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Hot Melt Coating: Development and Optimization of Controlled Release Formulation and Process of Oxcarbazepine

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Hot-melt coating process (HMCP) is being developed to formulate lipid based oral controlled release formulation system for anti-epileptic drug Oxcarbazepine. Pellets containing Active ingredient in the core portion were prepared by extrusion spheronization process with use of appropriate filler and binder. These core pellets were then coated using hot-melt coating technology with different levels of solid lipid material and a hydrophilic component. Formulation and Process parameters were optimized to achieve targeted drug release profile and other target product profile with particular focus on HMCP. Quality by design (QbD) with DOE approach was used for designing and development of the formulation, by putting risk assessment (FMEA, Fish-bone diagram), screening (by Plackett Burman), and optimization (by CCC) studies. Appropriate 'design space' was proposed based on the optimization studies. The results demonstrated that the level of Low melting coating component and a hydrophilic component influenced the drug release rate from the formulation, and the rate of release could be optimized by varying the amount of

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these components in the formulation. Processing parameters like Temperature of the coating solution and atomization air, Atomization air pressure and Spray rate also affects the drug release rate and other parameters like coating efficiency and mean particle size. For optimized formulation, dissolution data model fitting was also carried out which adequately fits to Higuchi model suggesting that the drug release occurred predominantly by diffusion.

Keywords: Hot-melt coating process; multi-particulate formulation; controlled release; design space; risk assessment; oxcarbazepine.

1. INTRODUCTION

Coatings are applied during formulation development of Pharmaceutical dosage forms with the different objectives like superior aesthetic quality (e.g., color, texture, mouth feel, and taste masking), to impart physical and chemical protection for the drugs in the formulation, and modification of drug release rate. Most film coatings are applied as aqueous- or organic-based polymer coatings. Both organic and aqueous film coating have their own limits. Solventless coating technologies can overcome many of the limitations associated with the use of solvents (e.g., solvent exposure, solvent disposal, and residual solvent in product) in formulation coating. Solventless processing reduces the overall cost by eliminating the tedious and expensive processes of solvent evaporation/disposal/treatment. In addition, processing time can be significantly reduced using these technologies because there is no drying and evaporation step. Few such Solventless coating techniques are hot-melt coating, Compression coating, electrostatic spray powder coating, supercritical fluid-based coating, dry powder coating, and photocurable coating [1].

In hot melt coating technology, the coating material is applied in its molten state over the substrate. Hence, solvent use is fully eliminated. This process of applying coating material in molten form offers several benefits and has potential for a wide variety of applications in pharmaceutical formulation. Some Low melting materials only are suitable as a coating material in hot melt coating. For sustained release applications, coating excipients of special interest can be categorized broadly as (i) Natural or Synthetic waxes, (ii) Hydrogenated Vegetable Oils and (iii) Polyglycolyzed glycerides [2].

For successful implementation of hot-melt coating, coating or spraying equipment is critically important. The top spray or bottom spray fluidized Bed can be modified suitably for hot-melt coating due to its capability to maintain the product temperature close to the congealing temperature of the melt [3]. The molten liquid is transferred to fluidized bed and is atomized into small particles/droplets by applying pressurized atomizing air through a binary nozzle. As atomization air pressure is increased, droplets shall become smaller and more discrete. Thus, application of lower spray rate and higher atomization air pressure shall favor smaller droplet formation [4].

Typically, some modification needs to be done in any fluidized-bed coating equipment to make it suitable for the application in hot melt coating [5]. Detailed evaluation of coating equipment and related processing conditions, including fluid bed equipment, has been reported by Mehta [6]**.** The changes are made in existing equipment so that it should enable delivery of molten material on the substrate in the fluidized bed. System should facilitate the transfer of molten material at low viscosity in molten state without any solidification or hardening of the melt, which shall result in discontinuity of the flow during process. To achieve this, delivery tube and spray nozzle, through which molten material is to be passed, can be enveloped with circulating hot air. Hot air supply can be obtained through an electric heating tower. A container of the molten material also needs to be maintained at higher temperature with use of heating device. The spray gun inside the expansion chamber should also be well insulated. This is required to prevent the re-melting of coating material on the substrates, when they come in contact with the spray gun while falling back into the bed.

Four processing stages are involved in the Hot-melt coating process. Pre-warming of equipment, pre-heating of the substrate, coating material melting and spraying on the substrate, and cooling and solidification of the coating [7]. During whole coating process, coating melt is maintained at a constant higher temperature, which shall be 30-40°C higher than the melting point of the material [8]. Hot melt coating process

is critical and has some processing challenges due to the need of maintaining constant elevated temperatures during the liquid storage and spraying through the nozzle during application [9].

Oxcarbazepine, an anti-epileptic drug, was selected for the present study. It is well-documented that in Oxcarbazepine as controlled release dosage forms, peak–trough fluctuations are markedly reduced, and would provide various advantages over the immediate release formulations [10]. Also, the multi-particulate formulations are having advantage over single unit matrix tablets that dose is spread out along the length of the intestine and there is lower risk of the variability and dose dumping.

The main objectives of this study are: (i) to assess the feasibility of HMCP in formulating a low-melting lipid based sustained release multi-particulate oral drug delivery system for high dose, anti-epileptic drug – Oxcarbazepine, with the target of achieving controlled release of drug over an extended period of about 12 h for reduced dosing frequency and improved patience compliance, and (ii) to apply QbD and DOE optimization studies for achieving a robust formulation and manufacturing process. Stearic Acid was used as a low melting lipid material for application in HMCP as release controlling material, as it is chemically inert and possess suitable physical properties (i.e. melting point of about 70^{o}C).

The *in vitro* % drug release data were also analysed using Higuchi diffusion model to assess the release mechanism of the tablets.

2. MATERIALS AND METHODS

Oxcarbazepine was supplied from CTX Lifesciences, India. Microcrystalline cellulose (Avicel® PH 101) was obtained from FMC Corporation, and HPMC (Hydroxy Propyl Methyl Cellulose) (Methocel E5) was supplied from Du-Pont. The low-melt coating component, Stearic Acid (Hysterene 5016), was supplied by PMC Biogenix. Sodium Dodecyl Sulphate (SDS) were purchase from S.D. Finechem. All chemical reagents used were of analytical grade.

2.1 Preparation of Pellets with Extrusion Spheronization

Oxcarbazepine core pellets containing about 60% (w/w) of drug along with other excipients like Microcrystalline Cellulose (as a diluent) and Hypromellose E6 (as a binder) were prepared by wet granulation method. Granulation was carried out in Rapid Mixer Granulator, followed by extrusion in twin screw extruder (0.8 mm screen) and spheronization using 2 mm chequered plate. Pellets were then dried in a tray dryer for about 60 min at 60^{o}C temperature.

2.2 Processing using Hot-Melt Coating Process

Dried core pellets were fractioned with ASTM 18/25 mesh sieve and were further processed for hot melt coating. A modified bottom spray fluid-bed granulator (Glatt, GPCG 1.1) was used to suit to the principle of hot melt coating process. There are controls to regulate and monitor inlet air temperature (T_1), fluidizing air volume and spray rate of the molten coating material. Pre-heated atomized air (which is having temperature of 20-30°C higher than the melting point of the coating material) was used for atomization of molten material through a binary nozzle. The nozzle used in process is enveloped with hot air supply. Other important processing parameters to consider are Bed temperature (T_2), outlet air temperature (T_3) and atomizing air pressure in binary nozzle. These parameters were adjusted according to the properties of coating material like melting point and viscosity of the molten lipid, batch size and equipment capabilities. All-important processing parameters were monitored throughout the coating process.

2.3 Experimental Design

The QbD concept was followed in the design and development of hot melt coated pellets of Oxcarbazepine solution and was done as per ICH Q8 – Pharmaceutical Development [11]. Risk assessment studies were conducted to recognize critical material attributes (CMAs) and critical process parameters (CPPs). The Plackett Burman screening design of experiments (DOE) was used to recognize the most critical CMAs (Critical Material Attribute) and CPPs (Critical Process Parameters). Based on screening study data, critical formulation variables and critical process variables were optimized using Central Composite Design. Response surface DOE was applied for optimization of Formulation and Process. The DOE data were analysed, and the design space was generated by an overlap plot, confirmation experiments were carried out to recognize the accuracy and robustness of the

generated model. A checkpoint batch was selected from the obtained “design space”.

