INVESTIGATION OF PHYSICO-CHEMICAL PROPERTIES OF LIPID-BASED EXCIPIENTS IN A HOT-MELT FLUID BED COATING PROCESS

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ABSTRACT OF THE THESIS

Investigation of physico-chemical properties of lipid-based excipients in a hot-melt fluid bed coating process

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Fluidized bed coating process is widely used in the pharmaceutical industry. In the case of lipid-based excipients as a coating material, the coating process requires an additional operation of melting the coating material prior to its application. Thus the process is said to be a hot melt fluid bed coating process. The objective of this study is to understand the hot-melt fluid bed coating process for coating of lipid-based excipients onto drug crystals to produce orally disintegrating granules. Orally disintegrating granules are a 'direct to mouth' dosage form and offers better patient compliance by making it easier to swallow the medication in the form of granules. However, for such dosage form, it is imperative to have a drug product with an immediate release profile and a good taste masking to mask the unpleasant taste of the active ingredient. In this work, a parametric study using a fractional factorial design of experiments was carried out to understand the influence of process parameters on thickness of the coating layer, dissolution rate of the API and taste masking ability of the coating material. With the help of analysis of the factorial design, an optimal design space to achieve desired quality of the drug product was found. In this work, in addition to the parametric study, an experimental study to understand polymorphism of the coating layer was also performed. Lipids tend to exhibit polymorphism. The presence

of an unstable crystal form in the product may result in storage instabilities and in turn affect the dissolution rate of the drug. Therefore, the influence of fluidization air temperature and emulsifier content on polymorphism of the coating layer was studied in detail. Thermal analysis of the coated granules helped understand the melting and crystallization behavior of different polymorphs exhibited by the coating layer. The results of this work suggests that a more detailed investigation of kinetics of crystallization and phase transformation of lipids is required for its application as a coating material for pharmaceutical products.

DEDICATION

This dissertation is lovingly dedicated to my parents, Santosh Hate and Snehal Hate for their constant love, encouragement and support throughout my life.

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CHAPTER 1

INTRODUCTION

1.1 Overview of the fluid bed coating process

The coating process is one of the fundamental unit operation practiced in several chemical engineering industries such as pharmaceuticals, food, detergent, cosmetics, fertilizers, etc. that handle solid particulate materials. This process is generally required to protect powders or particulate matter from the environment, to improve appearance, taste or odor, to delay or control the release of active ingredients or to functionalize powder [20]. The coating thickness can vary from nanometers to micrometers depending upon its purpose. There are different ways to introduce coating agent in the system: dispersed or dissolved in a solvent, molten or applied in the form of very fine dry powder. The introduction of a liquid in a particulate system leads to formation of liquid bridges between wetted particles and results in agglomeration of particles. More resistant agglomerates are formed by solidification of the coating material, which is usually promoted by heating or evaporation of the solvent or by cooling of the coating material in the case of melt coating. However distinction between coating and agglomeration is difficult. Depending on the expected effect of size enlargement or achieving specific functionalities, the coating process is called as agglomeration or coating respectively. In order to achieve coating of particulate material, particles must be thoroughly mixed and the coating material must be applied to the moving bed particles efficiently. Particle mixing can be carried out either by

mechanical actions (rotating drums or pans) or by combination of mechanical and pneumatic actions (fluidized beds, spouted beds) [20].

The most widespread equipment for coating of the solid particles in the industry is a fluidized-bed coater. In a fluidized bed, air used to raise particles in the bed and the flow rate of air is determined by particle minimal fluidization velocity to ensure homogeneous partition of all the bed particles. The coating solution is continuously sprayed onto particles using a nozzle and the particles receive some amount of coating material every time they pass through the spray zone in the fluidized bed [4]. Particle growth occurs either by coalescence of two or more particles or by layering of solids onto the surface of particles. Coalescence refers to two or more particles coming in contact with each other to form a single particle. Layering includes bonding of additional finer particles onto existing granules. In case of coating process, particle growth is by surface layering wherein the wetted particles dry sufficiently before collision and thus avoid agglomeration. This mechanism is a slow and an even growth process which creates well rounded and uniform granules with an ‘onion skin’ layered structure [8]. In order to achieve particle growth by the surface layering mechanism, the fluidized bed coating process needs optimal process control.

The fluidized beds, in addition to desirable characteristics of isothermicity, high heat and mass transfer rates and good particle mixing, allows elementary operations such as wetting, mixing, evaporation, drying or solidification and granulation (size enlargement or agglomeration) to be carried out in a single piece of apparatus. Therefore contrary to

coating technologies such as rotating drums or pans, there is minimal need for subsidiary drying units for evaporation of solvents. However, along with these advantages, there are some disadvantages of fluidized beds that may limit successful operations [5]. Improper process design can result bed quenching, wherein excessive particle growth occurs and the minimum fluidization velocity of granules exceeds the operating velocity or wet agglomerates are formed and they are too strong to be fragmented and too large to be fluidized. There is also a possibility of occurrence of spray congealing (solidification of molten coating material before deposition onto the solid particles). Subsequent formation of larger agglomerates can lead to defluidization phenomena and change the behavior of fluidized bed. Higher values of operating parameters can cause the spray congealing effect and lead to non-uniform or thin coating deposition on the solid particles and loss of coating material due to deposition on fluid bed wall [5, 6]. In this complex process of fluid bed coating, several process and product variables affect the product quality. Hence, to obtain optimal process design, it is imperative to study the influence of each of the process variable on the final product attributes.

The fluidized bed coating process has been known and used in industry for past several years. There is considerable literature available on investigation of process variables on performance of fluid bed systems. Link and Schlunder [8] developed an experimental set-up to investigate the particle-forming mechanism in a fluidized bed and observed that droplet momentum and concentration of suspension influences the adhesion probability, thus affecting the particle-growth rate. Saleh et al. [3] and Hemati et al. [5] studied the influence of fluidizing gas velocity, atomizing air and liquid flow rates, liquid

concentration, initial bed mass and particle size on growth rate, operation efficiency and agglomerate fractions. They concluded that fluidizing gas velocity is the most important factor affecting the coating efficiency. They also suggested that a decrease in initial particle size lead to higher rate of agglomeration due to stronger inter-particle adhesive forces. With respect to initial particle size distribution, it was noted that a narrow particle size distribution leads to an excessive formation of agglomerates. On the other hand, in the case of a relatively broader size distribution, the particle growth is mainly controlled by the layering mechanism [20]. Hemati et a.l [5], in addition, reported that increase in air humidity resulted in an increase in agglomeration. Moreover, they noted that for a higher particle porosity, a non-growth period was observed, attributing it to sprayed solution being deposited inside pore volume. The effect of fluidizing velocity and concentration of the coating solution on the growth rate was pronounced in the case of porous particles [20]. Hede et al. [11] investigated the influence of coating solution viscosity, pH and stickiness on the tendency of agglomeration. A salt solution showed lower tendency of agglomeration than a polymer solution. The increase in mass fraction of hydrophobic component in the coating formulation reduced the tendency of agglomeration [20]. Viscosity has an influence on atomization behavior of the liquid and larger droplets were observed with increase in viscosity. In addition, viscosity also affects quality of deposition. In the case of high viscosity liquids, the evaporation of liquid takes place before equilibrium contact angle is reached [20]. The influence of properties of coating solution was found to be closely related to humidity and temperature in the fluidized bed. Experimental studies were carried out by Maronga and Wnukowski [9] to investigate the temperature and humidity profiles in fluidized bed coating process. They developed a procedure to deduce the

distribution of temperature, pressure and humidity in different parts of bed. This study of temperature and humidity profile is an important tool in process optimization as it was found that different fluidizing temperatures may result in coating layers with different characteristics, even for the same coating material [10].

1.2 Introduction to a hot-melt fluid bed coating process

Although several authors have reported a thorough study of fluid bed coating process, the influence of process variables varies with growth kinetics, local conditions, and number of components [7]. In the literature cited above, the coating material generally required the use of solvent for dissolving or dispersion. The organic solvents offer faster evaporation, however these solvents are expensive, flammable and toxic. This calls for solvent disposal/recovery and safety issues and add to the processing cost. A simple, efficient, cost-effective alternative is to use of molten lipid-based excipients as coating material. For such solvent-less coating, the hot-melt coating process affords several benefits and potential for wide variety of applications in pharmaceutical industry [12]. In this process, the coating material is kept in its molten form and sprayed onto the substrate. It is a rapid process as coating material is applied directly onto the particle within very short time. Hot-melt coating can be carried out in two ways. The first consists of spraying a hot melted material in a cooled bed of particles, in which it has sufficient time to spread before solidification. The second procedure includes introduction of coating material in the system prior to coating operation in powder form and then heating up to a temperature close to the melting temperature of the coating material at limited regions of the bed. This results in spreading of molten coating material over the bed particles and further

solidification of the deposited coated layer. The former procedure is more widely used in the pharmaceutical industry.

Jozwiakowski et al. [13] studied the hot melt coating process in a fluid bed unit with top-spray technique to coat hydrogenated cottonseed oil on sugar based granules. They used response surface methodology to estimate optimum operating conditions for dissolution, particle size and coating density. Higher atomizing air pressure and slower spray rate resulted in less agglomeration and particle size of coated granules was found to be directly proportional to spray rate and inversely proportional to atomizing air pressure. Barthelemy et al. [14] investigated a novel hot melt coating agent in a bottom-spray fluid bed granulator. They observed that hot melt coating techniques are useful for both spheroidal particles and granules despite of differences in density, porosity and surface properties. The most important parameters were found to be molten lipid temperature and atomization air pressure. In a study conducted by Knezevic et al. [15], process parameters of hot-melt fluid bed coating were optimized and a design space was proposed, considering 'Quality by Design' concept wherein it is important to build quality into a product with an understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. They studied the influence of amount of lipid in the formulation on rate of drug release concluding that granule composition influenced the drug release pattern and increase in amount of coating reduced the release rate. Kulah and Kaya [16] explored the hot-melt coating process in fluid bed for coating of fine powder of Cefuroxime Axetil

with stearic acid. They also developed a thermodynamic model of mass and energy balances for scaling up of the process.

Lipid-based excipients are basically substances containing fatty acids. The selection of lipid-based excipient as coating material for a desired drug release is very critical. One of the useful indicator is hydrophilic-lipophilic balance (HLB) that is based on water solubility and polarity of the lipid. This is indirectly related to wettability of the coating material. Lipids have a tendency to exist in different crystalline structures: pseudo-hexagonal sub α-, hexagonal α-, orthorhombic β'- and triclinic β-form, β-form being thermodynamically most stable. These forms differ in their melting points, crystallization rate and solubility in water [21]. The transformation from thermodynamically instable to stable polymorph, however results in reduction of wettability, change in drug release after storage and formulation instability. There are several ways in which polymorphism of the lipid-based excipients and formulation stability can be controlled such as tempering during processing (operating at temperatures ranging between the melting point of α- and β-form), tempering after processing or maturing, addition of crystallization seeds, avoiding of melting or addition of polymorphic modifiers [21]. The most common approach and one used in this study to control polymorphism is use of emulsifiers as polymorphic modifiers. Emulsifiers control the nucleation rate, crystal growth and morphology and accelerates the transformation to the stable β-form. Use of emulsifiers offers advantage of low process temperatures and complete transformation before storage. However, excess of emulsifier can lead to storage instabilities such as phase separation. Therefore, pre-formulation studies

are important with respect to polymorphic and morphological behavior at different process conditions [21].

1.3 Objective

The objective of this research is to investigate a hot-melt fluidized bed process for coating of drug crystals with lipid-based formulations to produce orally disintegrating granules (or a "direct to mouth" dosage form). Orally disintegrating granules (ODGs) are a relatively newer technological development in the pharmaceutical industry. These fast dissolving drug delivery systems are "direct to mouth" dosage form that can be swallowed directly without a liquid. ODGs offer better patient compliance especially for population groups with swallowing difficulties and also improves bioavailability of the drug [1]. However, the unpleasant taste of active ingredients induces negative sensory response and hence taste masking of the active ingredient is of critical importance. Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Most common techniques of taste masking include adsorption onto or complexation with carriers and spray coating of drug particles [2]. Fluidized bed is an efficient technology for coating. It is preferred for its good particle mixing, temperature homogeneity, high heat transfer rates and uniform coating onto the solid particles [3]. In this study, granules were coated by the hot-melt coating process in a fluidized bed. The coating material used in this study is a lipid formulation containing lipid and an emulsifier. A fractional factorial design of experiment was considered to study the influence of process parameters and coating formulation on coating thickness, dissolution rate of the drug and taste masking by the coating. As stated in previous paragraphs, the lipid-based formulations used for the coating

material have tendency to exhibit polymorphism. In order to have a stable coating it is crucial to achieve a stable polymorph of the lipid coating at the end of the process. Moreover, addition of the spray liquid increases complexity of thermodynamic interactions in the bed rendering the coating process prone to undesirable product quality. So far, there is no study done that co-relates influence of process parameters and polymorphism of the coating material. Therefore, a further aim of this work was to study the product and outlet temperature profile during the process to predict polymorphism of the lipid coating.

