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Application of design of experiments for development and characterization of coprocessed excipients using *Lapidium Sativum*

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***Abstract*---**The development of novel excipients with enhanced functionality has been explored using particle engineering by co-processing. The aim of this study was to improve the functionality of Lapidium Sativum for direct compression by co-processing with MCC pH 101 and PVP K30 in optimized proportions. Design of Experiment (DoE) was employed to optimize the composition of the co-processed excipient using the desirability function and other supporting studies as a basis for selecting the optimized formulation. The co-processed excipient was thereafter developed by the method of spraydrying. Flow and compaction studies of coprocessed excipient were carried out in comparison to its parent component and physical mixture. Tablets were prepared by direct compression (DC) containing Venlafaxine hydrochloride (100 mg) as a model for poor compressibility. Tablets produced with CPE were satisfactory and conformed to USP specifications for acceptable tablets. The application of DoE was successful in optimizing and developing a starch-based co-processed excipient that can be considered for direct compression tableting.

***Keywords*---**application design, experiments development, characterization coprocessed excipients, Lapidium Sativum.

Introduction

Recent years have seen a shift in the composition of pharmaceutical formulations, with excipients being the primary focus [1]. Definitions are provided by the International Pharmaceutical Excipients Council. The compounds that are

included in a final product are called excipients. Dosage forms other than the active medication that are used in pharmaceuticals components of. Excipients have been subjected to the required testing for safety and are components that are incorporated into a drug delivery system in order to assist the during the manufacturing process, the processing of the drug delivery system, improve the drug's stability, bioavailability, and patient acceptance, or improve its overall effectiveness. Any additional characteristics that contribute to the overall safety and efficiency of the drug delivery device either while it is being stored or while it is being used [2]. Excipients with many uses and optimal utilization both have the potential to medication manufacturing costs can be reduced to the benefit of pharmaceutical companies. Development as well as assistance in the innovation of medicinal formulations.

Tablets, which were manufactured by either wet granulation, dry granulation, or the direct compression process, are the solid pharmaceutical dosage form that are utilised the most frequently. When compared with the wet granulation technique, direct compression tableting has a number of advantages, including fewer processing steps, simplified validation, elimination of heat and moisture, economy, and improved drug stability[3]. These advantages have led the majority of pharmaceutical manufacturing industries to switch to direct compression tableting. Tablets can be made directly from powder blends of active components and acceptable excipients by a procedure known as direct compression (DC), which is also abbreviated as 'direct compression'. According to Villanova et al. (2011), one of the prerequisites for direct compression is that the excipient that is utilised in the formulation has to have good flow and compression properties.

There are very few excipients that have all of the optimal qualities that are necessary for direct compression. The creation of new chemical excipients, new grades of existing materials, and new combinations of existing materials are all potential routes to obtaining excipients with enhanced functional capabilities. An intriguing possibility for product enhancement is the use of novel combinations of ingredients already in use. Because the majority of formulations comprise a number of different excipients, one intriguing approach for enhancing the functionality of excipients is to create new combinations of excipients that are already in use. Coprocessing, also known as particle engineering, is the act of taking two or more different excipients and combining their properties in order to create a new one with enhanced functioning.

Co-processing is based on the new concept of two or more excipients interacting with one another at the sub-particle level. The purpose of this interaction is to offer a synergy of functionality improvement while also disguising the unwanted features of the individual excipients[4,5]. Coprocessing results in the development of excipients that granulate and have superior qualities when compared to physical mixtures of components or individual components [6]. Coprocessing leads to the formation of excipients that granulate.

Material and Methods

Extraction of Mucilage from Lapidium Sativum

The seed of *Lepidium sativum* contains the mucilage in the outer covering of the seed. The mucilage is enmeshed in the hard covering of the seed. The seeds were soaked in distilled water for 12 hrs. The swollen material was transferred to the blender and blended for 10 min. The mass was then passed through eight-fold of muslin cloth. Acetone was added in ratio 1:1 in the filtrate to precipitate out the mucilage content. The precipitates were separated using separating funnel and lyophilized. The powder was characterized and used further in the development of coprocessed excipient using spray drying method.

