Drug Development and Industrial Pharmacy, 23(5), 441-449 (1997)

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Development of Hot Melt Coating Methods

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EVOLUTION OF PHARMACEUTICAL COATING TECHNOLOGY

Modern pharmaceutical coating, as practiced today, is a mature and routine pharmaceutical unit operation which facilitates efficient modification of biopharmaceutical properties, organoleptic properties, and/or stability of various dosage forms. The evolutionary course of coating technology to its current status in pharmaceuticals spans over this century and deserves mention at the outset of this review. Van Savage and Rhodes recently published an excellent historical review of developments in sustained-release coating technology of tablets (1). Similar reviews offering comprehensive description of tablet coating have also been published by Seitz et al. and Porter (2,3).

The origins of modern pharmaceutical coating can probably be traced back to the confectionery kitchens of the early 19th century (4). Pharmacists of that period adopted the "art" of pan coating from confectioners and used it primarily to increase the palatability of bitter medicaments. Also, coating was done as part of extemporaneous compounding in small batches, and no specialized equipment was available. By the end of first half of this century, the art of sugar coating had been perfected and became the standard of that period. Yet, there were few developments of great significance in coating technology during that period.

The introduction of film coating in 1953 probably marks the onset of "the era of contemporary pharmaceutical coating." This introduction along with innovations in the area of polymeric coatings and development of precise and efficient coating equipment facilitated the rapid transformation of coating technology from a skilled art into a science-based, versatile unit operation in pharmaceutical formulation. The inception of perforated pans and fluid bed coaters provides, arguably, the most significant milestones in the design of newer coating equipment and allow for precise, efficient, and elegant coating of a variety of dosage forms irrespective of batch size. Alternatively, many different polymers have also been evaluated in the past four decades, but the three which remain most popular even to this day are: cellulose acetate, ethylcellulose, and methacrylic acid copolymer.

Apart from the quest for superior performance, an important determinant in the evolution of contemporary coating technology has been the dynamic regulatory environment in the pharmaceutical community. Compliance with requirements of regulatory agencies such as the U.S. Food and Drug Administration (FDA), Envi-

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ronmental Protection Agency (EPA), and Occupational Safety and Health Administration (OSHA) has strongly influenced progress in this area. The clear shift to aqueous polymeric coatings in recent years can be substantially attributed to regulatory compliance, among other factors.

But even aqueous polymeric coating methods suffer from some shortcomings and certainly are not the "end." In the present environment of global competition and cost containment in the pharmaceutical industry, it is necessary to develop novel coating processes which are simple, efficient, precise, and cost-effective, and allow easy compliance with regulatory requirements. Under such demanding circumstances, the promise of hot melt coating methods is attractive and their development forms the central theme of this article.

HOT MELT COATING METHODS

Introduction

Traditionally, almost all coating methods require the use of solvents in which the coating material is either dissolved or dispersed. Initially, organic solvents were in vogue, but stringent regulatory constraints have been responsible for changing the preference to aqueous-based coating systems.

In hot melt coating methods, the coating material is applied in its molten state over the substrate. Hence, the necessity for the use of any solvent is fully eliminated. Lipids, waxes, and fatty bases are the most suitable coating materials in hot melt coating and are discussed later. This strategy of applying coating material in molten form offers several benefits and potential for a wide variety of applications in pharmaceutical formulation.

Advantages and Disadvantages

Hot melt coating methods offer many advantages over current and conventional coating techniques. Firstly, hot melt methods do not require the use of a solvent (aqueous or organic), deeming them unique solvent-free coating techniques. As there is no solvent to be evaporated, the processing times are much shorter than for current practices. Consequently, the tedious and expensive processes of solvent disposal/treatment associated with organic solvents are eliminated. Also, the routine of compliance with regulatory directives for the use of organic solvents is fully precluded, making hot melt coating environment-friendly.

Although aqueous-based coating systems are currently in vogue, they are not completely flawless. The irresolvable difficulty encountered with aqueous coating systems is the validation of coating dispersions for control of microbial presence. In fact, it is almost impossible to control microbial presence or growth in coating dispersions without any compromise. Hot melt coating methods do not suffer from any such shortcomings. Further, the required weight gains with lipid materials are lesser than those commonly employed with polymers to achieve the same effect. Existing coating equipment such as a fluid bed coater can be easily modified to suit the requirements of hot melt coating. As lipid-based coating materials are relatively inexpensive and processing times are short, hot melt coating is also cost-effective.