CHAPTER 2

EXPERIMENTAL METHODS

2.1 Materials

Acetylcysteine-500 (N-acetylcysteine or N-ac), procured from PharmaZell GmbH (Germany), was used as the active pharmaceutical ingredient (API) in this study. The average particle size of Acetylcysteine crystals was approximately 500 μm as measured by QICPIC (Sympatec GmbH, Germany). Acetylcysteine, a mucolytic agent, has a sour taste and it is undesirable to directly swallow without a liquid. Hence, lipid formulations were used to mask the unpleasant taste of the API. Dynasan 116 (triglyceride with palmitic acid or Tripalmitin) and Dynasan 118 (triglyceride with stearic acid or Tristearin) obtained from Cremer Oleo (Germany), served as a primary coating material. The thermal properties of the two lipids are given in Table1. Emulsifier was added to the lipid in coating formulation as it aids in faster transformation of lipid coating to a stable polymorph and also accelerates the release of API from the coating [22]. TWEEN® 65 (Polyoxyethylene glycol sorbitan tristearate) procured from Croda GmbH (Germany), was used as an emulsifier.

Table 1: Thermal Properties of Tripalmitin and Tristearin [17]

Lipid	**Melting Point (^{0}C)**		
	α-form	**β'-form**	**β-form**
Tripalmitin	44.7	56.6	66.4
Tristearin	54.5	64.5	72.5

2.2 Equipment

The coating process of Acetylcysteine crystals was carried out in a laboratory scale fluidized bed equipment by INNOJET VENTILUS® IEV 2.5 (INNOJET Herbert Hüttlin, Germany). The lipids, available in solid state at room temperature, are melted in INNOJET HOTMELT DEVICE® IHD 1 and fed to the spray nozzle in fluid bed unit by a peristaltic pump. The fluid bed is equipped with INNOJET booster ORBITER® at the bottom of the product container to allow fluidization of the particles. The molten coating material is sprayed through INNOJET INH 1 hot-melt spray nozzle located at the center-bottom of the fluid bed unit. The liquid is sprayed from the inner most part of the nozzle. The atomizing air is sprayed from the surrounding part of the nozzle, which in turn atomizes the spray liquid. INNOJET filter SEPAJET®, installed in upper part of the fluid bed unit, continuously entraps the dust present in outlet air stream and the outlet air is recirculated back into the filters such that entrapped dust is fed back to the process. The entire process is controlled using a control software and the data is administered and analyzed in a datalogger software.

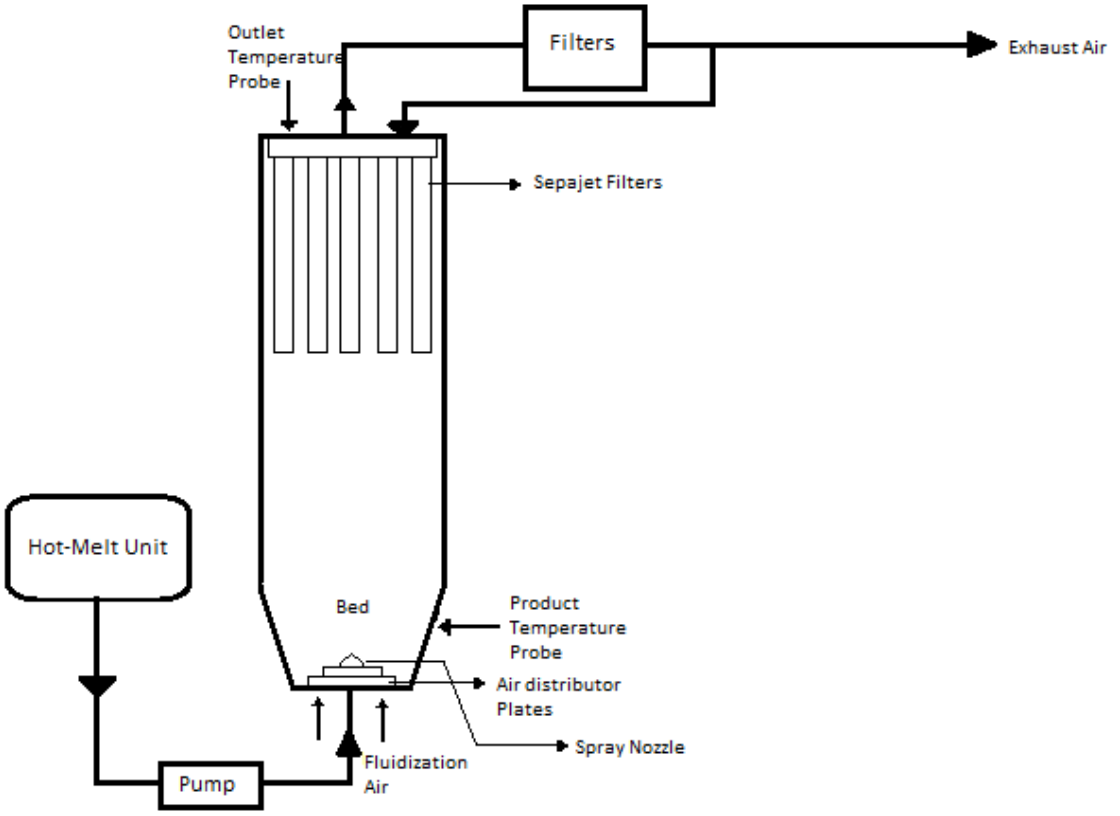

Fig 1: A schematic of the hot-melt fluidized bed unit.

2.3 Coating process

Lipid and emulsifier were melted together in a stainless steel container of the hot-melt unit using an electric heater and the molten formulation was homogenized by continuous stirring. The molten coating formulation was then pumped through the connections into the spray nozzle. In order to keep the coating formulation in molten state, the holt-melt unit was kept at a temperature of 100 ^{0}C throughout the process. The product container was mounted onto the fluid bed unit and air distributor plates and spray nozzle were fixed in their position. All the connections with hot-melt unit were set up for

continuous flow of coating material in the fluid bed. The fluid bed equipment was sealed. The inlet air flow was switched on and adjusted to the desired flow rate. Temperature of inlet fluidizing air was selected such that the molten lipid formulation sprayed onto the particles recrystallized immediately. A batch of 300 g of API crystals was loaded into bed and was allowed to fluidize for some time in order to break any aggregates formed during storage and achieve thermodynamic equilibrium in the equipment. Once equilibrium was achieved, the coating material pump was turned on (rpm relative to spray rate desired) and atomizing air pressure was set to desired value. This marked beginning of the coating process. All process parameters were held constant till the end of the process. The end-point or process time was marked by the coating amount. The process parameters considered for parametric study of the factorial design of experiments are given in Table 2. Additional set of experiments were carried out to understand polymorphism of the coating layer, as given in Table 5. Lipid used in parametric study was Tripalmitin and one used in polymorphism study was Tristearin. A different lipid, Tristearin, was used in the case of polymorphism study, because it takes longer time for phase transformation of Tristearin as compared to Tripalmitin. Thus, it is easier to differentiate between different polymorphs.

2.4 Design of Experiments

A five factor, two level factorial design of experiments was considered to study the effect of process parameters and coating formulation on coating thickness, dissolution rate of API and taste masking by the coating. The factors considered in the design are spray

rate, spray pressure, air flow rate, coating amount and emulsifier content. Table 2 shows the low and high level of each parameter of the DOE. As 2^{5-1} fractional factorial was considered, 19 experiments including three center points were performed. The response variables evaluated in this study are thickness of coating layer, dissolution rate and taste masking by the coating material.

Table 2: Process parameters included in the design of experiments

Parameters	Low Level	High Level
Spray Rate (g/min)	2	8
Spray Pressure (bar)	0.8	1.4
Air Flow Rate (m^3/hr)	30	45
Coating Amount (%) w.r.t. API mass	25	40
Emulsifier Content (%) w.r.t. coating amount	10	20
Inlet Air Temperature (^{0}C)	25	
Batch (g)	300	

2.5 Analytical Methods

2.5.1 Content Assay

The content of the coated granules were obtained by first cryomilling the sample and then dissolving them in a buffer solution to analyse the content. 6 g of coated N-ac particles were grinding in a cryomill (Retsch Haan, Germany) for 5 minutes at 25 Hz and cooled by nitrogen to -196^{0}C. Further the cryomilled samples were weighed in a volumetric flask (such that API weighs 600 mg) and dissolved in 100 ml of phosphate buffer (pH 6.8). The flasks were kept in ultra-sonic bath for 15 minutes while shaking every 3 minutes for 1 minute so as to break the coating layer. The solution was then filtered through a nylon

membrane filter and diluted to 1000 ml. The dilution were further filtered through MCE membrane into HPLC vials and analysed in HPLC (Waters 2996 PDA Detector HPLC system).

2.5.2 Dissolution test

Dissolution test of the coated granules was carried out in Dissolution Tester DT 820 - USP apparatus 2 (Erweka, Germany) operating with water warmed to 37°C. The dissolution vessels were filled with 900 ml of 0.1 N hydrochloric acid (pH 1.1). The dissolution solutions containing samples (weighed such that API weighs 600 mg) were continuously stirred at 100 rpm with the help of paddles and the test was carried out for 60 min. Aliquots of 1 ml were automatically taken after 1, 5, 10, 15, 20, 30, 45 and 60 min with the help of an on-line sampling system and the concentration was determined in HPLC (Waters 2996 PDA Detector HPLC system). The optimal limit for the dissolution rate was set to 85% of API release within 30 min (immediate release). The efficiency of the taste masking was determined by the N-ac release during the first minute of dissolution. The optimal limit was set to a maximum release of 1.4% of N-ac after 1 min of dissolution.

2.5.3 High Pressure Liquid Chromatography (HPLC) Analysis

The HPLC analysis of the samples obtained from the dissolution test and the content assay was performed by using a Synergi Fusion RP 4 µm column (80 Å, 250 mm x 4.6 mm) and pre-column of an Atlantis® T3 (5 µm). The solution containing 5% acetonitrile in water (pH 1.6) was used as mobile phase. The sample injection volume was 20 µL with a run-time of 20 minutes and the flow rate was set to 1 mL/min. The temperature of the column was maintained at 21°C and the temperature of the autosampler at 5°C. The

detection and data evaluation was performed with a diode array detector at the wavelength of 220 nm.

2.5.4 Thermal Analysis

The thermal properties of lipid formulations were obtained by Differential Scanning Calorimetry measurements in DSC 204 F1 Phoenix from NETZSCH (Selb, Germany). 5-6 mg of samples were taken in aluminum pans. Melting temperature of Tristearin was found at heating rate of 25 K/min and Tripalmitin was found at heating rate of 40 K/min. The recrystallization temperature of both the lipids was found at cooling rate of 10 K/min.

2.5.5 Particle Size measurements

The particle size distribution of the granules was obtained using high speed analysis sensor QICPIC (Sympatec GmbH, Clausthal-Zellerfeld, Germany) with a dry disperser RODOS/L. The range of particle size measured in this equipment was 20 µm to 3000 µm. The feeding rate was 30%, 400 frames per second were taken, the injector diameter was 4 mm and the air pressure was 1 bar. The particle size distributions d_{10}, d_{50}, and d_{90} were determined for all hot-melt coated samples.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Experimental Results

The design of experiments considered five parameters to study the influence of those parameters on coating thickness (measured as average of difference between median diameter of initial and final particle), dissolution rate (measured by percentage release of API in 30 min) and taste masking ability (measured by percent release of API in 1 min). Table 3 includes experimental combinations of 2^{5-1} fractional factorial design including three center points and results for each combination. The design of experiments and analysis of variance of the response variables is evaluated in statistical design software, MODDE 10.1.

Table 3: Results of response variables for DOE experiments.

