

Formula Optimization of Rifampicin Dry Powder Inhalation with Chitosan-Xanthan Carrier Using Response Surface Methodology

Silvia Surini*, Rahmadina Providya, Kurnia Sari Setio Putri

Laboratory of Pharmaceutics and Pharmaceutical Technology Development, Faculty of Pharmacy, Universitas Indonesia, Depok, 16424, Indonesia.

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ABSTRACT

This study was aimed to obtain an optimum formula of rifampicin dry powder inhalation (DPI) with chitosan-xanthan (CX) as a carrier by spray drying method using response surface methodology (RSM). Fourteen experimental formulas were designed statistically by Box Behnken method by varying three parameters namely concentration of CX solution, rifampicin/CX ratio, and inlet temperature of the spray dryer. The entrapment efficiency (EE), particle size, and drug release in pH 7.4 (pulmonary condition) and pH 4.5 (pulmonary macrophages condition) of the rifampicin DPI were characterized. The optimum formula of rifampicin DPI was obtained using Design Expert software. The obtained DPI from those 14 formulas possessed EE of 112.00–149.08% and average particle sizes of 0.599–5.506 μm . Rifampicin release in phosphate buffer medium pH 7.4 was 6.54%–22.95% and in pH 4.5 was 12.02–48.60%. The Design Expert predicted that the optimum formula would be obtained with a concentration of CX solution of 0.5%, a ratio of rifampicin to CX 1:1, and inlet temperature of the spray dryer at 143°C. The optimized formula produced a rifampicin DPI with EE of 108.9%, the particle size of 1.177 μm , and the rifampicin release of 14.49% (at pH 7.4) and of 37.97% (at pH 4.5).

INTRODUCTION

Pulmonary drug delivery system is increasingly investigated due to its potential to deliver the drug directly into the lung to provide higher local effect and target specific cells in the lung (Park *et al.*, 2013). Rifampicin administration for latent tuberculosis (TB latent) therapy through peroral route may cause many adverse effects (such as hepatotoxicity, indigestion, altered renal function, and others) (FDA, 2016). Moreover, high-frequency of rifampicin administration in such long periods of time can cause difficulties for patients to always adhere to the medication, causing intolerance or resistance by *M. Tuberculosis* (Park *et al.*, 2013). Therefore, pulmonary delivery of rifampicin is considered as prospective strategy to reduce administration doses, minimize side effects, and improve the effectiveness of rifampicin therapy.

In pulmonary drug delivery systems, solid form (dry powder inhalation) offers advantages over liquid formulation such as solution or suspension, due to its physical and microbial stability (Zhou, 2013). Dry powder inhaler should possess particular characteristics to be delivered into the lower airway, including spherical shape and particle size of 1-5 μm (Hickey, 2004). For this purpose, spray-drying method offers the best approach to produce spherical shape powder with size of 1–5 μm (Keshani, 2015).

In a dry powder preparation, a carrier excipient plays an essential role in delivering the drug into its target of pulmonary macrophages. The excipients should be non-toxic to the lungs, facilitate drug preparation and administration, promote consistent drug release, and protect the drug from degradation (Patel, 2015). It is known that rifampicin formulations with chitosan carriers may increase particle uptake by pulmonary macrophages (Park *et al.*, 2013). Thus chitosan was selected as a drug carrier in latent TB therapy. Based on previous research (Putri, Sulistomo & Surini, 2017), the combination of chitosan with xanthan gum can form a polyelectrolyte complex (Esteban and Severian, 2005; Hamman, 2010) which has a better swelling index at pH 5 than

*Corresponding Author

Silvia Surini; Laboratory of Pharmaceutics and Pharmaceutical Technology Development, Faculty of Pharmacy, Universitas Indonesia, Depok, 16424, Indonesia. E-mail: silvia@farmasi.ui.ac.id

the swelling index on a chitosan alone. Therefore, rifampicin dry powder prepared using polyelectrolyte complex chitosan and gum xanthan as a carrier was expected to exhibit better drug release in pulmonary macrophages.

During preparation of rifampicin dry powder by spray drying method, several factors influence the characterization of the powder (Bolton and Bon, 2010). Therefore, those factors need to be optimized to obtain the best formula. Optimization using response surface methodology (RSM) allows the formulator to estimate the exact system in the formulation process, as well as the method, can determine the optimum conditions significantly (Hussain, 1991). In this study, Box Behnken design was used to design fourteen formulas by varying three parameters: concentration of CX solution, rifampicin/CX ratio, and inlet temperature of the spray dryer. The entrapment efficiency (EE), particle size, and drug release in phosphate buffer medium pH 7.4 (pulmonary condition) and medium pH 4.5 (pulmonary macrophages condition) of the obtained dry powder were then characterized and analyzed by Design Expert software to find the best formula.

MATERIALS AND METHODS

Materials

Rifampicin was procured from Shenyang Antibiotic, China. Chitosan was obtained from Bio Chitosan, Indonesia; gum xanthan was purchased from Tongliao Huanghelong Bioengineering, China, and other chemical reagents.

