Journal of Pharmaceutical Research International

33(26B): 80-102, 2021; Article no.JPRI.67760
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Development and Optimization of Controlled Release Formulation and Process of Levetiracetam with Hot Melt Coating Technology

Nilam Patel[1*] and Rupal Jani[2]

[1]Parul Institute of Pharmacy and Research, Parul University, P.O. Limda, Ta: Waghodia, Dist. Vadodara-391760, Gujarat, India.
[2]Department of Pharmaceutics, Parul Institute of Pharmacy and Research, Parul University, P.O. Limda, Ta: Waghodia, Dist. Vadodara-391760, Gujarat, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author NP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author RJ read and approved the final manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i26B31485
Editor(s):
(1) Dr. Mohamed Salem Nasr Allah, Weill Cornell Medical College, Qatar.
Reviewers:
(1) Efren Hernandez Baltazar, Universidad Autónoma del Estado de Morelos, Mexico.
(2) Rahmat Satoto, Indonesian Institute of Sciences, Indonesia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/67760

Original Research Article

Received 20 February 2021
Accepted 23 April 2021
Published 28 April 2021

ABSTRACT

Conventional coating processes are based on aqueous or organic solvent system, resulting in the lengthy and tedious processes where use and removal of solvents consumes lots of energy and resources. Also, solvent disposal is a critical issue considering environmental hazard.Hot melt coating process avoids use of solvent and is short and energy-efficient process. Here, Hot-melt coating process (HMCP) is being developed to formulate lipid based oral controlled release formulation system to deliver highly water soluble Biopharmaceutical Classification System (BCS) class-I drug Levetiracetam. 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 lipid and a hydrophilic component. Formulation and Process parameters were optimized to achieve targeted drug release profile and other target product profile with particular focus onHMCP. Quality by design (QbD) with DOE approach was used for designing and development of the formulation, by putting risk

**Corresponding author: E-mail: nilampatel@qmedica.in;*

assessment Failure Mode and Effect analysis (FMEA, Fish-bone diagram), screening (by Plackett Burman), and optimization by Central Composite Design (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 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; levetiracetam.

1. INTRODUCTION

Coatings are an essential part in formulation development of pharmaceutical dosage form. Coatings are applied to achieve 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 dryingand 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 fluidizedBed can be modified suitably for hot-meltcoatingduetoitscapability to maintain theproduct temperature closetothecong ealingtemperature of themelt [3]. The molten liquid is transferred to fluidized bed and is atomized into small particles/droplets by applying pressurized atomizing air througha 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, hasbeen 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 spraygun inside the expansion chamber should also be well insulated. This is required to prevent the re-meltingof coating material on the substrates, when they comein contact with the spraygun 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 meltingand spraying on the substrate, and cooling and solidificationof the coating [7].During whole coating process, coating melt is maintainedat 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 liquidstorage and spraying through the nozzle during application [9].

Levetiracetam, a high dose, highly soluble anti-epileptic drug [10] was selected for the present study. It is well-documented thatLevetiracetam as controlled release dosage forms would provide various advantages over the immediate release formulations, recommended for multiple dosing, like reduced fluctuations of plasma drug levels, reduced adverse effects and more patient compliance [11]. 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 – Levetiracetam,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. Glyceryl Behenate 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

Levetiracetamwas supplied from Hetero Drugs Limited, 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, Glyceryl Behenate (Compritol 888 ATO), was supplied byGattefosse. All chemical reagents used were of analytical grade.

2.1 Preparation of Pellets with Extrusion Spheronization

Levetiracetamcore 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, 40 rpm, room temperature) and spheronization using 2 mm chequered plate. Pellets were then driedin a tray dryer at 60^{o}C temperature for about 60 minutes.

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 processis 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 QbDconcept was followed in the design and development of hot melt coated pellets of Levetiracetam solution and was done as per ICH Q8 – Pharmaceutical Development [12]. 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. 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 wereanalysed, 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 [13]. 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 Levetiracetam. In FMEA methodology each variable was scored in terms of severity (S), detectability (D), and probability (P) [14]. 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 [15] 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 andabove 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 [16].

2.5 Screening study (Plackett Burman design)

The Plackett Burman screening study DOE design was used for screening of significant factors influencing product CQAs [17]. 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 [18]. 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 [19]. It predicts all the interactions, especially the secondorder- 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’’ [20]. 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 [21].. 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 hot melt coated pellet formulation was determined by weighing crushed sample equivalent to 100.0 mg of Levetiracetam 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 209.0 nm using a validated UV-

Visiblespectrophotometer method [22] (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 [23]. Mean pellet size was calculated according to the equation given below [24]:

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

Equation 1 Calculation of Mean Particle Size (µm)

2.9.3 Friability of the pellet

The Friability of hot-melt coated pellets was evaluated by ElectrolabGranule 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. at 240 strokes per min for 2 min and sieved 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.

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.

Other micromeritic properties like Bulk density and Tapped density were also evaluated as per the procedure described in USP General Chapter <616> - Method I. Compressibility Index and Hausner ratio were calculated as per the procedure described in USP General Chapter <1174> [25].

2.9.5 Drug release study

Dissolution studies (six replicates for each experiment) were performed using the basket method – apparatus I (USP 43), at 100 rev./min, 37^0C, with 900 ml of dissolution fluid (Buffer pH 6). Dissolution fluid was prepared by dissolving 6.8 g of potassium dihydrogen phosphate and 0.2 g of sodium hydroxide in 1 L of water. pH of 6.0 was adjusted with 1 N sodium hydroxide. The pellets were placed in dry basket and attached to the shaft. The 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 209.0 nm in an UV-Visiblespectrophotometer (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. Higuchi model-based drug release kinetic was applied here, for the following two reasons.

i) Generally, Reservoir-Based Controlled Release Systems with insoluble/non-biodegradable polymers follows diffusion-controlled drug release kinetic [26].
ii) 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 [27].