FACTORS							RESPONSES		
Exp No	**Spray Rate (g/min)**	**Spray Press. (bar)**	**Air Flow Rate (m3/hr)**	**Emul. Cont. (%)**	**Coating Amount (%)**		**Thickn-ess (um)**	**N-ac release in 1 min (%)**	**N-ac Release in 30 min (%)**
					Theore-tical	**Measu-red**			
1	2	0.8	30	10	40	42.52	82.17	0.07	15.62
2	8	0.8	30	10	25	28.39	71.52	0.28	37.16
3	2	1.4	30	10	25	24.07	29.01	4.59	77.7
4	8	1.4	30	10	40	41.28	84.77	0.38	41.93
5	2	0.8	45	10	25	28.14	52.31	0.41	43.53
6	8	0.8	45	10	40	41.83	82.54	0.14	6.19
7	2	1.4	45	10	40	41.5	73.41	0.22	10
8	8	1.4	45	10	25	25.09	43.33	7.06	71.59
9	2	0.8	30	20	25	26.63	43.89	1.96	98.72
10	8	0.8	30	20	40	41.48	206.1	3.46	90.83
11	2	1.4	30	20	40	41.46	40.58	1.37	93.38
12	8	1.4	30	20	25	23.54	39.3	9.82	92.58
13	2	0.8	45	20	40	37.84	68.7	2.61	93.06
14	8	0.8	45	20	25	28.76	50.65	2.1	97.8
15	2	1.4	45	20	25	27.01	14.91	2.64	95
16	8	1.4	45	20	40	37.92	76.55	0.86	85.57
17	5	1.1	37.5	15	32.5	34.44	62.2	0.98	84.23
18	5	1.1	37.5	15	32.5	30.96	60.53	0.52	78.26
19	5	1.1	37.5	15	32.5	33.94	54.45	0.83	82.49

Analysis of variance was carried out to evaluate parameters influencing the output variables. Model fit was calculated using the partial least square method. Analysis of the design is shown in Table 4. It can be concluded from the model validity values that models were significant as the values were positive. The R^2 and Q^2 values shown in Table 4 tells how well the model fits the response and how well the model predicts new data respectively. Reproducibility values show good reproducibility of the process for all the three response variables. The coefficient plot and response contour plot were generated to evaluate the experimental results and observation. The coefficient plot helped in evaluating the significance of process parameters on response variables. The contour plot helped in illustration of the response surface and further estimate the optimized design space for the process. Both the plots were developed by editing and fitting the model.

Table 4: Design analysis for response variables

	Thickness (Response 1)	**Dissolution Rate (Response 2)**	**Taste masking (Response 3)**
R^2	0.782	0.883	0.931
Q^2	0.722	0.831	0.825
Model Validity	0.275	0.44	0.79
Reproducibility	0.98	0.99	0.94

3.1.1 Influence of process parameters on coating thickness

The coating thickness is a measure of particle growth of the coated granules. The particle size of the coated granules were measured in terms of d10, d_{50} and d90 values of the size distribution. The d_{50} measurements were considered in the evaluation and the average of the difference between d_{50} of initial drug crystal and d_{50} of coated granules was

reported as the coating thickness. From the analysis of variance and regression analysis, spray rate, spray pressure and coating amount were found to be significant factors influencing the coating thickness. This can be seen in the coefficient plot (in Figure 2) obtained by design analysis at confidence level of 95% and the values of regression coefficients are given in Table 5. The magnitude of coefficient is highest for coating amount, followed by spray pressure and spray rate.

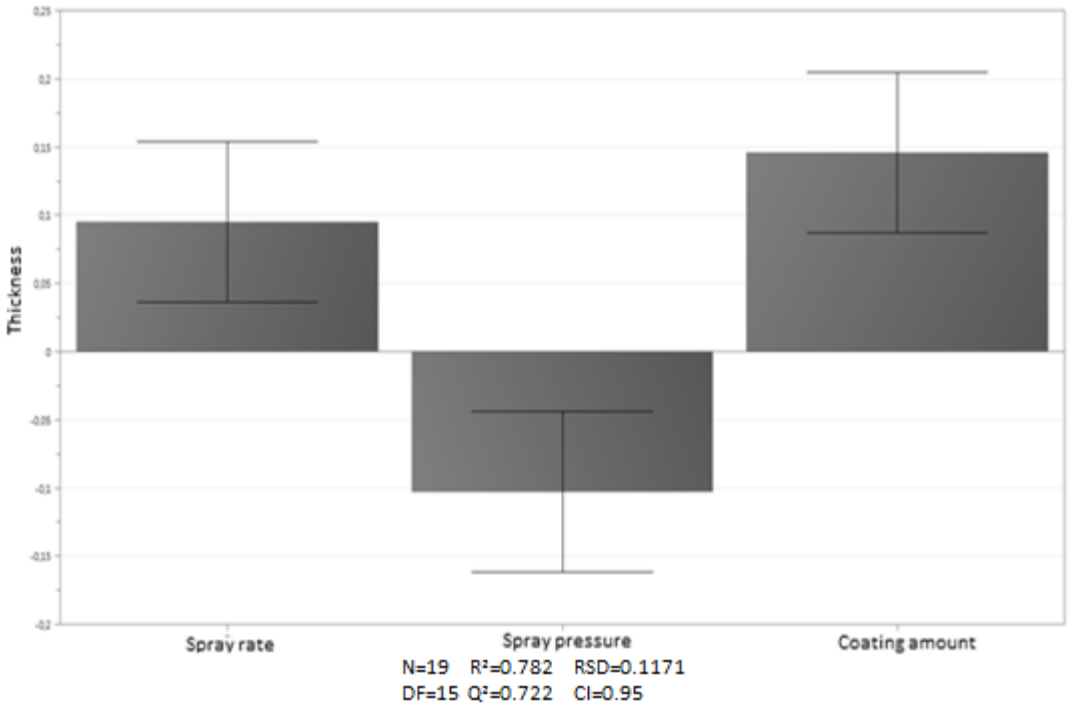

Fig. 2: Coefficient plot obtained from analysis of DOE to indicate significant factors influencing coating thickness.

Table 5: Coefficients of regression analysis for coating thickness

Significant factors	Coefficient (scaled and centered	Confidence Interval
Spray Rate	0.0949	0.0588
Spray Pressure	-0.1030	0.0583
Coating Amount	0.1462	0.05883

Experimental observations and results were further quantitatively analyzed using a 4D response contour plot. A 4D response contour plot for the coating thickness is shown in Figure 3. The significant factors, namely spray rate, spray pressure and coating amount were varied at low level, center level and high level. From the trends observed in Figure 3, at low level of coating amount a lesser coating thickness, in the range of 20-60 μm, was observed. As coating amount was increased from the low level to high level, the thickness of the coating increased from 60 μm to 200 μm. The increase in coating thickness at higher level of coating amount can be attributed to higher amount of coating material and longer process time. The spray pressure from the nozzle showed considerable influence on coating thickness and its influence is negative in nature. The spray pressure influences the size of spray liquid droplet such that an increase in spray pressure results in decreases in the droplet size and reverse is observed at low spray pressures. For higher spray pressure and lower droplet size, the amount of sprayed liquid deposited on the bed particles is less, resulting in a thinner layer of coating material. Therefore, with an increase in spray pressure a decrease in the coating thickness was observed. On the other hand, a thicker coating layer was observed for low spray pressures. There was some influence of spray rate observed on the coating thickness. Spray rate influences the spray liquid droplet size and rate of deposition of the liquid or melt onto the solid particles. A higher spray rate resulted in larger spray liquid droplets and a faster deposition of liquid and hence thicker coating layer was observed.

The influence of each of the significant process parameters discussed above, on the coating thickness is considerably dependent on corresponding values of the other parameters. In the case of low coating amount, the coating thickness increased with

increase in the spray rate and decreased in the spray pressure, though the change in the thickness was not very significant and varied only in a small range of 20 – 60 µm. However, at higher coating amount, increase in spray rate and decrease in spray pressure resulted in formation of agglomerates. The effect of spray rate was profound at low values of spray pressure as larger spray liquid droplets were formed and lead to more deposition of spray liquid onto solid particles of the bed. This effect can be seen in the results of content assay wherein, more than expected coating amount was noted as a result of thicker coating layer. Due to the deposition of larger droplets of spray liquid, the material did not recrystallize completely and liquid bridges were formed between two or more wetted particles, thus resulting in agglomeration. Formation of agglomerates caused defluidization of the bed or uncontrolled fluidization and resulted in an undesirable process. A density distribution of an effective coating run (DOE 18) and an agglomeration run (DOE 10) is showed in Figure 4. The broader particle size distribution due to agglomeration can be clearly seen in the figure. On the other hand, certain values of process parameters also lead to spray congealing phenomena. The spray congealing effect was observed at higher values of spray pressure due to formation of smaller spray liquid droplets. These small spray liquid droplets crystallized before coming in contact with the bed particles. Thus, some amount of coating material was sprayed directly onto the filters and fluid bed wall. For a process resulting in spray congealing, a thinner coating layer was thus observed. The influence of spray pressure was more profound at lower spray rate, lower coating amount and higher fluidization air flow rate. Such process conditions lead to a thinner layer of coating material on the solid particles. The coating efficiency was poor in both the cases of agglomeration and spray congealing. The impact on coating thickness is higher at high value of coating

amount as compared to its low value. This impact is also dependent on values of spray pressure and spray rate. The results suggests that coating amount, spray pressure and spray rate has combined effect on coating thickness and all three parameters need to be optimized to achieve desired thickness. There is no specification limit set for coating thickness in this study as desired operating conditions are based on taste masking efficiency of the coating material (discussed in following sections). In order to obtain a thicker coating, coating amount and spray rate can be operated at higher values however spray pressure should also be increased correspondingly so as to prevent agglomeration. However, a more desired operating scenario would be use of low amount of excipients. Therefore, further optimized studies need to be carried out in order to use less coating material, but at the same time a desired dissolution rate and taste masking are satisfied. For this reason we need to perform in vivo studies to obtain the correlation between the response variables.

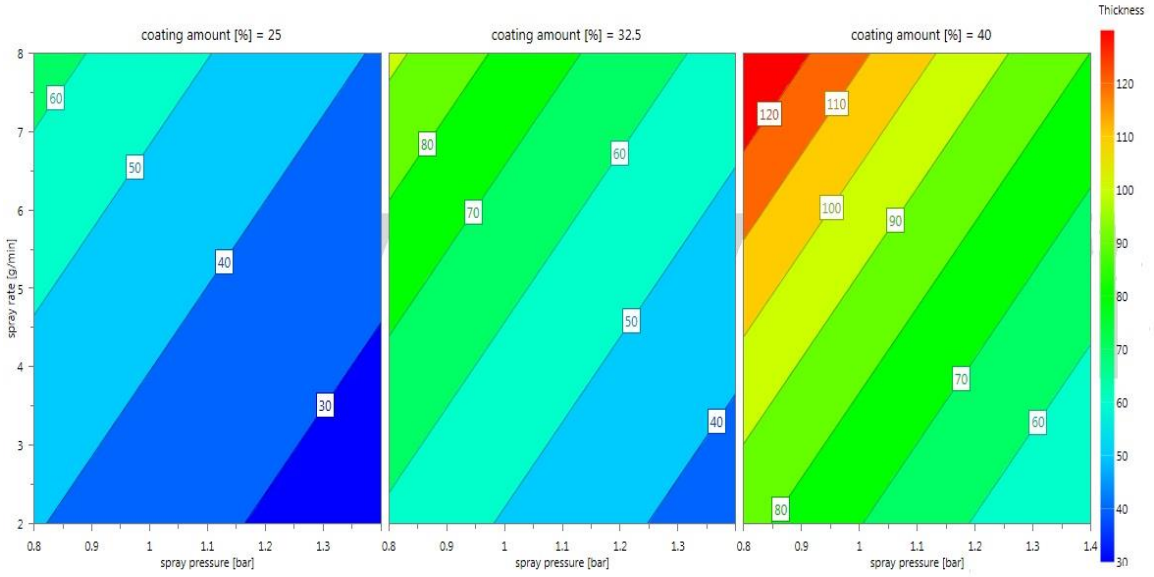

Fig.3: 4D response contour plot representing influence of significant process parameters on coating thickness.