Preparation of chitosan-xanthan excipients

Chitosan-xanthan excipients (CX) was prepared based on previous research (Stefaniak, 2011) conducted by Argin-Soysal, Kofinas, and Lo, which has been modified, by mixing chitosan solution and xanthan gum solution (1: 1) at pH 4.3-4.5. After the reaction process was completed, the stirring process was continued for 24 hours. The obtained precipitation was then washed with deionized water five times and dried in the oven at 70°C.

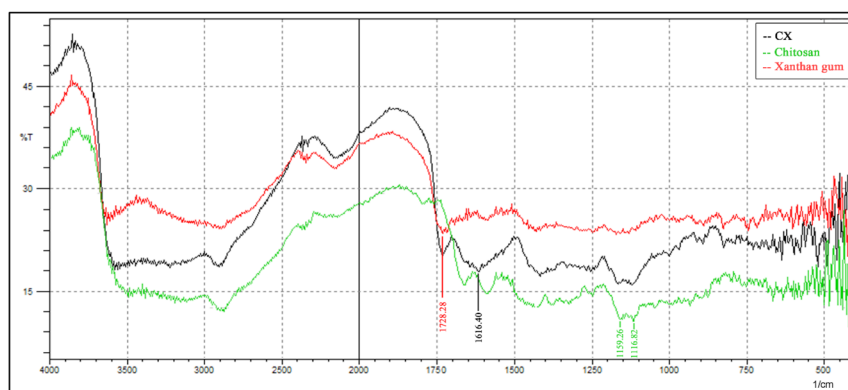


Fig. 1: Infrared spectrum of CX, chitosan, and gum xanthan.

Characterization of CX

CX was characterized by its functional group and viscosity. The functional group of CX was analyzed using Fourier Transform Infra Red (FTIR-8400 S Shimadzu, Japan) at wave numbers 400 to 4000 cm^{-1} (Varshosaz *et al.*, 2015). The IR spectrum obtained from the chitosan-xanthan polyelectrolyte complex was compared with each IR spectrum of chitosan and gum xanthan. The viscosity of CX was tested by viscometer Brookfield.

Preparation of rifampicin dry powder inhalation

The experimental design used in this research was Box-Behnken design, and 14 formulas were obtained from this model (Table 1). The CX was dissolved in the deionized water with concentration variations according to the formula, and rifampicin powder was dispersed into the CX solution. The solution was sprayed with a spray dryer (BUCHI *Mini Spray Dryer* B-290, German) with a flow rate of 25 mL/min, 100% aspirator, and inlet temperature variation according to each formula. The obtained dry powder was collected.

Table 1: Parameters of rifampicin dry powder formulas from Box-Behnken design.

F	Parameters		
	CX concentration (% b/v)	RIF: CX ratio	Inlet temp. (°C)
1	0.1	1:2	120
2	0.5	1:2	120
3	0.1	1:2	160
4	0.5	1:2	160
5	0.1	1:1	140
6	0.5	1:1	140
7	0.1	1:3	140
8	0.5	1:3	140
9	0.3	1:1	120
10	0.3	1:1	160
11	0.3	1:3	120
12	0.3	1:3	160
13	0.3	1:2	140
14	0.3	1:2	140

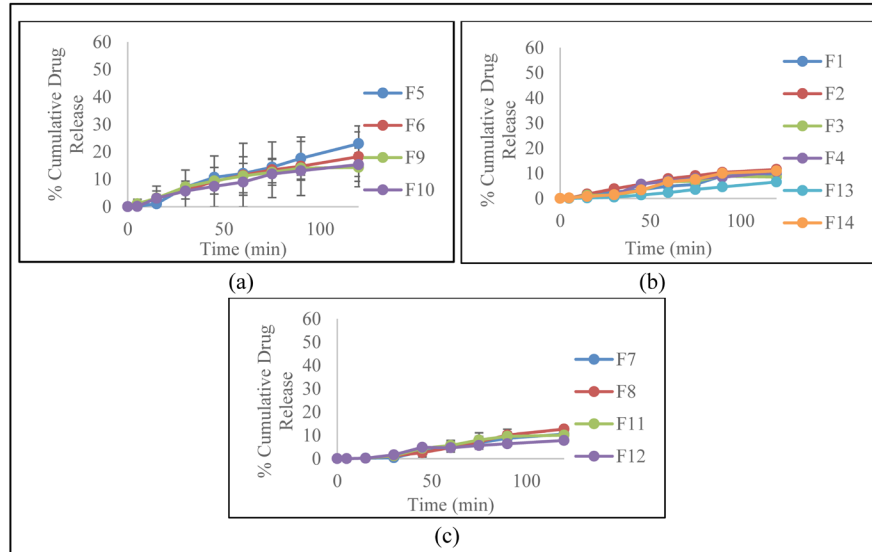


Fig. 2: Rifampicin release profile in medium phosphate buffer + SDS 0.05% pH 7.4 with RIF: CX ratio (a) 1:1, (b) 1:2, (c) 1:3.