The conventional basic Higuchi equation is represented by

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

Equation 2 Higuchi dissolution kinetic equation

Where, Q is the cumulative amount of drug released in time t per unit area (%), Co is the initial drug concentration (µg) , Cs is the drug solubility in the matrix (µg/ml) 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

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

Equation 3 Simplified Higuchi equation

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 [28]. 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 (^oC) and Atomization air temperature (^oC); E: Inlet air temperature (^oC), 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 (^oC), Atomization air temperature (^oC) 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-factor2-level-12 run Plackett Burman screening study was designed using Design Expert 11 experiment design software and the responses were Y1 and Y2.

As observed from Table 3, Y1 and Y2 ranges from 12 to 77% and 62 to 96%, respectively, forthe 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 6 hr time points, 1 hr from which demonstrates initial burst release while 6 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 34% to 50%, as given in Table 2.

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 <0.0001 (significant), F-value of 39.11, and p-value for “lack of fit” of 0.8462 (not significant).

$$Y1= 41.54 – 3.00*A +4.50*B-0.2500*AB \quad (1)$$

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.

3.3.2 Discussion on Response Surface Regression: % Drug Released at 6 hr (Y2)

With the studied combination of two independent variables, response factor (i.e. % Drug Released at 2 hr) varies from 66% to 88%, as given in table above.

ANOVA was performed to evaluate the model significance. As revealed in the analysis of variance Table 4, 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 0.0002 (significant), F-value of 20.57, and p-value for “lack of fit” of 0.8358 (not significant).

$$Y1= 77.15 – 4.50*A + 6.50*B + 0.0000*AB \quad (2)$$

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 6 hr while increasing the level of hydrophilic component shall result in more faster drug release profile.

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 6 hr, respectively), operating ranges of formulation variables A and B were defined. Target ranges for Y1 is from 40-45% and for Y2 from 77-83%. 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). As indicated in pareto chart, Temperature of coating material and Spray have effect over the coating efficiency and Atomization air pressure over the % drug release. These processing variables showed an impact on both the responses i.e. % Drug Released and Coating Efficiency (%). As

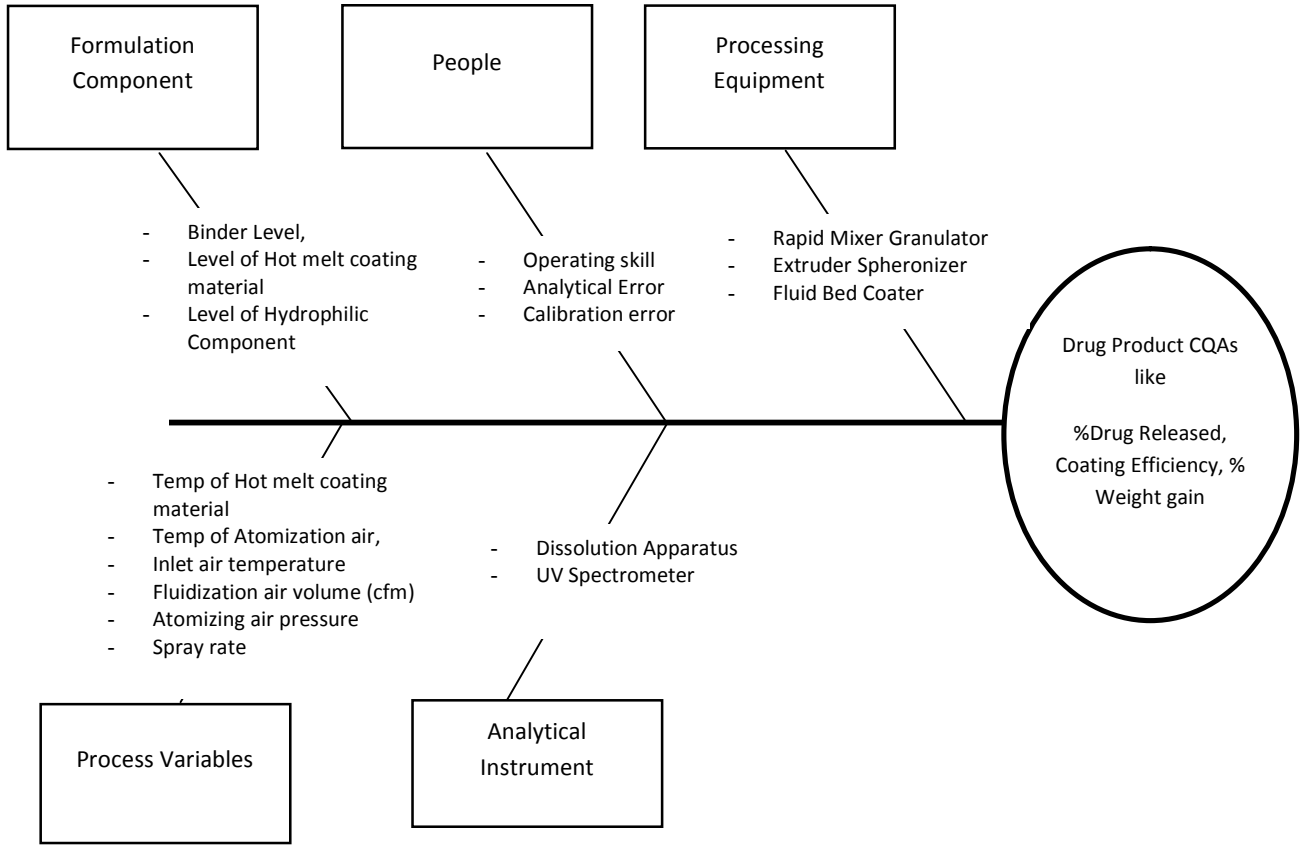

Fig. 1. Fishbone diagram illustrating possible factors which can impact Drug Product CQAs

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	100	600	50	80	35	30	40	1	38	66
OS-2	100	200	50	110	55	30	5	1	77	92
OS-3	100	200	50	110	35	120	40	4	62	83
OS-4	100	600	10	110	55	120	5	1	17	96
OS-5	50	600	10	110	55	30	40	4	12	85
OS-6	50	200	10	110	35	120	40	1	62	82
OS-7	100	200	10	80	55	30	40	4	48	68
OS-8	50	200	10	80	35	30	5	1	62	82
OS-9	50	200	50	80	55	120	5	4	65	77
OS-10	50	600	50	80	55	120	40	1	42	62
OS-11	50	600	50	110	35	30	5	4	39	88
OS-12	100	600	10	80	35	120	5	4	12	68