2.4 Risk Assessment

Failure mode and effect analysis (FMEA) is a form of risk assessment that uses a step-by-step approach to identify a possible failure in design, process, and or product enabling analysis to eliminate or reduce future failure [12]. Based on early experimental data and prior knowledge FMEA method was further applied in the risk analysis of the parameters influencing the Hot melt coated pellets of Oxcarbazepine. In FMEA methodology each variable was scored in terms of severity (S), detectability (D), and probability (P) [13]. Here, severity is term for the extent with which the parameter can affect the safety and efficacy of the final product, detectability is a chances of detection when there is a failure and probability is the chances of occurrence of failure. For each risk, severity, detectability and, probability scores were multiplied together to produce a ‘‘risk priority number’’ (RPN), which represents the overall magnitude of the risk [14]. Here, S, D, and P values are ranging from 1 to 5, where 1 being the best case value, 5 being the worst-case value and 3 being the moderate. With this values, RPN risk numbers of 1 to 5 is feasible. A threshold of RPN 60 and above is set for variables (formulation, process and, delivery device) that potentially affect CQAs of the final product and are to be taken further for a screening study, while factors with an RPN 60 or lower are eliminated from the study [15].

2.5 Screening study (Plackett Burman Design)

The Plackett Burman screening study DOE design was used for screening of significant factors influencing product CQAs [16]. Design Expert 11 was used for the screening study. After achieving the significant Formulation and Process factor by Plackett Burman screening study, further optimization studies were conducted.

2.6 Optimization Studies (Modified Central Composite Design)

Formulation optimization and process optimization studies were carried out by Response Surface Methodology (RSM) using Design Expert 11. RSM is one of the most commonly used experimental designs for optimization because it allows evaluating the effects of multiple factors and their interactions on one or more response variables [17]. Modified Central Composite Design (Face centered) was applied in the study. Central Composite Design is spherical, rotatable, and most widely used for model-based parameter estimation [18]. It predicts all the interactions, especially the second order- quadratic ones between the variables and the responses.

2.7 Establishment of the Design Space

ICH Q8 (R2), 2009 defines the design space as ‘‘the multidimensional combination and interaction of material attributes and process parameters that have been demonstrated to assure quality’’ [19]. With application of QbD concept, appropriate design space can be created and wider design space indicates more robust and flexible process, where some variations can be accommodated [20]. In this study, RSM is used in optimization studies to establish design space.

2.8 Confirmation Test of Model and Checkpoint Batch

To confirm the accuracy and robustness of the model, a checkpoint batch was chosen from the “experimental region” as the optimal batch. Formulations at those compositions were prepared, evaluated, and compared the experimented value with the predicted value**.**

2.9 Characterization of Hot Melt Coated Pellets

2.9.1 Determination of drug content

The drug content in HMC pellet formulation was determined by weighing crushed sample equivalent to 100.0 mg of Oxcarbazepine and dissolved in 25 ml distilled water. The sample solution was the solution was sonicated for 25 minutes and solution was further diluted to obtain concentration 10 µg/mL and absorbance was measured at 258.0 nm using a validated UV-Visible spectrophotometer method (Shimadzu®, UV-1800, Japan).

2.9.2 Size Distribution

Size distribution of the HMC pellets were determined by Sonic Sifter (Advantech). More efficient process will result in more uniform size pellets and narrow particle size distribution. Mean pellet size was calculated according to the equation given below [21]:

$$d\ avg = \Sigma \frac{\%\ retained\ X\ Avg.sieve\ aperture}{100}$$

2.9.3 Friability of the pellet

The Friability of hot-melt coated pellets was evaluated by Electrolab Granule Friabilator (EGF-1, Electrolab, India). Friability test was performed as per the Ph. Eur. 2.9.41 (Method B). 10 g of pellets (screened through 25-30#) were placed in glass container (105 mL), which was then installed in apparatus. Sample was oscillated for 120 s at frequency of 140 oscillations/min. Granules were sieved and weighed again. Also the % LOD measurement was carried out before and after test and the factor is taken into calculation. 3 samples were tested and the mean value was calculated.

$$F = \frac{m1(100-T1)-m2\ (100-T2)}{m1}\ X\ 100$$

Where,

F - Friability;
T1 - percentage loss on drying before the test (mean of 2 determinations);
T2 - percentage loss on drying after the test (mean of 2 determinations);
m1 - mass of pellets before the test, in grams;
m2 - mass of pellets after the test, in grams

2.9.4 Angle of Repose and other micromeritic properties

The angle of repose was measure with fixed cone height method for each sample. Here, glass funnel with an internal diameter of 5 mm was fixed to a height of about 1 cm over a solid surface. Samples were then allowed to flow through funnel until the height of the cone reach to the height of the edge of the funnel orifice. The angle of the cone is then recorded by measuring the diameter and height of the cone. This test should be performed in triplicate for each sample.

2.9.5 Drug release study

Dissolution studies (six replicates for each experiment) were performed, as per the method recommended in USFDA dissolution recommendation, using apparatus II (paddle) with sinker, at 75 rev./min, 37^{0}C, with 900 ml of dissolution fluid (1.0% SDS in Deionized Water (degassed)) [22]. Dissolution time points were 1, 2, 4, 6, 8, 10 and 12 hours. Dissolution fluid was prepared by dissolving 10 g SDS (Sodium Dodecyl Sulphate) in 1 L of water. The pellets were placed in basket type sinker. The paddle shaft was lowered in to the dissolution vessel. The amount of drug released was determined by withdrawing 10-ml samples at various time intervals and measuring the absorbance at 258.0 nm in an UV-Visible spectrophotometer (Shimadzu®, UV-1800, Japan). Equal amounts of dissolution media were replaced after withdrawal of each sample.

2.10 Dissolution Modelling

The release of a drug from a formulation generally involves both dissolution and diffusion. Different mathematical equations-based models can define drug dissolution and/or release from DDS. In the modern era of controlled-release oral formulations, the Higuchi equation is considered one of the widely used and the most well-known controlled-release equation [23].

The conventional basic Higuchi equation is represented by

$$Q = A\sqrt{D(2Co - Cs)Cs\ t}$$

Where, Q is the cumulative amount of drug released in time t per unit area, Co is the initial drug concentration, Cs is the drug solubility in the matrix and D is the diffusion coefficient of the drug molecule in the matrix.

After simplifying the above equation, Higuchi equation can be represented in the simplified form

$$Q = K_H\ X\ t^{1/2}$$

Where, K_H is the Higuchi dissolution constant.

3. RESULTS AND DISCUSSION

3.1 Risk Assessment

Risk identification and risk analysis are two basic components of risk assessment [24]. Risk assessment was conducted by systematically summarizing all the possible variables that could impact the product quality. Risk assessment is to be done based on the prior knowledge, available literature or preliminary experimental studies. To categorise the potential risks and corresponding causes, a fish-bone diagram was built. As shown in Fig. 1. As the objective of the study is to have controlled release formulation with targeted drug

release profile, % drug released is one of the most critical CQA. As these are preliminary screening studies, only one dissolution time point (i.e. 1 hr) was selected, based on the preliminary studies where % drug release at 1 hr shows high discrimination with formulation and process changes. Another response factor included in the study was % coating efficiency which is a measure of consistent and efficient process. RPN number was scored using FMEA methodology for those factors coming from the formulation component, people, process, manufacturing equipment and analytical instruments. The RPN scores using FMEA methodology is demonstrated in Fig. 2. A risk analysis study identified nine high-risk factors, whose RPN numbers are greater than 60 and that may have a potential impact on CQAs. From these listed independent variables, 3 Formulation variables and 6 processing variables found to have an RPN number more than 60. These includes A: Level of Binder, B: Level of Hot melt coating material (% w/w), C: Level of Hydrophilic component (% w/w), D: Temperature of hot melt coating material (°C) and Atomization air temperature (°C); E: Inlet air temperature (°C), F: Fluidization air Volume (cfm), G: Spray Rate (g/min) and H: Atomizing Air Pressure. From these, variable D i.e. Temperature of hot melt coating material (°C), Atomization air temperature (°C) shall be further evaluated as a confounded variable and so shall be varied simultaneously and shall be considered as a single variable. So now these 8 factors were used in Placket Burman design for further screening and to reach to the critical factors influencing selected CQAs.

3.2 Plackett Burman's Screening Design Study

Plackett Burman's screening design study could evaluate and screen main important factors from the all possibly listed large number of factors. These shortlisted factors can then further be used in next stage optimization studies. Each factor was evaluated at low (-) and high (+) levels in the study design, as summarized in Table 1. The response evaluated were % Drug Released at 2 hr (Y1) and Coating efficiency (Y2). The objective of this study was to recognize the most significant factors affecting the CQAs. An 8-factor 2-level-12 run Plackett Burman screening study was designed using Design Expert 11 experiment design software and the responses were Y1 and Y2.

