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Flexibility of Custom Design over Simplex Lattice Design in Co-Processed Excipient Formulations

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ABSTRACT

Custom design is a modeling technique that puts forward customized formula in a pharmaceutical formula optimization. The components may be adjusted to the formula constraints. However, these designs sometimes do not accommodate all the components used. In addition, its effectiveness is not necessarily optimal when compared with standard designs such as simplex lattice design (SLD). This study used computerized variations of microcrystalline cellulose PH 101 (MCC PH 101), lactose, and Kollidon K30. Custom design and SLD were compared using the Design Expert software based on previous research data. Hardness and tapping index became test parameters to assess the design effectiveness. The obtained optimum formula was MCC PH 101 : lactose : Kollidon K30 each at 80% : 10% : 10% for SLD. Unlike this finding, the custom design resulted in the absence of lactose proportion in its optimum formula. The predicted custom design had better hardness and tapping index than those of SLD instead.

Keywords: *custom design, simplex lattice design, co-processed excipient*

1. INTRODUCTION

Simplex lattice design (SLD) is part of mixture design in formula optimization (Muteki et al., 2007). It requires balanced formula, which can consist of two or more variables (Martinello et al., 2006). SLD also requires that no single variable be proportionately more prominent than the others. This design may be applied in processing pharmaceutical preparations or other preparations constituting a non-pharmaceutical formula (Belay et al., 2017; Fithri et al., 2017; Meinhart et al., 2017; Varanda et al., 2017; Zhang et al., 2014). Furthermore, such design has the advantage of high validity in modeling and predicting the results of a formula. In addition to SLD, a custom design can also be applied to a formula with non-proportional variables (Furlanetto et al., 2011). Such design has been used in several pharmaceutical studies, including in research into the making of co-processed excipient (CPE). Custom design is a non-lattice and non-centroid mixture design that puts more emphasis on customization of non-proportional formulas following the requirement defined by formulators. Both SLD and custom design can be performed through manual or computerized calculation using software such as Design Expert.

Kusuma et al. (2017) used microcrystalline cellulose PH 101 (MCC PH 101), lactose, and Kollidon K30 via spray drying to create new excipients with physical modification but without changing the chemical structure (Gonnissen et al., 2008; Kusuma et al., 2017). MCC PH 101 is a powerful filler binder for direct compression of tablet. Lactose is also tablet or capsule filler though its flowability and compactibility is inferior compared to MCC PH 101 (Edge et al., 2000). Meanwhile, kollidon K30 is a binder which being activated by moisture or water addition on tablet formulation. At the dry form, kollidon K30 has the best flow speeds compared to MCC PH 101 and lactose (Gonnissen et al., 2008; Kusuma et al., 2014).

Such CPE processing attempted to gain the benefits of its constituent components, including the compactibility and good flow properties (Awaluddin et al., 2017; Kusuma et al., 2014; Radojevic dan Zavaliangos, 2017). MCC PH 101, lactose, and kollidon K30 were mixed and spray dryed to obtain CPE powder. Flowability in the form of tapping index and compactibility displayed as hardness had been obtained and evaluated to determine the best design. It resulted in an optimum formula with a comparison of the three constituent components. However, such formula did not reflect all the involved components as lactose was omitted from the result (Kusuma et al., 2017). In addition, the result has not been able to outperform the compactibility and flow properties of MCC PH 102, the standard filler-binder material (Edge et al., 2000). Therefore, this present study aimed to overcome these problems as trough computerization an optimum formula would be achieved based on the previous research data.

2. EXPERIMENTAL SECTION

2.1. Materials

The study was fully computerized. This study involved the Design

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Expert software using previous research data (Table 1). SLD model was created with tablet hardness (TH) and tapping index (TI) taken from earlier research as the response parameters (Kusuma et al., 2017).

