Designing optimal formulations for hot-melt coating

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ABSTRACT

Hot-melt coating (HMC) as a solvent-free technology grants faster and more economic coating processes with reduced risk of dissolving the drug during the process. Moreover, traditional coating equipment can be modified to enable the HMC process. Despite the indubitable advantages and feasibility of the process, HMC is not well-known to pharmaceutical industry and its employment is still limited. The main aspect hindering the widespread application of this technique is the need of materials alternative to the conventional polymeric coatings.

The current work reviews the published HMC formulations and describes the properties that have led to their selection. As these materials are mainly solid lipid excipients, attention should be paid to their crystallization and solid state behavior, and their impact on the performance of coated drug products, particularly on the stable drug release profile.

Although different drug release profiles can be easily tailored, much development work is needed to respond to the unmet requirements of a stable formulation. Ensuring stable solid-state behavior and providing a mechanistic understanding of the macroscopic properties are essential steps towards fulfilling these requirements and establishing of HMC as advanced coating technology for manufacturing of pharmaceutical products.

1. Introduction

In the pharmaceutical industry, hot-melt coating (HMC) technology has been introduced as a modification of the film-coating technology, in which the coating material is supplied as a melt instead of a solution or dispersion. The driving force for the implementation of HMC is to evade the use of solvents and all the resulting constrains of their use (Jones and Percel, 1994; Bose and Bogner, 2007). Therefore, pan coaters, fluid beds and spouted beds can be adapted to atomize molten coating formulations, and coat diverse substrates from drug crystals up to tablets or capsules (Tuerck and McVean, 1973; Jones and Percel, 1994; Achanta et al., 1997; Weiss and Meisen, 1983; Jozwiakowski et al., 1990; Becker et al., 2016; Lopes et al., 2016).

HMC offers significant technical advantages, namely faster and cheaper coating processes, reduced risk of dissolving drug during the process and the microbial contamination of coating formulations is unlikely (Jannin and Cuppok, 2013). Although this technique has been well described since the 1990s (Jones and Percel, 1994) and it is a well-controlled process (Stocker et al., 2017; Hohl et al., 2017; Markl et al., 2015), its application is scarce in the production of coated dosage forms. The main aspect hindering the widespread of HMC is the fact that common polymeric coating materials cannot be employed by this technique, instead HMC formulations primarily make use of solid lipid excipients whose properties are not yet fully evaluated to render an optimal pharmaceutical coating. The aim of the current work is to review the published HMC formulations and to address the critical characteristics of coatings that needs to be satisfied during development stage. This review focuses on the critical material attributes required for development of robust HMC formulations. Description of manufacturing processes, improvements in their constructions and developed process analytical technology (PAT) strategies for controlling and in-line monitoring of HMC process are not the scope of this review and can be found elsewhere (Jannin and Cuppok, 2013; Becker et al., 2015; Jones and Percel, 1994; Achanta et al., 1997; Stocker et al., 2017)

2. Published HMC formulations

HMC formulations have been applied to oral solid dosage forms to provide functional coatings rather than for aesthetic or identification purposes. The most common application of these coatings is to modify the release profile of drugs (Jannin and Cuppok, 2013), while the most promising application is probably the taste and odor masking of drugs, especially when applied to high-dose drugs whose tablet formulation would result in a dosage form too large to be easily swallowed (Becker et al., 2016). As detailed below, several other applications of HMC formulations have been investigated, namely: to provide a physical

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Table 1
HMC formulations listed accordingly to their functionality. *Drug not disclosed.