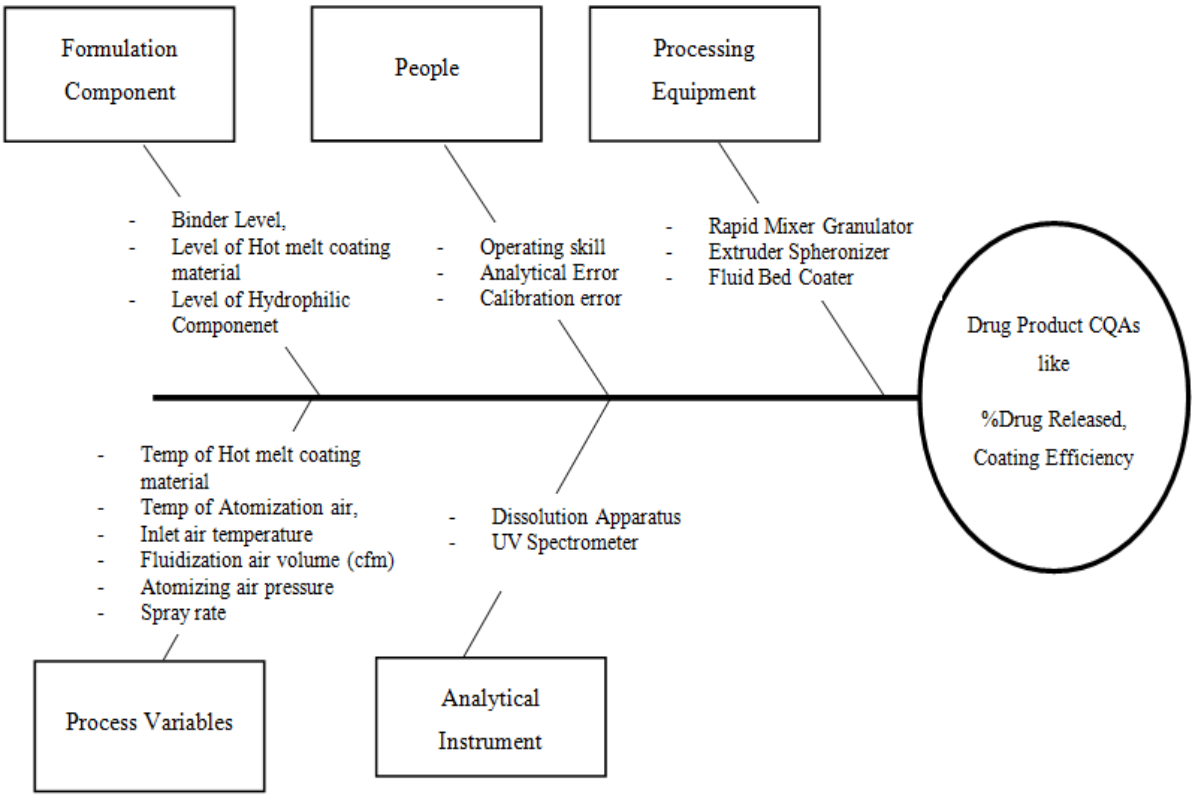

Fig. 1. Fishbone diagram illustrating possible factors which can impact Drug Product CQAs

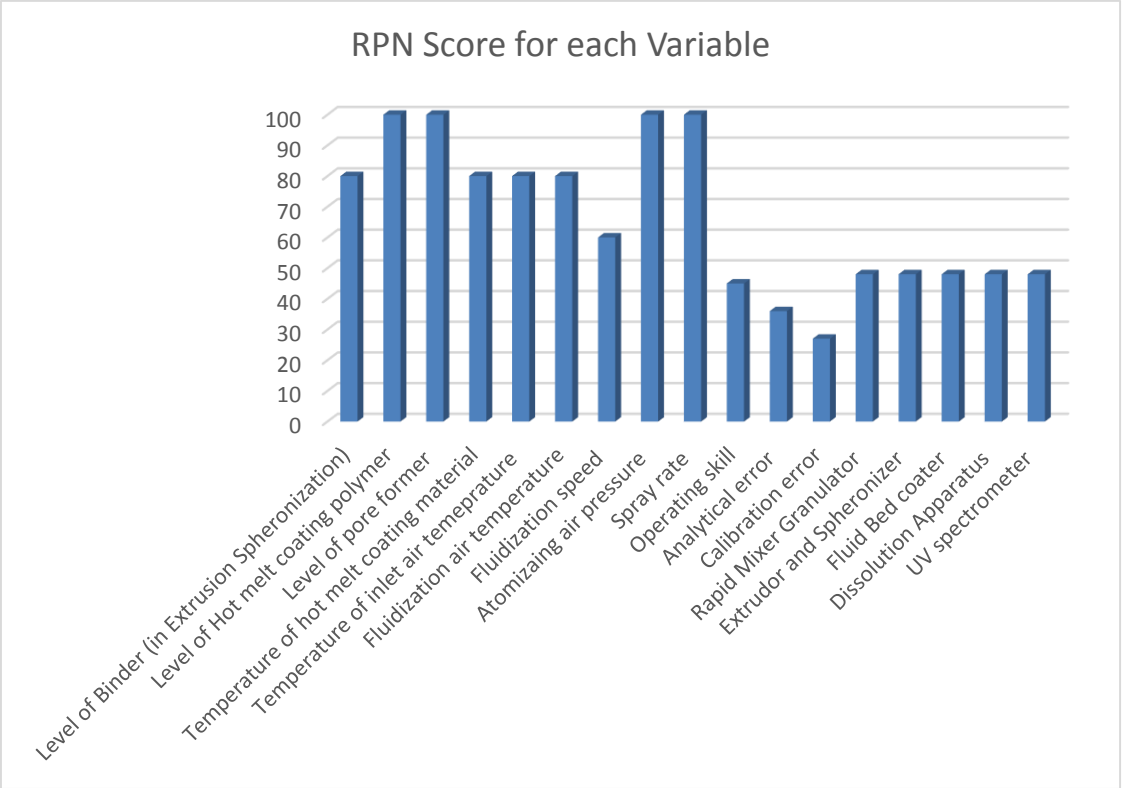

Fig. 2. RPN scores for the variables listed in Fish bone diagram

As observed from Table 3, Y1 and Y2 ranges from 7 to 57% and 65 to 97%, respectively, for the various experiments conducted in the range being studied. Fig. 4, indicates that among all of the factors, Level of Low melting material, Level of hydrophilic component and Atomizing Air pressure significantly influence Y1- % Drug Released at 2 hr. Another dependent response variable % Coating efficiency is significantly influenced by the temperature of the coating material and Atomizing Air and Spray rate. All other factors can be rated as less significant factors and shall be held constant for all further optimization trials.

Thus, these five significant variables were further evaluated for their impact on drug product quality attributes and interactions using Central Composite Design (Response Surface Methodology).

3.3 Optimization of Formulation

After screening results from the Plackett Burman design, this optimization study intended at understanding the effects and interactions between the critical formulation variables, which are A: Level of Hot melt coating material (% w/w), B: Level of Hydrophilic component (% w/w). As these Formulation variables demonstrated an impact only on the % Drug Released (as studied in Plackett Burman design), so in these formulation optimization studies, only drug release is included as a response factor. As these are more detailed formulation optimization studies, 2 time points are included in % drug release. These are 1 hr and 10 hr time points, 1 hr from which demonstrates initial burst release while 10 hr demonstrates the release pattern at later time points. Also these time points are shown to be most discriminating from the preliminary evaluation studies. Table 5, depicts the levels used for selected parameters and results for the experiments conducted. The optimization study was carried by Modified Central Composite Design (Face Centred) [Design: full, run: 13, Blocks: 1, total centre point 5 (alpha 1.0).

3.3.1 Discussion on response surface regression: % Drug released at 1 hr (Y1)

With the studied combination of two independent variables, response factor (i.e., % Drug Released at 2 hr) varies from 14% to 40%, as given in Table 2.

Table 1. Plackett Burman screening design of experiments and results

Batch ID	Formulation Variables			Processing Variables					Response Factor	
	A Level of Binder	B Level of Hot melt coating component	C Level of Hydrophilic Component	D Temperature of Hot melt coating material	E Inlet air temperature	F Fluidization air volume (cfm)	G Spray rate (g/min)	H Atomizing air pressure (bar)	Y1 % Drug Released at 2 hr (%)	Y2 Coating Efficiency (%)
OS-1	70	350	35	80	35	30	40	1	37	68
OS-2	30	350	5	110	55	30	40	4	10	75
OS-3	70	50	35	110	55	30	5	1	57	85
OS-4	30	350	35	80	55	120	40	1	37	65
OS-5	70	50	35	110	35	120	40	4	49	83
OS-6	30	350	35	110	35	30	5	4	29	97
OS-7	70	50	5	80	55	30	40	4	33	75
OS-8	30	50	5	110	35	120	40	1	44	72
OS-9	30	50	5	80	35	30	5	1	36	68
OS-10	30	50	35	80	55	120	5	4	51	78
OS-11	70	350	5	80	35	120	5	4	7	80
OS-12	70	350	5	110	55	120	5	1	15	85