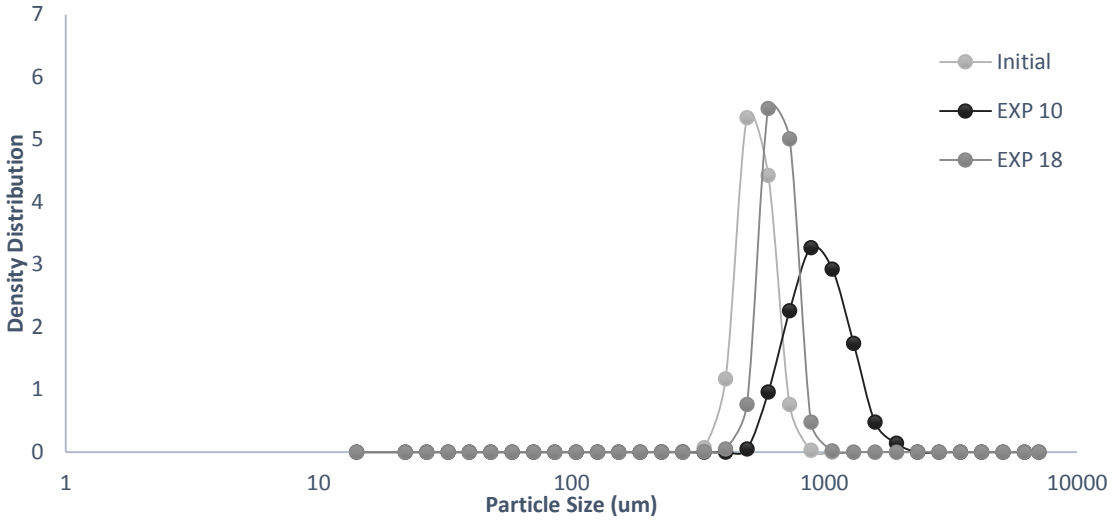

Fig. 4: Particle size distribution of raw material (NAC crystals) and coated granules from experiment 10 and 18. The figure shows change in PSD upon agglomeration (in the case of experiment 10).

3.1.2 Influence of process parameters on dissolution rate

The dissolution rate of the hot-melt coated drug particles was measured by performing dissolution tests and dissolution data was collected at specific intervals over 60 minutes. The result of dissolution rate was evaluated in terms of percentage of API dissolved in 30 minutes. For immediate release profile, it is necessary for drug product to attain more than 85% of drug release within 30 minutes. Experimental observation showed that longer time was taken to achieve % dissolution for particles coated at higher value of the coating amount and lower value of the emulsifier content, especially at higher spray pressure and higher fluidizing air flow rate. Figure 5 shows dissolution profile for granules coated at low and high level of coating amount and emulsifier content. It can be clearly seen that at high level of the coating amount and low level of the emulsifier content, the dissolution of API obtained after 60 minutes is only 25%. On the other hand, faster

dissolution is obtained at low level of the coating amount and high level of the emulsifier content. In this case, 85% of API is dissolved in less than 15 minutes. These observations are in correspondence with the design analysis results as discussed below.

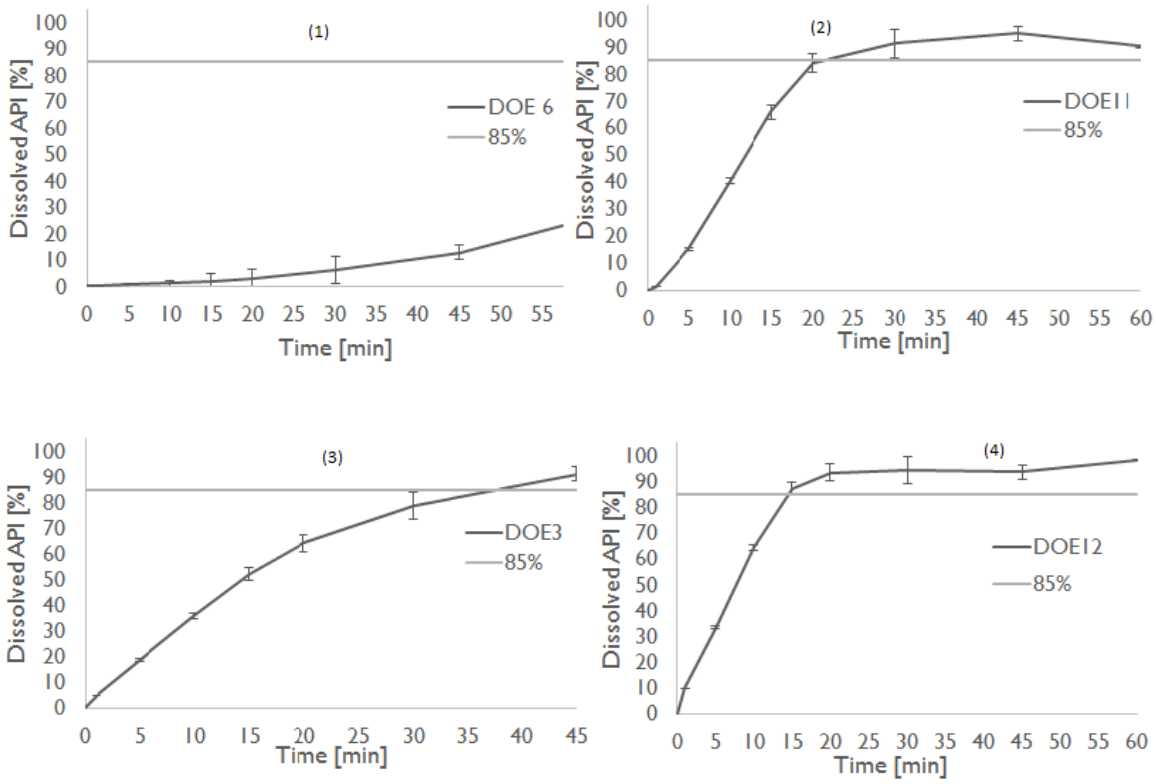

Fig. 5: Dissolution profile of the coated drugs: (1) 40% CA and 10% Emul. (2)40% CA and 20% Emul. (3) 25% CA and 10% Emul. (4) 25% CA and 20% Emul.
**CA=coating amount, Emul=emulsifier content*

The coefficient plot for the study of influence of process factors on dissolution rate obtained from DOE analysis showed emulsifier content and coating amount as the significant terms, as seen in Figure 6. Emulsifier content has larger magnitude of the regression coefficient as compared to coating amount, Table 6.

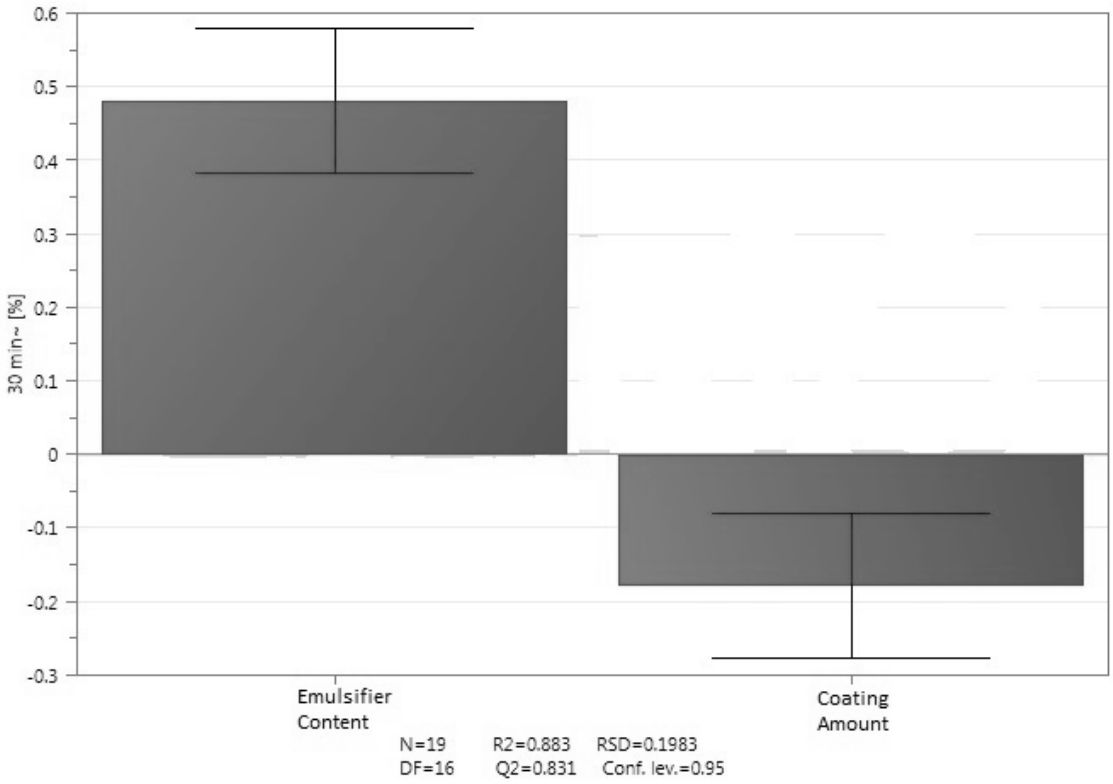

Fig. 6: Coefficient plot obtained from analysis of DOE to indicate significant factors influencing dissolution rate of the coated granules.

Table 6: Coefficients of regression analysis for dissolution rate

Significant factors	Coefficient (scaled and centered	Confidence Interval
Emulsifier Content	0.4811	0.099
Coating Amount	-0.1785	0.099

The response contour plot, shown in Figure 7, helped in quantitatively analyze the influence of emulsifier content and coating amount on dissolution rate by varying them at low, center and high level. According to the analysis of variance and regression analysis, emulsifier content was found to be the most influencing factor on dissolution rate. Higher

dissolution rate was observed for particles coated with coating formulation containing high emulsifier content. This agrees with the previous literature mentioned in section 1.2, as emulsifier helps dissolve the lipid coating faster in water owing to its surface activity (higher hydrophobic-lipophilic balance). At higher values of emulsifier content, more than 90% of API was dissolved within 30 minutes. The coating amount also showed significant influence on the dissolution rate. It can be seen in the Figure 7, that at low value of coating amount, a high percentage (more than 70%) of API was dissolved within 30 minutes. On the other hand, at high value of coating amount a thicker coating layer was observed and hence percentage of API dissolved within 30 minutes was very less. In some cases, the dissolution was only 20% even after 60 minutes. In such cases, it was not only the high coating amount that resulted in poor dissolution, but mainly low emulsifier content in the coating formulation. A low value of emulsifier content along with the high value of coating amount can lead to poor dissolution as emulsifier helps in faster dissolution of API. Other factors such as spray pressure and spray rate could have also resulted in poor dissolution at higher value of coating amount, particularly high spray rate and low spray pressure, due to formation of thicker coating layer.

Although spray pressure, spray rate and air flow rate are not indicated as significant process parameters influencing dissolution rate in the design analysis, experimental observations can help deduce their effect on drug release profile. Spray pressure significantly controls the coating thickness and at its high values, a thinner coating layer is formed. This could increase the dissolution rate considerably. Increase in spray rate can result in more deposition on coating material and thus decrease the dissolution rate due to thick coating layer. Air flow rate has relatively less influence on dissolution rate. However,

low air flow rate can result in poor fluidization and non-uniform deposition of coating, thus leading to poor dissolution rate.

The dissolution profile was also studied in the case of agglomeration and spray congealing phenomenon. The process conditions leading to agglomeration did not show much influence on dissolution rate due to poor coating efficiency. As the particles were not coated uniformly, a relatively faster dissolution was observed. In the case of spray congealing, due to loss of coating material on the filters and fluid bed wall, less amount of coating was deposited onto the solid particles. Hence, very rapid dissolution was observed. Both these cases are not desirable considering patient compliance as dissolution rate could vary with each batch or replicate.

A thick coating layer with poor dissolution rate is not acceptable for dosage form that is aimed for immediate release profile. Also, a very fast dissolution of drug is not desirable as this is at the cost of taste-asking ability of the coating layer (discussed in detail in the next section). Also, the amount of emulsifier in the coating formulation is limited by its low melting temperatures. Higher amount of emulsifier content can result in stickiness of the product and in turn affect product flowability.