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 6 hr
FS-1	450	25	46	82
FS-2	420	20	43	81
FS-3	450	20	41	79
FS-4	450	15	38	71
FS-5	420	25	50	88
FS-6	480	25	43	80
FS-7	450	20	41	77
FS-8	420	15	40	74
FS-9	480	15	34	66
FS-10	450	20	42	75
FS-11	450	20	40	77
FS-12	450	20	44	83
FS-13	480	20	38	70

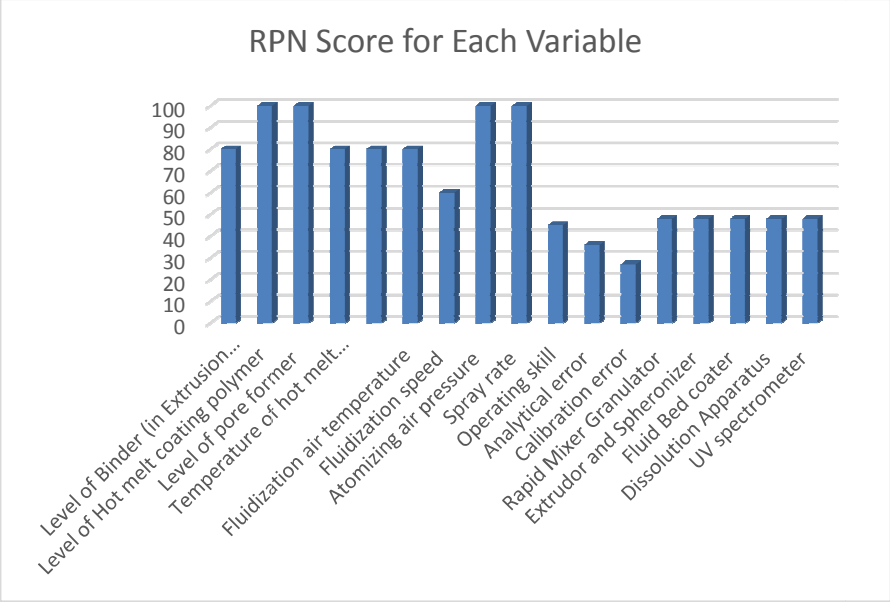

Fig. 2. RPN scores for the variables listed in Fish bone diagram

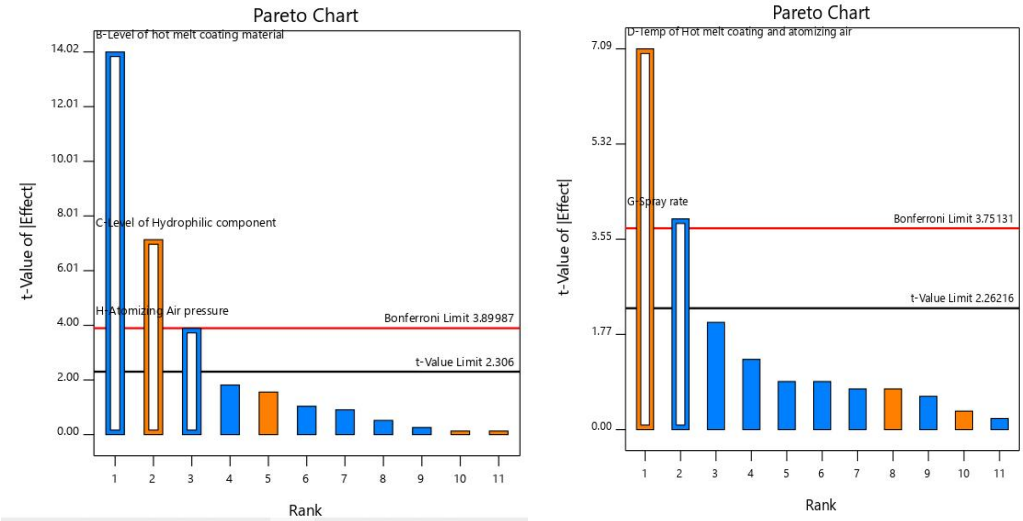

Fig. 3. Pareto chart showing t-value rank (a) Pareto chart for response Y1 % Drug Released at 2 hr (%) (b) Pareto chart for response Y2Coating Efficiency (%)(Variables with values above t-value threshold are selected as a significant variables)

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 6 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).

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	175.75	3	58.58	39.11	< 0.0001	Significant
A-Level of Low Melting Polymer	54.00	1	54.00	36.05	0.0002	
B-Level of Hydrophilic Component	121.50	1	121.50	81.12	< 0.0001	
AB	0.2500	1	0.2500	0.1669	0.6924	
Residual	13.48	9	1.50			
Lack of Fit	4.28	5	0.8562	0.3722	0.8462	not significant
Pure Error	9.20	4	2.30			
Cor Total	189.23	12				

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	375.00	3	125.00	20.57	0.0002	significant
A-Level of Low Melting Polymer	121.50	1	121.50	19.99	0.0016	
B-Level of Hydrophilic Component	253.50	1	253.50	41.72	0.0001	
AB	0.0000	1	0.0000	0.0000	1.0000	
Residual	54.69	9	6.08			
Lack of Fit	17.89	5	3.58	0.3890	0.8358	not significant
Pure Error	36.80	4	9.20			
Cor Total	429.69	12				

