RESEARCH ARTICLE

Optimization of Spray-Dried Co-Processed Excipients Using Design of Experiments: A Mixture Design Approach

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ABSTRACT

Co-processed excipient (CPE) are widely recognized for their ability to enhance the functional properties of pharmaceutical formulations, providing superior performance compared to unprocessed physical mixtures. They improve flowability and compactibility when combined with active pharmaceutical ingredients (API). In this study, Design of Experiments (DoE) was employed to revisit the spray-dried production of CPEs composed of microcrystalline cellulose (MCC), lactose (LAC), and povidone (POV). The responses evaluated were compressibility index (CI), hardness, yield, and moisture content (MC). A mixture design was utilized to assess the interactions between these excipients and their effects on the responses, with response surface methodology (RSM) used to model the data via Design-Expert software. The optimization process identified an optimal formulation composed of 90% MCC and 10% POV, achieving a hardness value of 7.39 kgf, CI of 30.37%, MC of 3.73%, and a yield of 57.97%. This study demonstrates that DoE can be effectively utilized to develop promising CPE formulations.

Keywords: Co-processed excipient, design of experiment, optimization, mixture design

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INTRODUCTION

Design of Experiments (DoE) techniques are frequently used in pharmaceutical research to systematically optimize formulations.[1] DoE enables researchers to study the effects of multiple variables simultaneously, providing a more robust understanding of how formulation and process parameters impact the final product quality.[2] The traditional trial-and-error approach to formulation design is gradually being replaced by the more systematic and efficient DoE methodology.[3] This shift represents a transformative leap in how pharmaceutical scientists approach formulation challenges, offering the potential for accelerated drug development and improved therapeutic outcomes.[4] The DoE approach has also been applied to the development of co-processed excipients (CPE). CPE is increasingly important in the pharmaceutical industry due to their ability to enhance the functional properties of formulations. These excipients are designed to provide superior performance compared to unprocessed physical mixtures, improving properties such as flowability and compactibility, especially when combined with active pharmaceutical ingredients (API) in tablet production.[5] CPE offers synergistic benefits that include enhanced compressibility and overall tablet performance, making it highly valuable in direct compression tablet manufacturing, where uniformity, stability, and efficacy are critical.[6] In earlier studies, spray drying has been employed to prepare CPE by processing mixtures of microcrystalline cellulose (MCC), lactose (LAC), and povidone K-30 (POV). MCC is widely used as a diluent and binder because of its excellent compressibility and flow properties, while LAC serves as a common filler to bulk up formulations.[7] POV acts as a binder, enhancing tablet hardness.[8] The combination of these excipients through spray drying offers a promising approach to achieving co-processed fillers with improved flow and compactibility.[9] However, despite the advantages, prior studies revealed certain limitations in the optimization process, particularly the exclusion of critical parameters such as yield and moisture content (MC). Yield reflects the efficiency of the manufacturing process, while MC directly affects the flowability and long-term stability of the granules. The exclusion of these key factors resulted in an incomplete understanding of the overall efficiency and processability of the CPE. Therefore, recalibration of the optimization model is necessary to incorporate these additional parameters and provide a more comprehensive analysis. In this study, previously excluded parameters such as yield and MC are incorporated to improve the optimization process, with the expectation of achieving better results. Traditional key parameters such as hardness and the compressibility index are still utilized to determine the optimal formulation.[10,11]

MATERIALS AND METHODS

This study is based on previous research that explored the influence of a mixture of three excipients: MCC, LAC, and POV, on four independent responses: compressibility index (CI), hardness, yield, and MC.[9] There were 12 spray dried formulations tested in this study (Table 1). A mixture design was employed to evaluate the interactions between the excipients and their effects on the responses, with response surface methodology (RSM) applied to model the data

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Table 1: Formula of spray dryed CPE comprising MCC, LAC, and POV.