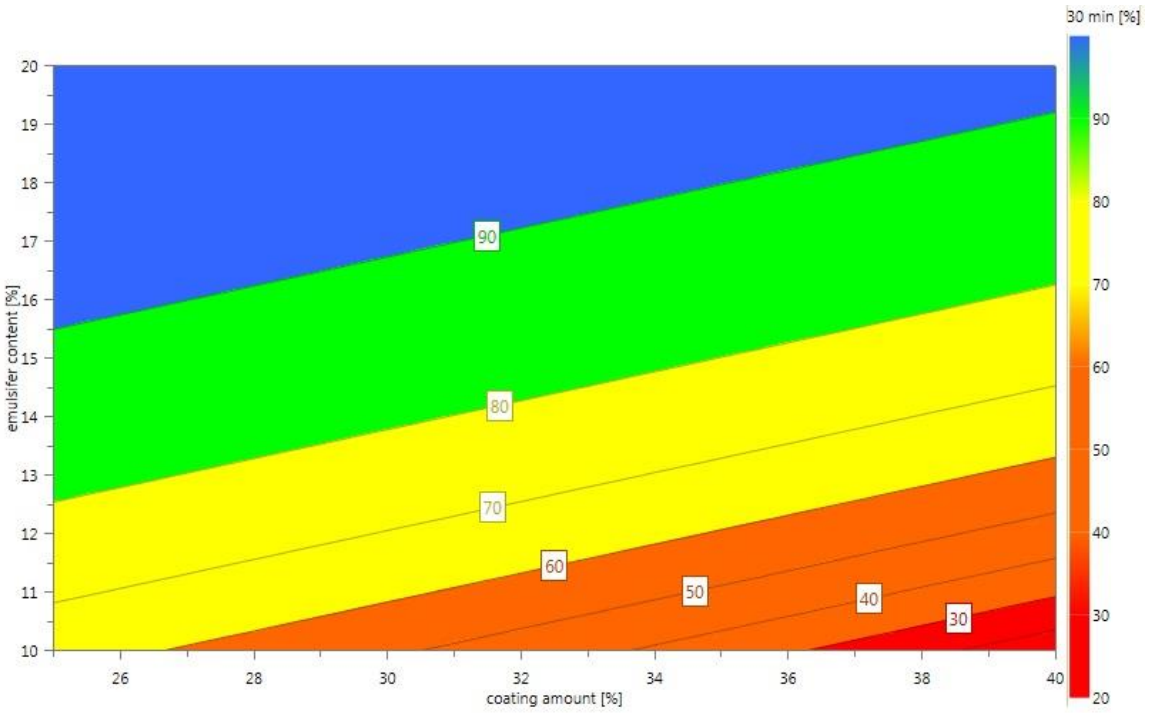

Fig. 7: A *response contour plot representing influence of significant process parameters on dissolution rate of the coated granules.*

3.1.3 Influence of process parameters on taste-masking ability

The taste masking ability of the coated granules can be qualitatively measured by tasting a specific amount of product from all the experiments and grading the taste masking ability on a scale. In order to quantitatively evaluate the taste-masking ability of the coating, data obtained from dissolution test can be used. In this study, taste masking ability is reported in terms of percentage of API dissolved in 1 minute in the dissolution tester. In vivo studies have been carried out to consider 1 minute as an indicator of taste masking efficiency, wherein volunteers reported maximum one minute to completely salivate and swallow one dose. Taste masking ability of the coating material is one of the important

response variable as a poor taste masked product will not be compliant to patients due to disagreeable taste and undesirable release profile.

Experimental observation showed that processes with higher amount of coating at low spray pressure resulted in better taste masking. A coefficient plot, shown in Figure 8, obtained from analysis of the design, showed that coating amount, emulsifier content and spray pressure are the significant factors influencing taste masking ability of the coating layer. In addition, it showed relatively significant influence of interactions between spray pressure, coating amount and emulsifier content. The emulsifier content and coating amount influenced taste masking ability the most, as seen in Figure 8 and Table 7.

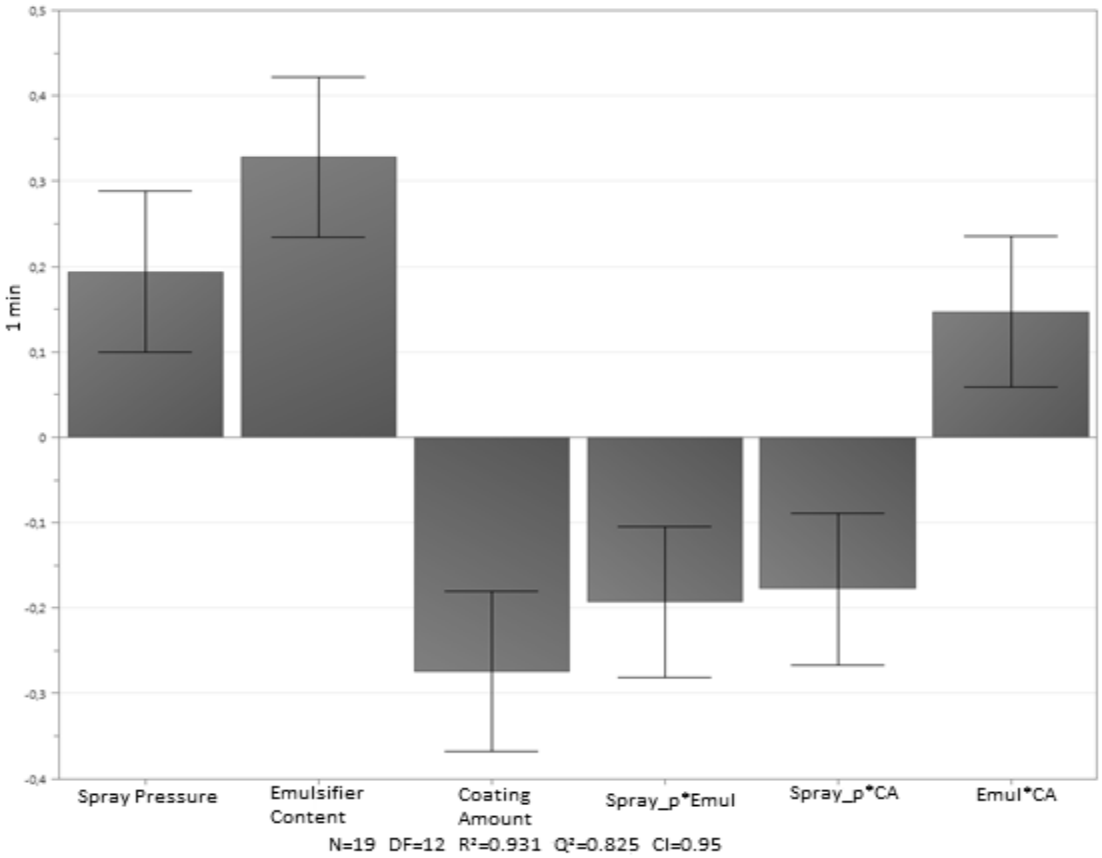

Fig. 8: Coefficient plot obtained from analysis of DOE to indicate significant factors influencing dissolution rate of the coated granules.

Table 7: Coefficients of regression analysis for taste masking ability

Significant factors	Coefficient (scaled and centered	Confidence Interval
Spray Pressure	0.1942	0.0939
Emulsifier Content	0.3282	0.0939
Coating Amount	-0.2744	0.0939
Sp_p*Emul	-0.1926	0.0885
Sp_p*CA	-0.1779	0.0885
Emul*CA	0.1475	0.0885

The 4D response contour plot shows influence of spray pressure, coating amount and emulsifier content on taste-masking at low, center and high level. From the Figure 9, it can be seen that at high level of coating amount, a good taste-masking was observed as the percentage of API dissolved in 1 minute is less. Conversely, at low values of coating amount, a faster dissolution of API was observed. The taste masking ability at low value of coating amount depends strongly on the interactions with other process parameters. As emulsifier aids in faster dissolution of API, a poor taste masking was observed at high value of emulsifier content. The taste masking can further deteriorate if a thin coating layer is present on the particle along with high amount of emulsifier in the coating formulation. Increase in spray pressure decreased the taste masking ability of the coating layer. This is due to smaller droplet size of the spray liquid deposited onto the solid particles. Moreover, at high value of spray pressure, due to smaller spray liquid droplet size, the sprayed liquid gets deposited on the fluid bed wall and filters, thereby resulting in spray congealing effect in the bed. A poor taste masking would then be observed. As the interaction coefficients are significant, their effect on taste masking can be clearly seen in Figure 8. The most dominant interaction amongst three significant factors is seen at low value of coating

amount. At this level, the dissolution is strongly influenced by spray pressure. An increase in spray pressure resulted in a thinner coating layer and hence more percentage of API was dissolved in one minute. On the contrary, for high emulsifier content, low coating amount and high spray pressure, the effect of interaction between process parameters was further pronounced and a very fast dissolution was observed. At higher level of coating amount, the interaction between coating amount and emulsifier content predominated. There was increase in dissolution with increase in emulsifier content. Relatively lesser influence of interaction between coating amount and spray pressure was observed at high value of coating amount. Therefore, better taste masking was observed at high level of coating amount, low level of emulsifier content and low level of spray pressure.

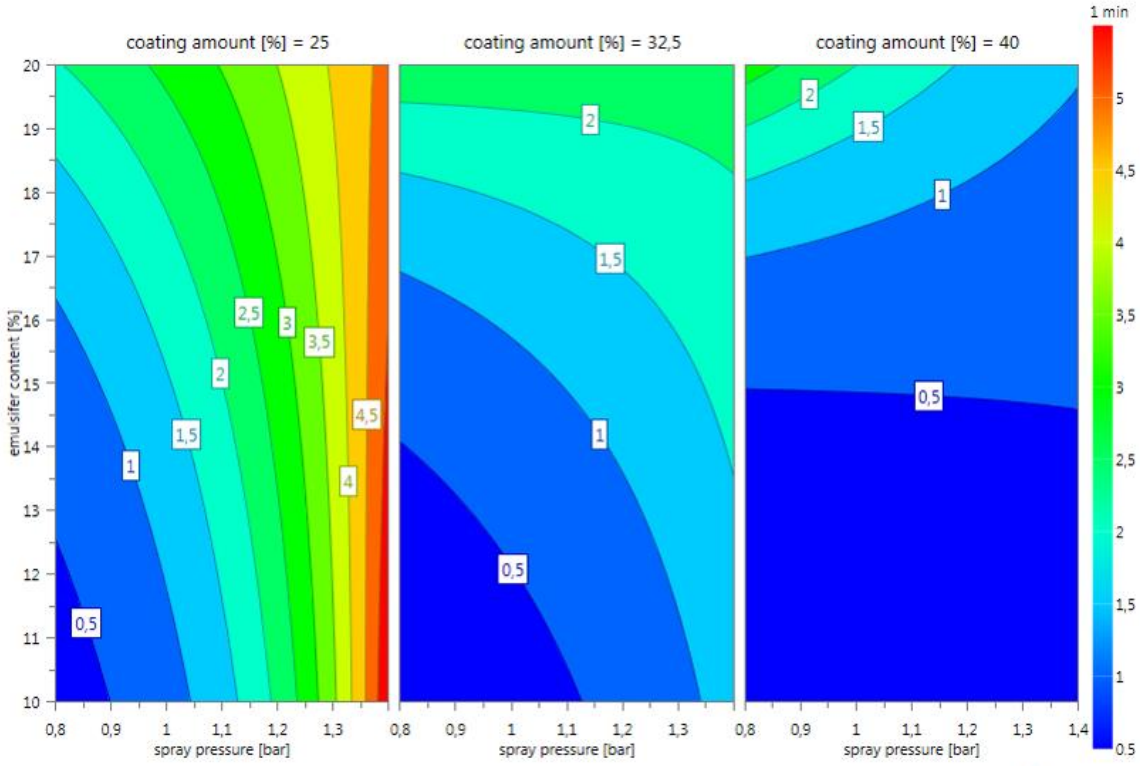

Fig. 9: 4D response contour plot representing influence of significant process parameters on taste masking ability of the coating material.

3.1.4. Desired operating conditions

The dissolution rate and taste masking ability are two most important response variables in this study. These variables determine performance of the coated granule or the dosage form. A product with an immediate release profile and a good taste masking is the most desired one. As both dissolution rate and taste masking should be achieved at the same time, the desirable range of these two variables is inter-related. Considering the results from this design of experiments and design analysis, an operating range can be found by evaluating the results for both dissolution rate and taste masking ability simultaneously. The process parameters having significant influence on both the response variables were considered. Figure 10 is a sweet plot developed by considering desirable values for both the response variables over the range of coating amount, emulsifier content and spray pressure considered in the DOE. It can be seen that desired operating conditions lie in a region where for any amount of coating material, an optimal emulsifier content and spray pressure is very important. For an immediate release profile, emulsifier content should increase with increase in coating amount at all levels of spray pressure. At high level of spray pressure, it is important to have high coating amount and high emulsifier content.