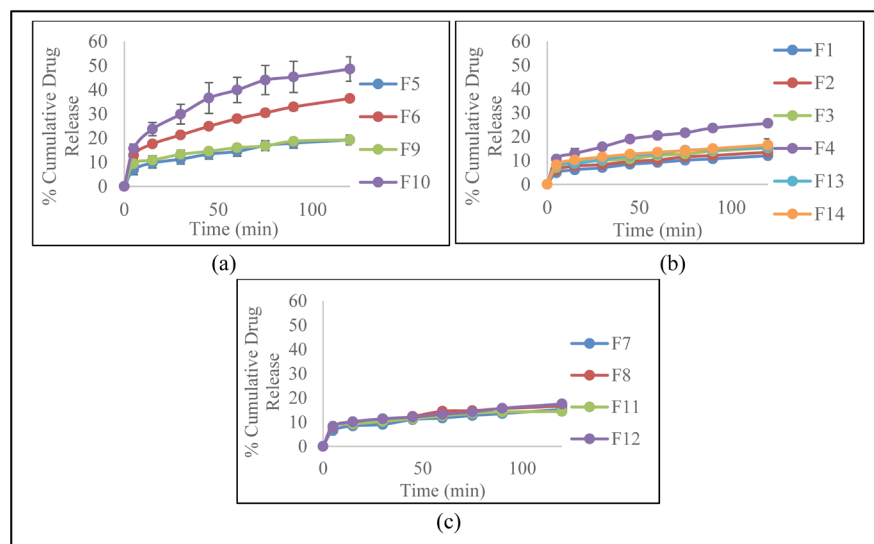


Fig. 3: Rifampicin release profile in medium potassium hydrogen phthalate pH 4.5 with RIF: CX ratio (a) 1:1, (b) 1:2, (c) 1:3.

Particle size distribution

Particle size distribution was determined using particle size analyzer with dynamic light scattering method (Chaudhary *et al.*, 2013). A total of 1 mg of powder was dissolved in 20 mL diethyl ether. The mixture was sonicated for 2 minutes and measured using Mastersizer 3000 MAZ 6240 (Malvern, UK).

Entrapment Efficiency

Dry powder equivalent to 25 mg rifampicin was dissolved in methanol in a 25 mL flask. Two milliliters of solution was dissolved into the phosphate buffer pH 7.4 in 100 mL measuring flask. The absorption was measured using UV-Vis spectrophotometer (UV-1800 Shimadzu, Japan) at maximum wavelength (British Pharmacopoeia, 2013). The level of

rifampicin was determined by using a linear regression equation. Percentage of entrapment efficiency (% EE) can be obtained using the formula:

$$EE (\%) = \frac{\text{Actual concentration of rifampicin}}{\text{Estimated concentration of rifampicin}} \times 100\%$$

Drug release

The medium used in drug release test was pulmonary simulation fluid and pulmonary macrophage simulation fluid. Pulmonary simulation fluid pH 7.4 was prepared from sodium phosphate buffer with 0.05% sodium dodecyl sulfate. The phagolysosomal lung macrophage simulation solution at pH 4.5 was prepared using 0.02 M potassium hydrogen phthalate with pH 4.5 (Stefaniak, 2011).

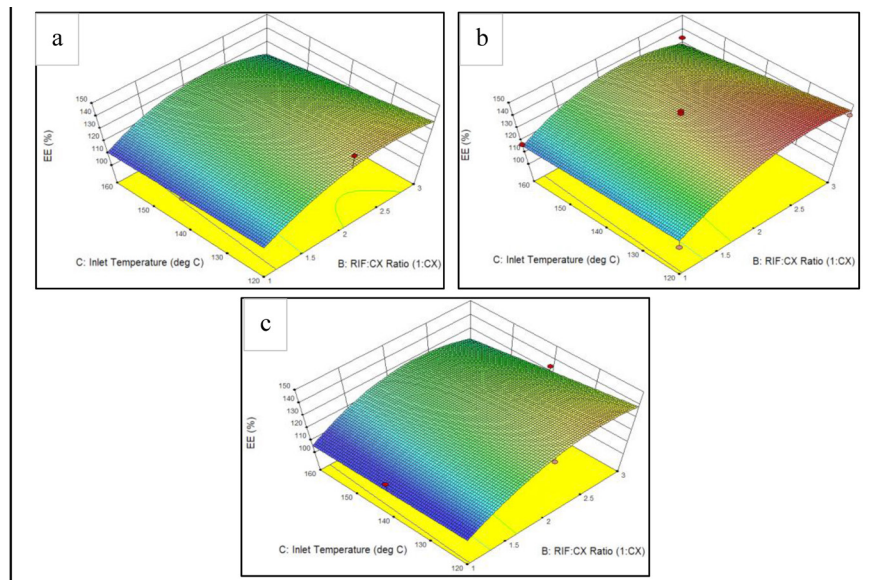


Fig. 4: Response surface of entrapment efficiency to RIF: CX ratio and inlet temperature in each CX concentration of (a) 0.1%. (b) 0.3%. (c) 0.5%.