Formula	MCC	LAC	POV	Hardness (kgf)	CI (%)	MC (%)	Yield (%)
1	0	50	50	3.54	42	5.29	34.05
2	0	70	30	3.83	38	4.43	39.10
3	0	90	10	2.43	44	4.25	37.05
4	17.5	52.5	30	3.61	48	4.84	39.43
5	17.5	52.5	30	3.73	44	5.16	35.01
6	30	30	40	3.95	52	5.08	29.48
7	45	45	10	4.43	34	3.11	38.16
8	45	45	10	4.81	36	3.31	46.06
9	46.67	16.67	36.67	4.38	44	4.29	52.94
10	50	0	50	4.94	46	5.42	51.44
11	70	0	30	6.69	24	4.96	46.84
12	90	0	10	7.39	38	4.11	64.26

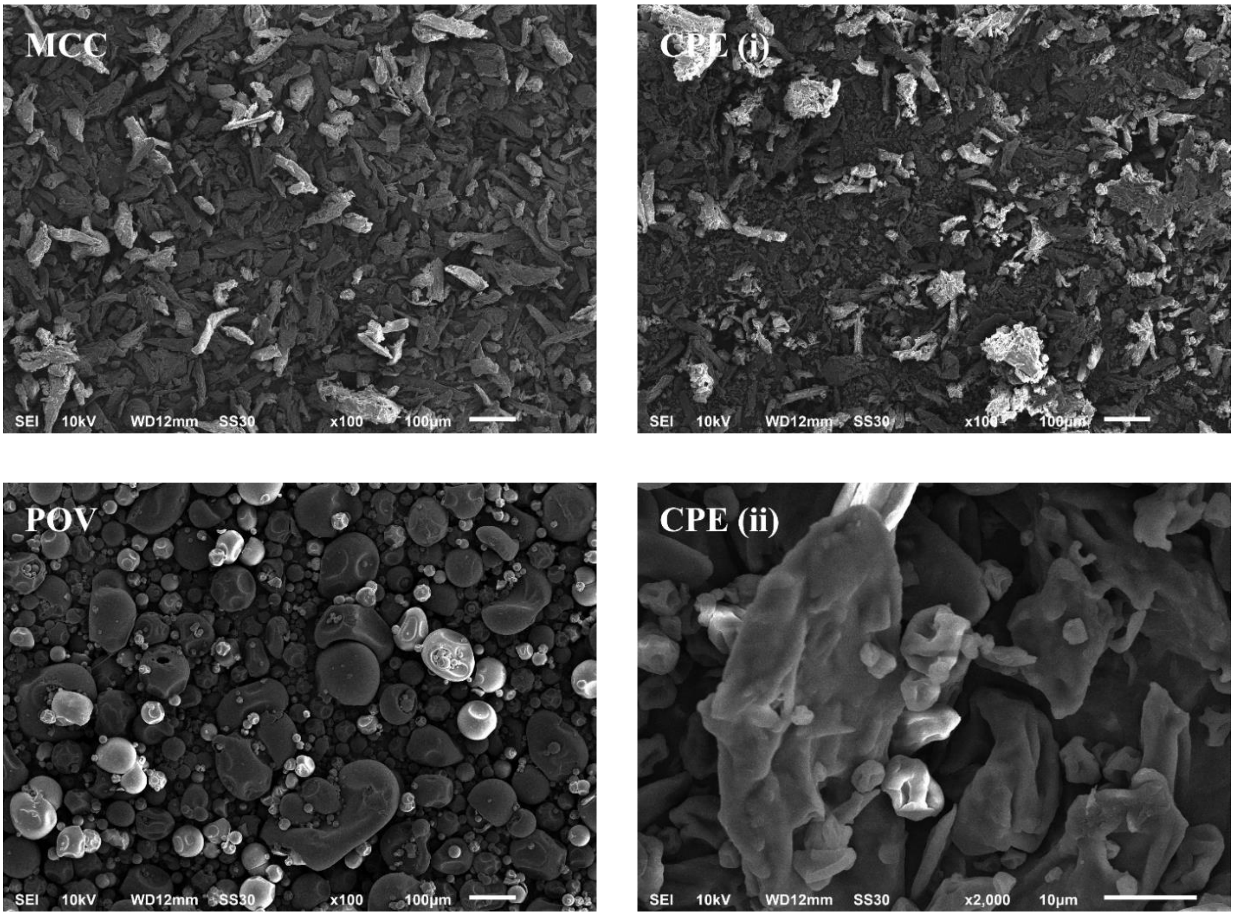

Figure 1: Morphology of spray dryed CPE comprising MCC, LAC, and POV.