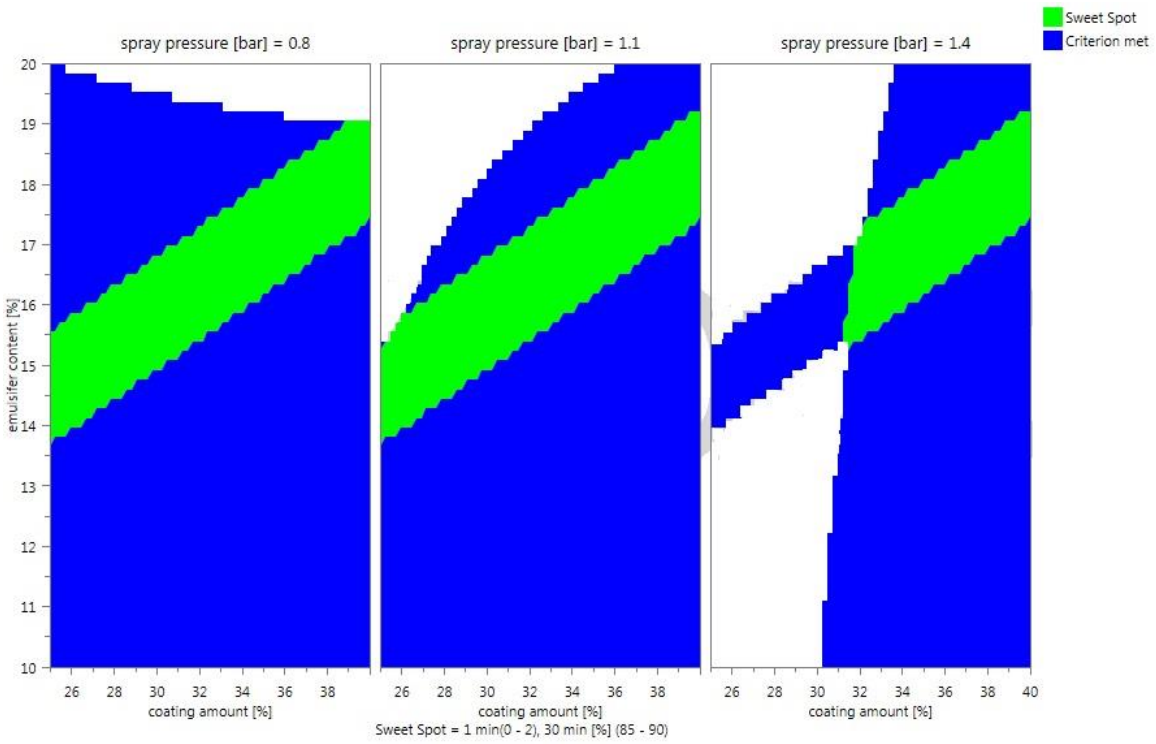

Fig. 10: Sweet Plot representing optimal operating region of the parameters influencing dissolution rate and taste masking.

Considering the process time and cost of the process, it would be desirable to work at higher values of spray rate and less amount of coating material. However, for high spray rates, the size of spray liquid droplets or corresponding spray pressure has to be considered to avoid agglomeration. Also, less coating material will reduce the cost of raw materials, but it is important to consider that desired dissolution rate and taste masking efficiency are achieved.

3.2. Polymorphism in triglycerides

Lipids exhibit the ability to form different crystalline structures or polymorphs. It is important to attain a stable polymorph to achieve good product quality and storage stability. In this research, a thorough study of temperature profile was carried out to understand the influence of process parameters and coating formulation on polymorphism of the coating layer. A set of experiments, apart from those included in design of experiment, were performed to study the polymorphic behavior. The product and outlet temperature profile throughout the process was studied for different formulations at same process conditions and DSC measurements were carried out on final granules to study the melting and re-crystallization curves.

3.2.1. Polymorphic Studies

Triglycerides have a tendency to display monotropic polymorphism, i.e., transition between polymorphs are irreversible and only possible when leading to a stable species. The occurrence of different crystalline structures depends on nature of fatty acid chains in the triglyceride, crystallization procedure and purity of the sample [18]. These crystalline states are characterized by subcell structures which define cross-sectional packing of aliphatic chains [19]. There are three most common crystal forms observed in triglycerides and in increasing order of stability, they are α, β’ and β. The crystalline properties of triglycerides are believed to be strongly influenced by thermal conditions. β’- and β-form are more influenced by thermal treatment than α-form [17]. Figure 11 shows melting and

recrystallization curve of Tristearin. Melting peak was obtained at 71.8°C and recrystallization peak was obtained at 47.9°C.

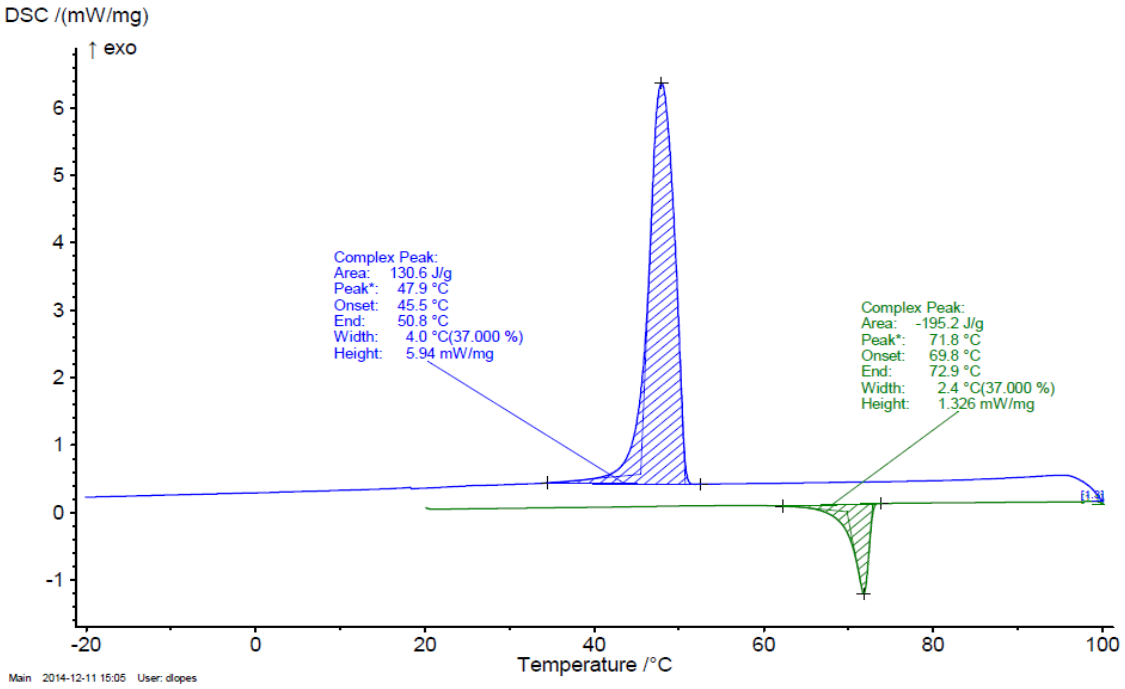

Fig. 11: DSC thermogram of Tristearin obtained at heating rate of 25K/min and cooling rate of 10K/min.

Experiments were carried out to study effect of process parameters, especially the temperature of fluid bed, on polymorphism. Two experiments were considered with similar process variables (as used in DOE) but carried out at two different inlet fluidization air temperatures of 25°C and 60°C. The coating formulation used in this study was a pure lipid (Tristearin) and no emulsifier was used. Tristearin was selected for polymorphism study because it shows slower transformation from unstable to stable polymorph and hence it is better to understand the transformation. A process carried out at 25°C resulted in coating layer with α-form crystals. On the other hand, a process carried out at 60°C resulted in

formation of β-form crystals. Figure 12 and Figure 13 show melting curves for coating layer obtained at the end of the process at two inlet air temperatures. Figure 12 shows two peaks at 57°C and 69°C indicating presence of α-form and some amount of β'-form respectively. Figure 13 shows peak at 73°C indicating presence of only β-form at the end of the process.

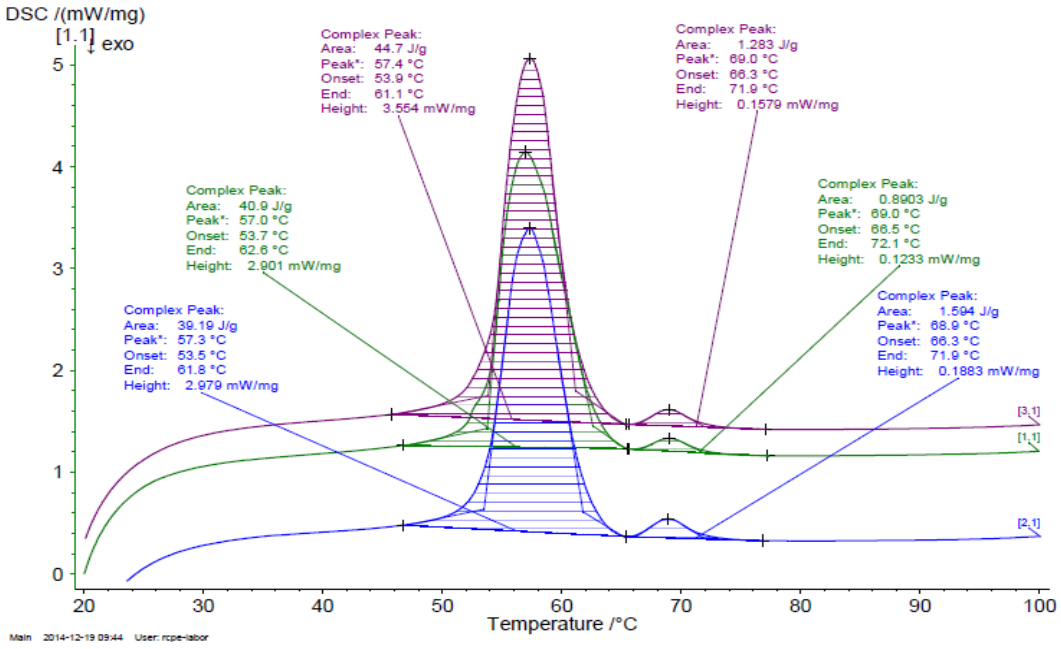

Fig. 12: DSC thermogram (@ heating rate of 25K/min) of granules coated at inlet air temperature of 25°C. Three curves are three replicates of DSC measurements of the sample.

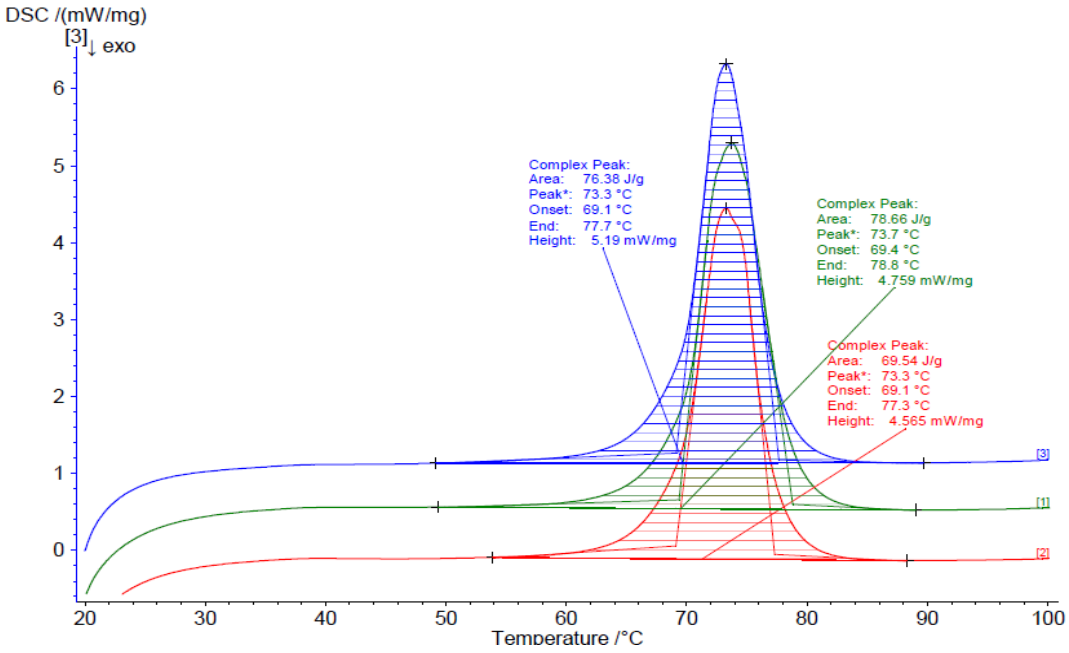

Fig. 13: DSC thermogram (@ heating rate of 25K/min) of granules coated at inlet air temperature of 60°C. Three curves are three replicates of DSC measurements of the sample.

