,[2] migration of hydrophilic drugs through the polymeric film, and physical instability of the polymeric film.[9] Less

noted challenges include inferior pharmaceutical elegance, product tackiness, and increased processing times due to film curing requirements.[3]

Hot-melt coating has received little attention in the literature. The desired coating is formed by application of the coating agent in the molten state with the aid of a spray nozzle. The temperature of the substrate bed is maintained slightly below the melting point of the coating agent, producing a congealed barrier. Early research concentrated on spray-congealing molten wax slurries.[10-13] Jozwiakowski et al. evaluated the hot-melt spray coating of fine granules in a fluid bed and optimized the process using response surface methodology.[14]

Hot-melt fluid bed coatings have presented unique challenges for the formulator. These challenges can be directly attributed to the molten viscosity and tendency of the coating agent to congeal prior to delivery onto the substrate. Many coating agents employed with this method require thinning with organic solvents for atomization. Furthermore, steam jackets, heated atomization air, and/or heating tape often have been necessary to prevent the coating agent from congealing within the spray lines and at the nozzle.[1, 14]

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.

Lipids are a large class of materials that includes fatty acids, glycerides, phospholipids, sphingolipids, waxes and sterols [Table1]. They are more or less digestible by lipases.[15] 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.[16]

Gibson provides a list of the most commonly used excipients for oral administration.[17] A normal diet includes a daily intake of 60-80 g of lipid mainly triglycerides. A normal adult's digestive system is powerful enough to hydrolyze around 100-140 g 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. Bile salt causes solubilization of lipids thereby enhancing bioavailability of drug therein formulation. [18]

1. Waxes: Waxes are obtained from animal, insect, vegetable, mineral, and synthetic sources.[19-26] 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.[27]

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) 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. [27]

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.[27] 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.[27]

Carbowaxes are water soluble and often used for taste masking or seal coating.[27] 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.

2. **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) and digestibility.[15] 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.[15] 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.[19-25]

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 USP 23. 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 by Gattefosse under the trade name Gelucire®. [23] 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.[28] 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).[29] Compositions for coating feedstuff additives for ruminants, and feedstuff additives are also coated using this technique.[30] Fatty acids with a melting point between 60 and 90◦C including stearic and behenic acid are also used as coating agents. 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. 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.[31] 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. Gelucire 43/01 has a nominal melting point of 50^{o}C and an HLB value of 13.[32]

3. 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.[33] 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.

Table 1: Examples of excipients used in hot-melt coating[19]

Excipient	Chemical composition	Characteristics	Applications	Examples
Animal fats	Clarified butter	MP ≈ 80 ◦C	Modified release	Cow ghee.
Fatty acids	Long chain fatty acids	MP = 60-90 ◦C	Modified release	Behenic acid, palmitic acid, stearic acid.
Fatty alcohol	Long chain fatty alcohol	MP = 50-55^{o}C	Modified release, Taste masking	Cetyl alcohol, wool alcohol.
Partial glycerides	Mixtures of mono-, di- and triglycerides	MP = 54-74 ◦C	Modified release, Taste masking, Lubrication.	Compritol® 888 ATO, Myvaplex™ 600, Precirol® ATO 5.
Polyoxyl-glycerides	Mixture of glycerides and esters of fatty acid and PEG	MP ≈ 50 ◦C, partially digestible.	Immediate release, modified release.	Gelucire® 50/02, Gelucire® 50/13.
Vegetables oils	Mixture of triglycerides, Free fatty acids, phospholipids.	MP = 60-71◦C, often digestible.	Taste-masking, modified release.	Hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenated soybean oil.
Waxes	Esters of fatty acids and long chain alcohols.	MP= 62-86 ◦C, hydrophobic.	Modified release.	Beeswax, carnauba wax, candelilla wax, hydrogenated jojoba oil, rice bran wax.

Where, MP is melting point in ^{o}C.

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).[34]

Nitrogen flushing can prevent oxidation in closed systems such as capsules.[35] 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.[36] α-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).[36] 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, and thermogravimetry.[37,38] Cyclic voltammetry is a rapid method used for identifying excipients in which the drug is more sensitive to oxidation, and for screening antioxidants.[39]

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.[40] 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.[41] 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.[42]

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).[43] 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. 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 physical methods to characterize waxes include color, Dilatometry, Goniometry, Hardness, melting point, refractive index, polymorphism, specific gravity, viscosity and water sorption. The chemical methods to characterize waxes include the determination of the acid value, iodine value, saponification value and peroxide value.