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

	Process Variables			Response Factors			
Batch ID	**X1 Temperature of Coating material and atomization air (°C)**	**X2 Spray Rate (g/min)**	**X3 Atomization Air pressure (bar)**	**Y1 % Drug Released at 1 hr**	**Y2 % Drug Released at 6 hr**	**Y3 Process Efficiency (%)**	**Y4 Mean Particle Size (µm)**
PS-1	110	5	3.5	42	77	92	658
PS-2	100	5	2.5	43	79	91	668
PS-3	100	10	2.5	43	82	91	682
PS-4	100	10	3.5	43	82	87	668
PS-5	100	10	2.5	44	80	89	678
PS-6	110	10	2.5	44	82	92	670
PS-7	100	10	2.5	45	82	91	685
PS-8	100	10	2.5	45	81	88	683
PS-9	90	10	2.5	45	82	84	695
PS-10	100	10	2.5	45	85	90	679
PS-11	90	5	3.5	45	79	75	685
PS-12	100	10	2.5	45	83	89	672
PS-13	90	15	3.5	46	84	87	702
PS-14	90	5	1.5	46	83	88	705
PS-15	110	15	3.5	46	84	92	672
PS-16	110	5	1.5	46	85	93	676
PS-17	100	10	1.5	47	85	87	693
PS-18	100	15	2.5	48	86	89	692
PS-19	110	15	1.5	50	87	92	682
PS-20	90	15	1.5	51	87	85	725

Table 6. Summary of ANOVA results of process variables optimization studies for response Y1

Source	**Sum of Squares**	**Df**	**Mean Square**	**F-Value**	**p-Value**	
Model	74.00	6	12.33	6.99	0.0017	significant
A-Temperature of Coating material and atomization air	2.50	1	2.50	1.42	0.2553	
B-Spray Rate	36.10	1	36.10	20.45	0.0006	
C-Atomization air pressure	32.40	1	32.40	18.35	0.0009	
AB	0.5000	1	0.5000	0.2832	0.6036	
AC	0.5000	1	0.5000	0.2832	0.6036	
BC	2.00	1	2.00	1.13	0.3065	
Residual	22.95	13	1.77			
Lack of Fit	19.45	8	2.43	3.47	0.0931	not significant
Pure Error	3.50	5	0.7000			
Cor Total	96.95	19				

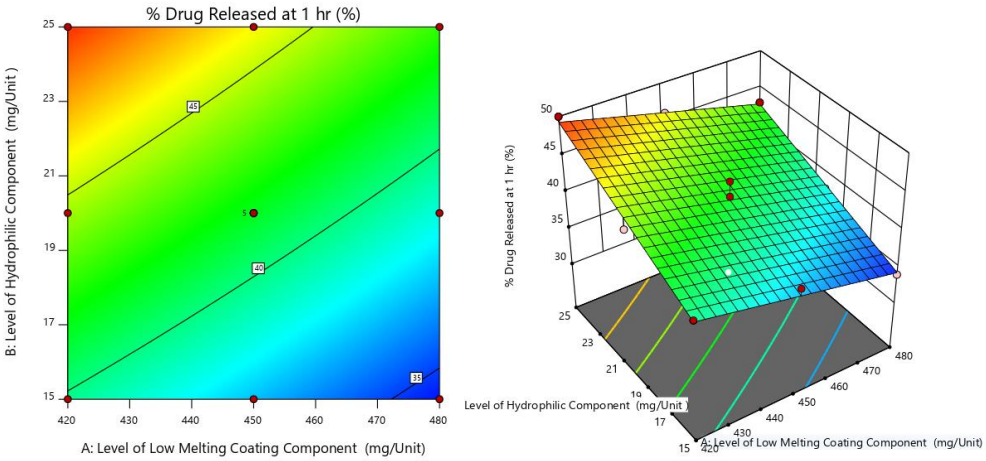

Fig. 4. (a) Contour plot of the formulation optimization studies demonstrating impact of variable A and B on response Y1 (b) 3d Surface plot the formulation optimization studies demonstrating impact of variable A and B on response Y1

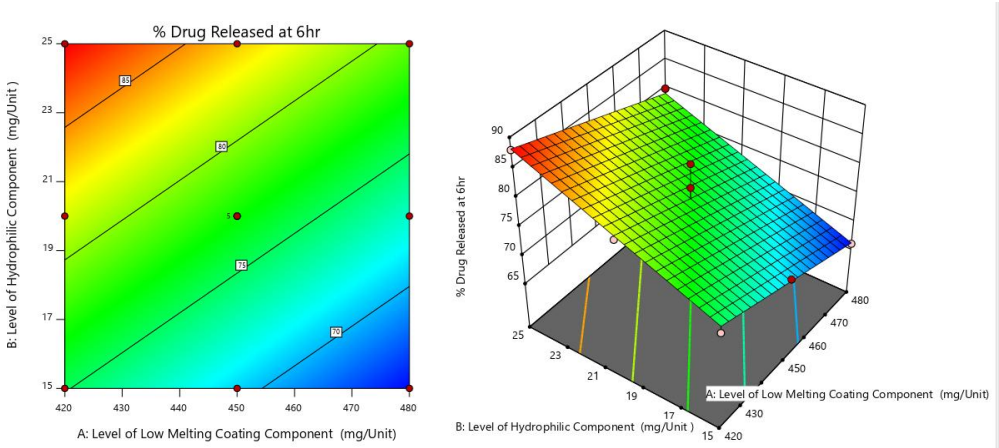

Fig. 5. (a) Contour plot of the formulation optimization studies demonstrating impact of variable A and B on response Y2 (b) 3d Surface plot the formulation optimization studies demonstrating impact of variable A and B on response Y2

3.4.1 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 42% to 51%, as given in Table 5.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) andC(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 0.0017 (significant), F-value of6.99, and p-value for "lack of fit" of 0.0931 (not significant).

Y1=45.45–0.5000*A+1.90*B-1.80*C+0.2500*AB -0.2500*AC -0.5000*BC.(3)

As per regression equation 3 in uncoded units, out of 2 significant variables, variable B showspositive effect while variable C shows negative effect on responseY1, 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.