using Design-Expert software.[12] Initially, the run data were analyzed to identify any potential outliers. Following this, the data were checked for possible transformations, which could be necessary to meet residual assumptions and validate the analysis of variance (ANOVA). This transformation was crucial when the ratio of maximum to minimum response was large, as it ensured a more accurate analysis. To determine the most suitable mathematical model for each response, several statistical parameters were evaluated, including the coefficient of determination (R^2), the adjusted R^2, and the F-value derived from ANOVA. Models with significant F-values ($p < 0.05$) were selected for further analysis. The model fit was assessed using diagnostic plots and residual analysis to ensure that the model assumptions were satisfied. If a significant lack of fit was detected, the model was refined by adjusting the experimental setup or transformations to improve its accuracy. The next step involved optimization, where overlay plots were generated to visually represent the interactions between the responses. The acceptance criteria for optimization were predefined based on literature references and experimental constraints. In this study, hardness and yield were set to be maximized, while CI and MC were minimized. All responses remained within their predefined ranges, thus no further adjustments to the limits were necessary. The importance and weight of all parameters were set equally, meaning that no single response was prioritized over others in the optimization

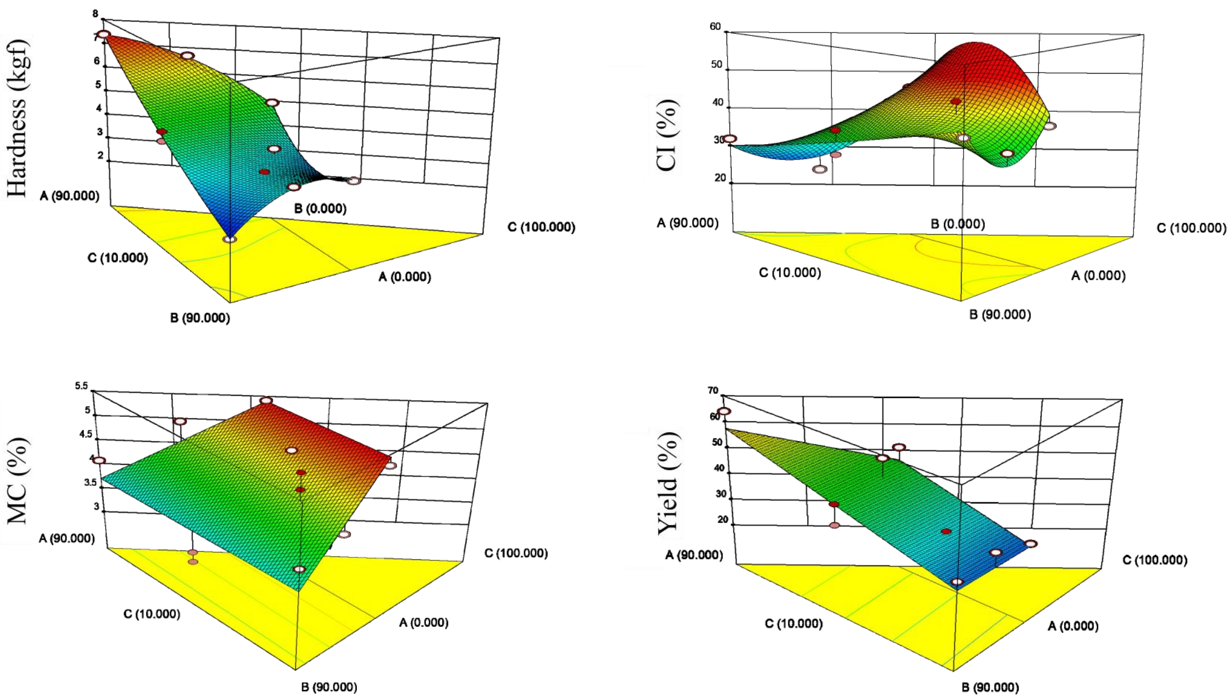

Figure 2: Optimization model of spray dryed CPE comprising MCC, LAC, and POV.

process. The solutions were determined by selecting the formulations with the highest overall desirability, which indicated the optimal balance of responses. Desirability functions provided the final composition of each component in the optimal formulation, specifying the percentage of MCC, LAC, and POV needed to achieve the target properties.