Method for Co processing

Spray drying

Polymer combination was employed for the purpose of spray drying. Lyophilized powder was dissolved in a 1:1 mixture of and IPA. The filler and binder was dissolved in a 1: 1 mixture of IPA and water. Both the solutions were mixed and colloidal silicon dioxide was added in a concentration of 0.5% w/w. The resultant mixture was kept under stirring and spray dried at an inlet temperature of 35 ± 3 °C with a pressure of 0.9 ± 0.1 bar and an air flow of 40–60 cfm to obtain co-processed polymer[7]**.**

Optimization of composition of coprocessed excipients using Design of Experiments

A Box Behenken design with 3 factors and 3 levels was selected for optimization of Excipient Blend[8]. Concentration of LSLP (X1), concentration of PVP K30 (X2) and Concentration of MMC pH 101 (X3) as significant independent variables affecting the CQAs and Hardness (Y1), Friability (Y2), In vitro disintegration time(Y3), T50 (Y4), Angle of repose (Y5) and Carr's Index (Y6) and Hausner's Ratio (Y7) were taken as dependent variables. Design Expert Software [Version 10.0.1, Stat ease Inc., Minneapolis, MN) was used to evaluate the effect of significant factors on dependent variables (CQAs). The experimental matrix of design is depicted in Table 1.

Table 1. Experimental Matrix of Box- Behnken Design for optimization of excipient blend

Std	A:LSLP	B:PVP K 30	C:MCC pH 101
1	10.5	0.5	80
2	20	0.5	80
3	10.5	5	80
4	20	5	80
5	10.5	2.75	75
6	20	2.75	75
7	10.5	2.75	85
8	20	2.75	85

9	15.25	0.5	75
10	15.25	5	75
11	15.25	0.5	85
12	15.25	5	85
13	15.25	2.75	80
14	15.25	2.75	80
15	15.25	2.75	80
16	15.25	2.75	80
17	15.25	2.75	80

Evaluation Parameters for Co- Processed Excipients
Precompression Characteristics
Angle of repose

The angle of repose was determined by the funnel method. The determination of angle of repose by this method is referred to as static angle of repose. Powder is poured onto the centre of the dish from the funnel that can be raised vertically until the maximum cone height (h) is obtained. The angle of repose can be calculated by the given formula, $\alpha = \tan^{-1}(h/r)$ where 'h' is height of pile and 'r' is radius of pile (As per USP method)[9].

Bulk density (BD)

Bulk density of various co-processed excipients was determined by USP bulk density apparatus (Electrolab). It was measured by pouring the weighed quantity of polymers into a 250 mL measuring cylinder, and the volume was noted. It is expressed in gm/mL and is given by Db = M/V where, M is the mass of polymer and V is the bulk volume of the polymer[9].

Tapped density (TD)

The tapped density was measured USP bulk density apparatus (Electrolab) by tapping the polymers of fixed mass for 100 and then 500 tapped until it reached a constant volume. It is expressed in gm/mL and is given by

$$TD = M/VT$$

where, M is the mass of powder, VT is the tapped volume of the powder[9].

Compressibility index (CI)

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula[9].

Compressibility index=Tappeddensity−BulkdensityTappeddensity×100

Hausner's ratio (HR)

It was calculated on the basis of bulk and tapped density data and given by

Hausner's ratio=Tapped density/ Bulk density

For the compressibility index and the Hausner's ratio[9],

Swelling capacity

The swelling capacity of the powder was estimated by a modification of the methods of Bowen and Vadino and Iwuagwu and Okoli. The tapped volume occupied by 5 g of the powder VX, was noted. The powder was then dispersed in 85.0 ml of water and the volume made up to 100 ml with more water. After 24 h of standing, the volume of the sediment, VV, was estimated [10]. The swelling capacity was computed as follows:

Swelling capacity = VV/VX

The mean of three determinations was calculated.

Hydration capacity

The hydration capacity (water retention capacity) was determined by the method of Ring. One gram of powder was placed in a centrifuge tube and covered with 10 ml of water. The tube was shaken intermittently over a 2 h period and left to stand for 30 min. This was then centrifuged for 10 min at 3000 rpm. The supernatant was decanted and the weight of the powder after water uptake and centrifugation, x was determined[11].