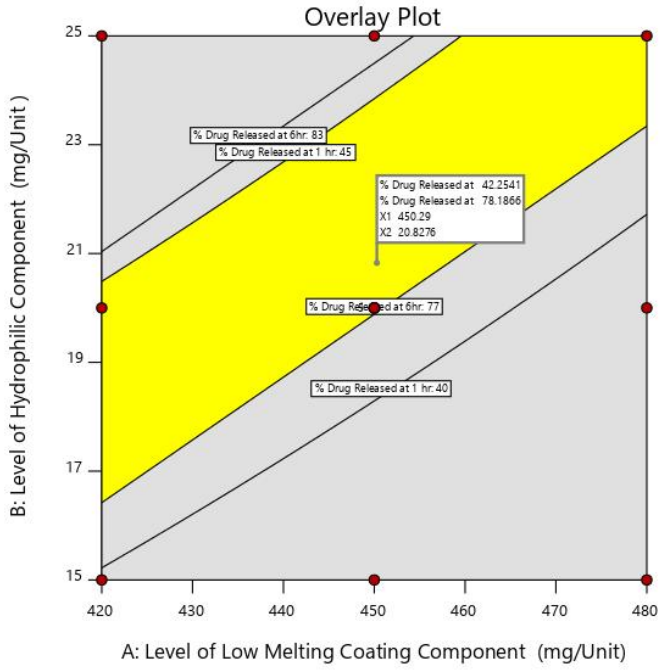

Fig. 6. Overlay plot demonstrating formulation design space

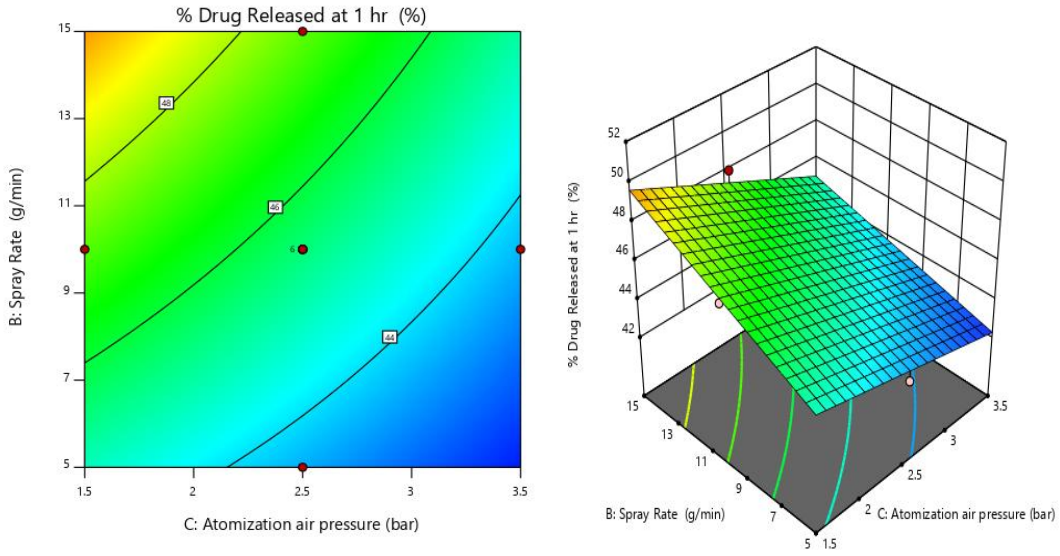

Fig. 7. (a) Contour plot of the process optimization studies demonstrating impact of variable B and C on response Y1 (b) 3d Surface plot the formulation optimization studies demonstrating impact of variable B and C on response Y1

3.4.2 Discussion on response surface regression: drug released at 6 hr (Y2) versus X1, X2 and X3\

With the studied combination of three independent process variables, response factor (i.e. % Drug Released at 6 hr) varies from 77% to 87%, as given in Table 5. 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 9.20, and p-value for "lack of fit" of 0.8184 (not significant).

Y1=82.75+0.0000*A+2.50*B-2.10*C+0.0000*AB -0.5000*AC +0.7500*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 6 hr, while increasing the Atomization air pressure shall result in the more controlled and retarded release at 6 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 93%, as given in Table 5. 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) (p-values < 0.05). There is no significant interaction between variable A*B or A*C. However, term B*C shows some level of positive interaction (p-values < 0.05). The model is significant in its prediction of Y3, as depicted by the p-value of 0.0007 (significant), F-value of 8.54, and p-value for "lack of fit" of 0.0556 (not significant).

Y1=88.45+3.90*A+0.9000*B-1.50*C+0.8750*AB +0.8750*AC +2.38*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.

Positive interaction effect of the X2 and X3 demonstrates that when spray rate and atomization air both are increased simultaneously than % coating efficiency is increased significantly.

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 658 to 725, as given in table 5. 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 17.46, and p-value for "lack of fit" of 0.1883 (not significant).

Y4=683.50-15.40*A+8.10*B-1.50*C-9.60C-2.12*AB +1.88*AC +0.6250*BC (6)

As per regression equation 5 in uncoded units, out of 3 significant variables, variable B shows positive effect whileA andC 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.

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	113.10	6	18.85	9.20	0.0005	significant
A-Temperature of Coating material and atomization air	0.0000	1	0.0000	0.0000	1.0000	
B-Spray Rate	62.50	1	62.50	30.49	< 0.0001	
C-Atomization air pressure	44.10	1	44.10	21.51	0.0005	
AB	1.421E-14	1	1.421E-14	6.932E-15	1.0000	
AC	2.00	1	2.00	0.9756	0.3413	
BC	4.50	1	4.50	2.20	0.1623	
Residual	26.65	13	2.05			
Lack of Fit	11.82	8	1.48	0.4979	0.8184	not significant
Pure Error	14.83	5	2.97			
Cor Total	139.75	19				

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	240.07	6	40.01	8.54	0.0007	significant
A-Temperature of Coating material and atomization air	152.10	1	152.10	32.48	< 0.0001	
B-Spray Rate	8.10	1	8.10	1.73	0.2112	
C-Atomization air pressure	22.50	1	22.50	4.80	0.0472	
AB	6.12	1	6.12	1.31	0.2734	
AC	6.13	1	6.13	1.31	0.2734	
BC	45.13	1	45.13	9.64	0.0084	
Residual	60.88	13	4.68			
Lack of Fit	53.54	8	6.69	4.56	0.0556	not significant
Pure Error	7.33	5	1.47			
Cor Total	300.95	19				