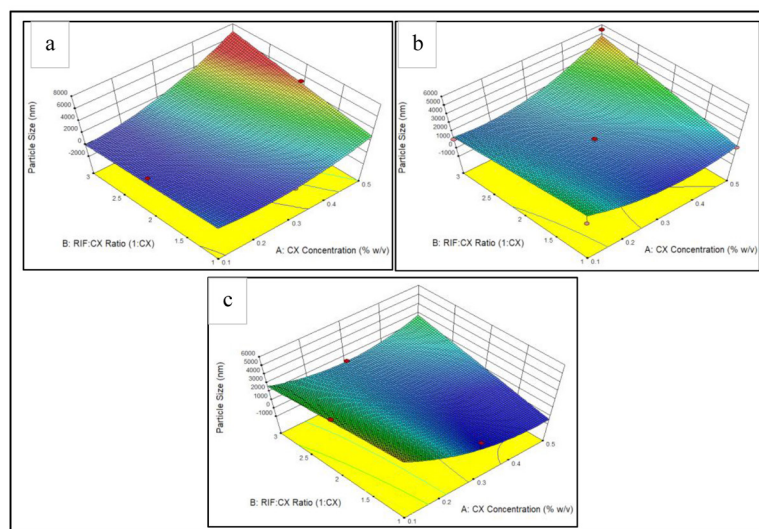


Fig. 5: Response surface of particle size to RIF: CX ratio and CX concentration in each inlet temperature of (a) 120°C, (b) 140°C, (c) 160°C.

The 900 mL buffer solution was heated to 37°C and dissolution test was performed at 100 rpm. Each powder was put into the dissolution basket, and the drug release test was performed three times (triple). At 5, 15, 30, 45, 60, 75, 90 and 120 minutes, 6 mL of samples were taken out and filtered using 0.45 μm Whatman filter (Son and McConville, 2009). The absorption of the sample solution was measured by a UV-Vis spectrophotometer at maximum wavelength.

Optimization of formulas with surface response methodology

The Box-Behnken design was applied to design the experiment. The minimum concentration was at position -1, and the maximum concentration was at point 1. Optimization of the formula in this research was using response surface methodology (RSM). The responses obtained from the fourteen formulas were

then analyzed using Design Expert 9.0.6.2 software outlined in several stages: transforming the data, observing the effects of factors on response, selecting model equations, ANOVA analysis, diagnostics, display output in graph contour, and surface response (Myers *et al.*, 2016).

RESULTS

Characterization of chitosan-xanthan excipients

Figure 1 showed that there was a new peak that appears on the 1616.41 cm^{-1} (amide group) wave number which was not present in the spectrum of chitosan and xanthan gum. In the spectrum of CX, there were also functional groups owned by chitosan and xanthan gum. At wave number 1116 cm^{-1} and 1159 cm^{-1} and wave number 3100 cm^{-1} to 3500 cm^{-1} with the

characteristic of peak width indicated existence of amine group ($-\text{NH}_3$) derived from chitosan. Also, the wave number 1728 cm^{-1} indicates the presence of carboxylic groups ($-\text{COOH}$) and

wave numbers 2400 cm^{-1} to 3400 cm^{-1} revealed the presence of carboxylic groups derived from xanthan gum.

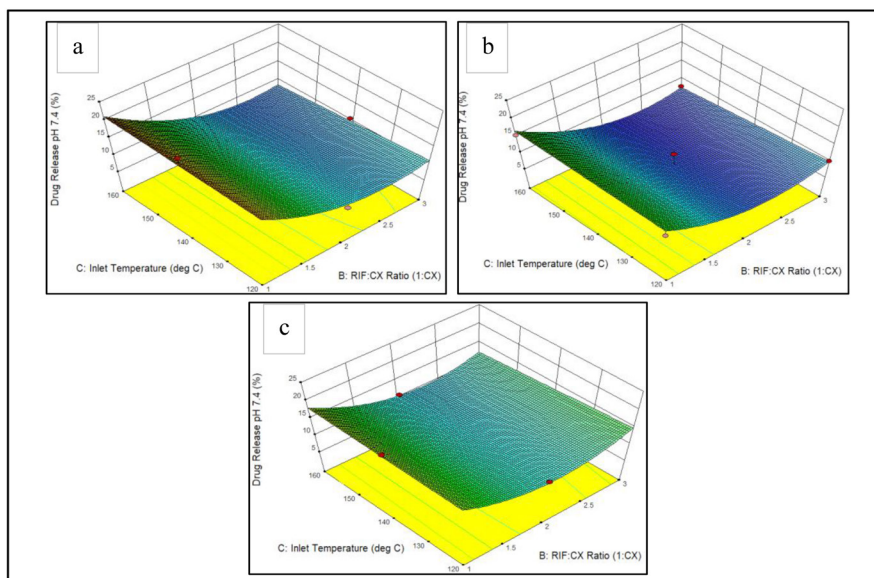


Fig. 6: Response surface of rifampicin release in medium pH 7.4 to RIF: CX ratio and inlet temperature in each CX concentration of (a) 0.1%. (b) 0.3%. (c) 0.5%.