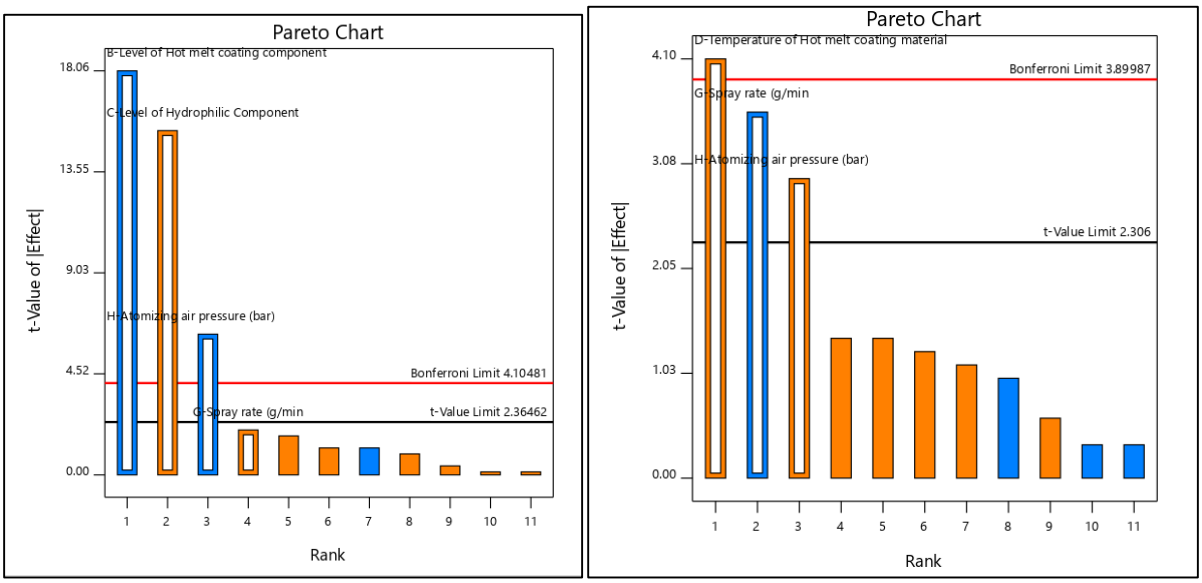

Fig. 3. Pareto chart showing t-value rank

Table 2. CCC optimization design of experiments for formulation variables and their results

Batch ID	Formulation variables		Response factor	
	A Level of Low Melting Coating Component	B Level of Hydrophilic Component	Y1 % Drug Released at 1 hr	Y2 % Drug Released at 10 hr
FS-1	300	40	26	85
FS-2	300	25	18	73
FS-3	300	40	23	82
FS-4	300	55	35	95
FS-5	330	40	21	79
FS-6	270	25	22	82
FS-7	330	25	14	74
FS-8	300	40	24	87
FS-9	270	55	39	97
FS-10	300	40	23	85
FS-11	270	40	40	97
FS-12	330	55	33	94
FS-13	300	40	27	87

ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 3, response Y1 was significantly affected by variable A (Level of Low melting coating component) and B (Level of Hydrophilic component) (p-values < 0.05). There is no significant interaction between variable A*B (p-values > 0.05). The model is significant in its prediction of Y1, as depicted by the p-value of 0.0004 (significant), F-value of 17.34, and p-value for “lack of fit” of 0.0533 (not significant).

$$Y1 = 26.54 - 5.50*A + 8.83*B + 0.5000*AB \quad (1)$$

As per regression equation 1 in uncoded units, out of 2 significant variables, variable X2 shows positive effect while X1 shows negative effect on response Y1, i.e. increasing the level of low melting coating component shall result in more controlled and slower drug release profile at 1 hr while increasing the level of hydrophilic component shall result in more faster drug release profile.

Table 3. Summary of ANOVA results of formulation variables optimization studies for Response Y1

Source	Sum of Squares	Df	Mean Square	F-Value	P-Value	
Model	650.67	3	216.89	17.34	0.0004	significant
A-Level of Low Melting Polymer	181.50	1	181.50	14.51	0.0042	
B-Level of Hydrophilic Component	468.17	1	468.17	37.43	0.0002	
AB	1.0000	1	1.0000	0.0800	0.7838	
Residual	112.56	9	12.51			
Lack of Fit	99.36	5	19.87	6.02	0.0533	not significant
Pure Error	13.20	4	3.30			
Cor Total	763.23	12				

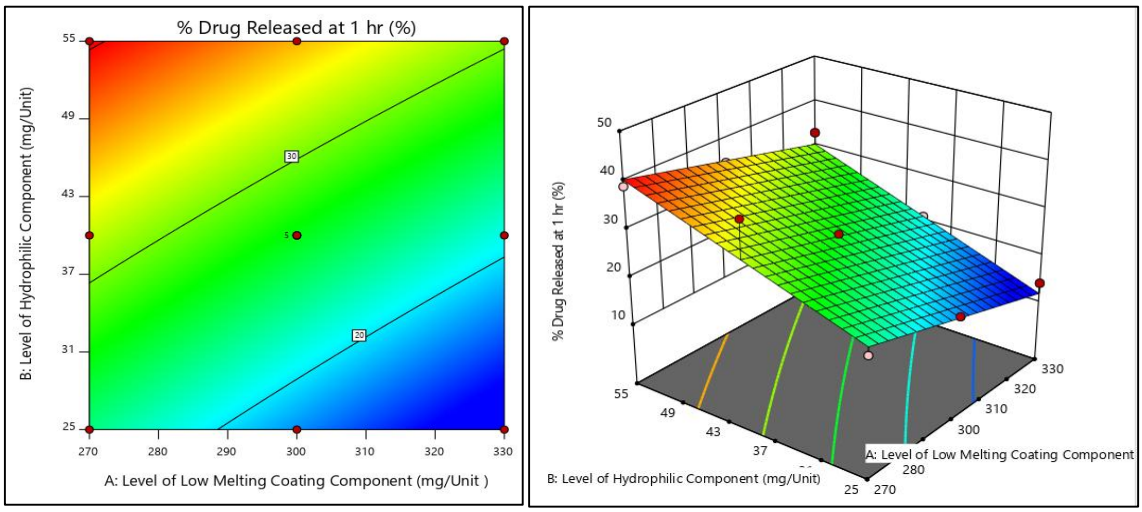

Fig. 4. (a) Contour plot of the formulation optimization studies demonstrating impact of variable A and B on response Y1 (b) 3d Surface plot the formulation optimization studies demonstrating impact of variable A and B on response Y1

3.3.2 Discussion on response surface regression: % Drug released at 10 hr (Y2)

With the studied combination of two independent variables, response factor (i.e. % Drug Released at 10 hr) varies from 73% to 97%, as given in table above.

ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 4. Summary of ANOVA results of formulation variables optimization studies for response Y2, response Y1 was significantly affected by variable A (Level of Low melting coating component) and B (Level of Hydrophilic component) (p-values < 0.05). There is no significant interaction between variable A*B (p-values > 0.05). The model is significant in its prediction of Y2, as depicted by the p-value of 0.0002 (significant), F-value of 21.27, and p-value for "lack of fit" of 0.1092 (not significant).

$$Y1= 85.92 – 4.83*A + 9.50*B + 1.25*AB...(2)$$

As per regression equation 2 in uncoded units, out of 2 significant variables, variable X2 shows positive effect while X1 shows negative effect on response Y1, i.e. increasing the level of low melting coating component shall result in more controlled and slower drug release profile at 10 hr while increasing the level of hydrophilic component shall result in more faster drug release profile.

Table 4. Summary of ANOVA results of formulation variables optimization studies for response Y2

Source	Sum of squares	df	Mean square	F-value	P-value	
Model	687.92	3	229.31	21.27	0.0002	significant
A-Level of Low Melting Polymer	140.17	1	140.17	13.00	0.0057	
B-Level of Hydrophilic Component	541.50	1	541.50	50.24	< 0.0001	
AB	6.25	1	6.25	0.5799	0.4659	
Residual	97.01	9	10.78			
Lack of Fit	80.21	5	16.04	3.82	0.1092	not significant
Pure Error	16.80	4	4.20			
Cor Total	784.92	12				