Function	Drug	Formulations (excipient family)	Reference
Extended release	Cefuroxime Axetil; Diclofenac sodium	Stearic acid (fatty acid)	Kulah and Kaya (2011) and Patil et al. (2012)
	Diclofenac sodium	Palmitic acid (fatty acid)	Patil et al. (2012)
	Propranolol hydrochloride	Precirol® ATO 5 (partial glyceride)	Sinchaipanid et al. (2004)
		Precirol® ATO 5 (partial glyceride) and Gelucire 50/02 (polyoxylglyceride)	
	Hydrophobic drug*	Partially hydrogenated cottonseed oil (hydrogenated vegetable oil)	Jozwiakowski et al. (1990)
	Theophylline monohydrate; Paracetamol	Compritol® 888 ATO (partial glyceride)	Barthelemy et al. (1999), Faham et al. (2000) and Knezevic et al. (2009)
	Beraprost sodium	Glyceryl monooleate (partial glyceride) and talc (mineral)	Guerin and Salle (2004)
		Glyceryl monopalmitate (partial glyceride) and talc (mineral)	
		Glyceryl trimyristate (triglyceride) and talc (mineral)	
		Cetyl alcohol (fatty alcohol) and talc (mineral)	
		Stearic acid (fatty acid) and talc (mineral)	
		Glyceryl palmitooleate (partial glyceride) and talc (mineral)	
Taste masking	Paracetamol	Precirol ATO 5 (partial glyceride), PEG 3000 (polymer) and calcium carbonate (release compound)	Kraahs et al. (2010)
		Stearic acid (fatty acid), Tween® 20 (surfactant) and calcium carbonate (release compound)	
		Stearic acid (fatty acid), PEG 3000 (polymer) and Amberlite IRP 88 (release compound)	
		Precirol ATO 5 (partial glyceride), PEG 3000 (polymer) and Amberlite IRP 88 (release compound)	
		Carnauba wax (wax) and triglyceryl monostearate (polyglycerol/surfactant)	Reo and Johnson (1999)
		Partially hydrogenated palm oil (hydrogenated vegetable oil) and sorbitan monostearate (surfactant)	
		Partially hydrogenated cottonsead oil (hydrogenated vegetable oil) and sodium stearoyl lactylate (surfactant)	
		Stearotex® K (hydrogenated vegetable oil) and triglyceryl monostearate (polyglycerol/surfactant)	
		Carnuba wax (wax) and sorbitan monostearate (surfactant)	
		Carnuba wax (wax) and decaglyceryl monostearate (polyglycerol/surfactant)	
	Cholestyramine	Stearic acid (fatty acid), partially hydrogenated soybean oil (hydrogenated vegetable oil) and PEG 3350 (polymer)	Bequette et al. (1995)
	N-acetylcysteine; caffeine; calcium acetate; ibuprofen; ibuprofen sodium; paracetamol	Dynasan® 116 (triglyceride) and Tween® 65 (surfactant)	Becker et al. (2016), Lopes et al. (2016) and Dandl et al. (2015)
Enhancement of Bioavailability	Meloxicam	PEG4000 (polymer) and Meloxicam (drug)	Khobragade et al. (2014)
		PEG6000 (polymer) and Meloxicam (drug)	
		PEG20000 (polymer) and Meloxicam (drug)	
		Gelucire 50/13 (polyoxylglyceride) and Meloxicam (drug)	
		Gelucire 50/13 (polyoxylglyceride), PVP K30 (polymer) and Meloxicam (drug)	
		Lutrol F68 (copolymer) and Meloxicam (drug)	
Gastroretentive	Metoprolol tartrate	Hydrogenated soybean oil (hydrogenated vegetable oil) and Metoprolol (drug)	Chansanroj et al. (2007a)
Lubricant	–	Compritol® 888 ATO (partial glyceride)	Jannin et al. (2003)

barrier to environmental storage conditions (Chen et al., 2010); to produce gastroretentive dosage forms (Chansaroj et al., 2007a); to enhance the bioavailability of poorly soluble drugs (Khobragade et al., 2014); and to provide lubrication to tablet excipients (Jannin et al., 2003).