Hydration capacity = x/y

Where x is weight of moist powder after centrifugation and y is weight of dry powder. The values of hydration capacity listed were the means of three determinations.

Post Compression Parameters

The prepared tablets are evaluated for hardness, friability, weight variation, thickness, length, assay, in vitro drug release, swelling index and fluid uptake studies[12].

Thickness and dimension

The thickness and dimension of the tablet in mm was measured using vernier calipers.

Hardness

Commonly used Monsanto type tablet hardness tester tested the tablet crushing strength. A tablet was placed between the anvils and the crushing strength, which caused the tablet to break, was recorded.

Friability

The friability of the tablets was measured in a Erweka friabilator. Randomly 20 tablets were selected and weighed (Wo). After 100 revolutions (speed-25 RPM), the sample of 20 tablets was de-dusted and weighed (W) again. Percentage friability was calculated from the loss in weight. Determinations were made in triplicate.

$$\%\text{Friability} = (\text{Initial weight} - \text{Final weight}) / \text{Initialweight} \times 100$$

Weight variation test

It was performed as per the method given in the US pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

***In vitro* dissolution studies**

In vitro dissolution of all formulations was carried out using USP dissolution testing apparatus II (paddle type, Electrolab, Mumbai, India) at 50 rpm. The dissolution test was performed using 500 mL of phosphate buffer (pH 6.8) as described in the USP monograph. Dissolution test was carried out for a period of 24 h. The temperature of the dissolution medium is maintained at 37 ± 0.5 °C. A aliquot (5 mL) of the solution was withdrawn from the dissolution apparatus at regular intervals and replaced with the same volume of pre-warmed fresh dissolution medium. The samples were filtered through a 0.45 μm membrane filter and diluted to 10 mL to get a suitable concentration with respective media. The amount of drug release was determined from the comparison with standard response of pure drug (As per USP monograph).

Compression Behavior Analysis

Heckel Plot

Data obtained over a range of compression pressure from 0.5 to 4 ton were analyzed by applying the Heckel equation. Heckel reported that the linear portion of the plot represents the densification process by particle deformation. Heckel parameters were thus derived by linear regression analysis of the straight-line portion of the Heckel plots. The yield pressure then was calculated from the reciprocal of the slope k of the regression line[13].

Kawakita equation

The volume reduction process changes from powder to powder due to differences in particle size and inter-particulate friction. Kawakita parameters were obtained by linear regression analysis. The parameter ‘a’ explains the initial porosity at zero pressure, which is corresponding to the total portion of reducible volume at maximum pressure. It also describes the relative volume reduction at the maximum number of taps[14].

Result and Discussion

Extraction of Mucilage from Lapidium Sativum

The process of extraction for mucilage from *Lepidium sativum* seeds was tedious. The stirring of soaked seeds was found prominent as mucilage in the seeds covering was leached out completely. The extraction yield of dries mucilage was 11.3% w/w. Further lyophilization of mucilage resulted in free-flowing powder[15].

Method of Coprocessing

The optimized conditions for spray drying are shown in Table 1**.**

Table 1.Conditions for Spray Drying

Sr. No.	Independent Variables	Optimized conditions
1	Inlet air temperature	55
2	Product temperature	30
3	Air Flow	90
4	Atomization pressure	30
5	Exhaust air temperature	40
6	Partition height	10
7	Spray Rate	20
8	viscosity	300

Optimization of composition of coprocessed excipients using Design of Experiments

Hardness

The Model F-value of 12.30 implies the model is significant. There is only a 0.04% chance that an F-value this large could occur due to noise.P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. Ifthere are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.Figure 1 represents the response surface plot for hardness.

