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Development of Prototype of Hard Capsule Shell Made from Goatskin Gelatin Using Simplex Lattice Design (SLD) as Optimization Method

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ABSTRACT

The objective of this study was to evaluate the application of the use optimization methods of Simplex Lattice Design (SLD) with special cubic models in the preparation formula of hard capsule based on goatskin gelatin. Three types of filler materials have been used in the manufacture of capsule shells, namely $MgCO_3$, tapioca starch (TS) and sago starch (SS). The basic ingredient was uses goatskin gelatin and aquadest as a solvent. The material formulation was calculated according to Simplex Lattice Design (SLD) using the equations Y = β1 (A) + β2 (B) + β3(C) + β12 (A)(B) + β13 (A)(C) + β23 (B)(C) + β123 (A)(B) (C). Based on these equations obtained seven formulas (three proportions formula 100% each component, three proportional formulas 50%: 50% for the mixture of two components and one formula 33.33% for the mixture of three components). The results obtained data related to the proportion of filler use in a mixture of materials. The superimposed contour plot shows that the proportion of the use of three types of filler ($MgCO_3$: TS: SS) in each mixture are (0.224 part: 0.055 part and 0.721 parts). Next, after further testing of the formula is then obtained properties of the capsule shell prototype, namely: thickness (0.35 mm), solubility (66.64%), and water vapor transmission rate (WVTR) (0.67 $g.H_2O.m^{-2}$ h^{-1}). The data obtained that the type of SS filler is the most dominant factor influencing in increasing the thickness and solubility properties of the capsule shell, while the filler TS is the most dominant increase in the nature of WVTR. The results of the study concluded that the application of the SLD optimization method could be applied in the preparation of hard capsule formulations made from goatskin gelatin with better properties.

Key words: Capsule shell, Filler, Goatskin gelatin, Prototype, Simplex lattice design

Introduction

Capsule shell is one of the pharmaceutical products that aims to protect consumers from the extreme taste and aroma of drugs such as bitter taste, sour or fishy. Capsule shells can be used as containers of various dosage forms, starting flour or powders, granules, pastes, liquids or semi-solids (Cole *et al*., 2008; Rampurna *et al*., 2017). In the packaging process of the preparation of the drug must have its own techniques.

There are two types of capsule shells in the market, namely capsule shell solid (hard capsule) and soft capsule. Commercial capsule shells commonly used in Indonesia are hard capsule. This type of capsule shell is made from gelatin, plasticizer, *filler*, dye and preservative. Plasticizer is an ingredient to improve the integrity and flexibility of capsule shell products (Kontny and Mulski, 1989).

Capsule shells are widely circulated, so far is a gelatin-based capsule shell from the skin or bovine bone. Gelatin is a biopolymer, which can be obtained by thermal denaturation or partial hydrolysis of collagen. This product is widely applied to food and non-food products to improve product consistency, elasticity and stability (Benjakul and Kittiphattanabawon, 2018). The use of nanocomposite polymers lately is in great demand because it has many advantages. One of them is the improvement of stabilization, thermal and mechanical properties and specific functional properties (Armstrong, 2015; Arul *et al*., 2017; Manikandan *et al*., 2017; Sundarrajan *et al*., 2012).

However, of course, gelatin-based capsules of leather or pig bones need to be watched. It is specialized in imported drug capsule shells. The potential use of pig gelatin on imported drugs is enormous. This is because the raw material of pig skin is by product of livestock is very cheap and not widely utilized (Said, 2015). The use of gelatin from pigs raises the problem especially related to the halalness of the product. Similarly, the use of gelatin from cows is directly related to the potential spread of bovine spongiform encephalopathy (BSE) and transmissible spongiform encephalopathy (TSE (Sadowska *et al*., 2003). The search for gelatin sources from halal and hygienic materials has been developed by several researchers on an ongoing basis (Abedinia *et al.,* 2017; Duan *et al*., 2018).

One effort to provide halal gelatin-based capsule shells is certainly indispensable. One potential source of gelatin for substituting pig gelatin is goatskin gelatin. This is because the properties and composition of gelatin from goatskin have similarities with skin and bone of cow gelatin.