1. Physical Characterization

1.1. 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.

1.2. 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.[44]

1.3. Goniometry: Goniometry is measure of the contact angle between the lipid coating surface and a droplet of water [Figure 1]. 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. [45]

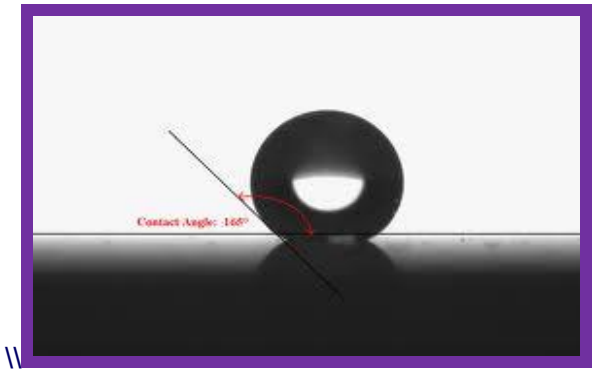


Figure 1: Measurement of contact angle between lipid surface and a droplet of water.

1.4. 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 [Figure 2].[46]

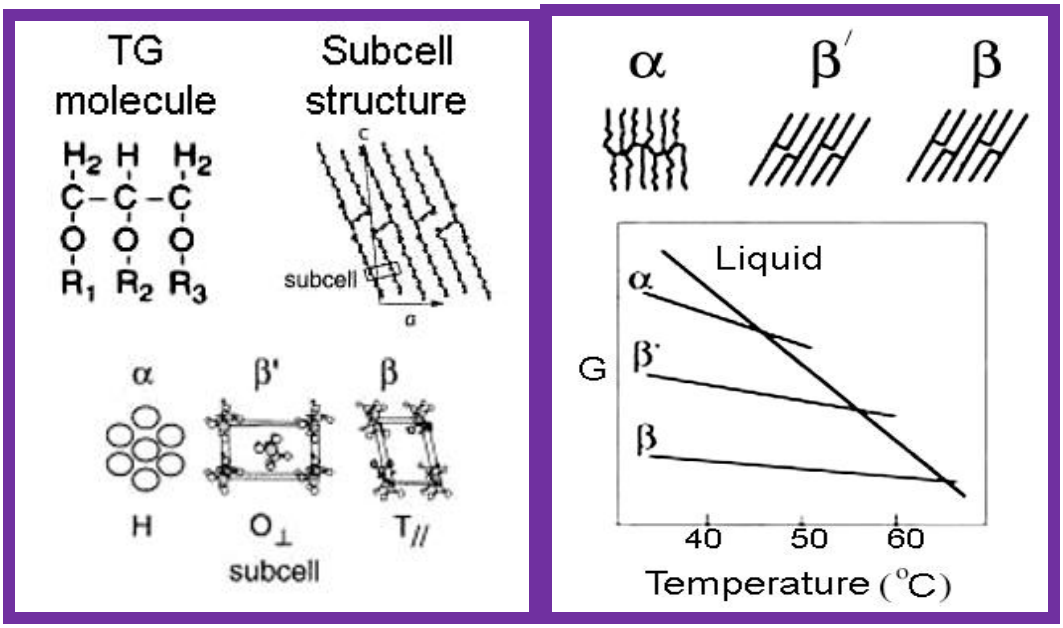
Figure 2: Penetration test apparatus.

1.5. 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.