Hardness = 4.87649 + -0.0526316 * LSLP + 0.711111 * PVP K 30 + -0.03 * MCC pH 101

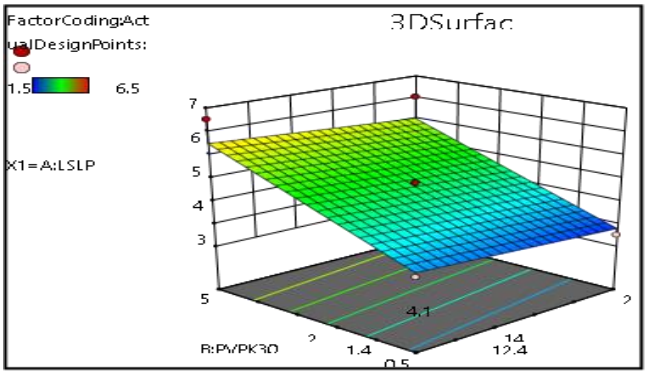

Figure 1. Response surface plot for Hardness

Friability

The Model F-value of 8.63 implies the model is significant. There is only a 0.21% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. Figure 2 represents the contour plot and response surface plot respectively for Friability.

Friability = 0.997957 + 0.0163158 * LSLP + -0.177222 * PVP K 30 + 0.00375 * MCC pH 101

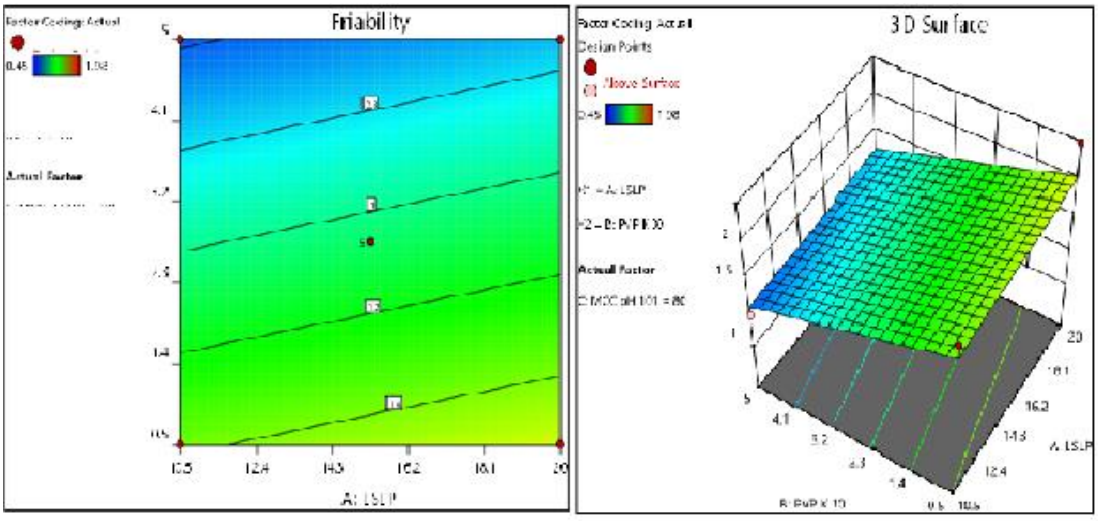

Figure 2. Contour plot and response surface plot for Friability

***In vitro* disintegration time**

The Model F-value of 5.82 implies the model is significant. There is only a 1.50% chance that an F-value this large could occur due to noise.P-values less than 0.0500 indicate model terms are significant. In this case B, A^2 are significant

model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. Figure 3 represents the contour plot and response surface plot respectively for in vitro disintegration time.

In vitro disintegration time= -2445.93 + 26.9725 * LSLP + -9.62846 * PVP K 30 + 59.3124 * MCC pH 101 + 0.299415 * LSLP * PVP K 30 + -0.0595789 * LSLP * MCCpH 101 + 0.149111 * PVP K 30 * MCC pH 101 + -0.802006 * LSLP^2 + -0.21684 * PVP K 30^2 + -0.36471 * MCC pH 101^2