The process of making hard capsule shells must have certain technology. This technology is related to the properties of capsule shells. This is related to the biological processes that occur in the human digestive tract. The process of formulation of the material in the manufacture of capsule shells determines its properties. In the pharmaceutical field, one of the optimization techniques of formula in drug mixing is applied in the simplex lattice design (SLD) method with contour plot technique. This optimization technique has also been widely applied in various fields of research, both pharmaceutical and other fields (Azevedo *et al*., 2011; Belay *et al*., 2017; Das *et al*., 2016; Fan *et al*., 2017; Kayacier *et al*., 2014; Sanka *et al*., 2016). The objective of this study was to evaluate the application of the use optimization methods of Simplex Lattice Design (SLD) with special cubic models in the preparation formula of hard capsule based on goatskin gelatin.

Materials and Methods

The main ingredients used in this study were goatskin gelatin (GsG) and glycerol as plasticizer. Three types of *filler* have been applied, namely: $MgCO_3$ (Merck), tapioca starch (TS) (pharmaceutical standard); sago starch (SS) (pharmaceutical standard) and aquades (pharmaceutical standard) as solvent. Commercial capsule shell No "0" (Brataco Chemika) (PT Kapsulindo Nusantara, Cibinong, West Java) was used as control, food grade standard dye Tartrasine CI 19140 and Ponceau 4R CI16255 (PT.Guna Cipta Multirasa, Jakarta).

Equipment: printed capsules from PVC material (modified), digital scales (Sartorius TE 214S), water bath (Memmert Type WNB7-45), oven (Memmert), beaker glass (Pyrex), measuring cup (Pyrex), stirrer, thermometer, cutter and volume pipette.

Determination of material composition formula

In this research will be applied three types of *filler* to be optimized in a mixture using SLD method, i.e. $MgCO_3$, TS and SS. The research begins by first testing some of the physical properties of the film that composes the capsule shell wall (according to predetermined optimization parameters). This data was used as the basic ingredients for composing and forming capsule shells. Physical test results were used as initial data, which is the result of response, for further processing with the help of software *design expert 8.0.4.trial*.

In accordance with the SLD method requirements for the three components, seven formulas were determined as initial experiments (F_1-F_7). The number of initial experiments was based on the 2^n-1 equation, where, the value of n = 3 (the number of components in the mix) (2^3-1 = 7). In this study three *filler* components ($MgCO_3$, TS and SS) were used. The basic formula of the ingredients used in making dough for a single batch process is as formula (I):

R/Goatskin gelatin (GsG)		10 g (10%)
Glycerol (plasticizer)		9 g (90%/g.gelatin)
$MgCO_3$	(A)	100 mg (1%/g. gelatin) (0-1 parts)….(Formula I)
TS	(B)	
SS	(C)	

The total *filler* used in the mixture is 100 mg (1%). The amount was calculated based on the amount of gelatin to be used in the mixture. The use of starch *filler* may inhibit the dissolution of the capsule. Therefore, starch was required in a formulation because it is associated with a drug dissolution process (Ku *et al*., 2011). The use of *filler* from the carragenan material does not affect the process at the time of in-vivo dissolution (Jones *et al*., 2012; Tuleu *et al*., 2007). The composition of the ingredient formulas used in the manufacture of capsule shells was presented in Table 1.

Determination of the optimum formula of the optimization parameter

The profile of mixed properties was determined by the SLD approach based on the equation (1): $Y = \beta 1(A) + \beta 2(B) + \beta 3(C) + \beta 12(A)(B) + \beta 13(A)(C) + \beta 23(B)(C) + \beta 123(A)(B)(C)$ where, Y=response (experimental results), A = proportion of $MgCO_3$ component; B = proportion of TS component; and C = proportion of SS component; $\beta 1$; $\beta 2$; $\beta 3$; $\beta 12$; $\beta 13$; $\beta 23$; $\beta 123$ = coefficient.