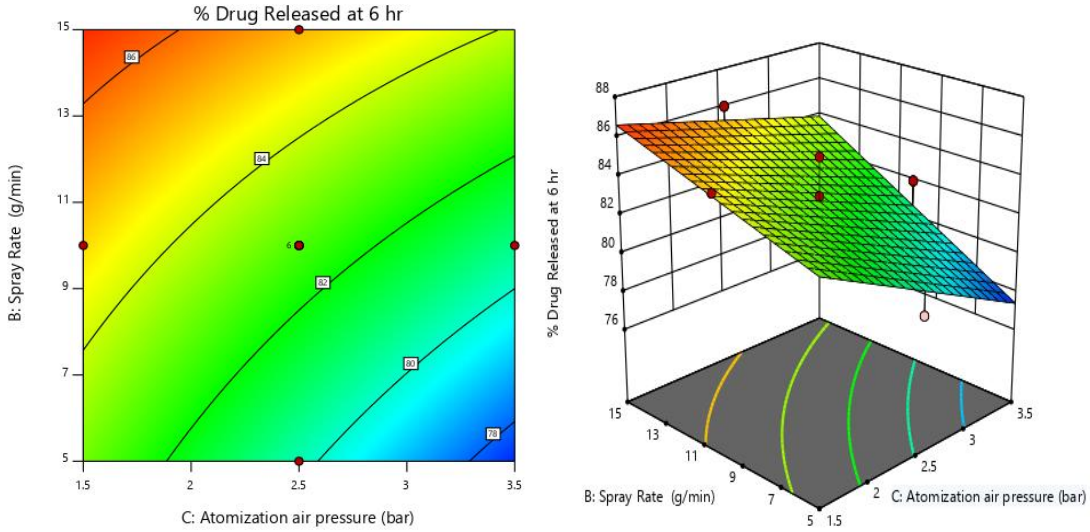

Fig. 8. (a) Contour plot of the process optimization studies demonstrating impact of variable B and C on response Y2 (b) 3d Surface plot the process optimization studies demonstrating impact of variable B and C on response Y2

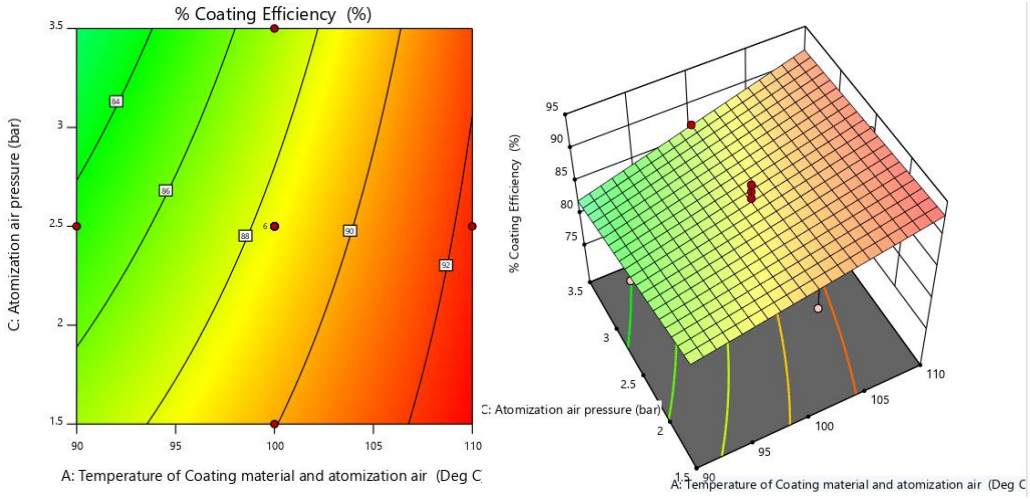

Fig. 9. (a) Contour plot of the process optimization studies demonstrating impact of variable A and C on response Y3 (b) 3d Surface plot the process optimization studies demonstrating impact of variable A and C on response Y3

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 ranges from 650-680µm. 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 110^{o}C. We get the maximum wide operating ranges for variables B and C, when variable A is set to its maximum value of about 110^{o}C. 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.

3.5 Confirmation 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 10. 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 werewithin 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 12. 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 650-680 µm after HMC. Also pellets are spherical in shape