To understand the influence of emulsifier content on polymorphism of the lipid coating layer, three experiments were carried out at same operating conditions but with different emulsifier content. Table 8 includes process parameters for the three experiments.

Table 8: Process parameters for experiments for polymorphism studies

Process Parameters	**Experiments**		
	1	**2**	**3**
Inlet Air Temperature	30°C	30°C	30°C
Spray rate	7 g/min	7 g/min	7 g/min
Spray Pressure	1 bar	1 bar	1 bar
Air flow rate	30 m^3/hr	30 m^3/hr	30 m^3/hr
Coating amount	50%	50%	50%

Emulsifier Content	10%	20%	30%

The polymorphism of the coating layer was studied with the help of DSC measurements of coated granules. The DSC thermograms of above mentioned experiments are shown in following figures. Figure 14 correspond to experiment with 10 % emulsifier in the coating formulation. There are two peaks observed, indicating presence of 15% of α-form crystals melting at 58°C and rest of the 75% of coating layer constituting β-form crystals melting at 72°C. The coated granules from process carried out with 20% emulsifier content (Figure 15) showed very small percentage (around 4%) of α-form crystals and most of the crystallized lipid layer converted to β-form. The product from process carried out with 30% emulsifier content (Figure 16) showed entire coating material converted in β-form with a single peak at 72°C. From this study it was concluded that higher percentage of emulsifier in coating formulation results in complete transformation of coating layer to β-form.

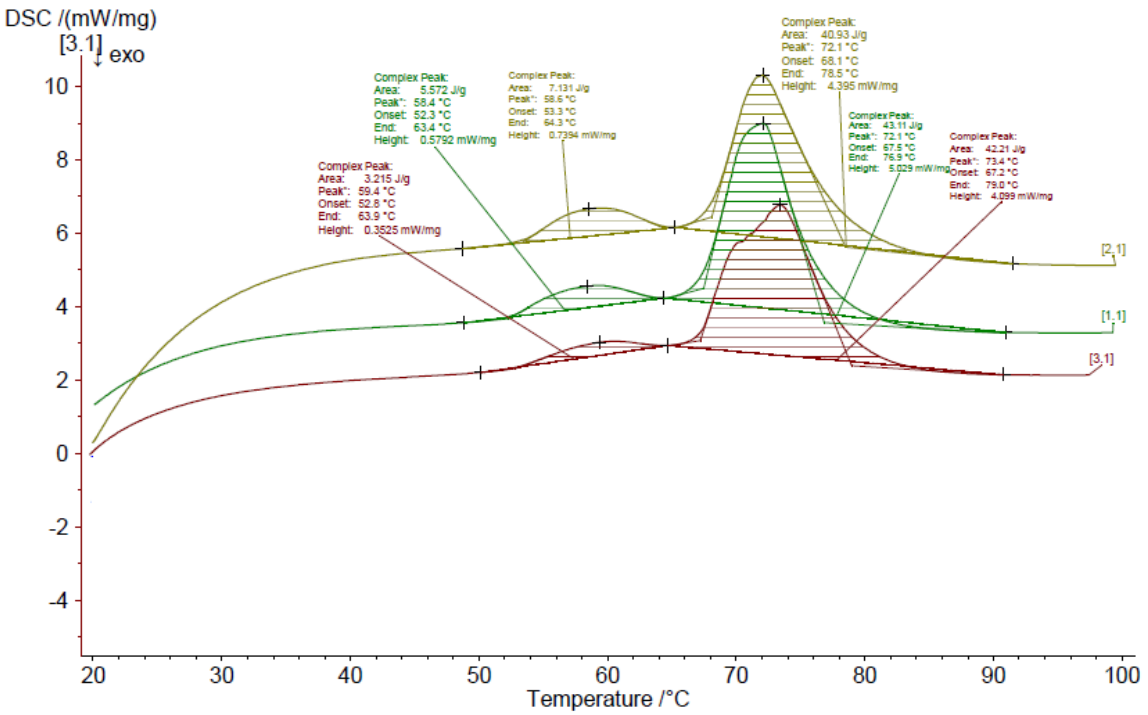

Fig. 14: DSC thermogram (@ heating rate of 40 K/min) of granules coated with 10% of emulsifier. Three curves are three replicates of DSC measurements of the sample.

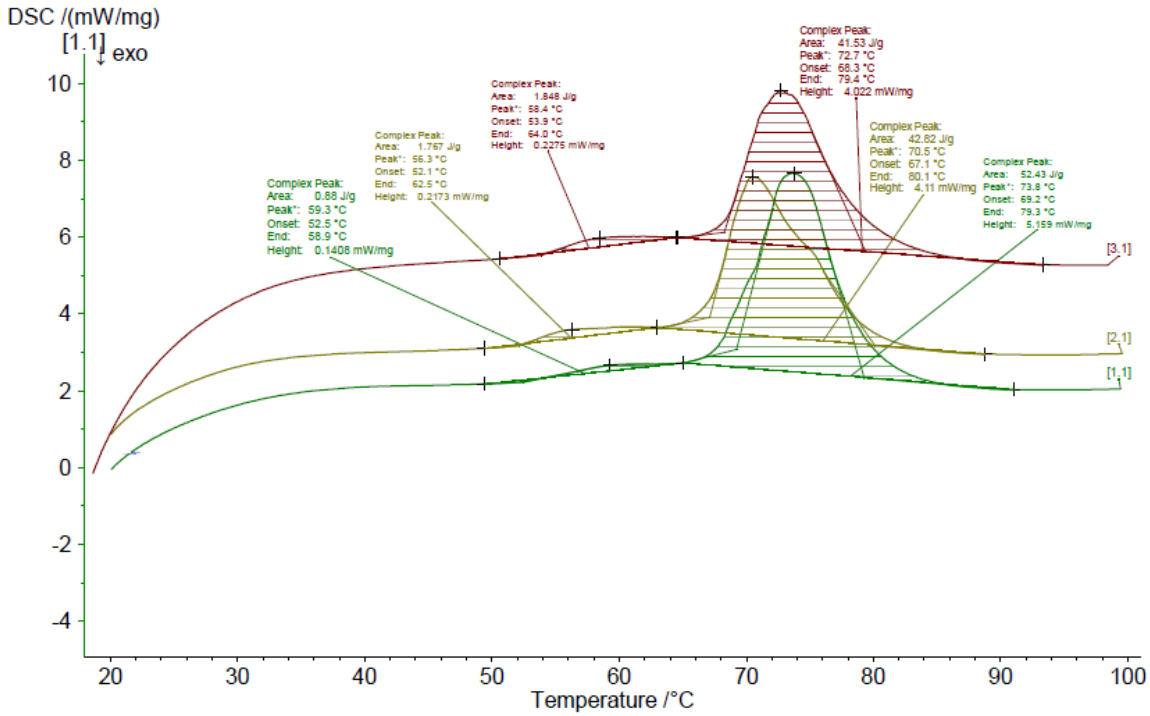

Fig. 15: DSC thermogram (@ heating rate of 40 K/min) of granules coated with 20% of emulsifier. Three curves are three replicates of DSC measurements of the sample.

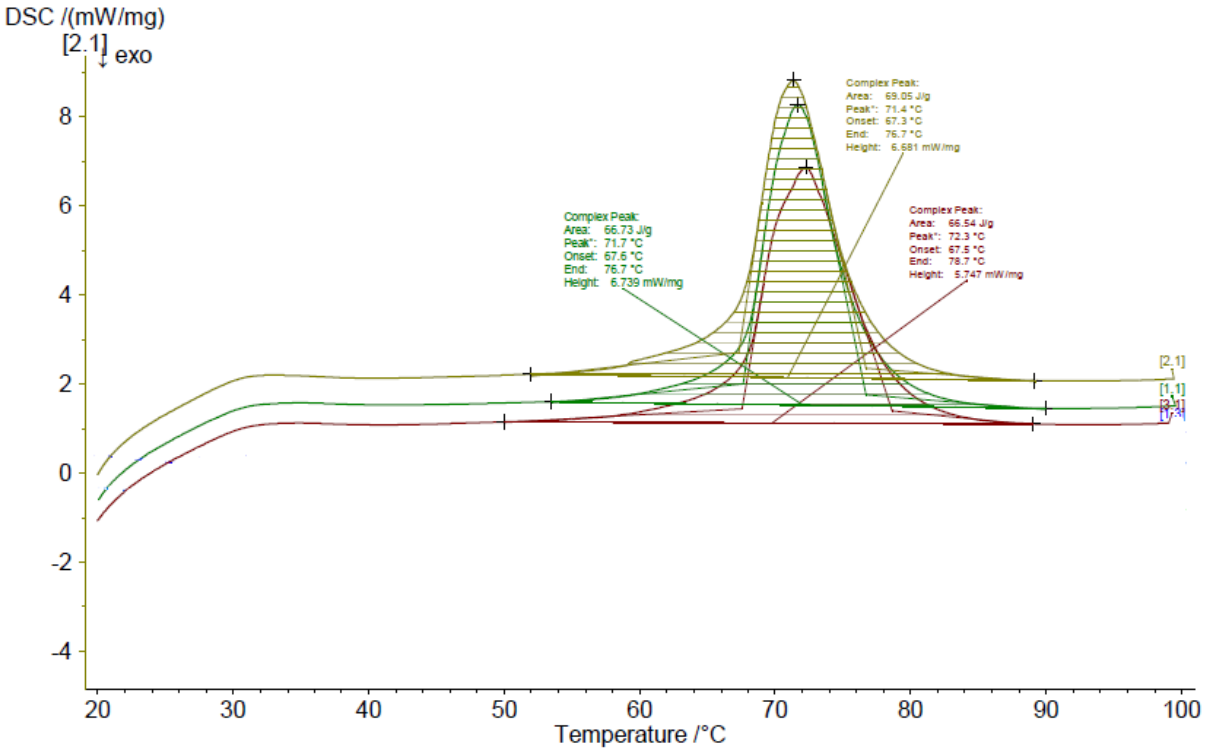

Fig. 16: DSC thermogram (@ heating rate of 40 K/min) of granules coated with 30% of emulsifier. Three curves are three replicates of DSC measurements of the sample.

As obtaining a stable polymorph is important for storage stability of the product, attempts were made to achieve β-form by end of the process. The process with 20% of emulsifier content in coating formulation was selected for this study. The process was first run till the coating amount was over (the conventional end point of the process). A second process was carried out at same operating condition but for longer process time. The process time was increased in this case by continuing the process for double the actual process time (process was continued even after no coating material was sprayed). This

increased the residence time of the product in the fluid bed. The DSC measurements were carried out for products from both the process and it was observed that increasing the process time resulted in complete transformation of coating layer to β-form. Figure 15 shows DSC measurements of the first process and Figure 17 shows DSC measurements of the second process. A clear change in percentage of α-form and β-form can be seen by comparing Figure 15 and Figure 17. The coating layer from the first process contained around 4% of α-form crystals. The coating layer from the second process showed presence of only β-form crystals. The presence of α-form in the coating layer in the case of the first process is from freshly sprayed coating material. Therefore, if the process is carried out only until the coating amount is present, there will be some amount of the coating deposited in α-form. However, if the process is continued for some more time under same process conditions (no liquid sprayed during the additional time span), complete transformation to β-form can be achieved, moreover at same kinetics. Thus this would prevent conversion of α-form to β-form under storage condition and it would eliminate risk of storage instabilities. Nevertheless, storage instabilities caused by phase separation may occur and it needs to be investigated.