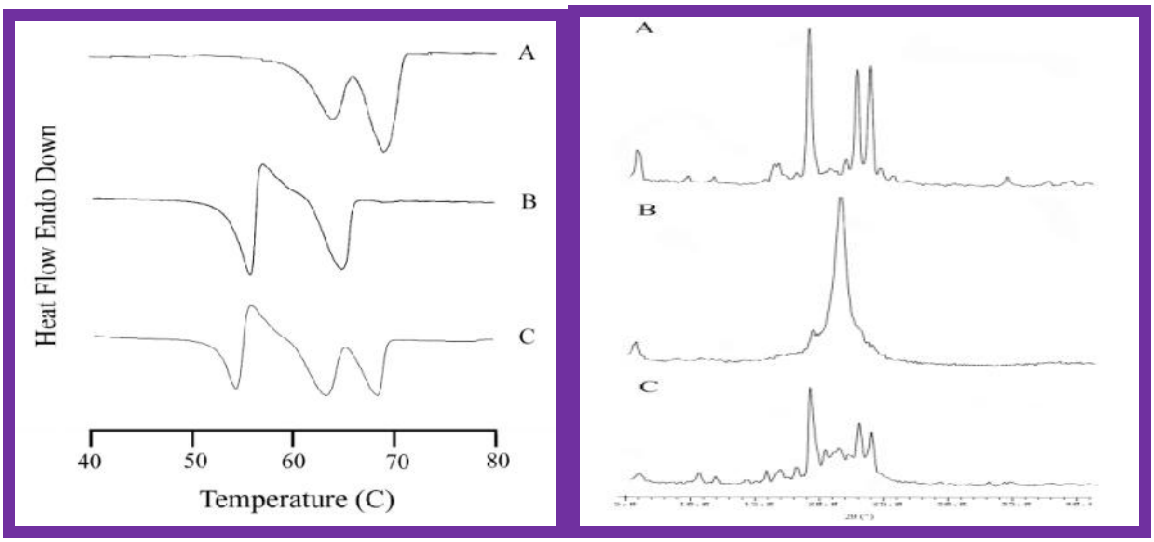
Differential scanning calorimetry (DSC) is a fundamental technique for the characterization of the thermal behavior of lipid excipients including their melting and solidification point, their phase transition temperature and the solid/liquid ratio. DSC can be coupled with X-ray diffraction (XRD) to gain a deeper insight into the polymorphic behavior of lipid excipients [Figure 3,4]. 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. Indeed, crystallization toward the thermodynamically most stable form can be achieved by seeding hydrogenated vegetable oils with triclinic crystals (0.1–30.0 wt %). 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. [47, 48]



A B

Figure 3: Polymorphism of TGs (A) and correlation between polymorphic forms and Gibb's free energy (B).



A B

Figure 4: DSC thermograms, performed at a heat rate of 5 °C/min, (A) and XRD patterns (B) of hydrogenated soybean oil.

1.6. Slip point test: 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.

1.7. Drop point test: 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 [Figure 5]. 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.

1.8. Smoke point: 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.

Figure 5: Drop point test.

1.9. Flash point: 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.

1.10. Cloud point: 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^{o}C for prolonged periods. A simple test to determine the ability of lipids to withstand cold temperatures without forming crystals.

1.11. Refractive Index: The sample (10 g) was melted on a water bath (60^{o}C constant temperature) till a clear solution was obtained. Refractive index was determined on Abbe's refractometer [Figure 6]. A drop of molten Sample was placed upon the surface of the prism A. On clamping the two prisms A and B, the liquid spreads as a film. Light reflected by a mirror M is then directed towards the prism system. On reaching the ground surface of A, the light scatters into the liquid film. This light is divided into bright and dark portions. When the edge of the bright portion coincides with the cross wire of the refractometer, note the refractive index on the scale. Either sodium vapour lamp or mercury vapour lamp is used as a light source. Refractometer should be calibrated against distilled water, which has a refractive index of 1.3325 at 25^{o}C.[49]

Figure 6: Table top Abbe's Refractometer.

1.12. 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 [Figure 7]. 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^{o}C.[50]

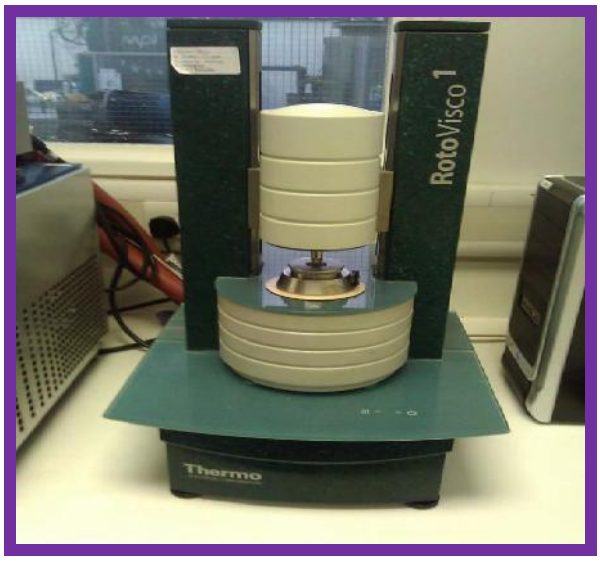


Figure 7: Measurement of viscosity using Viscometer.