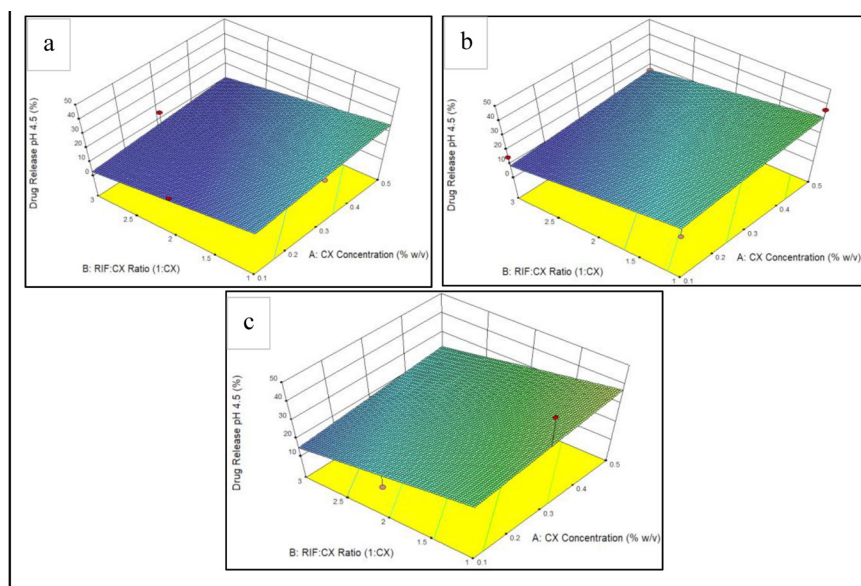


Fig. 7: Response surface of rifampicin release in medium pH 4.5 to CX concentration and RIF: CX ratio in each inlet temperature of (a) 120°C, (b) 140°C, (c) 160°C.

Particle size distribution

The particle size of the dry powder was depicted in Table 2. The mean diameter (d_{mean}) of particle size of rifampicin inhalation powder has a size range of $0.60\text{ }\mu\text{m}$ to $5.51\text{ }\mu\text{m}$. There were two formulas (F4 and F9) that were not within the required particle size range for the inhalation powder ($1\text{ }\mu\text{m}$ – $5\text{ }\mu\text{m}$). In the inhalation powder formulas with 0.3% CX concentration variables had the lowest average particle size ranges of $0.64\text{ }\mu\text{m}$ to $1.65\text{ }\mu\text{m}$, and in powders with 0.5% CX concentration variables had the highest average particle size range, i.e., $0.60\text{ }\mu\text{m}$ to $5.51\text{ }\mu\text{m}$.

Entrapment efficiency

Table 2 also showed the entrapment efficiency results of the application of dry powder formulations. It can be seen that the entrapment efficiency of the fourteen formulas were more than 100%, varied from 112.12% (F5) to 149.41% (F1). Based on the results obtained, it can be seen that the formula with the ratio RIF: CX 1:1 (F5, F6, F9, F10) had the average value of the entrapment efficiency closest to 100% that was $113.82\% \pm 2.20\%$. In the formula with the ratio RIF: CX 1:2 (F1, F2, F3, F4, F13, F14) had the highest average value of entrapment efficiency of

135.54% ± 11.06%. Besides, the formula for the ratio RIF: CX 1:3 had an average value of the high entrapment efficiency, i.e., 133.99% ± 6.66%.

Table 2: Parameters and responses of fourteen dry powder formulas.

F	Input variables			Output parameters				
	CX concentration (% b/v)	RIF: CX ratio	Inlet temp. (°C)	EE%	Particle size (d mean) (µm)	Rifampicin release in 24 hours		
						pH 7,4	pH 4,5	
1	0.1	1:2	120	149.08 ± 1.69	1.740	9.53 ± 0.87	12.02 ± 0.09	
2	0.5	1:2	120	133.80 ± 1.26	5.19	11.52 ± 1.92	13.53 ± 0.26	
3	0.1	1:2	160	125.76 ± 0.49	3.90	8.49 ± 2.90	15.29 ± 1.21	
4	0.5	1:2	160	122.48 ± 1.41	0.60	10.55 ± 0.78	25.64 ± 0.53	
5	0.1	1:1	140	112.00 ± 0.60	1.77	22.95 ± 6.49	17.35 ± 0.93	
6	0.5	1:1	140	113.71 ± 2.58	1.09	18.23 ± 9.02	36.40 ± 0.99	
7	0.1	1:3	140	125.75 ± 1.44	1.11	10.53 ± 1.83	15.23 ± 0.14	
8	0.5	1:3	140	134.39 ± 2.38	5.51	12.65 ± 1.04	16.56 ± 0.23	
9	0.3	1:1	120	112.01 ± 0.88	0.64	14.30 ± 7.06	19.30 ± 1.19	
10	0.3	1:1	160	117.02 ± 1.17	1.55	15.33 ± 4.34	48.60 ± 5.06	
11	0.3	1:3	120	141.90 ± 2.48	1.29	10.07 ± 3.32	14.38 ± 1.45	
12	0.3	1:3	160	134.29 ± 0.86	1.46	7.83 ± 1.07	17.46 ± 0.94	
13	0.3	1:2	140	144.47 ± 2.91	1.65	6.54 ± 3.02	15.58 ± 0.35	
14	0.3	1:2	140	142.47 ± 1.74	0.86	10.93 ± 0.76	16.56 ± 2.57	