Table 1 lists the published HMC formulations for different coating functions. Generally, these coating formulations comprise one solid lipid excipient that can be combined with a surfactant or a hydrophilic component acting as a pore former. Solid lipid excipients contain in their chemical structure long-chain saturated fatty acids that are solid at ambient temperature. The pharmaceutical excipients can be composed by free fatty acids or by the product of the esterification of these fatty acids with glycerol (mono-, di- and triglycerides), long chain alcohols (waxes) or synthetic molecules (e.g. polyethylene glycol, propylene glycol, polyglycerol). Hydrogenated vegetable oils comprise triglycerides (90–95%), but also fatty acids, phospholipids and unsaponifiable compounds (pigments, sterols and fat soluble vitamins). This results in batch to batch variability, and makes the hydrogenated vegetable oils less suitable for pharmaceutical purposes. In contrast, synthesized glycerides are manufactured by the partial or full esterification of fatty acids with glycerol, producing excipients with defined ratios of mono-, di- and triglcerides (Rosiaux et al., 2015).

As solid lipid excipients are generally hydrophobic materials, surfactants or hydrophilic substances are added in taste masking formulations to provide immediate drug release. A wide range of surfactants have been employed, from liquid to solid surfactants and from low to high hydrophilic-lipophilic balance (HLB), e.g. span 60 and sodium stearoyl lactylate with HLB values of 4.7 and 22, respectively (Table 1). These developments have been mainly empirical and there are no publications dedicated to the rational selection of surfactants for HMC formulations.

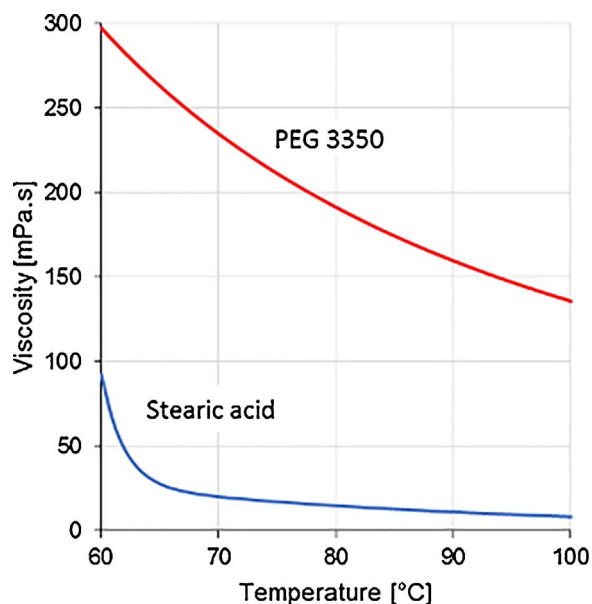The selection of hydrophilic substances has been limited to

Fig. 1. Rheogram temperature ramping curves of PEG 3350 and stearic acid (adapted from Wong et al., 2016).

polyethylene glycol of different molecular weights, with the exception of Kraahs et al. In their work, calcium carbonate and polacrilin potassium (Amberlite IRP88) were incorporated in the HMC formulations as release compounds (Table 1). The authors defined release compound as a compound which in the gastrointestinal tract either causes disruption or disintegration of the taste-masking layer. It was shown that the incorporation of this excipient significantly improves the release rate compared to samples without it (Kraahs et al., 2010).

Generally, the drug is incorporated in the substrate to be coated, alternatively, if the physico-chemical requisites are observed, the drug can be incorporated in the coating melt itself. Khobragade et al. studied the application of HMC to produce solid dispersions and improve the dissolution profile of drugs with low water solubility. In this study, nonpareils where coated with a melt suspension of crystalline meloxicam (< 15 μm) in PEG, Gelucire 50/13 or Lutrol F68 (Table 1). The authors observed that this strategy showed remarkable improvement in drug dissolution and that it can be a novel and practical approach for enhancement of bioavailability (Khobragade et al., 2014). However, further studies are necessary to evaluate the potential of HMC technology to produce enabling formulations.

Similarly, Chansanroj et al. incorporated metroprolol in hydrogenated soybean oil to coat nonpareils. The authors made use of the low density and high hydrophobicity of hydrogenated soybean oil to produce a gastroretentive dosage form, i.e. a dosage form that can float and be maintained uniformly distributed in the stomach where it releases the drug for a desired period of time (Chansaroj et al., 2007a). The floating property of multiparticulate systems coated with solid lipid materials and its implication in *in vivo* drug release needs to be addressed.