Making prototype of capsule shell

The procedure for making capsule shells refers to the standards established by Pharmacopoeia Indonesia (FI) (Anonymous, 1995). First of all, the optimized result formulas were then formed into a mixture of dough. The dough was then heated in a water bath at 70^{o}C for 40 min until homogeneous. Capsule printing process in the form of pin from PVC material (modification). Pin dipped into batter for 3 sec at

±45^{o}C temperature. Pin lifted from dough while rotated several times. The pin was then placed in

Table 1. Composition of the ingredient formula in the dough on the manufacture of the shell capsule for a single batch process using SLD method

Ingredients	Amount of ingredients						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
(Goatskin gelatin) (GsG) (g)	10	10	10	10	10	10	10
Glycerol (g)	9	9	9	9	9	9	9
$MgCO_3$ (mg)	100	0	0	50	50	0	33.3
TS (mg)	0	100	0	50	0	50	33.3
SS (mg)	0	0	100	0	50	50	33.3

F_1 (100% $MgCO_3$) ; F_2 (100% TS) ; F_3 (100% SS) ; F_4 (50% $MgCO_3$ + 50% TS) ; F_5 (50% $MgCO_3$ + 50% SS) ; F_6 (50% TS + 50% SS) ; F_7 (33.3% $MgCO_3$ + 33.3% TS + 33.3% SS). Each formula was made into 2 batches and each batch was tested 3 times.

reverse position and placed at room temperature for ±10 min. The pins were then dried in oven temperature 55^{o}C for 2 h until the dough dries. The dough that has dried on the pin was pulled up to form a capsule shell product. Capsule shells are made into 2 types, namely the body and head (cover).

Research design and data analysis

The study was designed using the SLD method of the spacial cubic model described as an equilateral triangle and displayed in a two-dimensional form with three corners. Statistical tests to compare the value of laboratory experiments with mathematical calculations were analyzed by one-way ANOVA. Furthermore, further tests using the comparison test according to Bonferroni (Steel and Torrie, 1991). The position of each formula point (F_1-F_7) in the two-dimensional plane as shown in Figure 1.

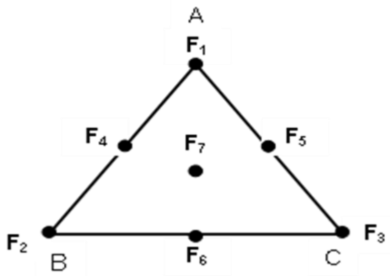

Figure 1. Design experiment of *spacial cubic* model using SLD method. A=$MgCO_3$; B=tapioca starch (TS); C=sago starch (SS); F_1 (100% $MgCO_3$) ; F_2 (100% TS) ; F_3 (100% SS) ; F_4 (50% $MgCO_3$ + 50% TS) ; F_5 (50% $MgCO_3$ + 50% SS) ; F_6 (50% TS + 50% SS) ; F_7 (33,3% $MgCO_3$ + 33,3% TS + 33,3% SS).

Result and Discussion

Determination of optimization parameters

Data from optimization parameters were selected from three types of test results of physical properties on the CSW produced based on seven mixed formulas. The optimization parameters are (1) the thickness, (2) the solubility and (3) the water vapor transmission rate (WVTR) on the CSW as presented in Table 2.

To get the description of contour plot model, it is necessary to limit the parameter value to be optimized. The value was taken from the test results using commercial capsule shell material (PT.Kapsulindo Nusantara) as a control. The thickness value is 0.359 mm ± 0.07; 85.48% ± 8.02 for solubility and 0.65 g.H_2O. $m^{-2}.h^{-1}$ for WVTR.

Thickness

Wall thickness in the capsule shell is one of the parameters optimized in this study. Thickness affects solubility. Thickness occurs because of the increase in the amount of polymer that makes up the wall of the capsule shell. The use of gelatin, plasticizers and filler types as basic ingredients affect the properties of the capsule shell.

Based on data of physical characteristics of the thickness of capsule shell wall (CSW)(Table 2), the equation according to SLD method is as follows: Y_1 = 0,294(A) + 0,301(B) + 0,304(C) + 0,054(A)(B) + 0,268(A)(C) + 0.074(B)(C) + 0.468(A)(B)(C) (equation 2) where, Y_1 = thickness of CSW (mm); A = proportion of $MgCO_3$ component (part); B = proportion of TS components (parts); C = proportion of SS component (part). The result of equation 2 is then made contour plot using design-expert program 8.0.4 Trial as presented in Figure 2(1).