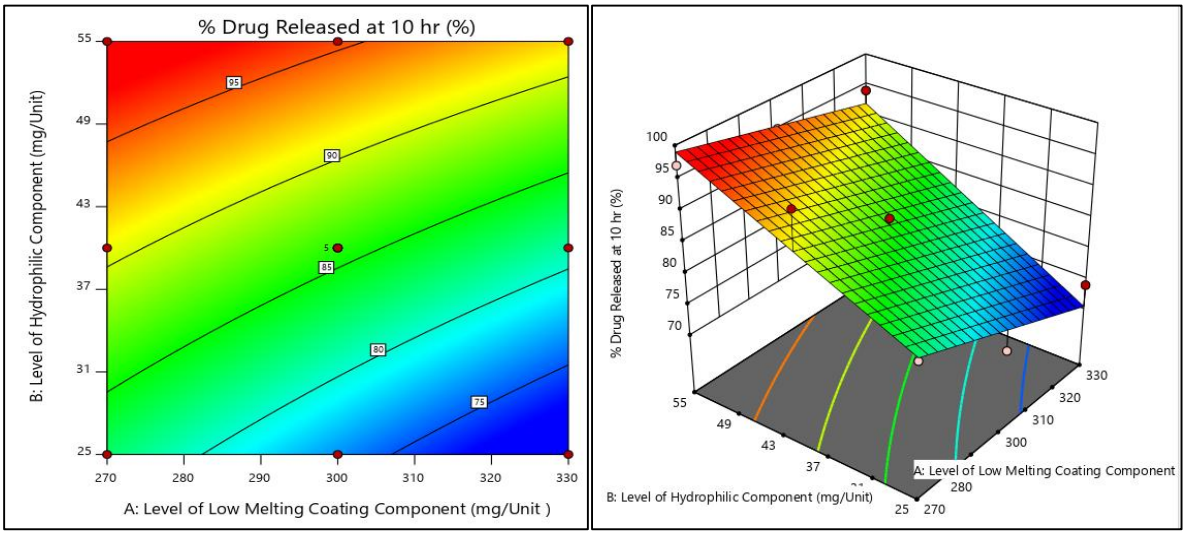

Fig. 5. (a) Contour plot of the formulation optimization studies demonstrating impact of variable A and B on response Y2 (b) 3d surface plot the formulation optimization studies demonstrating impact of variable A and B on response Y2

3.3.3 Establishment of the formulation design space

Based on the above formulation optimization studies and defined targeted ranges of Y1 and Y2 (% Drug released at 1 hr and 10 hr, respectively), operating ranges of formulation variables A and B were defined. Target ranges for Y1 is from 22-28% and for Y2 from 82-88%. In the Overlay plot given below, shaded area (in yellow) indicates the operating design space for variable A and B, where both the responses Y1 and Y2 shall fall in the target range.

3.4 Optimization of Manufacturing Process

As evaluated from the Placket-Burman design for factor screening, 3 processing variables are critical to evaluate which can impact the product CQA significantly. These are A: Temperature of Coating material and atomization air (^{O}C) (confounded variables), B: Spray Rate (g/min) and C: Atomization air pressure (bar). These processing variables showed an impact on both the responses i.e. % Drug Released and Coating Efficiency (%). As this is more intensive optimization studies, 2 dissolution time points are to be studied as a response factor of % drug release, similar to that used in Formulation optimization studies. Additionally, Mean particle size is also included as a response factor, as selection of processing parameters critically impact the uniformity of particle size distribution and agglomerates generation during process. Thus, in process optimization studies, total 4 responses are considered i.e. Y1: % Drug Released at 1 hr; Y2: % Drug Released at 10 hr;

Y3: Process Efficiency and Y4: Mean Particle Size. Table 5 demonstrates the levels used for selected parameters and results for the experiments conducted. The optimization study was carried by Modified Central Composite Design (Face Centred) [Design: full, run: 20, Blocks: 1, total centre point 6 (alpha 1.0).

3.4.1 Discussion on response surface regression: % Drug released at 1 hr (Y1) versus X1, X2 and X3

With the studied combination of three independent process variables, response factor (i.e. % Drug Released at 1 hr) varies from 22% to 31%, as given in table above. Factor having p values < 0.05 were considered as significant. ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 7, response Y1 was significantly affected by variable B (Spray Rate) and C (Atomization air pressure) (p-values < 0.05). There is no significant interaction between variable A*B, A*C or B*C (p-values > 0.05). The model is significant in its prediction of Y1, as depicted by the p-value of 0.0078 (significant), F-value of 4.93, and p-value for “lack of fit” of 0.2947 (not significant).

$$Y1= 25.35 – 0.5000*A +1.90*B-1.80*C+0.2500*AB -0.2500*AC -0.5000*B \quad (3)$$

As per regression equation 3 in uncoded units, out of 2 significant variables, variable B shows positive effect while variable C shows negative effect on response Y1, i.e. increasing the spray rate shall result in the faster dissolution at 1 hr, while increasing the Atomization air pressure shall result in the more controlled and retarded release at 1 hr.

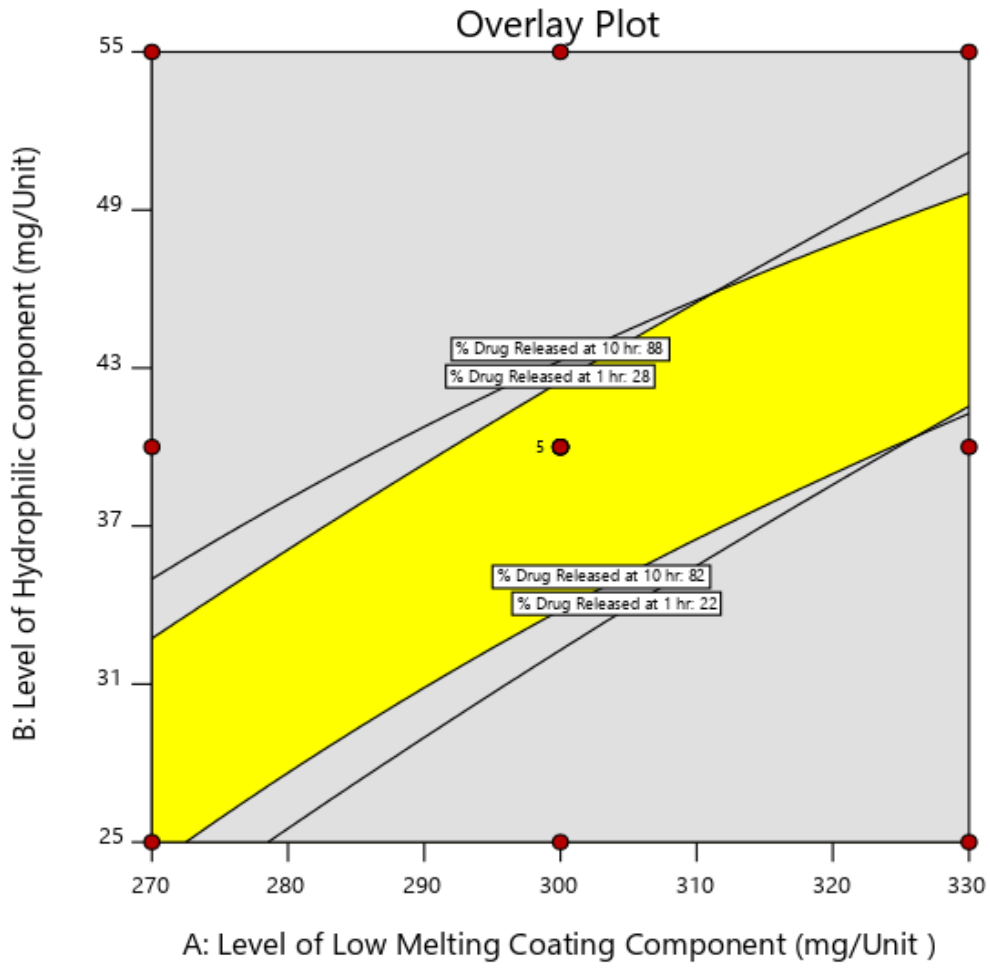

Fig. 6. Overlay plot demonstrating formulation design space

Table 5. CCC optimization design of experiments for process variables and their results

Batch ID	Process variables			Response factors			
	X1 Temperature of Coating material and atomization air (ºC)	X2 Spray Rate (g/min)	X3 Atomization Air pressure (bar)	Y1 % Drug Released at 1 hr	Y2 % Drug Released at 10 hr	Y3 Process Efficiency (%)	Y4 Mean Particle Size (µm)
PS-1	100	10	2.5	22	85	87	653
PS-2	100	10	2.5	25	87	90	658
PS-3	90	15	3.5	26	89	75	677
PS-4	90	5	1.5	26	87	86	682
PS-5	100	5	2.5	23	82	89	648
PS-6	100	10	2.5	25	86	85	660
PS-7	90	10	2.5	25	87	81	675
PS-8	100	10	1.5	27	91	83	672
PS-9	90	15	1.5	31	92	82	692
PS-10	100	10	2.5	23	87	89	667
PS-11	100	15	2.5	28	91	86	680
PS-12	100	10	2.5	25	89	87	652
PS-13	100	10	3.5	23	85	84	642
PS-14	110	5	3.5	22	79	86	640
PS-15	90	5	3.5	25	84	72	655
PS-16	110	15	3.5	26	88	89	645
PS-17	110	10	2.5	24	85	88	648
PS-18	110	5	1.5	26	90	90	651
PS-19	100	10	2.5	25	87	90	655
PS-20	110	15	1.5	30	87	89	662

Table 6. Summary of ANOVA results of process variables optimization studies for Response Y

Source	Sum of Squares	Df	Mean Square	F-Value	p-Value	
Model	74.00	6	12.33	4.93	0.0078	significant
A-Temperature of Coating material and atomization air	2.50	1	2.50	0.9985	0.3359	
B-Spray Rate	36.10	1	36.10	14.42	0.0022	
C-Atomization air pressure	32.40	1	32.40	12.94	0.0032	
AB	0.5000	1	0.5000	0.1997	0.6623	
AC	0.5000	1	0.5000	0.1997	0.6623	
BC	2.00	1	2.00	0.7988	0.3877	
Residual	32.55	13	2.50			
Lack of Fit	23.72	8	2.96	1.68	0.2947	not significant
Pure Error	8.83	5	1.77			
Cor Total	106.55	19				

3.4.2 Discussion on response surface regression: Drug released at 10 hr (Y2) versus X1, X2 and X3

With the studied combination of three independent process variables, response factor (i.e. % Drug Released at 10 hr) varies from 79% to 92%, as given in table above. Factor having p values < 0.05 were considered as significant. ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 7, response Y1 was significantly affected by variable B (Spray Rate) and C (Atomization air pressure) (p-values < 0.05). There is no significant interaction between variable A*B, A*C or B*C (p-values > 0.05). The model is significant in its prediction of Y2, as depicted by the p-value of 0.0005 (significant), F-

value of 4.75 and p-value for "lack of fit" of 0.0939 (not significant).