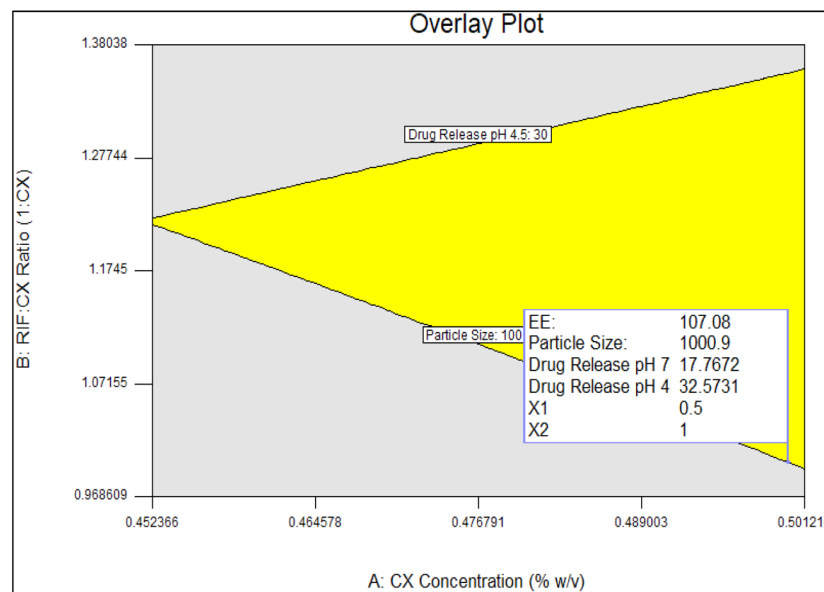


Fig. 8: Overlay plot graphic of optimization.

Drug release

Figure 2 and 3 show the release profile of dry powder rifampicin. At medium pH 7.4, CX was able to control rifampicin release significantly. At a medium of pH 4.5, all of the formulae released the drug immediately during first 5 minutes, in contrary to the release of rifampicin at a pH medium of 7.4. This result suggested that the excipient has a role in retaining rifampicin release in a pH medium of 7.4 to 15 minutes. Rifampicin was released higher in the medium pH 4.5, compared to its release in

a pH medium of 7.4. The release of rifampicin in a medium pH of 7.4 for 2 hours has the highest value obtained in the formula with ratio of RIF: CX 1:1. Similarly, in a medium pH of 4.5, the highest dissolution of rifampicin value for 2 hours is obtained in the formula with the ratio of RIF: CX 1:1.

Formula optimization with response surface methodology

The characterization results on fourteen formulas were input into Design Expert software, and the optimum formulas

were analyzed with response surface methodology. Correlation between input and output parameters was investigated. The results obtained is displayed at Table 3.

Table 3: The correlation of the input variable and output response.

Response	CX Concentration	Inlet temperature	RIF: CX ratio
Entrapment efficiency	-0.067	-0.299	0.631
Particle size	0.233	-0.081	0.262
Rifampicin release in pH 7.4	0.032	-0.072	-0.664
Rifampicin release in pH 4.5	0.309	0.458	-0.557

*correlation value > 0.5 is considered as strong correlation

In the data analysis, model of response surface methodology (RSM), such as linear, 2FI, quadratic, and cubic model, were evaluated. The model of polynomial equations for each response is selected based on the equations recommended by the program. The equation model is then modified so that it was significant to use. The Table 4 shows the selected model equations in each response.

The response variables were optimized based on the goal parameter specified as in Table 5. The parameters were combined, then the optimum region was obtained. The optimum point was shown in Figure 8.

Table 4: Model equations in each response.

Response	Model
Entrapment efficiency	Quadratic
Particle size	Quadratic
Rifampicin release in pH 7.4	Quadratic
Rifampicin release in pH 4.5	Linear

Table 5: Goals parameters in each response.

Response	Lower limit	Upper limit	Goals
Entrapment efficiency	100%	150%	Minimize
Particle size	1 μm	5 μm	In range
Rifampicin release in pH 7.4	0%	30%	In range
Rifampicin release in pH 4.5	30%	50%	In range

Characterization of the optimal formula

The predicted results obtained from the software were then characterized for its entrapment efficiency, particle size, rifampicin release at pH 7.4 and pH 4.5. The results were depicted in Table 6.