Other applications of HMC have been investigated. Jannin et al. showed that HMC technology can be employed to induce a more homogeneous repartition of Compritol ATO 888 as lubricant in lactose. Hot melt coating of lactose with Compritol ATO 888 resulted in decrease of required amount of lubricant from 3% to 0.5% for tableting of lactose (Jannin et al., 2003). Guerin and Salle incorporated talc in their HMC formulation as a "brittleness-inducing agent", however the effect of this component on the coating brittleness or any other mechanical properties was not demonstrated (Guerin and Salle, 2004). Finally, a coating of stearic acid and PEG 6000 was used to provide a protection barrier against moisture in herbal extract pellets (Chen et al., 2010). Although the hot melt technique employed in this work was spreading

coating instead of spraying coating, it shows that lipid coats can be employed for this purpose.

3. Properties of HMC formulations relevant for processing

The application of the coating as a melt instead of a solution or a dispersion provides indubitable advantages. However, the coating material for a HMC process must comprise a set of properties that limit the excipients that can be employed.

3.1. Viscosity-temperature relationship

As the coating formulation is air atomized on the substrate in its molten state, primarily HMC formulations must provide appropriate viscosity at an acceptable temperature to provide convenient flow for uninterrupted delivery by peristaltic pump and for nozzle atomization. It has been referred in the literature that the viscosity of the melts should be lower than 300 mPa.s (Bose and Bogner, 2007) at temperatures not higher than 150 °C (Jones and Percel, 1994; Jannin and Cuppok, 2013; Achanta et al., 1997). Traditional film-coating polymers (hydroxypropylmethylcellulose, polymethacrylate, polyvinyl acetate phthalate, etc.) are too viscous to be employed as HMC agents (Rowe et al., 2012). Alternative materials whose apparent viscosity can be successfully decreased with temperature have been employed (Table 1).

Wong et al. investigated the viscosity-temperature relationship of twelve excipients that are suitable to be sprayed as a melt, from which eight were solid lipid excipients (Wong et al., 2016). First, the authors showed that at 10 °C above their melting point, solid lipid excipients exhibit Newtonian flow. Then, the authors reported that in solid lipid excipients there is an initial steep decrease of viscosity with temperature followed by a phase in which a further increase in temperature no longer produces a significant viscosity change. In contrast, the viscosity of the polymeric excipients studied (PEG and Poloxamer) decreased gradually with temperature (Wong et al., 2016). Fig. 1 compares the viscosity-temperature relationship of stearic acid, representing a solid lipid excipient, with PEG 3350, representing a polymeric excipient. The viscosity of the melt will impact the droplet size, therefore it is required to select a melt processing temperature at which the viscosity does not oscillate significantly.

In a further work, Wong et al. quantified the impact of PVP-VA, ethyl cellulose and ibuprofen on the viscosity-temperature behavior of solid lipid excipients (Wong, 2015). Both polymers increased exponentially the viscosity of the formulations, while ibuprofen appeared to reduce these viscosities. The high viscosity of the resulting melts limited the concentration of polymeric additives (< 10%). These authors derived the temperature-independent parameter Tp, which is correlated with the viscosity and the median droplet size. The application of this parameter in formulation optimization seems to be more valuable than simple viscosity at predetermined temperatures (Wong et al., 2016).

Coating materials with high viscosity require higher atomizing air pressure which can cause additional mechanical stress in the process chamber, resulting in the pulverization of fragile substrates (Gowan and Bruce, 1992; Lopes et al., 2016). Smaller substrates require smaller droplet sizes in order to promote a uniform coating and prevent sticking (Ronsse et al., 2008; Srivastava and Mishra, 2010). Nonetheless, if the coating droplets congeal prematurely, it will result in poor spreading onto the substrate surface, and even in non-adhesion which produces coating dust particles that can clog the filters (Jones and Percel, 1994).