Based on equation 2 and Figure 2(1), it appears that the SS(C) *filler* is the most dominant component in the mixture determining the thickness properties of the CSW. It is characterized by the highest coefficient value (0.304), followed by TS (B)(0.301) and $MgCO_3$ (A) (0.294). The two most dominant interaction components determining the thickness of CSW were $MgCO_3$ Vs SS (AC) with the highest component proportion (0.268), followed by TS with SS (0.074) and $MgCO_3$ Vs TS (AB) (0.054). The interaction of three components (ABC) positively increases the thickness with a coefficient value of 0.468.

The concentration of dissolved solids can affect the thickness of the capsule shell film. The greater of the concentration of solids, the thicker the film will be produced (Garcia *et al*., 2000; Tapia-Blacido *et al*., 2005). Gelatin and plasticizers (glycerol) can experience an interaction process. This is because the glycerol molecule is hydrophilic and small. This molecule is very easy to enter between the protein chains that make up gelatin. Then the molecule will bind to form hydrogen bonds between amide groups in the protein structure (Gontard *et al*., 1993).

Solubility

Table 2. Characteristics of physical test results of optimization parameters on CSW produced using several types of formula using SLD method (mean±Sd)

Formula	Physical characteristics of capsule shell wall (CSW)		
	Thickness (mm)	Solubility (%)	Water vapor transmission rate (WVTR) ($g.H_2O.m^{-2}.h^{-1}$)
F_1	0,294±0,08	66,00±4,44	0,66±0,3
F_2	0,301±0,08	64,89±3,29	0,76±0,3
F_3	0,304±0,06	67,08±4,10	0,49±0,0
F_4	0,311±0,07	65,27±7,09	0,51±0,4
F_5	0,366±0,07	66,60±4,97	0,76±0,1
F_6	0,321±0,09	66,13±6,55	0,63±0,1
F_7	0,361±0,06	65,46±4,66	0,71±0,1

TS = tapioka starch; SS = sago starch ; S_d = *standard deviation*; F_1 (100% $MgCO_3$) ; F_2 (100% TS) ; F_3 (100% SS) ; F_4 (50% $MgCO_3$ + 50% TS) ; F_5 (50% $MgCO_3$ + 50% SS) ; F_6 (50% TS + 50% SS) ; F_7 (33,3% $MgCO_3$ + 33,3% TS + 33,3% SS).

Based on the calculated data on the solubility of the CSW (Table 2), the equation obtained according to the SLD method, namely: Y_2 = 66.00(A) + 64.89(B) + 67.08(C) - 0.7(A)(B) + 0.24(A)(C) + 0.58(B)(C) - 14.67(A)(B)(C) (equation 3), where, Y_2 = solubility value (%); A = proportion of $MgCO_3$ component (part); B = proportion of tapioca starch (TS) component (part); C = proportion of sago starch (SS) component (part). The result of formula (3) is then made contour plot using design-expert 8.0.4 trial as presented in Figure 2(2).

Based on the equations (3) and Figure 2(2) it appears that the SS(C) component is the most dominant component determining the solubility properties of the CSW in the mixture. It is characterized by the highest coefficient value (67.08), followed by $MgCO_3$ (A) (66.00) and TS (B) (64.89). The two most dominant interaction components determining the solubility were TS Vs SS (BC) with the highest component proportion (0.58), followed by $MgCO_3$ with SS (AC) (0.24) and $MgCO_3$ Vs TS (AB) (-0.7). The three-component interaction (ABC) negatively decreases the solubility by coefficient (-14.67). Starch as the largest component of *filler* has an effect on CSW solubility. The starch is composed of two major polymer units namely amylose and amylopectin. The use of plasticizers of polyethylene glycol (PEG) as a coating enhances the adhesion properties of capsule shells (Cole *et al*., 2002).