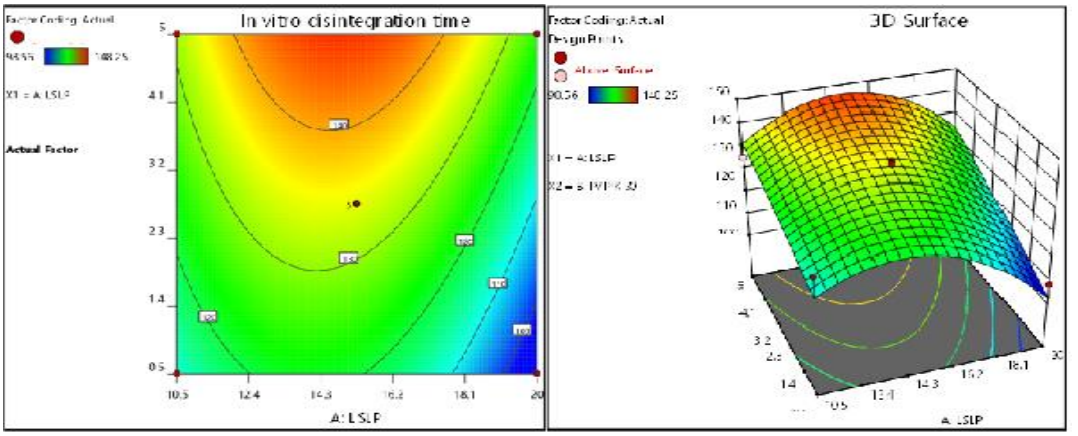

Figure 3.Contour Plot for In vitro drug release

T50

The Model F-value of 7.35 implies the model is significant. There is only a 1.23% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are notsignificant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. Figure 4 represents the contour plot and response surface plot respectively for T50.

T50= 198.445 + 0.532459 * LSLP + -5.38755 * PVP K 30 + -4.4942 * MCC pH 101 + 0.17076 * LSLP * PVP K 30 + -0.0115789 * LSLP * MCC pH 101 + 0.0155556 * PVP K 30 * MCC pH 101 + -0.0162881 * LSLP^2 + 0.510123 * PVP K 30^2 + 0.0293 * MCC pH 101^2

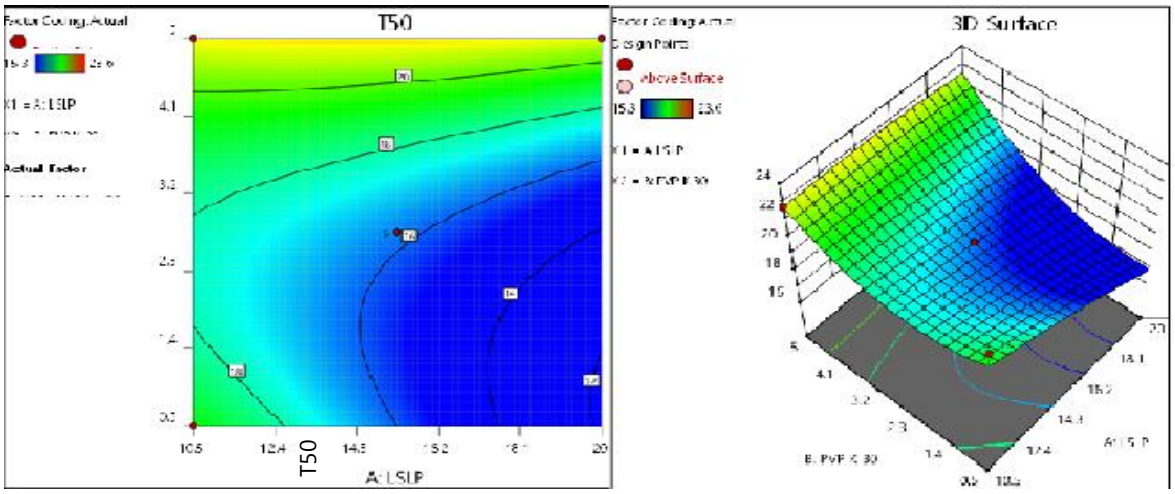

Figure 4. Contour Plot and Response surface plot for T50

Angle of Repose

The Model F-value of 121.54 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, BC, A^2, B^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model termsare not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.The Predicted R^2 of 0.9166 is in reasonable agreement with the Adjusted R^2 of 0.9855; i.e. the difference is less than 0.2. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 29.126 indicates an adequate signal. This model can be used to navigate the design space. The Lack of Fit F-value of 5.33 implies there is a 6.98% chance that a Lack of Fit F-value this large could occur due to noise. Figure 5 represents the contour plot and response surface plot respectively for angle of repose.