A difficulty in hot melt coating methods is maintaining adequate operator safety, as high temperatures, close to 200°C, are employed. Hence, adherence to safety and protective measures is important during coating. Also, the in vivo fate of lipidic coating material should be investigated.

Potential for Application

The potential for application of hot melt coating in pharmaceutical formulation is enormous. The applications of hot melt coating may be broadly categorized as:

1. Improvement of palatability of dosage forms.
2. Prevention of environmental degradation of dosage forms.
3. Retardation of drug release from dosage forms.

Prevention of environmental degradation comprises protection from physical degradation (light, humidity), protection from drug incompatibilities, and protection from physiological degradation (enzymatic breakdown in stomach, pH sensitivity). Controlled release of drug is probably the most popular objective of hot melt coating and is, hence, the main theme of this review.

Challenges in Development

Development of hot melt coating methods offers the following challenges:

1. Investigation of the batch variability of lipidic coating excipients and development of methods for evaluation of raw material.
2. Physicochemical characterization of coating excipients and evaluation of their functionality.

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3. Investigation of thermal behavior of lipid coating excipient and its interaction with the drug in the formulation.
4. Characterization of coating equipment for hot melt coating.
5. Investigation of drug release characteristics from the coated substrates.

DEVELOPMENT STRATEGY

This section attempts to describe the multitude of factors which require critical investigation in the development of hot melt coating methods. The physicochemical behavior of coating excipients and efficiency of coating process are probably the two most important considerations in hot melt coating. Hence, these topics form the focal point of the discussion below.

Coating Excipients

The hydrophobic coating materials (lipidic excipients) which are suitable for application in hot melt coating comprise waxes, fatty bases, and hydrogenated vegetable oils. The choice of the coating excipient depends primarily on its "function" (such as retardation of drug release rate, prevention of environmental degradation, and masking of unpalatable taste) in the dosage form. This discussion primarily focuses on hot melt coating aimed at retardation of drug release rate from the formulation.

Chemical Nature

The coating excipients most suitable for application in hot melt coating fall under the category of fats and waxes. Chemically, fats and waxes are hydrophobic substances consisting predominantly of glyceryl esters of fatty acids, also known as triglycerides. A triglyceride is the reaction product of 1 molecule of glycerol and 3 molecules of fatty acids to yield 3 molecules of water and 1 molecule of a triglyceride. If the three fatty acids are identical, the product is a simple triglyceride; when they are dissimilar, it is a mixed triglyceride. The chemical reaction in Fig. 1 shows the formation of a triglyceride. Structural isomers of the same triglycerides can be observed depending on the site of ester linkage and nature of the fatty acid. Monoglycerides and diglycerides can also be obtained if all the three hydroxyl groups of glycerol have not been esterified by the fatty acid.

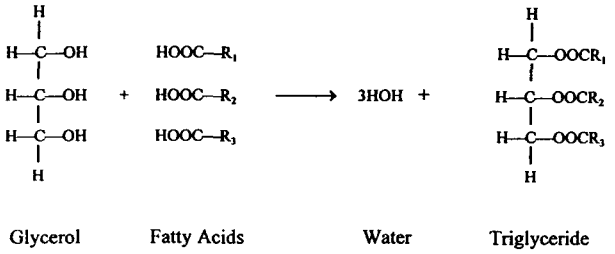

Figure 1. Formation of a triglyceride, where R_1, R_2, and R_3 denote any alkyl group.

Ideal Characteristics

The excipient characteristics ideally desired for application in hot melt coating are:

1. It should not undergo physical or chemical degradation at temperatures below 200°C.
2. It should have a melting point in the 75°–80°C range.
3. Its melt transition should occur over a narrow temperature range and it should not soften before melting.
4. Its thermal behavior in the range of 30°–200°C should be independent of the preparation, storage conditions, and thermal history.
5. It should not undergo any crystal modifications when subject to temperatures as high as 200°C.
6. It should be stable when subject to repeated heating–cooling cycles.
7. It should be available in varying HLB values.
8. Its melt viscosity should facilitate easy flow and spray.

