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 on HMCP. Quality by design (QbD) with DOE approach was used for designing and development of the formulation, by putting risk...
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 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 melting 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 remelting of coating material on the substrates, when they come in contact with the spray gun while falling back into the bed.

Keywords: hot-melt coating process; multi-particulate formulation; controlled release; design space, risk assessment; levetiracetam.
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].

Levetiracetam, a high dose, highly soluble anti-epileptic drug [10] was selected for the present study. It is well-documented that Levetiracetam 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-particle 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 multiparticulate 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°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

Levetiracetam was 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 by Gattefosse. All chemical reagents used were of analytical grade.

2.1 Preparation of Pellets with Extrusion Spheronization

Levetiracetam 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, 40 rpm, room temperature) and spheronization using 2 mm chequered plate. Pellets were then dried in a tray dryer at 60°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 (T1), 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 (T2), outlet air temperature (T3) 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 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 were reanalysed, 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 methodology 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 chance of detection when there is a failure and probability is the chance 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 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 [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 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” [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]:

\[
d_{\text{avg}} = \frac{\sum \% \text{ retained} \times \text{Avg. sieve aperture}}{100}
\]

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 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. 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°C, 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

\[
Q = A \sqrt{D(2Co - Cs)Cs \tau}
\]

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

\[ Q = K_H \times t^{1/2} \]

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 (°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 Plackett 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.

As observed from Table 3, Y1 and Y2 ranges from 12 to 77% and 62 to 96%, 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 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 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).

\[ Y1= 77.15 - 4.50*A + 6.50*B + 0.0000*AB \] (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.

3.3.2 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).

\[ Y1= 41.54 - 3.00*A + 4.50*B - 0.2500*AB \] (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.

3.3.3 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 (°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 |                      |                  |                          |                          |                          |                          |                          | 38                          | 66                          |
| OS-2     | 100 200 50 | 110 55 30 40 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 |
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

| 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                        | 89                        | 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                                                          | 15                    | 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) 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 0.0017 (significant), F-value of 6.99, and p-value for “lack of fit” of 0.0931 (not significant).

\[ Y1 = 45.45 - 0.5000A + 1.90B - 1.80C + 0.2500AB - 0.2500AC - 0.5000BC. \] (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.
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).

\[ Y1 = 82.75 + 0.0000A + 2.50B - 2.10C + 0.0000AB - 0.5000AC + 0.7500BC \] (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).

\[ Y3 = 88.45 + 3.90A + 0.9000B - 1.50C + 0.8750AB - 2.12*AC + 1.88*AC + 0.6250*BC \] (5)

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 Y3, 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 lower, it results in faster congealing resulting in more agglomerates generation and thus reduced coating efficiency. When while 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).

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

As per regression equation 5 in uncoded units, out of 3 significant variables, variable B shows positive effect 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.
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  | 6.89        | 4.56    | 0.0556  not significant |
| Pure Error                                     | 7.33           | 5  | 1.47        |         |           |
| Cor Total                                       | 300.95         | 19 |             |         |           |
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°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°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 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 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.

![Overlay Plot](image)

**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   | significance |
|----------------------------------------------|----------------|-----|-------------|---------|-----------|--------------|
| 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   |
| Hypermellose (6cps) #              | 62.50    | 62.50    | 62.50    |
| Purified Water $                   | q.s.     | q.s.     | q.s.     |
| Coating Composition               | 450.00   | 450.00   | 450.00   |
| Glyceryl Behenate                  | 20.00    | 20.00    | 20.00    |
| PEG 1500                           |          |          |          |
| Total Weight                       | 1720 mg  | 1720 mg  | 1720 mg  |

Processing Parameters

|                                    |          |          |          |
| Temperature of Coating material and Atomization air | 110°C   | 110°C   | 100°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 (°) | Bulk density (g/cm³) | Tapped density (g/cm³) | 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.

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