RESULTS AND DISCUSSION

In previous study, MCC, POV, and LAC were combined to form a CPE using spray drying. MCC, which has a fibrous powder form, and POV, which tends to be spherical, were blended. The spray-dried combination resulted in a mixture that still retained the physical characteristics of each component (Figure 1). It is observed that the particle size of POV is relatively large, with some particles reaching approximately 200 µm. In contrast, CPE appears to follow the size of MCC, exhibiting relatively smaller particle sizes, although the particles now tend to be more rounded compared to their initial form. Upon increasing the resolution of observation, it becomes evident that the MCC particles are coated by smaller POV particles following the spray drying process. The POV particles maintain their spherical or rounded morphology.[9] The process conducted in this study involves spray drying. Spray drying is a technique that converts a liquid into powder by spraying the liquid into hot air. Spray drying is used to produce particles with homogeneous sizes. This process provides flexibility in controlling particle morphology and size.[13] Spray drying has also been used in various other processes involving the combination of excipients, as well as with the active pharmaceutical ingredient (API). Hibbard utilized spray drying to produce ciprofloxacin salts with several types of aliphatic dicarboxylic acids, including hydroxypropyl methylcellulose (HPMC). Other research focuses on developing spray-dried Olipudase alfa, a parenteral therapeutic enzyme, in combination with excipients such as trehalose and arginine.[14,15] Modeling modifications can be applied to various existing experimental designs to enhance optimization outcomes. For instance, simple linear regression modeling can be expanded into more complex forms such as quadratic or cubic models. In this research, a careful reevaluation and modification of the approach were undertaken to achieve better optimization results, taking into account factors that may have been overlooked in previous studies.[16] The remodeling approach has also been undertaken by Sempértegui, who has conducted research in tissue engineering. He added more complex, three-dimensional structures to enhance the accuracy of the previous model, accommodating the complex configurations found in real tissues.[17] The current study employs a mixture design where one component exhibits variability in quantity, diverging from traditional designs that impose equal constraints on material proportions. Such an experimental setup closely resembles real-world tablet manufacturing scenarios, where asymmetry in the proportions of fillers and binders is common. This complexity in proportions highlights the interactions between MCC and LAC as fillers, alongside POV as a binder, which ultimately influence the characteristics of the final CPE. Consequently, the deviation from symmetrical proportions prevents the model from conforming entirely to a triangular shape, as illustrated in Figure 2. Notably, the POV proportion, which ranges from 10% to 50%, results in a truncated appearance on the response surface.[4] Yield was one of the variables that were skipped in the previous research. However, this variable is currently included. The yield itself is a number or percentage that shows the amount of results from a process. Yield in spray drying is influenced by various factors, including the physical properties of the

Table 2: Equation of spray dryed CPE model comprising MCC, LAC, and POV.

Parameter	Equation	Model
Hardness	0.0740 MCC + 0.0119 LAC - 0.0367 POV + 0.0002 MCC*LAC + 0.0012 MCC*POV + 0.0019 LAC*POV - 3.7844.10^{-5}* MCC*LAC* POV	Special cubic
CI	0.3836 MCC + 0.5845 LAC + 1.5799 POV - 0.0069 MCC*LAC - 0.0222 MCC*POV - 0.0254 LAC*POV + 0.0007 MCC*LAC*POV	Special cubic
MC	0.0331 MCC + 0.0340 LAC + 0.0750 POV	Linear
Yield	0.6079 MCC + 0.3405 LAC + 0.3260 POV	Linear