It is difficult to find an excipient which has all the above properties, and hence, the pharmaceutical scientist should exercise careful discretion in choosing the right excipient. Additionally, the coating excipient should have the necessary regulatory approval for use in pharmaceuticals.

Suitable Commercial Excipients

For sustained-release applications, coating excipients of special interest can be divided broadly as:

1. Natural and synthetic waxes
2. Hydrogenated vegetable oils
3. Polyglycolyzed glycerides

Table 1 lists a few coating excipients, along with their commercial sources, found favorable for hot melt coat-

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Table 1

Suitable Commercial Lipidic Excipients for Hot Melt Coating

Coating Excipient	Category	Commercial Source
Gelucires	Polyglycolyzed glycerides	Gattefosse
Stearines	Hydrogenated vegetable oils	Quest
Myvaplex 600	Glyceride	Eastman
PEG family	Ethylene glycol polymers	Union Carbide
Carnauba wax	Natural wax	Frank B. Ross
Ross wax #100	Synthetic wax	Frank B. Ross

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ing in our experience. Gelucires are a class of polyglycolyzed glycerides supplied by Gattefossè. Gelucires are specified by their melting point and HLB value (Gelucire 50/13 melts at 50°C and has an HLB value of 13), and various combinations of melting point and HLB value are available. Stearines are a family of partially hydrogenated vegetable oils and are used for "structuring" in the food industry.

Physicochemical Characterization and Excipient Functionality

> [P]harmaceutical scientists have become increasingly aware of the fundamental effects that excipients can exert on the bioavailability, bioequivalence, and stability of formulations; excipients can no longer be regarded simply as 'inert' or 'inactive' substances. (From *Handbook of Pharmaceutical Excipients*, 2nd ed., 1994)

The above statement demonstrates the importance of, and need for a thorough investigation of the functional effects of the excipient in dosage form development. Also, it is desirable to identify and examine excipient properties to which its "functionality" is sensitive. Such information would be a useful tool in engineering the performance of the dosage form. In this regard, the following excipient properties deserve special attention in the development of hot melt coating methods.

Molecular Weight and Hydrophobicity

Waxes are complex mixtures of high molecular weight organic compounds. But molecular weight of the glyceryl portion (C_3H_5) of a triglyceride is only 41. Hence, the remaining portion of the triglyceride (fatty acid residue) contributes greatly to the overall molecular weight. Molecular weight is a key physicochemical parameter and can provide information about the strength, flexibility, and rheological behavior of the material. It can also be correlated to the ability of the excipient to retard drug release.

Hussain and coworkers reported a simple method for the determination of molecular weight averages of fats and oils using size-exclusion chromatography (SEC) (5). They used SEC to determine the weight average (M_w), number average (M_n), and the Z average (M_Z) of various fats. Size-exclusion chromatography is a well-accepted technique to characterize synthetic polymers and has been extensively reviewed by Barth and coworkers (6). Size-exclusion chromatography studies were also employed by Arroyo et al. and Sánchez-Muniz et al. in the evaluation of sunflower oil (7,8).

Because of their preponderant weight in the glyceride molecules, fatty acids greatly influence the physical and chemical nature of glycerides. Any contributions that a fatty acid makes to hydrophobic character of triglycerides are limited to the amount of hydrophobic character in the fatty acid itself (9). Acid number and saponification number of waxes have been used as measures of interbatch variability. Acid number is defined as the number of milligrams of potassium hydroxide required to neutralize the free acids in 1 g of the substance, and saponification number is defined as the number of milligrams of potassium hydroxide required to neutralize the free acids and saponify the esters contained in 1 g of the substance (10). Hence, knowledge of acid and saponification numbers is useful in understanding the fatty acid moiety of the wax.

Thermal Behavior

Hot melt coating requires melting of the coating excipient and exposure to high temperature (about 200°C). Hence, complete investigation of the excipient's thermal behavior is important. Such an investigation should aim at elucidating the effects of thermal treatment of the excipient on:

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1. Physicochemical drug–excipient interactions
2. Excipient's ability to retard drug release rate
3. Stability of the dosage form

From this perspective, thermal and polymorphic behavior of the excipient, which are closely interrelated, deserve special attention (11).