2.1. Methods

SLD was selected from mixture tab in the Design Expert software. MCC PH 101, lactose, and kollidon K30 were used as mixture components. Each component was set in the range of 10-80%. Total of mixture components was 100%. Six simplex points were used with quadratic order. Four augment design were being selected with 1 block. There were four runs for replication from total of 14 runs. The response were tablet hardness (TH) and tapping index (TI). There were 3 runs which being omited due to unpresent in previous research data (Kusuma et al., 2017).

3. RESULTS AND DISCUSSION

The input value for SLD comes from custom designs. The SLD in this study used 11 formulas with 4 points of augmentation and replication. Replication is required to improve the validity of the model, while the augmentation value is used to improve the strength of the model (Dejaegher and Heyen, 2011). Three SLD formulas were not used because the value did not exist in the modeling, which were MCC PH 101 : lactose : Kollidon K30 at 10% : 10% : 80% (2 replications) and 21.67% : 21.67% : 56.67%, respectively.

The highest value of compactibility in the SLD is slightly less than 7 kg while the custom design is almost 8 kg. At its lowest position, the value of SLD compactibility reaches 2.87 kg, while the custom design is slightly lower at 2.43 kg. This lowest value is achieved when lactose concentration is most dominant from other materials, be it SLD or custom design. The CPE is intended to be a better filler binder for direct compression, thus requiring higher physical properties of compactibility. The higher the compactibility, the stronger the resulting filler excipient (Gonnissen et al., 2008).

The compactibility parameter is represented by the tablet hardness, a measure of the strength of CPE powder compressed into tablet then broken down at its axis (Gohel et al., 2012; Martinello et al., 2006; Nguyen et al., 2013). Both SLD and custom design showed good compactibility, which increased correspondingly with the addition of MCC PH 101, an excellent filler binder with high compactibility (Figure 1). The SLD indicated lower compactibility than that of the custom design obtained from a previous study (Kusuma et al., 2017).

Tablet hardness does not require any transformation to yield valid results in either SLD or custom design though it can be done to improve the validity of the model. Transformation may include an inversion, logarithm, square root, or others (Dejaegher dan Heyden, 2011). Meanwhile, the SLD model used on tablet hardness was quadratic, the third degree after mean and linear (Vera Candioti et al., 2014). It appears that the variables in SLD were simpler than those in custom design (Table 2). The custom design involved a special cubic model that uses variables of interaction among the three constituent components. This means that the components interact with each other in their contribution to tablet hardness (Pires et al., 2017).

The ANOVA assessed the validity of tablet hardness models in both SLD and custom design, showing significant results (Table 3). In addition, the result of lack of fit test was insignificant in both modeling types. The value of lack of fit suggests a model mismatch, in which the greater the value, the greater the inconsistency. Therefore, the insignificant lack of fit indicates good results (Dejaegher dan Heyden, 2011).

The visualization of tablet hardness model (Figure 1) depicts custom design as a truncated model because it did not take on equal proportions of its constituent components. In contrast, the shape of SLD model is an intact curved triangle, indicating the equivalence of its constituent components (Reynolds et al., 2017).

The next parameter is the flow properties represented by the tapping index. This value was obtained by tapping the powder on a measuring cup 100, 200, and 300 times or more until the reduction became constant. Such value is an indirect assessment of the flow since it is not produced by flowing the powder (Saifullah et al., 2016). Powder will come down along with every tap as particles fill the cavities underneath. More descending particles mean worse flow as it shows that the initial poured powder is not immediately able to fill the granule spaces (Ketterhagen, 2015).