3.2. Electrical resistance

Many substrate particles, especially smaller than 100 μm, are prone to adhere to machine surfaces as a result of static electricity. However, when spraying of certain coating formulations initiates, the static charge is dispelled (visually) and even very fine substrates fluidize

freely (Jones and Percel, 1994). Coating formulations that are poor conductors will retain the transferred charge (Eliasen et al., 1999) and the improvement of fluidization can be limited. The measurement of the electrical resistance of the coating melt may be helpful in the selection of the coating formulation. An electrometer and a measuring chamber made of polypropylene with parallel walls constructed of brass and polypropylene can be used to measure the bulk resistivity (Eliasen et al., 1999).

3.3. Crystallization of solid lipid excipients

Solid lipid excipients have been widely applied in HMC due to their optimal viscosity-temperature relationship that is intimately related with the fact that these are crystalline materials. The temperature at which the crystallization of the coating takes place will dictate the polymorphs and the structure of this polycrystalline matrix. This will impact critical dosage form attributes such as the mechanical properties and the drug release profile.

3.3.1. Polymorphism

The majority of solid lipid excipients contain glycerides that are known to crystallize into different polymorphic forms. These forms can loosely be described as α-form, β'-form and β-form, in order of increasing stability and melting point. They are characterized by their short d-spacing obtained by X-ray diffraction patterns as hexagonal (α-form), orthogonal (β'-form) and triclinic (β-form) (Fig. 2a). Additionally, all these forms have diffraction peaks at smaller angles which are referred as long d-spacing that are associated with the length of the molecule (Fig. 2b) (Idziak, 2012). Often, solid lipid excipients are a mixture of different components and the polymorphic behavior is more complex. In those excipients, melting range applies rather than melting point. A narrow range is advisable to prevent low melting fractions to agglomerate particles during process and during storage (Becker et al., 2015).

During a HMC process, the substrate is typically maintained 10–15 °C below the melting point of the α-form (Jones and Percel, 1994). When the melt droplets are spread onto the substrate at these temperatures, the nucleation of the α-form takes place (Fig. 3) (Lopes et al., 2015). This unstable crystalline form can transform into the more stable ones during process and/or during storage. If not controlled, it can cause polymorphic inhomogeneity from batch to batch or polymorphic transitions during storage. Due to the latent instability of the α-form, different approaches can be followed to obtain the coating in the stable β-form after the process. The crystallization of the most stable

form can be achieved by post-coating tempering (Chansaroj et al., 2007b), controlling the rate and temperature of crystallization during the process (Lopes et al., 2015) or by seeding with the β-form (Kakiguchi et al., 2003). Additionally, additives can be added in the coating formulation to promote the polymorphic stabilization at lower temperatures (Becker et al., 2016).

It is essential to investigate the thermal behavior of HMC formulations. It is good practice to characterize the thermal behavior of solid lipid excipients using differential scanning calorimetry (DSC). DSC thermograms provide useful information on the melting and the crystallization ranges that are necessary to select process parameters. Moreover, as different polymorphs have different melting points and enthalpies, the physical stability of the formulation can be characterized. Becker et al., used DSC to simulate the HMC process and predict the amount of polysorbate 65 required to promote the complete polymorphic stabilization of tripalmitin at low process temperatures (25–35 °C) (Becker et al., 2016).

3.3.2. Microstructure

While in film coating technology, the coating layer is typically in the amorphous state, in hot-melt coating the coating "shell" is a polycrystalline matrix (Rosiaux et al., 2015). At the nano- and meso-scale, the glycerides crystallites are lamellar structures with thickness thought to be 20–80 nm and lateral distances of 100–1000 nm (Fig. 2c) (Peyronel et al., 2015; Acevedo and Marangoni, 2010; Pink, 2012). These crystallites are arranged into spherulitic structures (Ueno et al., 2008) creating a polycrystalline matrix in which the minor components are trapped within nanospaces (Peyronel et al., 2015). The average crystallite thickness (D) of a lipid-based coating can be estimated from the first-order Bragg small angle X-ray scattering peak using the Scherrer equation (Acevedo, 2012). Relaxation nuclear magnetic resonance (NMR) and NMR diffusometry studies have described the evolution of glycerides crystal network microstructure (Adam-Berret et al., 2011). These studies could identify the decrease of the surface-to-volume ratio of the crystallites induced by Ostwald ripening and calculate the tortuosity of the sample.