Y1= 86.70 +0.6000*A+2.50*B-2.20*C-0.5000*AB -0.5000*AC +1.0000*BC…….(4)

As per regression equation 4 in uncoded units, out of 2 significant variables, variable X2 shows positive effect while X3 shows negative effect on response Y2, i.e. increasing the spray rate shall result in the faster dissolution at 10 hr, while increasing the Atomization air pressure shall result in the more controlled and retarded release at 10 hr.

3.4.3 Discussion on response surface regression: % Coating efficiency (Y3) versus X1, X2 and X3

With the studied combination of three independent process variables, % coating efficiency varies from 75% to 90%, as given in table above. Factor having p values < 0.05 were considered as significant. ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 8, response Y3 was significantly affected by variable X1 (Temperature of Coating solution and Atomizing Air) and X3 (Atomization air pressure)

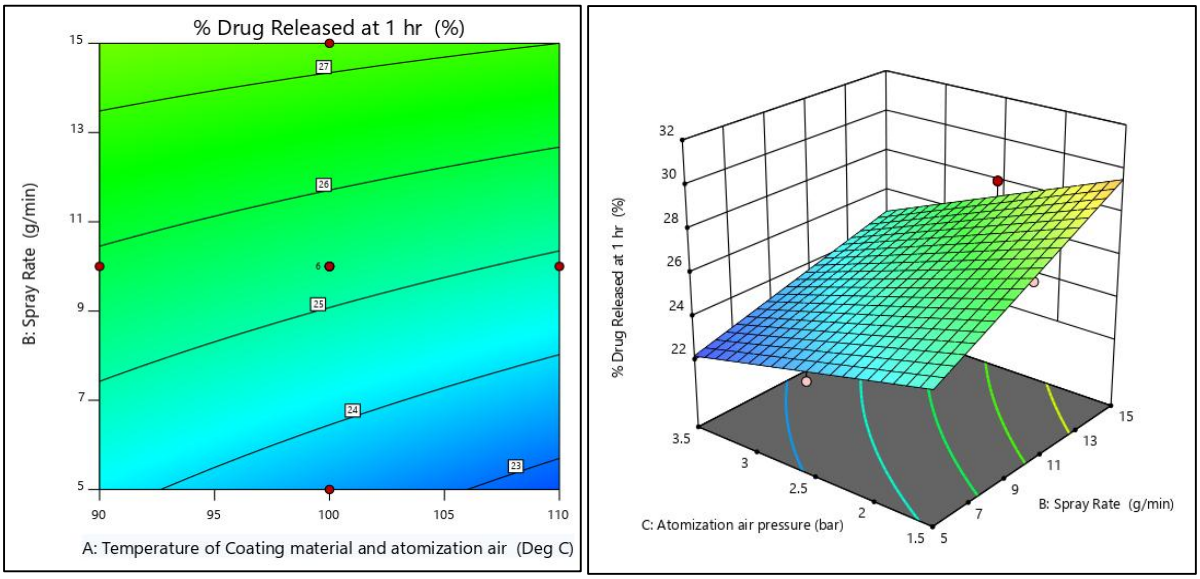

Fig. 7. (a) Contour plot of the process optimization studies demonstrating impact of variable B and C on response Y1 (b) 3d Surface plot the formulation optimization studies demonstrating impact of variable B and C on response Y1

Table 7. Summary of ANOVA results of process variables optimization studies for response Y2

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	126.50	6	21.08	4.75	0.0090	significant
A-Temperature of Coating material and atomization air	3.60	1	3.60	0.8111	0.3842	
B-Spray Rate	62.50	1	62.50	14.08	0.0024	
C-Atomization air pressure	48.40	1	48.40	10.90	0.0057	
AB	2.00	1	2.00	0.4506	0.5138	
AC	2.00	1	2.00	0.4506	0.5138	
BC	8.00	1	8.00	1.80	0.2024	
Residual	57.70	13	4.44			
Lack of Fit	48.87	8	6.11	3.46	0.0939	not significant
Pure Error	8.83	5	1.77			
Cor Total	184.20	19				

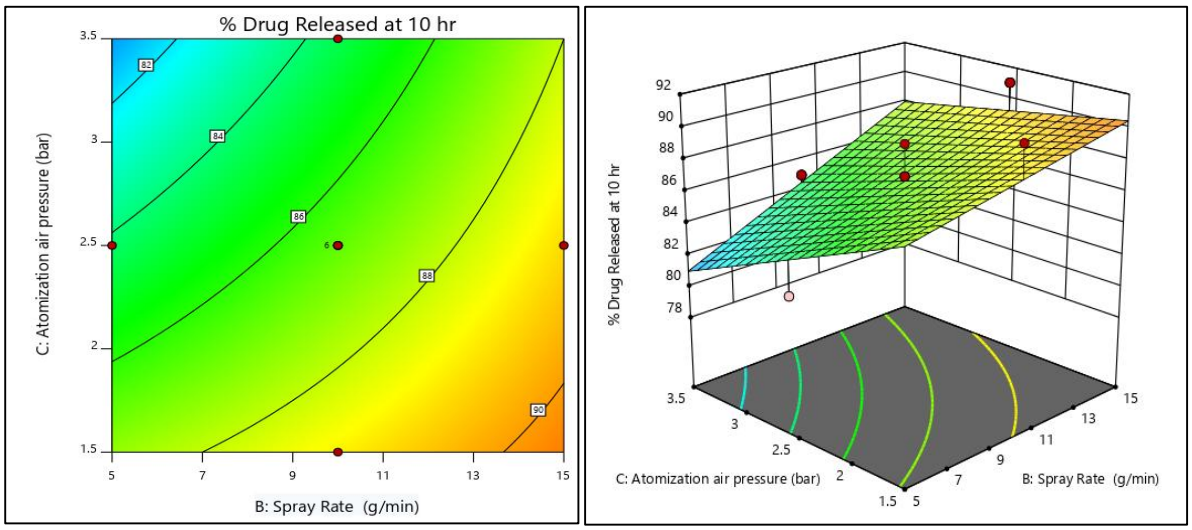

Fig. 8. (a) Contour plot of the process optimization studies demonstrating impact of variable B and C on response Y2 (b) 3d Surface plot the process optimization studies demonstrating impact of variable B and C on response Y2

Table 8. Summary of ANOVA results of process variables optimization studies for response Y3

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	321.97	6	53.66	5.25	0.0060	significant
A-Temperature of Coating material and atomization air	211.60	1	211.60	20.71	0.0005	
B-Spray Rate	0.4000	1	0.4000	0.0391	0.8462	
C-Atomization air pressure	57.60	1	57.60	5.64	0.0337	
AB	1.13	1	1.13	0.1101	0.7453	
AC	36.12	1	36.12	3.54	0.0827	
BC	15.12	1	15.12	1.48	0.2454	
Residual	132.83	13	10.22			
Lack of Fit	112.83	8	14.10	3.53	0.0906	not significant
Pure Error	20.00	5	4.00			
Cor Total	454.80	19				

(p-values < 0.05). There is no significant interaction between variable A*B or A*C or B*C (p-values >0.05). The model is significant in its prediction of Y3, as depicted by the p-value of 0.0060 (significant), F-value of 5.25, and p-value for "lack of fit" of 0.0906 (not significant).

Y1= 85.40 + 4.60*A – 0.2000*B-2.40*C+0.3750*AB +2.12*AC +1.37*BC…(5)

As per regression equation 5 in uncoded units, out of 2 significant variables, variable X1 shows positive effect while X3 shows negative effect on response Y3, i.e. increasing the temperature of coating solution and atomization air results in increased % of coating efficiency, while increasing the Atomization air pressure shall results in reduction in the % coating efficiency. This indicates when the temperature of the coating solution is lower, it results in faster congealing resulting in more agglomerates generation and thus reduced coating efficiency. While when atomization air pressure is higher, it may lead to sticking of some coating material to the wall of the fluidization chamber and thus resulting in reduced coating efficiency.