Angle of Repose= 1673.91 + -13.073 * LSLP + -31.6091 * PVP K 30 + -36.6217 * MCC pH 101 + 0.0311111 * LSLP * PVP K 30 + -0.00336842 * LSLP * MCC pH 101 + 0.336667 * PVP K 30 * MCC pH 101 + 0.422825 * LSLP^2 + 0.402469 * PVP K 30^2 +0.2182 * MCC pH 101^2

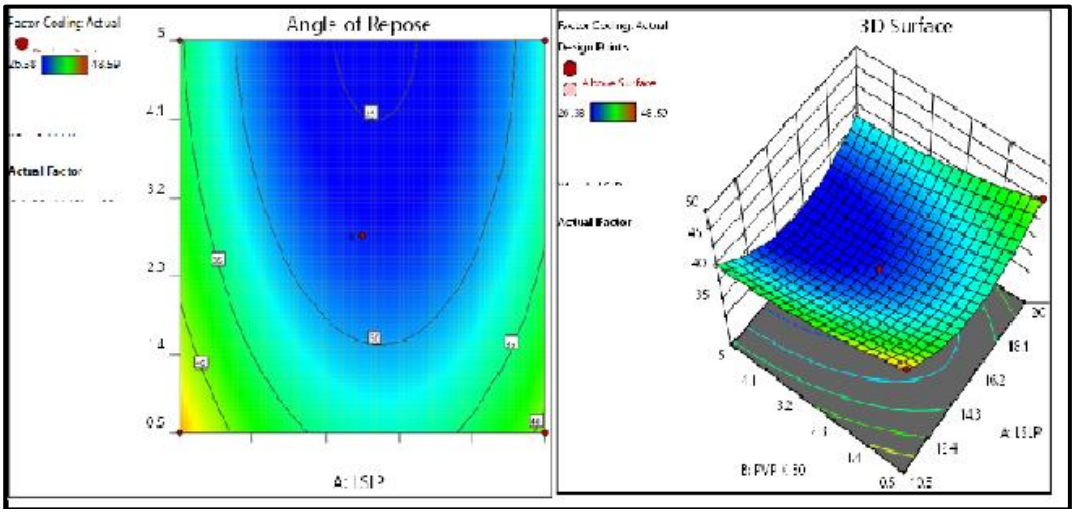

Figure 5. Contour Plot and response surface plot for Angle of Repose

Carr's Index

The Model F-value of 14.16 implies the model is significant. There is only a 0.10% chance that an F-value this large could occur due to noise.P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, BC, A^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms arenot significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.The Lack of Fit F-value of 148.90 implies the Lack of Fit is significant. There is only a 0.01% chance that a Lack of Fit F-value this large could occur due to noise. Figure 6 represents the contour plot and response surface plot respectively for Carr's Index.

Carr's Index = 709.461 + -2.91728 * LSLP + -11.8843 * PVP K 30 + -16.0585 * MCC pH 101 + -0.0210526 * LSLP * PVP K 30 + -0.0142105 * LSLP * MCC pH 101 + 0.128222
* PVP K 30 * MCC pH 101 + 0.125717 * LSLP^2 + 0.187951 * PVP K 30^2 + 0.09736
* MCC pH 101^2