Literature describing analytical techniques and methods for studying the thermal behavior of fatty waxes and glycerides has been widely published (11–17, 19–21). However, such reports have focused on thermal behavior and its significance in the formulation of suppositories, creams, and matrices for controlled release. But such methods can be appropriately modified to serve as investigative tools in the thermal characterization of excipients in hot melt coating.

Flaherty reported, in 1971, the application of differential scanning calorimetry in the characterization of hydrocarbon and natural waxes (12). Craig has recently reviewed thermal techniques to characterize materials in the solid or the molten state (13). This review focused on the utility of differential scanning calorimetry in studying the structure and properties of polyethylene glycols. He reported that differential scanning calorimetry is a highly versatile thermoanalytical technique. Simon and Süverkrüp performed a comparative evaluation of current techniques to characterize fatty bases (14). Busfield and Proschogo investigated the thermal properties of palm stearine using differential scanning calorimetry (15,16). They demonstrated that thermal treatment controls the physical state of palm stearine. They also found that heating rate influences nature of the transition the material can undergo and its observation during a differential scanning calorimetry scan. Craig and Newton reported the suitability of differential scanning calorimetry to detect solid-state changes in materials and thus facilitate their standardization (17). Létoffé et al. described the application of differential scanning calorimetry in conjunction with thermomicroscopy to study waxes in the crude oil industry (18). They reported that thermomicroscopy is useful in correlating morphological or structural changes with thermal effects observed by differential scanning calorimetry.

The report of Ginés et al. elaborating the interactions between cinnarizine and gelucire 53/10 further justifies the value of differential scanning calorimetry in investigating drug–excipient binary systems (19). This report employed differential scanning calorimetry and hot stage microscopy to demonstrate the ability of molten gelucire 53/10 to dissolve cinnarizine crystals. Sutananta and coworkers described the effects of aging on the thermal behavior of the gelucire family of excipients (20,21). These reports investigated the long-term stability of gelucires and heat treatment methods which accelerate the transformation to equilibrium form and structure of these glycerides.

Thus, differential scanning calorimetry can be employed to investigate the thermal behavior of excipients in hot melt coating. But investigations should be modified to reflect the appropriate temperature range of operation. Also, the behavior of excipients upon repeated heat–cool cycles should be investigated as such thermal treatment is likely to be employed during hot melt coating. Kotsiomiti and McCabe studied the stability of dental waxes upon repeated heatings (22). Thus, effects of thermal treatment on the excipient and subsequent drug–excipient interactions require complete examination in the development of hot melt coating methods.

Polymorphic Behavior

Most organic molecules can crystallize in several different ways, and these different lattice configurations of the same molecule are called *polymorphs* (23). Each of the structural isomers resulting from the esterification of glycerols by fatty acids can exist in alpha (α), beta prime (β'), or beta (β) polymorphic forms (11). The variability encountered in the observation of transition temperatures and melting point of triglycerides and fatty bases has been partially attributed to such complex polymorphism. In general, the morphology of glycerides is strongly dependent on thermal history of the samples. To a certain extent the morphology can be controlled by tempering or annealing (heating the material at a temperature higher than the melting point for a specified time duration) and the rate of cooling from the molten state (15). Also, it is well known that polymorphic changes can influence the intrinsic dissolution rate and other solid-state properties of materials (24). Hence, it is worthwhile to investigate the polymorphic behavior of excipients in hot melt coating.

DeMan and others studied the polymorphic behavior of hydrogenated oils using differential scanning calorimetry and x-ray crystallography (25). They investigated the crystallization temperatures of various oils. Busfield et al. also described the crystalline modifications in palm stearine and correlated these changes to thermal conditions (15). Hagemann and Tallent examined the polymorphism of 13 single-acid triglycerides as a function of the acyl group chain length and unsaturation using differential scanning calorimetry (26). Coben and Lordi

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employed x-ray diffraction and differential scanning calorimetry studies to characterize amorphous-to-crystalline transitions in several semisynthetic suppository bases (27).

Yap and coauthors reported a study comprehensively describing the polymorphic behavior of palm oil and related compounds (28). Simon and Süverkrüp also reported an isothermal variant of differential scanning calorimetry to study the crystallization of fatty suppository bases (14). They concluded that the crystallization behavior of fatty bases is a biphasic process, where the content of partial glycerides and the extent of supercooling determine the formation of crystal nuclei while final solidification level depends on the crystallization temperature.