1. 13. 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.[51]

2. Chemical Characterization

Standardization of lipids is necessary if it is to be used as an excipient in the pharmaceutical dosage form. The sample was evaluated for various analytical test to set the specification range, which is described below:

2.1 Acid value.

2.2 Reichert or Reichert-Meissl-Wollny value.

2.3 Polenske value.

2.4 Iodine value.

2.5 Peroxide value.

2.6 Saponification value.

2.1 Acid Value: The acid value is the number of milligrams of potassium hydroxide (KOH) required neutralizing one gram of the fat. The fat, after separation by melting the butter, is dissolved in a mixture of ethanol and diethyl ether and titrated with dilute alkali solution. [52-54]

Weigh accurately into 5-10 g of the sample into a 250 ml conical flask. Add 50 – 100 ml of the ethanol/ether mixture, which has been neutralized after the addition of 0.1 ml of phenolphthalein solution. Heat gently on water bath, if necessary, until the substance has completely melted. Titrate with 0.1 N potassium hydroxide, shaking constantly until a pink colour, which persists for 15 seconds, is obtained. The acid value is calculated by using the following equation (1.1).

$$\text{Acid value} = V \times 0.0561 \times 1000 / W \qquad (1.1)$$

Where,

V = volume in ml of 0.1 N KOH solution consumed during the titration,

W = weight in grams of sample taken.

Soluble volatile fatty acid values (Reichert Meissl–Wollny value): This standard specifies a reference method for the determination of water-soluble fatty acid values.
The soluble volatile fatty acid value (Reichert or Reichert-Meissl-Wollny value) is the number of millilitres of aqueous 0.1 N alkali solution required to neutralize the water-soluble volatile fatty acids obtained from 5 grams of fat under the specific conditions of method. The insoluble volatile fatty acid value (Polenske value) is the number of millilitres of aqueous 0.1 N alkali solution required to neutralize the water-insoluble volatile fatty acids obtained from 5 grams of fat under the specific conditions of method. [52-54]
After saponification of the fat with sodium hydroxide solution in glycerol, the soap solution was diluted with water and acidified with sulphuric acid. The volatile fatty acids are distilled and the insoluble fatty acids are separated from the soluble acids by filtration. The aqueous solution of soluble acids and the ethanolic solution of the insoluble acids are then titrated separately with a standardized alkali solution. The method is empirical as it determines only a part of these acids. Consequently, the specifications for procedure and apparatus must be followed rigorously in order to obtain accurate and reproducible results.

Weigh 5.00 ± 0.01 g of the sample into a flask. Add 20 g (16 ml) of glycerol and 2 ml of the sodium hydroxide solution (44 %) (Note: For supplying the sodium hydroxide solution, use a burette protected from the entry of carbon dioxide and clean the burette jet by rejecting the first few drops from the tap.) Heat the flask over a naked flame, avoiding overheating and shaking continuously until the liquid no longer foams and becomes clear. Allow the flask to cool to about 90°C, add 90 ml of freshly boiled distilled water of about the same temperature and mix. The liquid should remain clear. Add 0.6 to 0.7 g of pumice and then 50 ml sulphuric acid solution (1 N). Connect the flask immediately to the distillation apparatus and warm it gently until the free fatty acids form a clear surface layer.

Start heating and regulate the flame so as to collect in the measuring flask 110 ml of distillate in 19-21 min.,

taking the moment when the first drop forms in the condenser as the beginning of the distillation period. Regulate the water flowing in the condenser so as to maintain the temperature of the water leaving the condenser at 20 ± 1°C (Note: If the temperature of the cooling water exceeds 20°C as in tropical and sub-tropical areas, and if no special arrangements can be made, the measuring flask should stay in the water bath at 20± 1°C for about 1 hour). When exactly 110 ml of distillate has been collected, remove the burner immediately and substitute a small beaker for the measuring flask. Mix the contents of the measuring flask by gentle shaking and immerse the flask in a water bath at 20 ± 1°C for 10 to 15 minutes, the 110 ml mark on the flask being 1 cm below the level of the water in the water bath and the flask being turned from time to time. Stopper the flask and mix by inverting it 4 to 5 times without shaking. Filter the 110 ml of distillate through a dry medium speed filter paper, which fits snugly into the funnel. The filtrate should be clear (Note: The filter should be of such a size that 15 ml poured into it would fill it completely). Pipette 100 ml of the filtrate into a conical flask of 300 ml, add 0.5 ml of phenolphthalein indicator solution and titrate with the standardized aqueous alkali solution (0.1 N) to a pink colour persistent for ½ to 1 minute.