3.4.4 Discussion on response surface regression: Mean particle size (Y4) versus X1, X2 and X3

With the studied combination of three independent process variables, % coating efficiency varies from 642 to 692, as given in

table above. Factor having p values < 0.05 were considered as significant. ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 9, response Y3 was significantly affected by variable A (Temperature of Coating solution and Atomizing Air), B (Spray Rate) and C (Atomization air pressure) (p-values < 0.05). There is no significant interaction between variable A*B, A*C or B*C. The model is significant in its prediction of Y4, as depicted by the p-value of <0.0001(significant), F-value of 13.38, and p-value for "lack of fit" of 0.2900 (not significant).

Y4= 660.70 -13.50*A+8.00*B-10.0*C-2.00*AB +1.75*AC +0.7500*BC……..…(6)

As per regression equation 5 in uncoded units, out of 3 significant variables, variable B shows positive effect while A and C shows negative effect on response Y4, i.e. increasing the temperature of coating solution and atomization air pressure results in reduced mean particle size, while increasing the spray rate results in higher level of mean particle size value. This indicates when the temperature of the coating solution is higher and atomization pressure is high, coating material spreads more evenly which results in more uniform particle size distribution. While when spray rate is higher, then there might be some agglomeration or localized particle coating resulting in increased value of mean particle size.

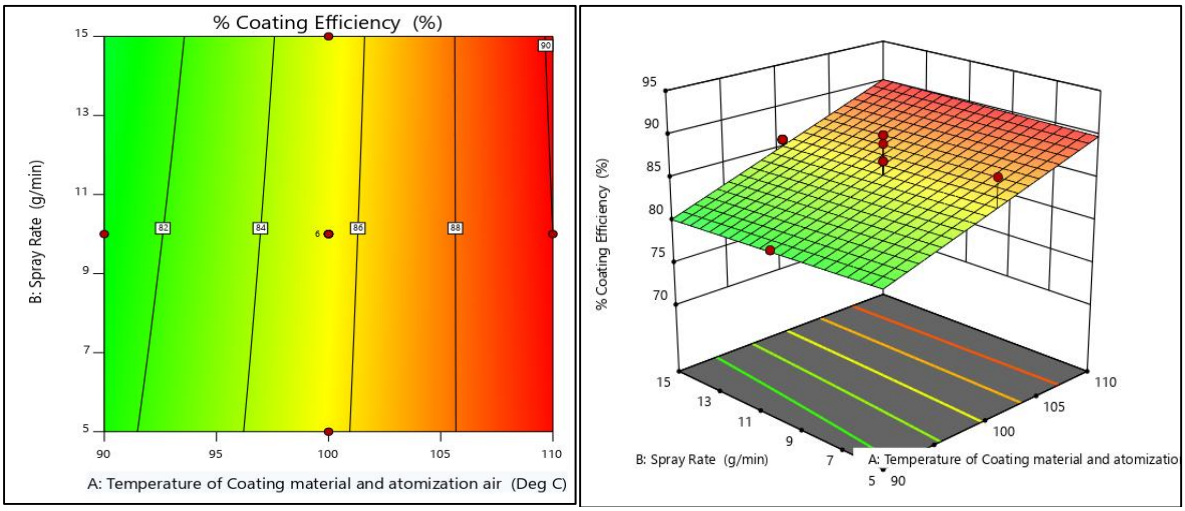

Fig. 9. (a) Contour plot of the process optimization studies demonstrating impact of variable A and C on response Y3 (b) 3d Surface plot the process optimization studies demonstrating impact of variable A and C on response Y3

Table 9. Summary of ANOVA results of process variables optimization studies for response Y4

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	3523.50	6	587.25	13.38	< 0.0001	significant
A-Temperature of Coating material and atomization air	1822.50	1	1822.50	41.51	< 0.0001	
B-Spray Rate	640.00	1	640.00	14.58	0.0021	
C-Atomization air pressure	1000.00	1	1000.00	22.78	0.0004	
AB	32.00	1	32.00	0.7289	0.4087	
AC	24.50	1	24.50	0.5581	0.4683	
BC	4.50	1	4.50	0.1025	0.7539	
Residual	570.70	13	43.90			
Lack of Fit	417.20	8	52.15	1.70	0.2900	not significant
Pure Error	153.50	5	30.70			
Cor Total	4094.20	19				

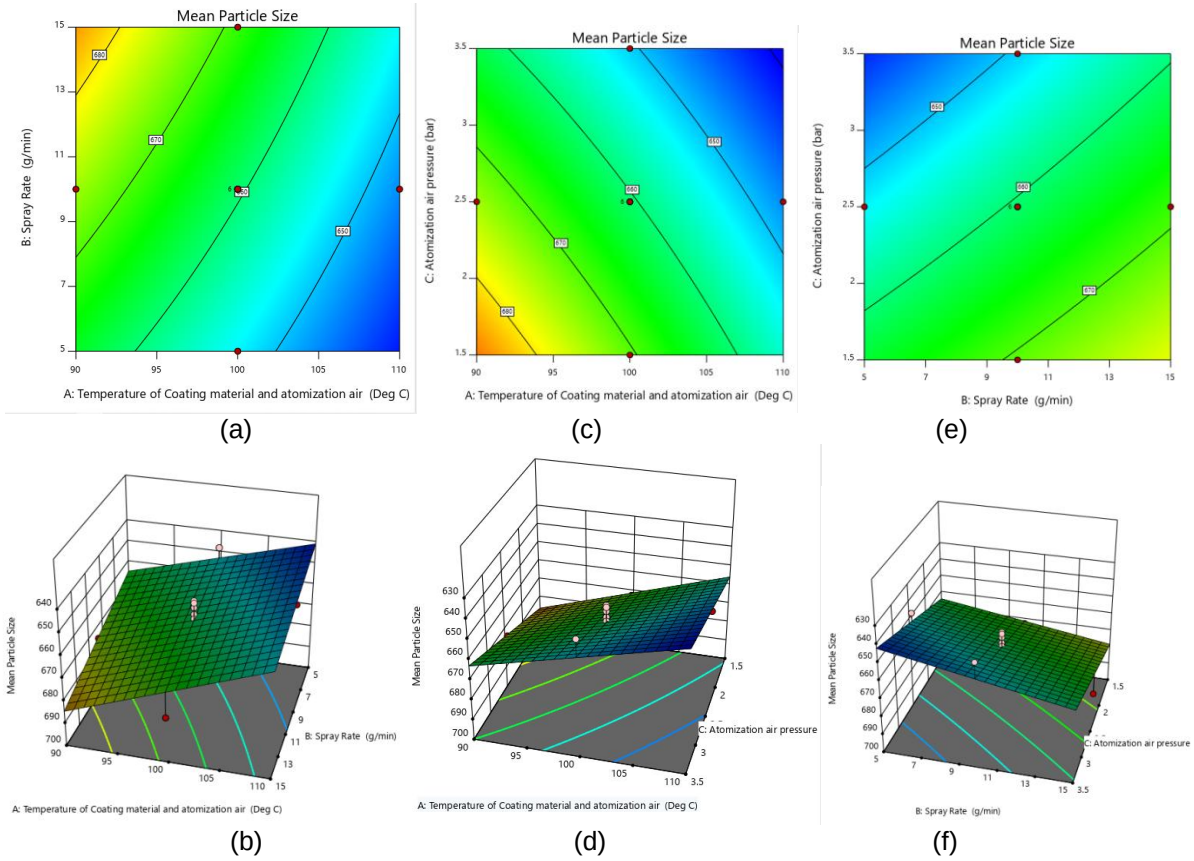

Fig. 10. (a) Contour plot of the process optimization studies demonstrating impact of variable A and B on response Y4 (b) 3d surface plot the process optimization studies demonstrating impact of variable A and B on response Y4 (c) Contour plot of the process optimization studies demonstrating impact of variable A and C on response Y4 (d) 3d Surface plot the process optimization studies demonstrating impact of variable A and C on response Y4 (e) Contour plot of the process optimization studies demonstrating impact of variable B and C on response Y4 (b) 3d Surface plot the process optimization studies demonstrating impact of variable B and C on response Y4

3.4.5 Establishment of the design space

Based on the above process optimization studies and defined targeted ranges of Y1, Y2, Y3 and Y4, operating ranges of processing variables A, B and C can be defined. Target ranges for Y1 is from 40-45% and for Y2 from 77-83%. Target range for %coating efficiency is from 85% to 100% and for mean particle size it ranges from 650-680µ. In the Overlay plot given below, shaded area (in yellow) indicates the operating design space for variable B (Spray rate) and C (Atomization air pressure), while keeping the A (temperature of coating solution and Atomization air) to 110ºC. We get the maximum wide operating ranges for variables B and C, when variable A is set to its maximum value of about 110ºC. When we reduce the value of variable A, then the operating ranges of variable B and C gets narrowed down in the design space. Thus, it can be said that process runs to its maximum efficiency when variable A is set at higher values. Thus, when we operate in this shaded design space, all four responses Y1, Y2, Y3 and Y4 shall fall in the target range and is wide enough to ensure product quality.