Rheology in Molten State

As the lipidic coating excipient is spray coated on the substrate in its molten state, an investigation of the rheological behavior of the coating material and its temperature dependence is required. Primarily, the melt viscosity of the coating excipient should facilitate convenient flow for uninterrupted delivery by a peristaltic pump and spray in the coating chamber. Hence, it may be necessary to spray the coating material at temperatures of about 60°–75°C above its melting point.

Bourret and coworkers studied the rheological behavior and its variation with temperature of the gelucire family of excipients (29). They reported that the apparent viscosity of these glycerides decreases exponentially with temperature and follows an Arrhenius-type relationship. In our experience, we have found that an optimal combination of flow pattern and temperature of the coating material needs to be achieved for efficient coating.

Coating Process

Modification of Coating Equipment

Typically, any fluidized-bed coating equipment can be modified to suit the needs of hot melt coating. Detailed evaluation of coating equipment and related processing conditions, including fluid bed equipment, has been reported by Mehta (30). In our experience, we have found the top-spray fluidized-bed coater to be most suitable for hot melt coating, due to its ability to operate with product temperature closest to the congealing temperature of the molten excipient. However, the use of a Wurster column in the fluid-bed coater can also be employed.

The changes made in existing equipment to facilitate hot melt coating should allow delivery of the molten material on the substrate in the fluidized bed without any discontinuity due to solidification or hardening of the melt. This can be achieved by the passage of hot air to envelop the delivery tube in the spray nozzle through which the molten coating material passes before being atomized and sprayed on the substrate. We have used an electric heating tower to obtain the hot air supply. Also, the tube delivering coating material from the reservoir to the spraying gun should be maintained at high temperature to prevent hardening of the molten coating material. A heating device to control the temperature of the coating material in the reservoir is also necessary. The spray gun inside the expansion chamber should be well insulated. This is required to prevent the remelting of coating material on the substrates, when they come in contact with the spray gun while falling back into the bed. A schematic sketch of the modified coating equipment used by us is shown in Fig. 2.

Excellent reviews of the processing conditions and the characterization of coating equipment for hot melt coating have been published by Jones et al. and Jozwiakowski et al. (31,32). Jozwiakowski and coworkers stated that increasing the length of the expansion chamber, making it conical in shape, and providing an alternate filter shaking facility to avoid interrupting fluidization in a conventional fluid bed coater is required for hot melt coating.

Statistical Experimental Design and Optimization

The application of optimization techniques to pharmaceutical systems has been thoroughly discussed by Schwartz et al. (33). Mathematical optimization techniques allow control of variability in desired responses and facilitate precision in product quality. Generally, optimization protocols in pharmaceuticals follow the completion of data collection based on a predetermined set of experiments. The generation of data for use in optimization protocols through rational experimentation forms the subject of statistical experimental design. Although a variety of experimental designs have been employed, the factorial design or some variation of it (full or fractional factorial) is probably the most popular design. Factorial designs allow the identification of both the main and interaction effects of factors. Statistical experimentation and multiple regression techniques allow correlation between the effect of a causative factor over a certain range and the responses of interest.

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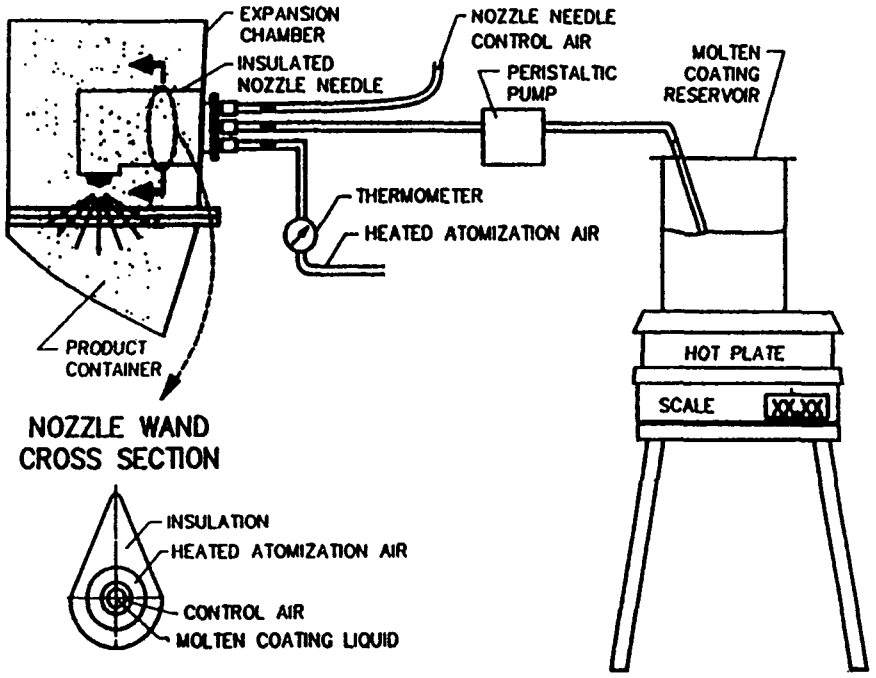