Conduct a blank test without sample and instead of saponifying over a naked flame, heat over a boiling water bath for 15 minutes. (Note: Not more than 0.5 ml of the standardized alkali solution should be required for the titration. Otherwise, new reagent solutions should be prepared).

The formula for calculating soluble volatile fatty acid value i.e. Reichert-Meissl value or RM value is given by equation (1.2).

$$\text{RM value} = 11 \times N \times (V_1 - B) \quad (1.2)$$

Where,

V_1 = number of millilitres standardized alkali solution (0.1 N) required for the sample,

B = number of millilitres of standardized alkali solution (0.1 N) required for the blank test,

N = exact normality of the standardized alkali solution (0.1 N).

Insoluble Volatile Fatty Acid Values (Polenske value): Rinse the filter with three successive 15 ml portions of distilled water at a temperature of 20 ± 1°C. Place the funnel with filter in the neck of a dry clean conical flask of 200 ml capacity. Dissolve the insoluble fatty acids by repeating the washing procedure using now 15 ml portions of ethanol (95–96 %). Titrate the combined ethanolic washings with the standardized aqueous alkali solution (0.1 N), using 0.5 ml of phenolphthalein indicator solution, to a pink colour persistent for ½ to 1 min. Insoluble volatile fatty acid value i.e. Polenske value is calculated by equation (1.3).

$$\text{Polenske value} = 10 \times N \times V_2 \quad (1.3)$$

Where,

V_2 = number of ml of standardized alkali solution (0.1 N) required for the sample.

N = exact normality of the standardized alkali solution (0.1 N).

The difference between results of duplicate determinations (results obtained simultaneously or in rapid succession by the same analyst) should not exceed 0.5 for the Reichert value and 0.3 for the Polenske value. [52-54]

Iodine Value: Iodine value is measure of unsaturation of fats and oils and hence their potential of oxidation. HMC materials react with iodine resulting in the addition of the iodine at the C=C double bond site. In this reaction, iodine tri-chloride reacts with the unsaturated bonds to produce a di-halogenated single bond, of which one carbon has bound an atom of iodine. Iodine value expresses number of milligram of iodine absorbed by 100 g of sample. In this method sample is treated with excess amount of iodine. Free iodine can be determined by back titration with sodium thiosulphate solution using starch solution as indicator.

Iodine Value Wijs Method: Preparation of Wijs Reagent is done by dissolving approximately 9 g of iodine tri-chloride in 1000 ml of a mixture of 700 ml concentrated acetic acid (99–100%) and 300 ml of carbon tetrachloride, both free from oxidizable matter. Determine the halogen concentration in the following way: run 5 ml of the solution from a burette into a flask, add 5 ml of 10% potassium iodide solution and 30 ml of water and titrate with 0.1 N sodium thiosulphate solution using starch solution as the indicator. Add the starch solution shortly before the end of titration. [52-54]

After the determination of halogen content of the iodine tri-chloride solution, add 10 g of iodine powder and swirl until enough of the iodine has dissolved such that the halogen content, determined as above, has increased

to considerably more than 1.5 times the original value. Filter or decant the clear solution and dilute it with a mixture of acetic acid and carbon tetrachloride, so that 5 ml of the solution is equivalent to 10 ml of the 0.1 N sodium thiosulphate solution. Keep the solution in dark in a tightly closed amber-coloured stoppered glass bottle. Preparation of Starch Solution by mixing 5 g of soluble starch and 10 mg of mercuric iodide in 30 ml water, add this mixture to 1000 ml of boiling water and boil further for 3 minutes. Sample is prepared for the determination of the iodine value use melted, clear, filtered and well-mixed sample.