Table 6: Characterization results of optimum formula.

F	Entrapment Efficiency (%)		Particle size (μm)		Rifampicin release pH 7.4 (%)		Rifampicin release pH 4.5 (%)	
	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted
FO1	108.9	107.1	1.177	1.001	14.49	17.8	37.97	32.6
FO2	108.9	107.5	1.617	1.500	15.3	17.6	22.52	30.8
FO3	109.32	110.1	2.089	1.300	26.34	17.0	21.28	30.0

DISCUSSION

In characterization of functional group analysis, the peak at the 1616.41 cm^{-1} wave number indicated the ionic interaction between the protonated $-\text{NH}_3^+$ of the amine group ($-\text{NH}_2$) in chitosan with $-\text{COO}^-$ dissociated from the carboxylic group ($-\text{COOH}$) in xanthan gum, forming a polyelectrolyte complex (Lankalapalli and Kolapalli, 2009). In the spectrum of CX, there are also functional groups owned by chitosan and gum xanthan. It shows that not all amine groups react with carboxylate groups because in the spectrum of CX there were still carboxylic and amine groups peaks in the spectrum of CX (Varshosaz *et al.*, 2015).

Preparation of rifampicin inhalation powder with spray dryer made based on three different parameters in each formulation, i.e., the concentration of CX solution, inlet temperature, and ratio RIF: CX. The concentration of the solution will affect the viscosity of the liquid, then change on the droplet size after spraying. It also may affect the powder yield and particle size response. The rifampicin ratio with CX will affect the formation of films of polymer against the drug so that the factor will affect the response of rifampicin release, the entrapment efficiency, and the particle size in the rifampicin dry powder (Paudel, 2013).

The average particle size values obtained were not entirely within the required particle size range for the inhalation powder (1 μm –5 μm) (Hickey, 2004). It may be due to the broad particle size distribution of powders, which was indicated by its relatively

large polydispersity index (PDI) (data not shown). The higher the value of PDI, the more heterogeneous the powder (Avadi, 2010). Based on the particle size results, the CX concentration in solution and ratio of RIF: CX affects the viscosity of the spray dried liquid, and the viscosity affects the size of the powder particles (Paudel, 2013). The viscosity affected the droplet size after spraying on the spray dryer, thus affecting the size of the resulted particles. The effect of RIF: CX ratio, CX concentration and inlet temperature to particle size of rifampicin DPI are depicted in Figure 5.

All formulas showed entrapment efficiency value higher than 100%; it might be due to properties of sprayed solution. The CX solution was slightly insoluble; thus it poorly flows into collecting tube of the spray dryer. The Buchi manual explained this condition might cause some excipient was left on the tube and unable to coat the API (rifampicin) perfectly (Büchi, 2015). Furthermore, coherently with Paudel *et al.*, our results also showed that entrapment efficiency in inhalation powder was influenced by the drug-polymer ratio (Table 3) (Paudel, 2013). The higher CX-rifampicin ratio, the higher entrapment efficiency value of the powder. Response surface of entrapment efficiency toward RIF: CX ratio and inlet temperature in various CX concentration can be observed in Figure 4.

Our results showed that rifampicin was released higher from the DPI in the medium pH 4.5 than in the medium pH 7.4 (Figure 2 and Figure 3). It was due to the higher solubility of

chitosan in acidic medium, thus coating layer of CX was dissolved better in medium pH 4.5 and released more rifampicin from the powder. Furthermore, our results also showed that rifampicin release was strongly influenced by Rif-CX (drug-polymer) ratio (Table 3). Higher polymer concentration increased coating layer of the powder, thus sustained drug release from the powder, both in medium pH 4.5 and pH 7.4 (Berger *et al.*, 2004). Response surface of rifampicin release in medium pH 7.4 and pH 4.5 toward RIF: CX ratio and inlet temperature in various CX concentration are presented in Figure 6 & Figure 7, respectively.

Based on the characterization results of the fourteen formulas, the optimization of dry powder formulas was carried out

with response surface methodology. The responses obtained from each formula were later incorporated into the experimental design. According to the obtained optimization, the response surfaces of the entrapment efficiency and the rifampicin release in medium pH 4.5 as well as pH 7.4 had the correlation values more than ± 0.5 to the RIF: CX ratio. It shows that the RIF: CX ratio gives the dominant influence over the three responses. The correlation value of 0.631 was obtained on the response of the absorption efficiency to the RIF: CX ratio, it showed the positive correlation value that was the higher the excipient ratio to rifampicin, the higher the entrapment efficiency obtained.