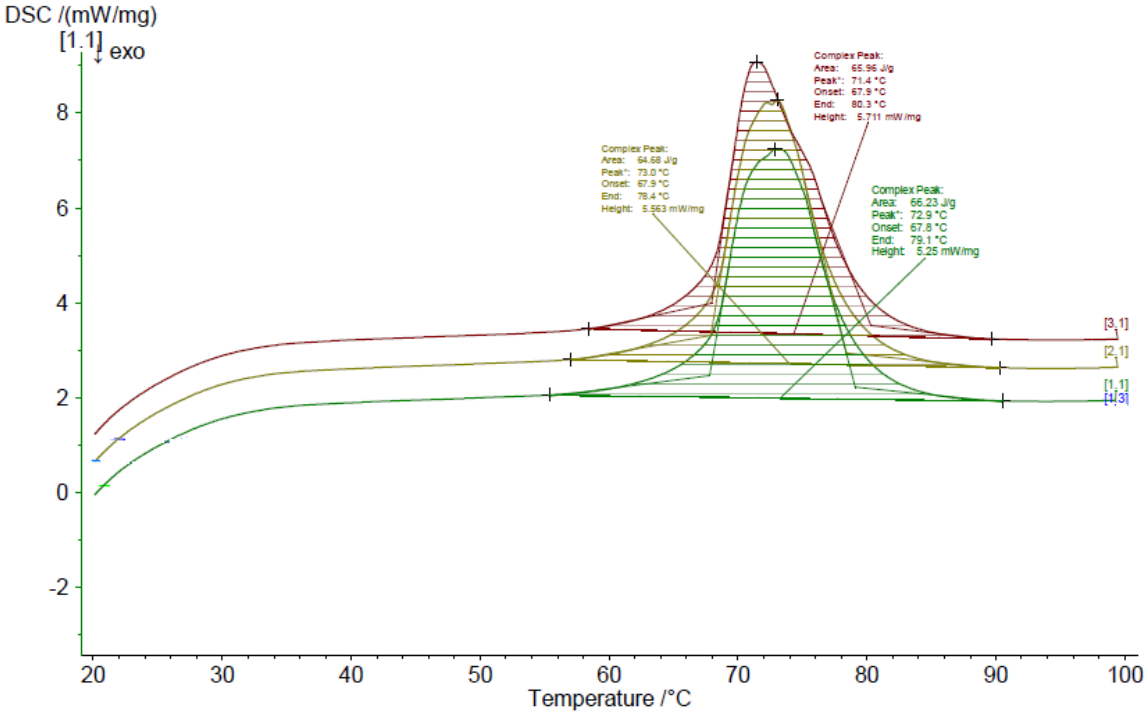

Fig. 17: DSC thermogram (@ heating rate of 40 K/min) of granules coated with 20% of emulsifier for longer time. Three curves are three replicates of DSC measurements of the sample.

3.2.2. Temperature Studies

With an objective to develop a predictive tool for influence of process parameters on polymorphism of the lipid coating, the product and outlet temperature profile over process time were studied in detail. It was hypothesized that any difference in product or outlet temperatures profiles of processes carried out with different percentage of emulsifier content can be attributed to the difference in heat of crystallization of α-form and β-form. Due to different heat of crystallization of the two polymorphs, there could be different amount of heat added to the product or outlet air stream and hence a difference in profile can be expected. Experiments mentioned in Section 3.2.1 in Table 5 were considered and

temperature profiles were studied in detail. Figure 18 shows product and outlet temperature profile of the processes with three formulations with different emulsifier content.

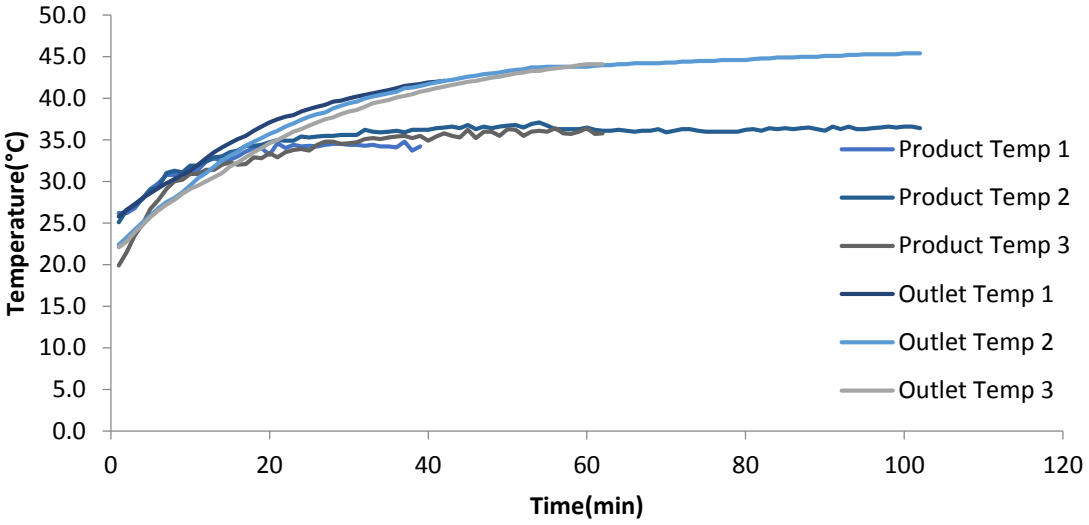

Fig. 18: Product and outlet temperature profile of the process with three different formulations.

As hypothesized, the product or outlet temperature of three different formulations did not vary. Similar temperature profiles were observed for all the three formulation. This similar temperature profile could be attributed to lesser influence of heat of crystallization as compared to influence of inlet air temperature and temperature of spray air on heat balances in the fluid bed unit (the latter temperatures were constant for three process).

The aim of this study was to develop a thermodynamic model for the process and further use the model as a predictive tool for polymorphism of the coating layer. However, as it was observed, there was no difference in the temperature profile for different formulations. Hence it can be concluded that it is not possible to predict polymorphism using a thermodynamic model.

CHAPTER 4

CONCLUSIONS AND FUTURE WORK

In this research, a hot-melt fluid bed process was thoroughly studied for coating drug crystals with a lipid-based formulation. The use of fractional factorial design of experiments helped in evaluating influence of process parameters on quality of coating by conducting only few set of experiments. With the help of design analysis, the influence of each process parameter on the coating thickness, rate of dissolution and taste masking ability can be concluded. The conclusions of desired operating conditions are based on achieving an immediate release profile and a good taste masking. The coating amount had significant influence on coating thickness, rate of dissolution of API and taste masking ability by the coating layer. At higher values of coating amount, a thicker coating layer with poor dissolution rate and a good taste masking was observed. Emulsifier content showed significant influence on dissolution rate and taste masking ability. An increase in emulsifier content resulted in faster dissolution of API and a poor taste masking. This effect was pronounced at low values of coating amount. The effect of spray pressure was dominant in the case of coating thickness and taste masking. Higher spray pressure resulted in less deposition of coating material onto the solid particles. Thus, at high values of spray pressure, thinner coating layer, faster dissolution of API and a poor taste masking was observed. At low values of spray pressure there are chances of agglomeration, particularly for high values of coating amount and low value of spray rate. The influence of spray rate was dominant in the case of coating thickness. The coating thickness increased with increase in spray rate, due to more deposition of coating onto the solid particles. The effect

of air flow rate was found to be the least significant. Though, low value of air flow rate, particularly at low spray pressure and high spray rate can lead to agglomeration.

The polymorphism of lipid is an important phenomena and needs more attention while considering lipid-based formulations. A study based on effect of emulsifier content and fluid bed temperature was carried out to understand their influence on polymorphism. It was also observed that for a pure lipid formulation, temperature of the fluid bed plays an important role. At lower fluidization air temperature, it is difficult to achieve stable β-form and thus lead to risk of storage instabilities. By adding emulsifier to the lipid formulation, it was found that emulsifier improved the rate of transformation of less stable α-form to more stable β-form. Increase in emulsifier content reduced the percentage of α-form in the coating layer at the end of the process.

In order to use lipid-based formulations in the coating process of a pharmaceutical product, it is very important to study physico-chemical properties of the lipid. To completely understand polymorphism and control it in the coating process, further studies are necessary. Detailed studies can be carried out to develop an optimal formulation for coating of drug crystals by studying different lipids and their recrystallization kinetics. Investigation of kinetics of phase transformation will be very helpful in this study and can help in developing a predictive tool for polymorphism. This will give a direct correlation between process parameters and polymorphism of the lipid coating thus saving the loss of raw material and resources in performing experiments.

REFERENCES

1) A. C. Liang, L. H Chen, *Fast-dissolving intraoral drug delivery systems*, Expert Opinion on Therapeutic Patents, 11 (6), 2001, 981-986.

2) D. Douroumis, *Practical approaches of taste masking technologies in oral solid forms*, Expert Opinion on Drug Delivery, 4 (4), 2007, 417-426.

3) K. Saleh, R. Cherif, A. Hemati, *An experimental study of fluidized-bed coating: influence of operating conditions on growth rate and mechanism*, Advanced Powder Technology, 10 (3), 1999, 255–277.

4) B. Guignon, A. Duquenoy, and E. D. Dumoulin, *Fluid bed encapsulation of particles: principles and practice*, Drying Technology: An International Journal, 20 (2), 2002, 419-447.

5) M. Hemati, R. Cherif, K. Saleh, V. Pont, *Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics,* Powder Technology, 130 (1–3), 2003, 18–34.

6) P. D. Hedea, P. Bach, A. D. Jensen, *Batch top-spray fluid bed coating: Scale-up insight using dynamic heat- and mass-transfer modelling,* Chemical Engineering Science, 64 (6), 2009, 1293–1317.

7) S. Wernera, J. R. Jonesa, A. Patersona, Richard H. Archera, David L. Pearce, *Air-suspension particle coating in the food industry: Part I — state of the art*, Powder Technology**,** 171 (1), 2007, 25–33.

8) K. C. Link, E. Schlünder, *Fluidized bed spray granulation: Investigation of the coating process on a single sphere*, Chemical Engineering and Processing: Process Intensification, 36 (6), 1997, 443–457.

9) S. J. Maronga, P. Wnukowski, *Establishing temperature and humidity profiles in fluidized bed particulate coating*, Powder Technology, 94 (2), 1997, 181–185.

10) E. Horvath, Z. Ormos, *Film coating of dragee seeds by fluidized bed spraying methods*, Acta Pharm Tech., 35, 1989, 90-96.

11) P. D. Hede, P. Bach, A. D. Jensen, *Fluidised bed coating with sodium sulphate and PVA/TiO2, 2. Influence of coating solution viscosity, stickiness, pH and droplet diameter on agglomeration*. Ind. Eng. Chem. Res., 48, 2009, 1905–1913.

12) A. S. Achanta, P. S. Adusumilli, K. W. James, and C. T. Rhodes, *Development of Hot Melt Coating Methods*, Drug Development and Industrial Pharmacy, 1997, 23(5), 441-449.

13) M. J. Jozwiakowski, D. M. Jones, R. M. Franz, *Characterization of hot melt fluid bed coating process for fine granules*, Pharmaceutical Research, 7 (11), 1990, 1119-1126.

14) P. Barthelemya, , J.P Laforêta, N Faraha, J Joachim, *CompritolÒ 888 ATO: an innovative hot-melt coating agent for prolonged-release drug formulations*, European Journal of Pharmaceutics and Biopharmaceutics, 47 (1), 1999, 87–90.

15) Z. Knezevic, D. Gosak, M. Hraste, D. Rausl, M. Z. Khan, *Application of Hot-Melt Coating Process for Designing a Lipid Based Controlled Release Drug Delivery System for Highly Aqueous Soluble Drugs*, Chem Pharm Bull (Tokyo), 57(5), 2009, 464-71.

16) G. Kulah, O. Kaya, *Investigation and scale-up of hot-melt coating of pharmaceuticals in fluidized beds*, Powder Technology, 208 (1), 2011, 175–184.

17) M. Kellens, H. Reynaers, *Study of the Polymorphism of Saturated Monoacid Triglycerides I: Melting and Crystallization Behaviour of Tristearin*, European Journal of Lipid Science and Technology, 94 (3), 1992, 94–100.

18) F. Lavigne, C. Bourgaux, M. Ollivon, *Phase transitions of saturated triglycerides*, Journal de Physique IV, 3 (8), 1993, 137-140.

19) K. Sato, *Crystallization behaviour of fats and lipids - a review*, Chemical Engineering Science, 56 (7), 2001, 2255-2265.

20) A.D. Salman, M.J. Hounslow and J. P. K. Seville (eds.), Coating and Encapsulation Processes in Powder Technology – Handbook of Powder Technology, Elsevier, 2007.

21) K. Becker, S. Salar-Behzadi, A. Zimmer, *Solvent-free melting techniques for the preparation of lipid-based solid oral formulations*, Pharmaceutical Research. (Accepted)

22) K. Becker, D. Haack, S. Salar-Behzadi, A. Zimmer, *Oral pharmaceutical composition comprising taste-masked N-Acetylcysteine*, EP Patent 13163638.3, 2013.