Weigh accurately 0.4 to 0.45 g of the sample in a clean dried Erlenmeyer flask. Dissolve the fat in 15 ml of carbon tetrachloride and add by means of a burette exactly 25 ml of the Wij's reagent. Close the flask with its stopper, mix carefully and leave it standing for 1 hour in the dark. Add 20 ml of potassium iodide solution and approximately 150 ml of distilled water and mix. Titrate with 0.1 N sodium thiosulphate solution (use 2 ml of starch solution as the indicator), swirling the liquid constantly. Add the starch solution shortly before the end of the titration. Carry out a blank test, using the same quantities of the reagents without sample. Calculate the iodine value by means of the following equation (1.4).

$$\text{Iodine value} = 1.269\ (b - a) / w \qquad (1.4)$$

Where,

a = number of ml of 0.1 N sodium thiosulphate used in the blank test,

b = number of ml of 0.1 N sodium thiosulphate solution used in the titration with the sample present, and

w = weight of sample taken for the analysis.

The results of triplicate determinations should not differ by more than 0.4.

Peroxide Value: The peroxide value means the number of milligram equivalents of oxygen per kilogram of anhydrous fat. The Peroxide Value (PV) test is useful for predicting shelf life when used together with other tests during a shelf life study. In contrast, it is not always useful in quality control, especially in the absence of sensory evaluation and other tests. There are several known mechanisms and pathways for the decomposition of lipids and the subsequent production of a rancid flavor-aroma. Although, there are various methods that an analytical chemist can use to look for chemical indicators of rancidity, a single test is not necessarily conclusive. [52-54]

Weigh 5.0 g of sample accurately into 250 ml stoppered conical flask, add 30 ml of a mixture of 3 volumes of glacial acetic acid and 2 volumes of chloroform swirl until dissolved and add 0.5 ml of standard saturated potassium iodide solution. Allow standing for exactly one minute, with occasional shaking, adding 30 ml of water and titrate gradually, with continuous and vigorous shaking, with 0.01M sodium thiosulphate until the yellow colour almost disappears. Add 0.5 ml of starch solution and continue the titration, shaking vigorously until the blue color just disappears (a ml). Repeat the blank titration without HMC material (b ml). The volume of 0.01 M sodium thiosulphate in the blank determination must not exceed 0.1 ml. The peroxide value is calculated from the following equation (1.5).

$$\text{Peroxide value} = 10\ (a - b) / w \qquad (1.5)$$

Where,

w = weight of sample in grams.

Saponification Value: The saponification number is the number of milligrams of potassium hydroxide required to neutralize the fatty acids resulting from the complete hydrolysis of 1g of fat. It gives information concerning the character of the fatty acids of the fat- the longer the carbon chain, the less acid is liberated per gram of fat hydrolyzed. It is also considered as a measure of the average molecular weight (or chain length) of all the fatty acids present. The long chain fatty acids found in fats have low saponification value because they have a relatively fewer number of carboxylic functional groups per unit mass of the fat and therefore high molecular weight. [52-54]

Accurately weigh 2 g of Sample in 250 ml borosilicate glass flask fitted with reflux condenser. Add 25 ml of 0.5 M ethanolic potassium hydroxide and little pumice powder and boil under reflux on a water bath for 30 minutes. Add 1 ml of phenolphthalein solution and titrate immediately with 0.5 N hydrochloric acid solution (a ml). Repeat the procedure for blank titration without sample (b ml). Calculate the saponification value from the following equation (1.6).

$$\text{Saponification value} = 28.05\ (b - a) / w \qquad (1.6)$$

Where,

w = weight of HMC material in grams.

Conclusions

Looking at the several advantages of hot-melt coating over conventional coating, this technique has growing the demand by regulatory authorities. Hot-melt coatings techniques are widely used to provide drug protection, to increase aesthetic value of products, to reduce acidity if vitamins, to provide lubrication and modified drug release. These methods are economic, fast, reproducible and safe. Lipid coating is the smart alternative for conventional polymer coating as they need melting before application directly on the substrate. Majority of lipids are obtained from natural, semi-synthetic and synthetic sources, and depending upon sources of the lipids, the physico-chemical properties of them may change. Therefore it is essential to standardize them for reproducibility, safety and efficacy of pharmaceutical dosage form is necessary. The selection of the right lipid for the application requires knowledge of their physico-chemical properties and its associated effect on drug release.

Rational design may be achieved using *in vitro* methods or other markers to better predict the dynamic changes of a lipid formulation *in vivo*. The recent FDA's critical path initiative offers an excellent opportunity for enhancing regulatory sciences and fostering development of novel dosage forms such as lipid-based formulations. Good product quality and product performance can be maintained with the rational design of a hot-melt coated dosage form.

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