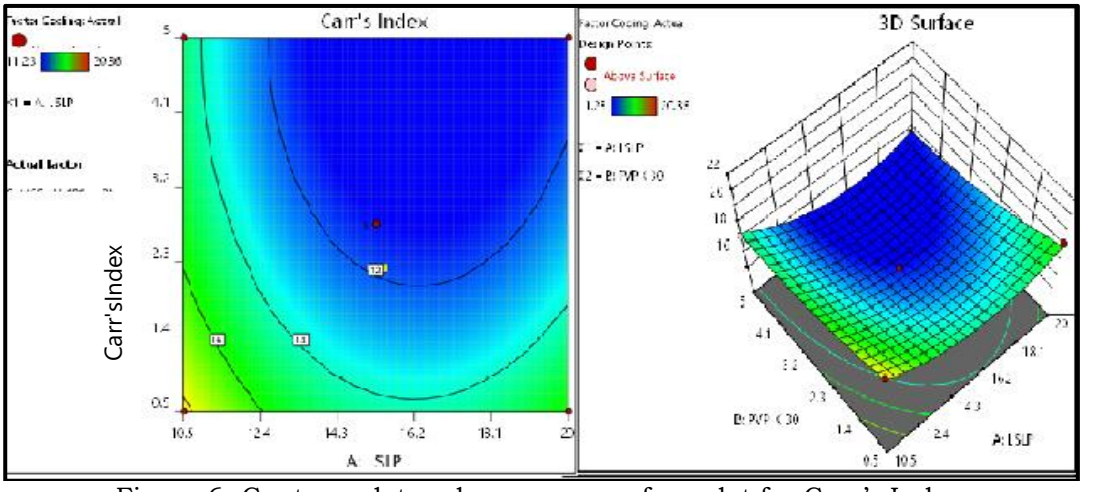

Figure 6. Contour plot and response surface plot for Carr's Index

Hausner's Ratio

The Model F-value of 21.01 implies the model is significant. There is only a 0.03% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, AC, BC, A^2, B^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms arenot significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. Figure 7 represents the contour plot and response surface plot respectively for Hausner's Ratio.

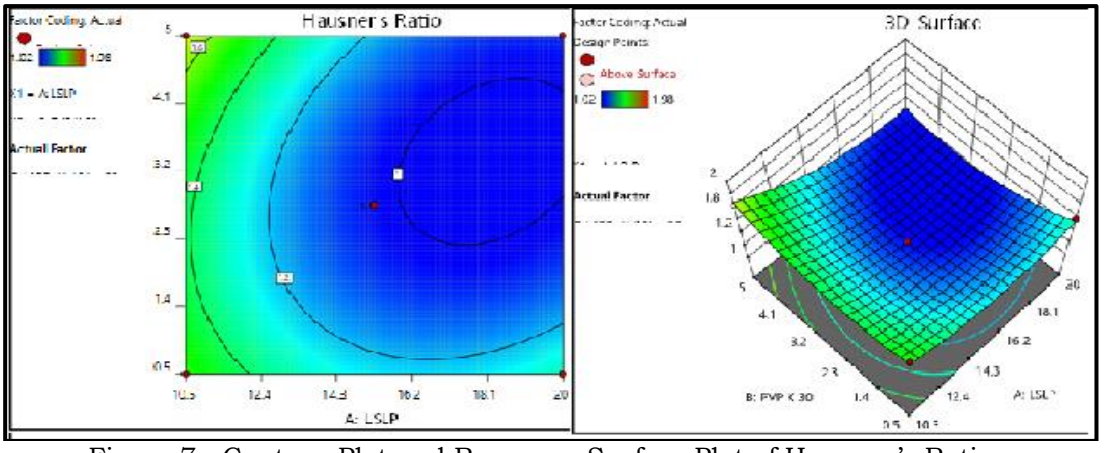

Figure 7. Contour Plot and Response Surface Plot of Hausner's Ratio

Optimization and validation of model

The prediction power of a mathematical model generated must be validated. The checkpoint was prepared by taking one batch from the overlay plot generated using Design Expert optimization function by "trading off" CQAs. Hardness values were kept between 2-5 kg/cm2, in vitro disintegration time was kept from 100 to

130 seconds. Friability values were set between 0.6-1% while T50 was kept between 16 to 24 min. Angle of repose, Carr's Index and Hausner's Ratio were kept 26-35, 11-18 and 1.02-1.5 respectively. After applying these constraints, an overlay plot was generated to identify a zone where each of product criteria was complied. Figure shows the generated overlay plot, the yellow region in the plot is the area where all product criteria are satisfied is called as design space. Another region (green colour) inside the yellow region is considered as control space. In control space, even small changes are made in independent variables the dependent variables will give results which are within the acceptable limits. Based on this control region, three check point batches were obtained using graphical optimization and were prepared and the values of response were produced in the software and the PRESS values ranged below 5% suggesting the model is validated.