The organization of the coating structure can be visualized by polarized light microscopy (Fig. 4a). In this case, sample manipulation is required and a hot-stage can be employed to simulate the HMC process (Lopes et al., 2017). Coated substrates can be analyzed by scanning electron microscopy (SEM) in which only the surface of coatings can be described. A typical surface phenomenon in glycerides is the so-called "lipid blooming" (Fig. 4b) (Lopes et al., 2015). This phenomenon has been connected with the polymorphic transition from unstable α-form

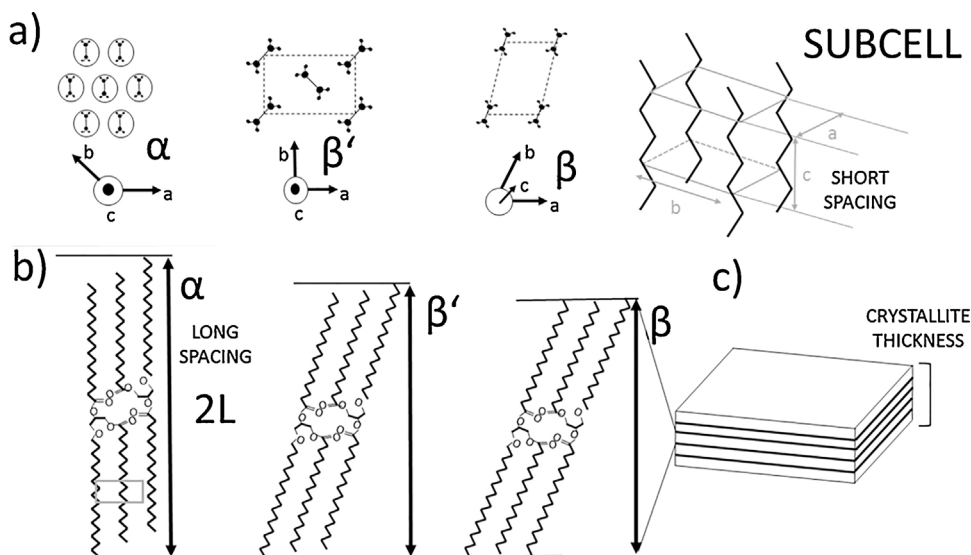**Fig. 2.** (a) Schematic of the three common subcells found in TAG polymorphs (α-, β', and β-forms). (b) Sketch of the vertical packing of TAG molecules in full extended two 2L (α-form) and in tilted 2L (β'- and β-forms). (c) Schematic 3D representation of a TAG crystallite showing the different lamellas packed together and the crystallite thickness dimension. Reproduced from Idziak, 2012.
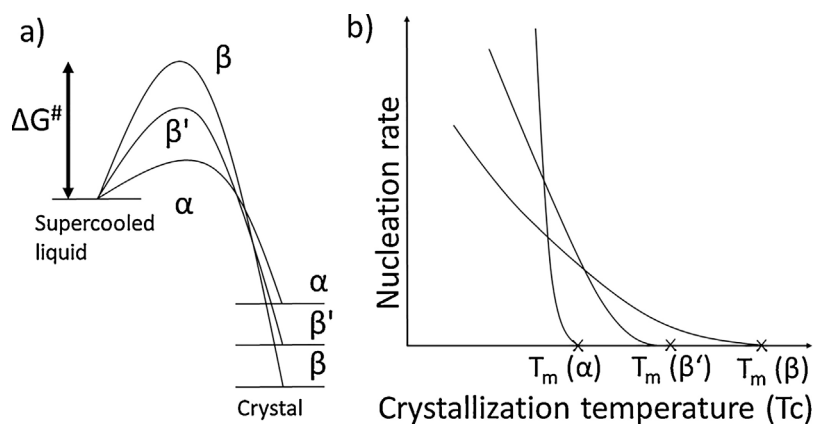
Fig. 3. Schematic illustraton of (a) activation free energy for nucleation (ΔG#) and (b) nucleation rate of α-, β', and β-forms of TAGs. Reproduced from Sato et al., 2013.