3.5Confirmation test of the model and checkpoint batches

To evaluate the accuracy and robustness of the obtained model, a confirmation test batch was manufactured. Following 3 batches were executed with the optimized formulation. Processing parameters were selected from the obtained design space. Batch was analysed for all 4 response factors. Details of the Formulation and processing parameters for the 3 checkpoint

batches are shown in Table 1. All 3 batches were evaluated for the critical parameters and then the observed values are compared with the responses predicted by obtained design space model. Responses. All obtained results were within the 95% CI of the predicted value. Thus, based on data, it can be concluded that obtained model is valid and relevant.

3.6 Characterization of Hot-Melt Coated Pellets

The results of the evaluation of HMC pellets are summarized in [Table 2]. Core pellets prepared by extrusion-spheronization process demonstrate good micromeritic properties. However, hot melt coating with lipid excipient resulted in further improvement of the micromeritic properties. The pellets are having very narrow and uniform size distribution, as observed from the results where pellet size range from about 641-665 µm after HMC. Also pellets are spherical in shape with very smooth surface. Angle of repose results were approximately 22- 25º for all formulations indicating excellent flow properties of HMC pellets. Values of Friability are negligible, where maximum friability value is about 0.32%, which indicates good mechanical strength of pellets. This value can be due to the loss of some coated wax due to attrition forces in friability testing.

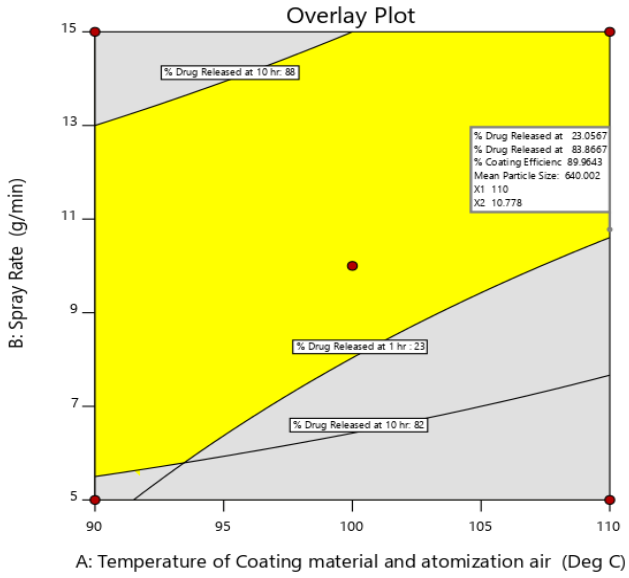

Fig. 21. Design space for processing variables (Spray rate (B) and Atomization air pressure (C), when Temperature of the coating solution and atomization air (A) is set to its maximum value

Table 1. Formulation and process parameter details for the confirmation batches

Ingredients	Formulation		
	F1	F2	F3
Core Pellet Composition			
Oxcarbazepine	600.00	600.00	750.00
MCC (Avicel PH 101)	350.00	350.00	437.50
Hypromellose (6cps)	50.00	50.00	62.50
Purified Water	q.s.	q.s.	q.s.
Coating Composition			
Stearic Acid	300.00	300.00	300.00
PEG 1500	40.00	40.00	40.00
Total Weight	**1340 mg**	**1340 mg**	**1340 mg**
Processing Parameters			
Temperature of Coating material and Atomization air	110 ºC	110 ºC	100ºC
Spray Rate	7 g/min	11 g/min	9 g/min
Atomization Air Pressure	2.5 bar	3.0 bar	3.3 bar

Table 11. Actual and Predicted values for the response variables in confirmation batches

Batch ID→	Batch F1		Batch F2		Batch F3	
Response Variables	**Predicted (90% CI)**	**Actual**	**Predicted (90% CI)**	**Actual**	**Predicted (90% CI)**	**Actual**
Y1 - % Drug released at 1 hr	23.56 (19.77-27.35)	22	24.205 (20.43-27.98)	23	23.61 (19.99-27.23)	24
Y2 - % Drug released at 10 hr	84.90 (79.85-89.95)	82	85.25 (80.23-90.27)	87	84.28 (79.46-89.10)	83
Y3 - % Coating Efficiency	89.895 (82.23-97.56)	87.8	90.035 (82.42-97.65)	91.2	83.3 (75.99-90.61)	86
Y4- Mean Particle Size (μ)	643.6 (627.72-659.48)	648	644.35 (628.56-660.14)	651	650.98 (635.82-666.14)	658

Table 12. Evaluation of hot-melt coated pellets

Formulation	Drug Content	Friability	Angle of Repose	Bulk density	Tapped density	Housner's Ration	Carr's Index	Mean pellet Size
	(%)	**(%)**	**(^{0})**	**(g/cm^3)**	**(g/cm^3)**			**(μm)**
F1	99.2%	0.15	23.6	0.87	0.92	1.05	5.43	648
F2	100.4%	0.09	24.8	0.89	0.95	1.07	6.32	641
F3	98.5%	0.32	22.3	0.92	0.98	1.07	6.12	665

Time (Hr)	Sq. Rt of Time (Hr)	% Drug Released
0	0	0
1	1	26
2	1.4	33
4	2	47
6	2.5	62
8	2.8	75
10	3.1	88
12	3.5	98

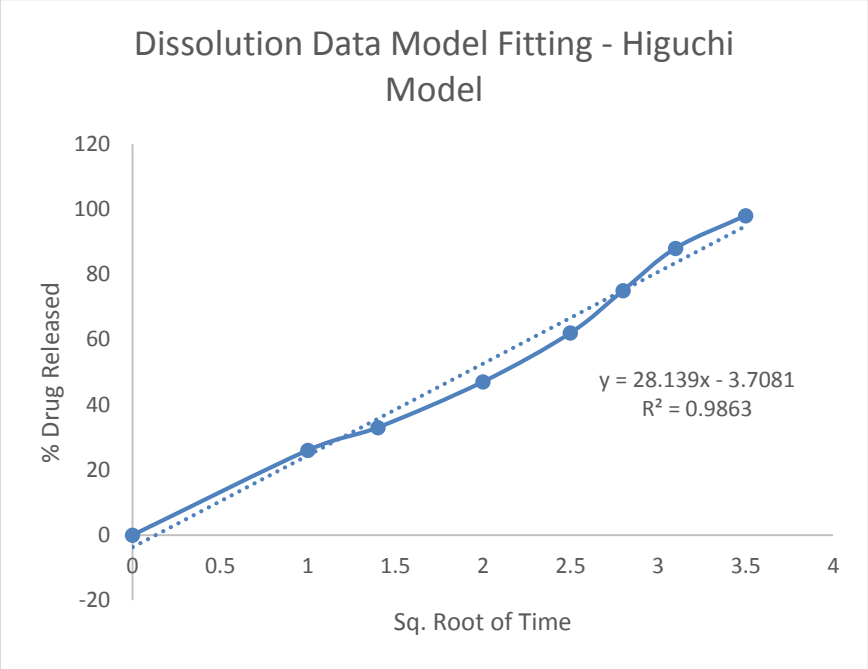

Fig. 12. Higuchi model kinetic release of oxcarbazepine hot melt coated pellets

3.7 Dissolution Modelling

Here, % drug released (cumulative) was plotted against the square root of time. Graph demonstrate reasonable linearity indicating that Formulation follows Higuchi model dissolution kinetic.

As correlation coefficient is higher for the above plot so we can interpret that the prime mechanism of drug release is diffusion-controlled release mechanism.

4. CONCLUSION

Present study aims to develop a pellet formulation coated with hot melt coating technique which is solventless cost effective technology for coating of tablets and multiparticulate system. Based on initial risk assessment, different formulation and process variables were screened for criticality using plackett-burman screening design. Based on the screening, critical formulation and process variables were then optimized using central composite experimental design (response surface methodology). Critical response factors evaluated in the design are %drug release at 1 hr, % drug release at 10 hr, % Coating efficiency and Mean particle size. After optimization, confirmation batches were also executed within the obtained design space to check the validity of model, which showed consistent similarity between the actual and predicted values. All other characterization studies of the optimized formulation pellets, demonstrates good strength and micromeritic properties. Dissolution modelling in Higuchi model demonstrates the predominant diffusion-controlled drug release from the formulation. Thus, hot melt coating can be effectively applied for development of controlled release formulation of high soluble drug substances.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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