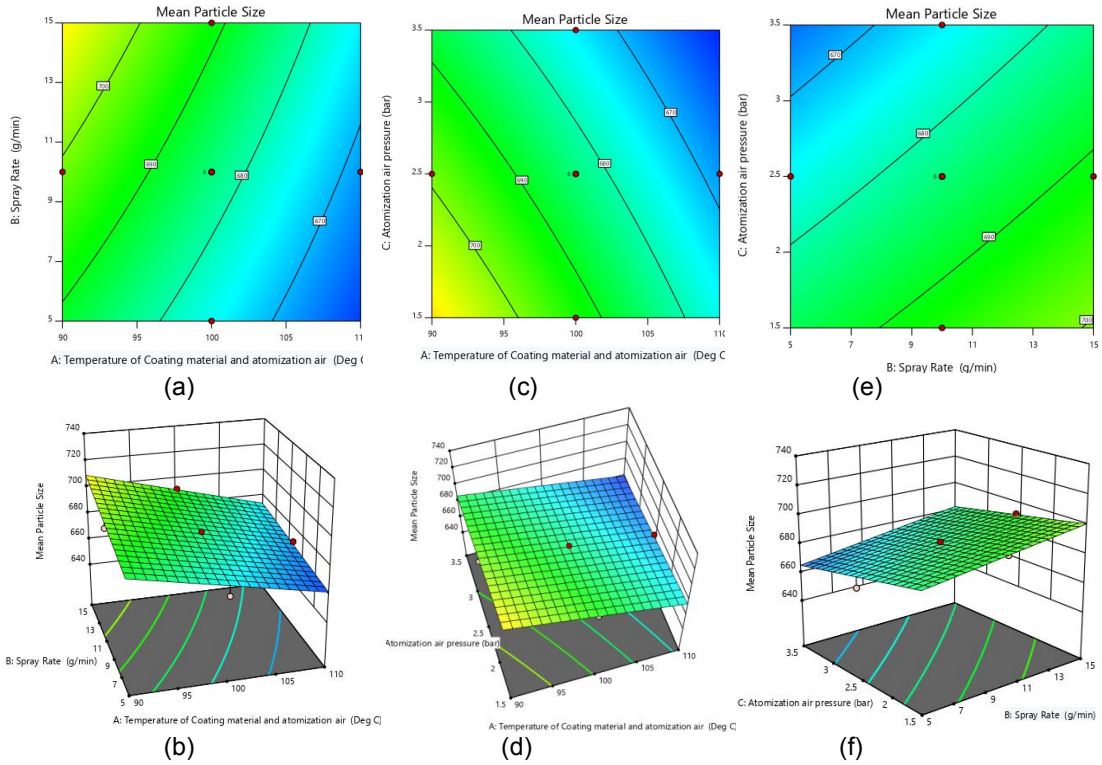

Fig. 10. (a) Contour plot of the process optimization studies demonstrating impact of variable A and B on response Y4 (b) 3d Surface plot the process optimization studies demonstrating impact of variable A and B on response Y4 (c) Contour plot of the process optimization studies demonstrating impact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

with very smooth surface. Angle of repose results were approximately 21- 25° for all formulations indicating excellent flow properties of HMC pellets. Values of Friability are negligible, where maximum friability value is about 0.12%, 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.

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.

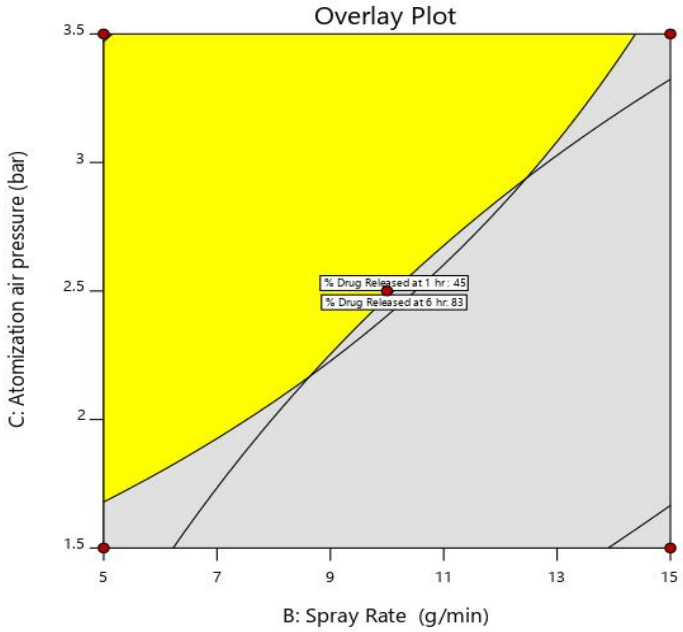

Fig. 11. Design space for processing variables (Spray rate (B) and Atomization air pressure (C), when Temperature of the coating solution and atomization air (A) is set to its maximum value

Time (Hr)	Sq. Rt of Time (Hr)	% Drug Released
0	0.0	0
1	1.0	42.7
2	1.4	55.8
4	2.0	71.4
6	2.5	81.2
8	2.8	90.5
12	3.5	99.9

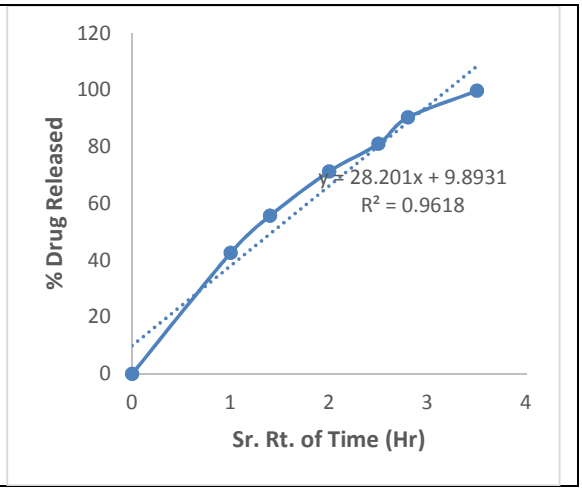

Fig. 12. Higuchi model Kinetic Release Of Levetiracetam Hot Melt Coated Pellets

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	4016.67	6	669.45	17.46	< 0.0001	significant
A-Temperature of Coating material and atomization air	2371.60	1	2371.60	61.87	< 0.0001	
B-Spray Rate	656.10	1	656.10	17.12	0.0012	
C-Atomization air pressure	921.60	1	921.60	24.04	0.0003	
AB	36.12	1	36.12	0.9424	0.3494	
AC	28.13	1	28.13	0.7337	0.4072	
BC	3.13	1	3.13	0.0815	0.7797	
Residual	498.33	13	38.33			
Lack of Fit	391.49	8	48.94	2.29	0.1883	not significant
Pure Error	106.83	5	21.37			
Cor Total	4515.00	19				

Table 10. Formulation and Process Parameter details for the confirmation batches

Ingredients	Formulation		
	F1	F2	F3
Core Pellet Composition			
Levetiracetam #	750.00	750.00	750.00
MCC (Avicel PH 101) #	437.50	437.50	437.50
Hypromellose (6cps) #	62.50	62.50	62.50
Purified Water $	q.s.	q.s.	q.s.
Coating Composition			
Glyceryl Behenate	450.00	450.00	450.00
PEG 1500	20.00	20.00	20.00
Total Weight	**1720 mg**	**1720 mg**	**1720 mg**
Processing Parameters			
Temperature of Coating material and Atomization air	110^{o}C	110^{o}C	100^{o}C
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	43.7 (42.3-45.0)	42.2	44.3 (43.0-45.6)	44.8	43.7 (42.7-44.7)	44.1
Y2 - % Drug released at 6 hr	81.3 (79.8-82.7)	81.7	82.0 (80.6-83.5)	80.3	80.5 (79.3-81.5)	81.4
Y3 - % Coating Efficiency	92.3 (90.1-94.6)	93.3	92.3 (90.1-94.4)	91.8	86.7 (85.1-88.3)	85.9
Y4- Mean Particle Size (µ)	664 (658-670)	670	665 (659-671)	661	674 (669-679)	672