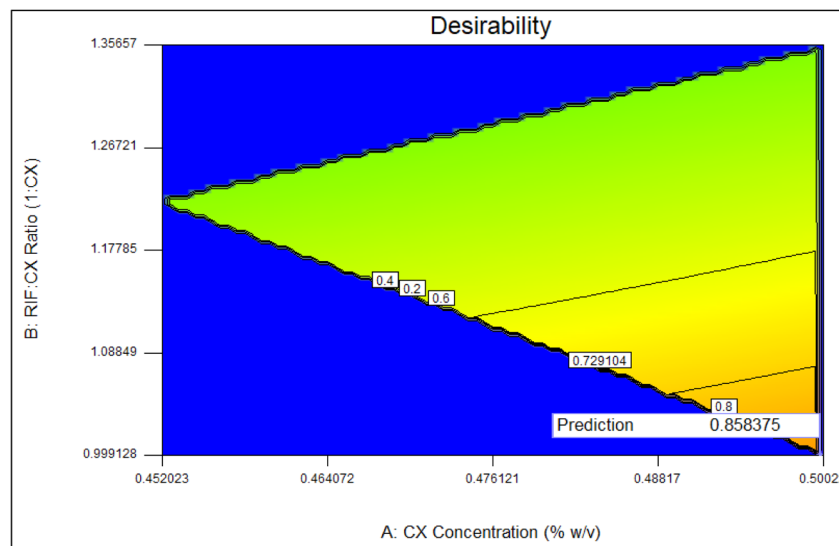


Fig. 9: Desirability graphic of optimization.

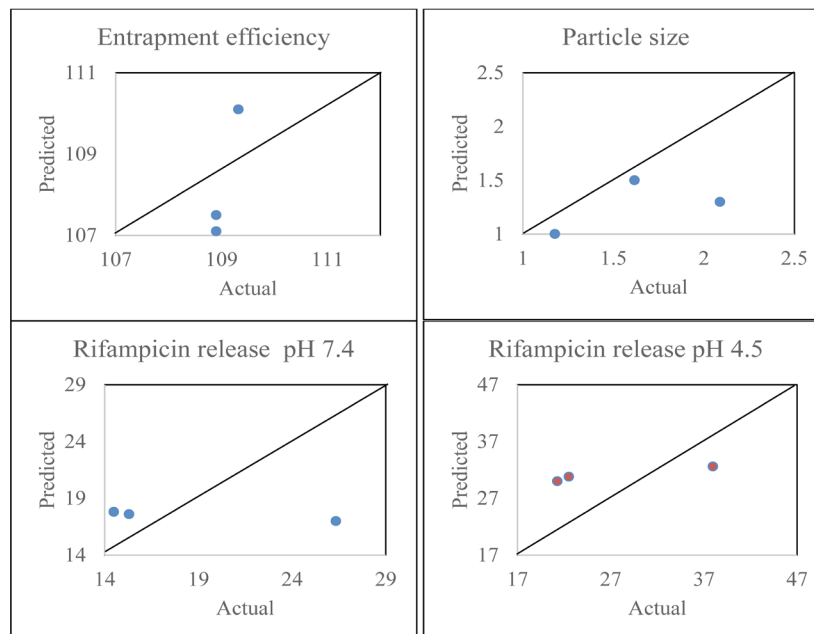


Fig. 10: Actual vs predicted of the optimum formula.

In response to the release of rifampicin, a negative correlation was obtained. The value of -0.664 was obtained in the response of rifampicin release in the pH medium of 7.4 and the value of -0.557 was obtained in the response of rifampicin release in the pH 4.5 medium to the RIF: CX ratio factor. It can be interpreted that the greater the ratio of excipients to rifampicin, the less the number of rifampicin being released. In the particle size response, the correlation value for the three input variables was <0.5 , indicating that the input variables only have small effect on the particle size. The correlation value between the particle size and the concentration of CX solution and the RIF: CX ratio is 0.233 and 0.262, so it can be interpreted that the concentration factor of CX and RIF: CX gave little influence on the particle size. The higher the concentration of CX solution and the RIF: CX ratio, the bigger particle size obtained.

The optimization result was obtained at the CX concentration 0.5%, inlet temperature 143°C , and the ratio of RIF: CX 1:1, with the response value of entrapment efficiency 107.1%, particle size $1,001\ \mu\text{m}$, rifampicin release in pH 7.4 17.8% and pH 4.5 32.6%. At that point, the desirability value was 0.86 (Figure 8 and Figure 9) thus the actual response-obtained from the input factor at the optimum point may not be the same as predicted.

Table 6 and Figure 10 showed that the predicted response value does not match perfectly to the actual response value. It was due to the desirability value is only 0.86; thus the actual result was slightly different to the prediction. However, with high prediction value, the obtained-response was close to the prediction.

CONCLUSION

The RSM successfully designed an optimum formula of Rifampicin DPI at the point of 0.5% CX concentration, RIF: CX ratio 1:1, and inlet temperature at 143°C , which produced rifampicin DPI with EE of 108.9%, particle size of $1.177\ \mu\text{m}$, and the release of rifampicin of 14.49% at pH 7.4 and 37.97% at pH 4.5.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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