The lowest IP on SLD is at 33.7 where MCC PH 101 is the most dominant, while the highest value, more than 60%, is obtained when kollidon K30 is most dominant (Figure 1). The lowest and highest IP values in custom design are 24 and 52% respectively with the same composition as the SLD, which is the lowest dominant MCC PH 101, and the highest when the K30 kollidon is dominant. All SLD as well as custom designs showed an increase in the tapping index in accordance with the addition of Kollidon K30. Increased tapping index indicates worse flow prop-

Table 1. CPE formulation using Simplex Lattice Design

Formula	MCC PH 101 (%)	Lactose (%)	Kollidon K30 (%)	TH (kg)	TI (%)
1	80	10	10	6.83	34.84
2	10	80	10	2.87	42.51
3	45	45	10	4.61	35.2
4	45	10	45	4.46	48.09
5	10	45	45	3.44	50.56
6	56.67	21.67	21.67	5.35	38.57
7	21.67	56.67	21.67	3.69	41.95
8	33.33	33.33	33.33	3.99	48.65
9	80	10	10	6.83	34.84
10	10	80	10	2.87	42.51
11	45	45	10	4.61	35.2

Table 2. SLD and custom design (CD) predictive equation of tablet hardness (TH) and tapping index (TI)

Parameter	Predictive Equation
TH_{SLD}	6.84A+2.88B+2.89C-0.99AB-1.72AC+2.10BC
TH_{CD}	7.55A+2.46B-3.34C-1.56AB+8.81AC+15.12B-26.11ABC
TI_{SLD}	33.74A+41.04B+62.35C
TI_{CD}	36.01A+45.87B+168.31C-22.94AB-213.75AC-222.79BC+555.44ABC