to polymorphs with increased stability (Mayama, 2009). Lopes et al. has shown that blooming can be avoided if HMC process is carried above the melting point of the α-form and the crystallization of more stable forms is induced (Lopes et al., 2015). However, the blooming and polymorphic transformation showed small impact on the drug release profile. More importantly, the size and organization of crystallites into spherulites dictated by the crystallization process dramatically affected the drug release (Lopes et al., 2015). Despite the stable polymorphism, the microstructure of solid lipids is dynamically evolving. This can negatively impact the drug release profile during storage, especially in the case of a solid lipid excipient/surfactant mixture (Lopes et al., 2017).

4. Properties of HMC formulations relevant for product performance

In order to save time and costs in the development of a coating formulation, it is important to screen critical coating properties before the actual coating process is carried out. The performance of coated products may be predicted by evaluating isolated coatings. Methods commonly used to prepare isolated coatings include casting and spraying techniques.

4.1. Water uptake, erosion and floating

Hydrophobic lipid-based coatings can be used to retard the drug release from the final dosage form. This is achieved by controlling the amount and rate of medium penetration into the drug core and the erosion of the coating layer itself (Rosiaux et al., 2015). Solubility parameters and HLB values can be used to quantify the hydrophilic character of the formulation (Griffin, 1954). However, the penetration of water from the dissolution medium is not only dependent on the chemical structure of the formulation but also on the microstructure and interaction in the solid state of the different components of the formulation. For example, even though the chemical structure is stable during storage, the drug release kinetic might change due to polymorphic or microstructural changes (Lopes et al., 2015, 2017). The study of the water uptake and erosion of a coating formulation stored at defined storage conditions will be a good indication of the drug release stability. Furthermore, the evaluation of water uptake and erosion can be used to predict the impact of the dissolution medium on the drug release profile (Siepmann et al., 2007).

As solid lipid excipients have a relatively low pycnometric density, are typically hydrophobic and can form a porous system, the hot-melt coated particles might float and be retained in the gastric compartment until complete drug release (Chansaroj et al., 2007a). This strategy can be followed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects of irritating drugs (Chen et al., 2014). However, this property can be unwanted in the development of enteric dosage forms and can result in unpredictable *in vivo* performance. The floating properties can be studied during water uptake and erosion studies. The time required to reach the water surface (floating lag time) and the period of time during which the film constantly floated on the water surface (floating duration) can be evaluated (Baumgartner et al., 2000).

4.2. Mechanical properties

The mechanical properties of coating layers are crucial in the designing of high quality coats, especially for sustained drug release in which coating cracks can promote burst release (Siepmann and Siepmann, 2008). Typically, lipid-based coatings have a high content of
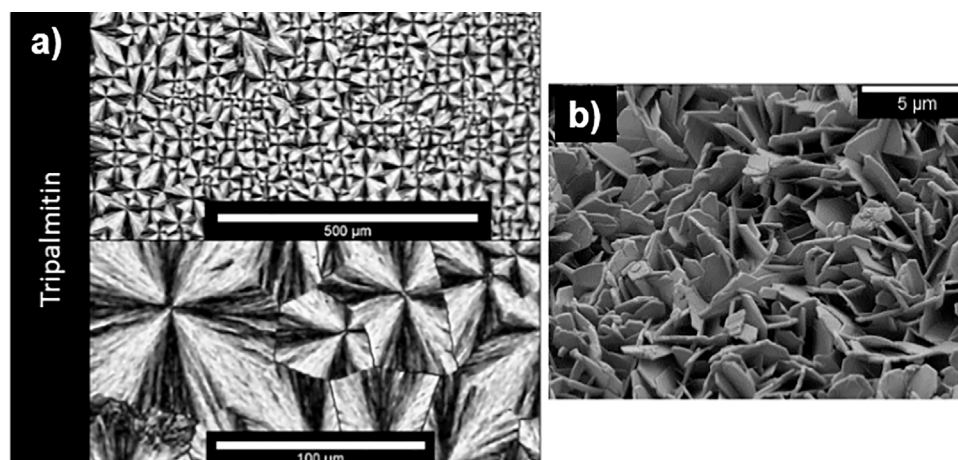