The starch contains 75% soluble amylopectin (Moorthy, 2004). This is because, on the starch there is a complex structure of amylose-subtituen groups that cause the swelling power increases. This can prevent the amylose component more difficult to dissolve (Thirathumthavorn and Charoenrein, 2006). Therefore, it will result in decreased starch solubility. The addition of hydroxypropyl cellulase as a coating may increase the capacity of the capsule shell to improve its solubility properties (Dvorácková *et al*., 2010).

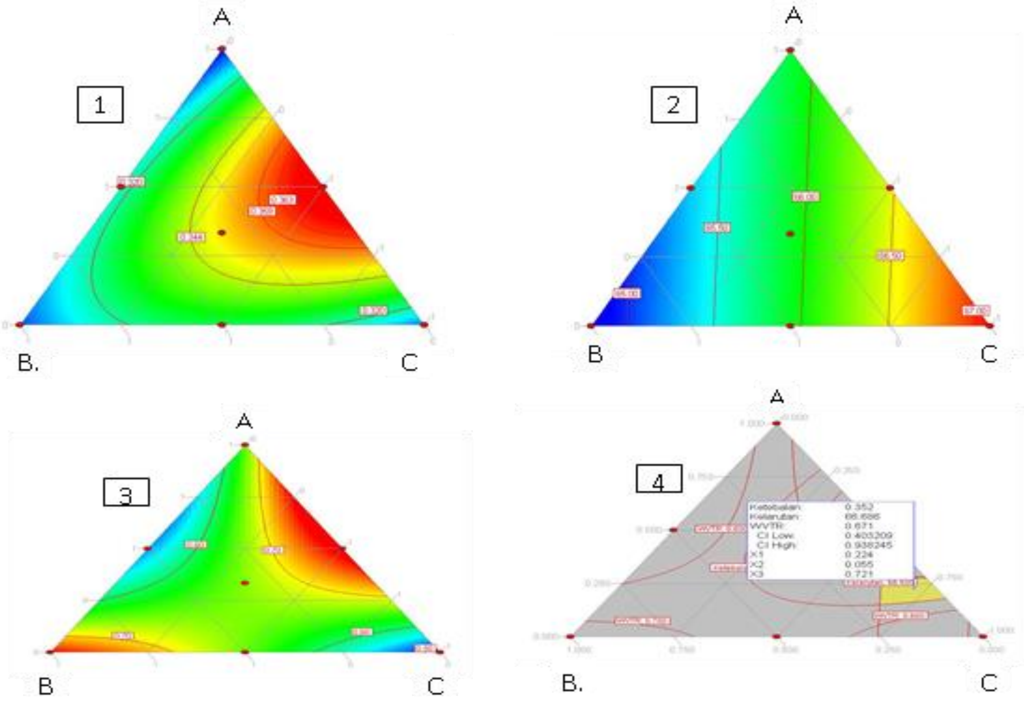

Figure 2. Contour plot model for each parameter, thickness (mm) (Figure 2(1)), solubility (%) (Figure 2 (2)), water vapor transmission rate (WVTR) ($g.H_2O.\ m^{-2}.h^{-1}$) (Figure 2(3)) on the CSW and superimposed contour plot (Figure 2(4))

optimization of capsule shell material formula using SLD method; A = $MgCO_3$; B = TS; C = SS); The images are presented in 2-dimensional format using the *8.0.4 trial design-expert* program.

Water vapor transmission rate (WVTR)

Based on the data in Table 2, then calculated the WVTR value on the CSW. The calculation result was obtained by equation (4) according to SLD method, that is: Y_3 = 0.66(A) + 0.76(B) + 0.49(C) – 0.8(A)(B) + 0.74(C) + 2.1(A)(B)(C), where, Y_3 = value of WVTR ($g.H_2O.m^{-2}.h^{-1}$); A = proportion of $MgCO_3$ component (part); B = proportion of TS component (part); C = proportion of SS (part). The result of equation (4) was then made contour plot using *design-expert program 8.0.4 trial* as shown in Figure 2(3).