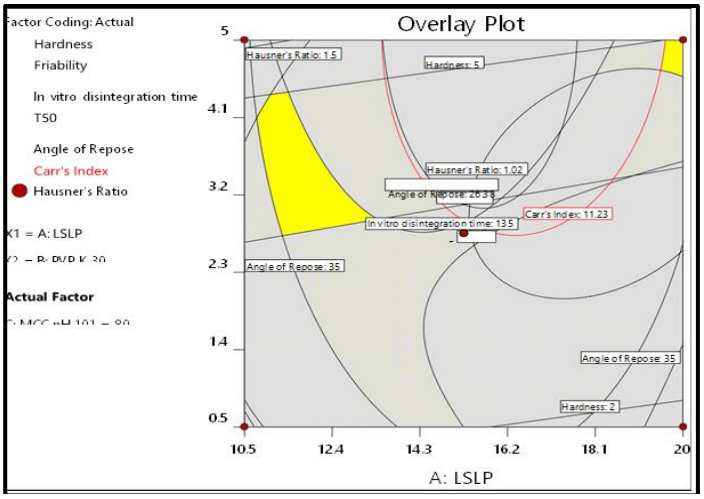

Figure 8. Overlay Plot

Table 2. Results of Checkpoint batch along with calculated PRESS values

Response	Predicted	Observed	Predicted Error
Hardness	3.629411765	3.65	0.564061241
Friability	1.059411765	1.02	- 3.8638985142
In vitro disintegration time	134.288	133.56	-0.545073375
T50	16.26	16.98	4.240282686
Angle of Repose	27	27.22	0.808229243
Carr's Index	11.362	11.3	-0.548672566
Hausner's Ratio	1.026	1.01	-1.584158416

Validation of QbD methodology was accomplished by preparing six check point formulations and comparing their observed responses with those predicted ones. The prediction error (i.e., bias) for the CQAs varied between -1.58 to 4.24 with overall mean ± SD as -0.98% ± 0.22.

Compression Behaviour Analysis
Heckel Plot

The data of Heckel equation are shown in Table 7.32 and 7.33. It summarizes the values of 'Py', which states that mean yield pressure of CP4 (1.9277) is lesser than physical mixture (2.052). A lower value of 'Py' of CP4 represents a higher degree of densification as compared to physical mixture, while the higher value of 'Py' indicates higher yield strength, requiring higher force for initiating deformation.

Kawakita Plot

The physical mixture has higher 'a' value (0.296) than P4 (0.2) which could be attributed to large amount of voids between them (Table). The less 'a' value of P4 is due to the smaller size and spherical shape of the particles, which would facilitate efficient packing. The '1/b' values for P4 and physical mixture are 0.5 and 0.74 respectively. Thus, physical mixture requires greater force to reduce to one half of its original volume than CPE1. The larger 'b' value of P4 (2) than physical mixture (1.34) implies that comparatively less resisting forces could occur for P4 during compression.

Conclusion

The use of particle engineering via co-processing has been investigated in order to investigate the possibility of developing innovative excipients that have improved functionality. The purpose of this research was to determine whether or not co-processing with MCC pH 101 and PVP K30 in proportions that were optimised may increase the functionality of Lapidium Sativum for direct compression. The desirability function and other supporting studies were used as a basis for selecting the optimised formulation, and the Design of Experiment (DoE) method was used to optimise the composition of the co-processed excipient. Following that, the approach of spraydrying was utilised in order to develop the co-processed excipient. Flow and compaction studies of the coprocessed excipient were conducted, and the results were compared to those of the parent component and the physical combination. As a model for poor compressibility, tablets containing 100 milligrammes of venlafaxine hydrochloride were manufactured by the process of direct compression (DC). Tablets made with CPE were of a satisfactory quality and met all of the requirements set forth by the USP for approved tablets. DoE was successfully applied in order to optimise and produce a starch-based co-processed excipient that is suitable for direct compression tableting. This excipient can be evaluated for use in this tableting method.

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