Figure 2. Modifications to a conventional fluid-bed coater to suit hot melt coating and cross section of insulated spray nozzle wand.

However, causative factors and their ranges of operation should be empirically chosen.

Several reports of application of optimization techniques to pharmaceutical systems have appeared recently (34–38). Renoux and coworkers employed a full factorial experimental design to improve the industrial production of tablets by direct compression (34). Khan et al. reported the application of a second-order Box–Behnken design to optimize the levels of polymer, diluent, and the compression force in the formulation of controlled-release tablets (35). The use of experimental design in the study of ruggedness and robustness of analytical methods in validation of assays has been reported by Torbeck (36). Bouckaert and coauthors have published the optimization of a wet-granulation procedure using central composite and full factorial designs (37). We have recently employed response surface methodology and multiple regression to control and counteract the inherent variability in the determination of wet-granulation end point and the effect of such variability on tablet properties such as friability, hardness, and disintegration time (38). Röscheisen and Schmidt investigated the effects of compression force and lubricant concentration on the lubricant effectiveness, disintegration time, and hardness of effervescent tablets using simplex optimization and two-factor full factorial design (39).

Thus, experimental design and optimization protocols are valuable tools to rationally, efficiently, and scientifically refine formulations and processes. Their utility and value in hot melt coating is indisputable and is discussed in the next section.

Optimization of Coating Process

Jones and Percel cite the product bed temperature and droplet size of the molten material being sprayed as key process variables in hot melt coating using a top-spray fluid-bed coater (31).

The temperature in the coating zone determines the adhesion to, and spreading of the coating material over the substrate. If the temperature is very high the coating material may not adhere to the substrate, whereas if it is too low, it may not spread on the substrate. This in turn affects the surface properties of the coated substrates and, hence, the nature of drug release from them.

Droplet size and its uniformity is very important. Droplet size is influenced by the atomization air pressure, viscosity of the molten coating material, and the spray rate. Typically, droplet size should be smaller

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relative to the substrate size for effective coating. Higher atomization pressure leads to smaller droplet size. As discussed earlier, the melt viscosity should facilitate satisfactory atomization. Spray rate affects the coating quality and the degree of agglomeration. Other important process variables are temperature of the molten material and atomization air, batch size, and substrate size. Hence, an optimization protocol for hot melt coating should include all these process variables in the experimental design, so that their effects can be systematically studied.

Jozwiakowski and coworkers employed a modified central composite design to optimize the release rate from a hot melted coated formulation (32). They coated drug-loaded sugar beads with Stearine 07. The independent factors in their design were temperature of atomization air and molten wax, spray rate, and atomization air pressure; and the measured responses included bulk density, flow, and percentage drug dissolution. They used multiple regression, response surface methodology, and contour plots for optimizing the measured responses.

CONCLUSION

The stringent regulatory environment and the ever-changing requirements of the pharmaceutical industry have, once again, determined the evolutionary course of modern pharmaceutical coating technology. The unique feature of hot melt coating methods is that they do not require the use of any solvent, and this probably marks the advent of "the era of solvent-free coating techniques." The promise and potential of hot melt coating methods is very attractive. It is believed that the efforts of researchers will help circumvent challenges in the development of these coating techniques and lead to further beneficial innovation.

ACKNOWLEDGMENT

The generous financial support and access to library and laboratory resources provided by SmithKline Beecham Consumer Healthcare to A.S.A. is gratefully acknowledged.

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