Fig. 4. a) Polarized light micrographs of tripalmitin at low and high magnification (from Lopes et al., 2017); b) Scanning electron microscopy micrographs of a tristearin coating showing lipid blooming (Lopes et al., 2015).

crystalline triglycerides resulting in reduced plasticity (Gonzalez-Gutierrez and Scanlon, 2012). PEGs and lower melting point fractions might act as plasticizers of solid lipids. However, mechanical characterization of pharmaceutical HMC coatings is not available.

Basic research has focused on the mechanical properties, including tensile strength, Young's modulus, and elongation (Gonzalez-Gutierrez and Scanlon, 2012). These mechanical data have also been used to make predictions regarding the long-term stability of coated dosage forms. Common methods used to evaluate mechanical properties of films include microindentor probe analysis, puncture and shear tests, and stress relaxation (Felton, 2007).

4.3. Water vapor permeability

Lipid-based coatings have been used as barriers to protect moisture-sensitive drug from atmospheric water and improve the stability of drugs that degrade by hydrolytic mechanisms (Chen et al., 2010). The water vapor permeability coefficient is used to evaluate the effectiveness of a particular coating as a barrier to water. Water vapor permeability is commonly evaluated using water sorption/desorption isotherms determined by Dynamic Vapor Sorption (DVS).

4.4. Adhesion

Poor adhesion between the film coating and the surface of the substrate may result in flaking or peeling of the coating from the solid substrate during storage, which could significantly jeopardize film functionality (Felton, 2007). On the other hand, reduced adhesion between the coating and the oral mucosa improves the ease of swallowing (Smart et al., 2015; Drumond et al., 2017).

In pharmaceutical products, the strength of interfacial bond that affects adhesion is primarily affected by hydrogen bond formation. Dipole-dipole and dipole-induced interactions also occur to a lesser extent. Factors that affect the type or the number of bonds formed between the coating and the solid surface will influence coating adhesion. Therefore, the adhesion of non-polar lipid-based excipients to the substrate may result in poor adhesion. The surface roughness of the substrate can improve the coating adhesion. The peel test or the butt adhesion test can be implemented to assess the coating-substrate adhesion (Felton, 2007).

4.5. Volume contraction

The volume contraction of a HMC formulation can be characterized by dilatometry. The change in volume with temperature has been studied for oils and fats and informative tables can be found in the literature where the expansivity (ml/g/K) and the melting dilation (ml/g) are available for glycerides and fatty acids (Craig, 1957). The volume contraction upon crystallization is the consequence of a more dense packing mass at several scales and is connected with the polymorphism and microstructure. High stable polymorphic forms show the most dense structuring and therefore higher degree of volume contraction (Ehlers, 2012).

It might be expected that a high degree of volume contraction will promote coating defects. In that case the addition of non-crystalline excipients may be able to "repair" small defects caused by volume contraction (Khan et al., 2014).

5. Conclusions and future perspectives

HMC provides unique technological advantages over the state of the art solvent coating techniques resulting in a more economic process. However, the HMC formulations have been limited to solid lipid excipients and their inherent crystalline behavior poses a new paradigm in coating technology. Development of HMC formulations have shown that drug release profiles can be easily tailored, nevertheless much

development work is required to provide excipients with stable solid-state behavior, ensuring the stable shelf-life of pharmaceutical products. Moreover, a mechanistic understanding of the macroscopic properties, essential for advanced and stable coating behavior, is missing. Providing portfolios of HMC excipients with defined coating properties is an unmet requirement for establishing HMC as advanced coating technology for manufacturing of pharmaceutical products.

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