liquid material, operational parameters such as temperature and air flow speed, and the design of the spray drying equipment itself. Success in achieving high yields requires optimization of these parameters to suit the characteristics of the material being processed and the final application goals of the product. Yield is not only reflects process efficiency but also closely relates to the quality of the final product. High yields may indicate that most of the input material has been converted into powder, but this must still be balanced with optimal product quality.[9] MC is a critical parameter in pharmaceutical formulations, significantly influencing the physical properties and stability of the final product. High MC can result in undesirable characteristics such as stickiness and clumping, which impair the flowability of the CPE. Furthermore, elevated moisture levels can promote the chemical degradation of active ingredients, negatively impacting the efficacy and shelf life of the formulation. Therefore, maintaining an optimal MC is essential for ensuring both the manufacturability and quality of pharmaceutical products.[18] The study focused on selecting a statistically significant model while maintaining hierarchical structure. Hardness and CI were modeled using a special cubic model (Figure 2), while MC and yield were represented by linear models [19,20]. For the hardness parameter, MCC emerged as the most dominant factor, followed by LAC. Surprisingly, POV, commonly used as a binder, reduced the hardness (Table 2). The combination of two or three of these materials showed no significant impact on hardness values. While interactions are present, they are relatively minor compared to the main effects of individual excipients. Conversely, POV had the greatest influence on CI, with LAC and MCC contributing to a lesser extent. This indicates that a higher proportion of POV is detrimental to improving flow properties. POV also played a major role in increasing MC, likely due to its hygroscopic nature, which elevates the moisture content of the spray-dried powder.[21] For yield, MCC was the primary contributor, and an increased proportion of MCC consistently resulted in improved yield.[22] The optimization strategy aimed to maximize hardness and yield while minimizing CI and MC. High hardness ensures that the CPE possesses excellent compactibility, which is expected to enhance compressibility when mixed with active ingredients[23]. High yield signifies process efficiency, while a low CI indicates better flow properties [24]. When used as a filler, this CPE is expected to improve the flow characteristics of the active ingredient[25]. On the other hand, maintaining a low MC is crucial, as high moisture content can lead to stickiness and complicate further processing of the material.[26] The optimization results for the four parameters identified the optimal formula as comprising 90% MCC, 0% LAC, and 10% POV. The fact that LAC was assigned a proportion of 0% suggests that the optimal CPE is solely composed of MCC and POV. This formulation achieved a hardness value of 7.39 kgf, a CI of 30.37%, MC of 3.73%, and a yield of 57.97%. In contrast, Tofiq (2020) found that LAC played a more prominent role in CPE formulations focusing solely on MCC and LAC, likely due to the absence of a binder like POV in his study.[27] The optimization demonstrated a strong desirability of 0.824, with a predicted yield exceeding 55%. Given that spray drying was used in conjunction with a highly hygroscopic material such as POV, this result is particularly commendable. The moisture content is within an acceptable range for tablet compression[10]. Notably, both the moisture content and yield responses were excluded from model determination and optimization in earlier studies, but were included here, ensuring a more comprehensive optimization that balances all relevant factors rather than focusing solely on hardness and CI. Compared to previous research, the hardness estimate in this study is slightly higher at 7.39 kgf versus 7.33 kgf, while the CI also shows a slight increase, at 30.37% versus 29.33%. Although these differences appear marginal, the inclusion of the additional responses—yield and moisture content—adds considerable value, as these crucial parameters were previously overlooked, further enhancing the robustness of the optimization.

CONCLUSIONS

This study demonstrates the effectiveness of using DoE for optimizing the development of CPE. By employing a mixture design, the interactions between MCC, LAC, and POV were systematically evaluated. The optimization identified the optimal CPE composition as 90% MCC and 10% POV, which resulted in desirable functional properties, including a hardness of 7.39 kgf, CI of 30.37%, MC of 3.73%, and a yield of 57.97%. Although the process can generally be further improved, a yield greater than 50%, is already quite satisfactory. Additional optimization of process parameters, such as solvent selection and adjustment of inlet and outlet temperatures, can be undertaken to enhance these results even further.

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