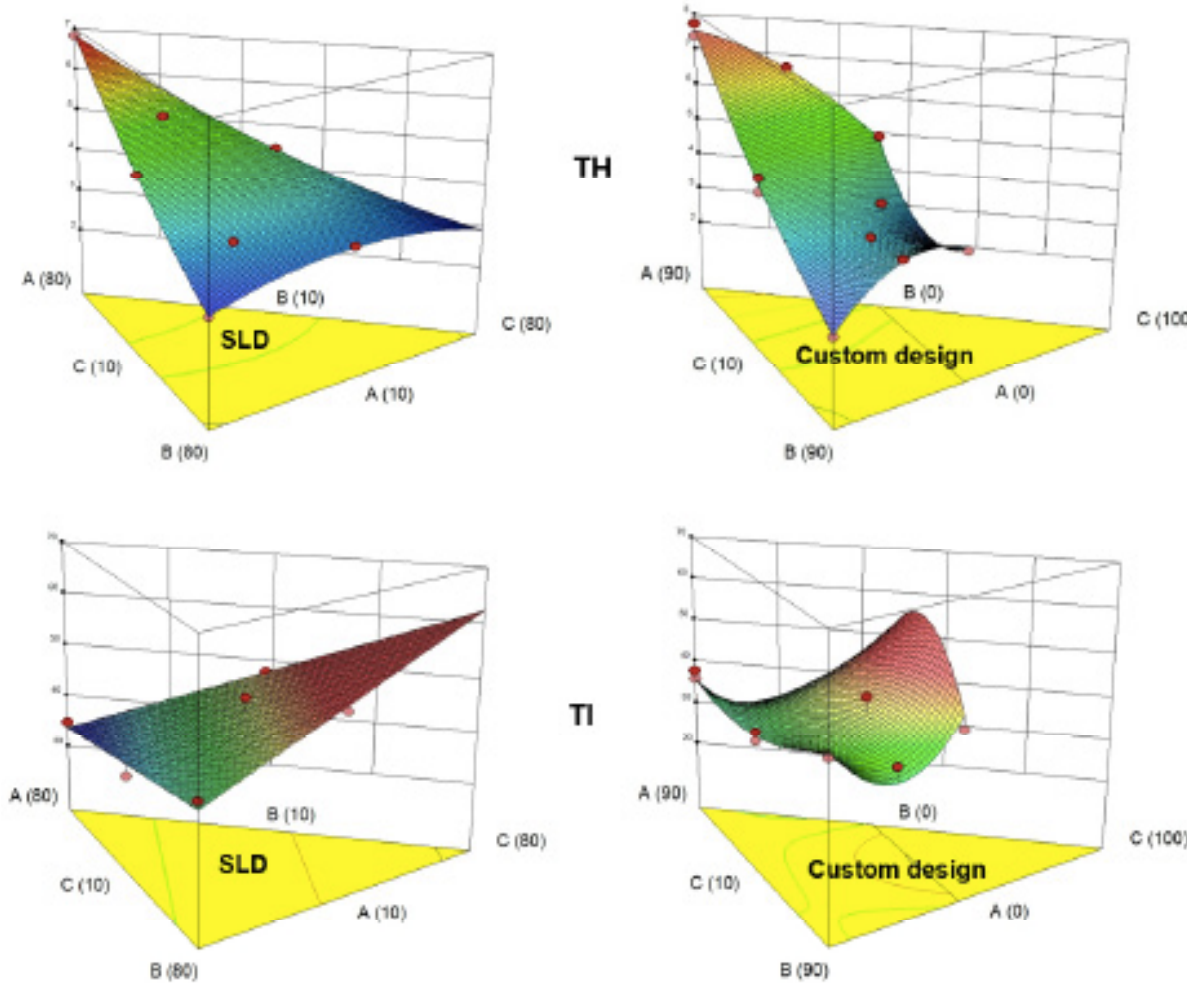

Figure 1. SLD and custom design model of tablet hardness (TH) and tapping index (TI)

erties of granules. Kollidon K30 is a very hygroscopic material that makes granules sticky (Gonnissen et al., 2008; Kusuma et al., 2014), producing an adverse affect on the granule flow properties. The tapping index of SLD was higher than that of the custom design from the previous research.

Similar to tablet hardness, tapping index requires no transformation in SLD or custom design (Table 3). The modeling used in tapping index was linear, which is simply a sum of the three components involved (Dejaegher dan Heyden, 2011). Meanwhile, custom design used the same model as the one for tablet hardness, namely special cubic.

The ANOVA test for the tapping index of SLD and custom design showed significant results. Additionally, the value of lack of fit was insignificant in both models. The shape of SLD model for tapping index was an intact straight curved triangle, indicating a linear model. On the other hand, that of the custom design was not intact since Kollidon K30 only composed a maximum of 50% proportion.

The determination of optimum formula was performed by the numerical optimization in Design Expert. The ranges, targets, and limits were set for both test parameters. The compactibility represented by tablet hardness requires a maximum value to acquire the best filler-binder, while the flow properties represented by tapping index need a minimum value for the best result (Reynolds et al., 2017).

The optimum formula for SLD consists of MCC PH 101 : lactose : Kollidon K30 at 80% : 10% : 10%, respectively. This value differs from that of custom design, which omits lactose proportion. The prediction presented in Table 4 for custom design has instead a better value than SLD for both tablet hardness and tapping index. The hardness of the tablet is 0.4 kg higher, and the tapping index has a 4.2% difference. However, in SLD, the lactose component retains a portion in the optimum formula, which is 10%.

4. CONCLUSION

The obtained optimum formula was MCC PH 101 : lactose : Kollidon K30 each at 80% : 10% : 10% for SLD, with worse hardness and tapping index than those of custom design. Custom design is highly flexible for pharmaceutical preparations that have non-uniform component proportions in the formula. Aligning the number of components in a formula with SLD will only reduce its flexibility, which in turn worsens the test results.

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Table 3. SLD and custom design (CD) parameters of tablet hardness (TH) and tapping index (TI)

	TH		TI	
	SLD	**CD**	**SLD**	**CD**
Model	quadratic	special cubic	linear	special cubic
Transformation	none	none	none	none
p-value	6.6×10^{-7}	7.6×10^{-6}	4.9×10^{-5}	0.020
Sig.	significant	significant	significant	significant
Lack of fit	insignificant	insignificant	insignificant	insignificant

Table 4. SLD and custom design prediction of tablet hardness (TH) and tapping index (TI)

	MCC PH 101	**Lactose**	**Kollidon K30**	**TH**	**TI**
SLD	80%	10%	10%	6,8 kg	33,7%
Custom design	79.60%	0%	20.40%	7.2 kg	29.50%

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