Table 12. Evaluation of hot-melt coated pellets

Formulation	Drug Content (%)	Friability (%)	Angle of Repose (^{0})	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Housner's Ration	Carr's Index
F1	98.7%	0.09	23.8	0.83	0.92	1.11	9.78
F2	99.2%	0.11	24.2	0.91	0.98	1.08	7.14
F3	98.9%	0.12	21.5	0.85	0.93	1.09	8.60

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 6 hr, % Coating efficiency and Mean particle size. By optimizing level and ratio of low melting polymer and hydrophilic pore former, targeted drug release profile can be achieved by hot melt coating technology. Processing parameters like temperature of the coating material, Spray rate and Atomization air pressure need to be optimized for the robust formulation and process. 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 AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bose S, Bogner R. Solventless Pharmaceutical Coating Processes: A Review Pharmaceutical Development and Technology.
2. DOI: 10.1080/10837450701212479.
3. Achanta AS, Adusumilli PS, James KW, Rhodes CT. Development of Hot Melt Coating Methods. Drug Development and Industrial Pharmacy.1997;23(5):441-449.
4. Jones DM, Percel PJ. Coating of Multiparticulates Using Molten Materials. In: Isaac G. S. editors. Multiparticulate Oral Drug Delivery ed. CRC Press, Taylor & Francis Group;1994.
5. Jozwiakowski MJ, Jones DM, Franz RM. Characterization of a hot-melt fluid bed coating process for fine granules. Pharm. Res. 1990;7(11):1119–1126.
6. Sudke SG, Sakarakar DM. Hot-Melt Coating: An Innovative Pharmaceutical Coating Technique. Journal of Pharmaceutical Research & Clinical Practice. 2013;3(1):16-26.
7. Mehta AM. Aqueous Polymeric In: McGinity J.W. editors. Coatings for Pharmaceutical Dosage Forms. New York: Marcel Dekker; 1989.
8. Kennedy JP, Niebergall PJ. Development and optimization of a solid dispersion hot-melt fluid bed coating method. Pharm. Deve. Technol. 1996;1(1):51–62.
9. Jozwiakowski MJ, Jones DM, Franz RM. Characterization of a hot-melt fluid bed coating process for fine granules. Pharm.Res.1990;7(11):1119–1126.
10. Jones, DM, Percel, PJ. Coating of Multiparticulates Using Molten Materials. In: Multiparticulate Oral Drug Delivery ed. CRC Press, Taylor & Francis Group; 1994.
11. Package Leaflet: Information for the patient : Keppra 500 mg film-coated tablets. Available: https://www.ema.europa.eu/en/documents/product-information/keppra-epar-product-information_en.pdf.

12. Ulloa CM, Towfigh A, Safdieh J. Review of levetiracetam, with a focus on the extended release formulation, as adjuvant therapy in controlling partial-onset seizures. Neuropsychiatric Disease and Treatment. 2009;5:467-476. DOI: 10.2147/ndt.s4844.
13. https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf
14. QI Essentials Toolkit: Failure Modes and Effects Analysis (FMEA) Tool. Institute for Healthcare Improvement; 2017. Available: http://www.ihi.org
15. Risk Priority Number (from Failure Modes and Effects Analysis). Institute for Healthcare Improvement; 2011. Available: http://www.ihi.org
16. Kiran DR. Failure Modes and Effects Analysis. Total Quality Management. 2017;373–389. DOI:10.1016/b978-0-12-811035-5.00026-x
17. Vogt FG, Kord AS. Development of quality by design analytical methods. J Pharm Sci. 2011;100:797–812.
18. Link : https://www.isixsigma.com/tools-templates/design-of-experiments-doe/when-and-how-to-use-plackett-burman-experimental-design/
19. Aydar AY. Utilization of Response Surface Methodology in Optimization of Extraction of Plant Materials; 2007. DOI: 10.5772/intechopen.73690
20. Bhattacharya S. Central Composite Design for Response Surface Methodology and Its Application in Pharmacy. Intech Open; 2020. DOI: 10.5772/intechopen.95835. Available:https://www.intechopen.com/online-first/central-composite-design-for-response-surface-methodology-and-its-application-in-pharmacy
21. U.S. Food and Drug Administration. Guidance for Industry: Q8 (R2) Pharmaceutical Development.; 2009.
22. Stosch MV, Schenkendorf R, Geldhof G, Varsakelis C, Mariti M, Dessoy S, Vandercammen A, Pysik A, Sanders M. Working within the Design Space: Do Our Static Process Characterization Methods Suffice?. Pharmaceutics. 2020; 12:562. DOI:10.3390/pharmaceutics12060562
23. Panchumarthy R, Niharika A, Anusha H, Himaja V, Afzal SK. A simple validated UV spectrophotometric method for quantitative analysis of Levetiracetam in pharmaceutical dosage form Indian Journal of Research in Pharmacy and Biotechnology. ISSN: 2321-5674(Print); 2320 – 3471(Online)
24. Fekete R, Zelko R, Marton S, Racz I. Effect of the formulation parameters on the characteristics of pellets. Drug Dev Ind Pharm. 1998;24(11):1073-1076.
25. PatilAT, Khobragade DS, Chafle SA, Ujjainkar AP, Umathe SN, Lakhotia. Development and evaluation of a hot-melt coating technique for enteric coating. Braz. J. Pharm. Sci.Jan./Mar. 2012;48(1) [Link]
26. United States Pharmacopoeia; 2014.
27. Yang W, PierstorffE. Reservoir-Based Polymer Drug Delivery Systems. Journal of Laboratory Automation. 2012;17(1):50-58
28. Gouda R, Baishya H, Qing Z. Application of Mathematical Models in Drug Release Kinetics of Carbidopa and Levodopa ER Tablets. J Develop Drugs. 2017; 6:171.
29. U.S. Food and Drug Administration. Guidance for Industry: Q9 Quality Risk Management; 2006.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/67760