Based on equations (4) and 2(3), it appears that the *filler* component of TS (B) is the most dominant component determining the WVTR in the mixture. It is characterized by the highest coefficient value (0.76), followed by $MgCO_3$ (0.66) (A) and SS (0.49) (C). The most dominant two-component interaction determines the rate of WVTR is $MgCO_3$ Vs SS (AC), with the highest component proportion (0.74), followed by TS(B) Vs SS(C) (0.24) and $MgCO_3$ Vs TS (AB) (-0,8). The three-component interaction (ABC) positively increases the vapor transmission rate by the coefficient value (2.1). Starch as a component of the CSW also affects the WVTR because the starch is a derivative of a hydrophilic polysaccharide. According to Greener and Fennema (1989), polysaccharides have hydrophilic properties with a higher WVTR ability than fat. Further described by Chillo *et al*. (2008), film components made from starch materials have a significant effect on WVTR values.

Determination of optimum formula

Based on the calculation results obtained mathematical equations for the three physical properties of the CSW using SLD, i.e Y_1 (equation for thickness), Y_2 (equation for solubility) and Y_3 (equation for WVTR). Each of these equations can be made contour plot of three predefined parameters. Based on the contour plot, it can be combined to form superimposed contour plot as shown in Figure 2(4). In determining the contour of the region based on the optimum physical properties, it is necessary to first determine the parameters interval that meets the requirements. In this regard, the limit of the optimization parameter values was selected from values close to the properties of commercial capsules as controls.

Based on Figure 2(4), the limit value for thickness is in the range value of 0.344-0.359 mm with the assumption that, the value closest to the thickness of commercial capsule (0.359 mm), solubility with the value range 66.5-67%. This value is still significantly different from the solubility of commercial capsules (85.48%), but in general the solubility value that can be achieved for the seven initial formulas (F_1-F_7) is 67.27% maximum. If we use a reference value above 67%, then on the determination of the optimum formula, the optimization region for 3 types of parameters can not be met. The WVTR value was selected in the range of 0.60-0.70 $g.H_2O.m^{-2}.h^{-1}$. This value was used with reference to the minimum constraint to obtain an optimization area for three types of parameters, however, theoretically it can be explained that the desired properties are the CSW which has the least (low) of WVTR value.

Each component part (Figure 2(4)) was then transformed into mg units of *filler* material. The result will be obtained an optimum formula for a one-time mixing process (batch). The composition of the ingredients in each process of mixing the composition is as follows:

R/GsG	10 g
Glycerol	9 g
$MgCO_3$ (A)	22,4 mg (X1)
TS (B)	5,5 mg (X2)
SS (C)	72,1mg (X3)…..(Formula II)

Based on the formula (II), then conducted experiments in the laboratory to make capsule shell products. The products that have been obtained are further tested to obtain data related to the value of thickness, solubility and WVTR. This value was then compared with the theoretical response as a result of mathematical calculations. Based on equations (2), (3) and (4), then mathematically calculated. The calculation results were obtained as presented in Table 3. Based on the experimental results in the laboratory and the theoretical response (Table 3) then further verified theoretically to determine the degree of validity of the formula obtained.

Verify the optimum formula

The verification process aims to examine the validity of mathematical equations obtained. The value of the experimental results that did not differ significantly with the theoretical

Table 3. Theoretical response value based on the mathematical calculation of optimization parameters of CSW using SLD method

Optimization parameters	Theoretical response
Thickness (mm)	Y_1 = 0.294(0.224) + 0.301(0.055) + 0.304(0.721) + 0.054(0.224)(0.055) + 0.268 (0.224)(0.721) + 0.074(0.055)(0.721) + 0.468(0.224)(0.055)(0.721) = 0.353 ≈ 0.35 mm.
Solubility (%)	Y_2 = 66.00(0.224) + 64.89(0.055) + 67.08(0.721) – 0.7(0.224)(0.055) + 0.24(0.224)(0.721) + 0.58(0.055)(0.721) – 14.67(0.224)(0.055)(0.721) = 66.640 % ≈ 66.64%
WVTR ($g.H_2O.m^{-2}.h^{-1}$)	Y_3 = 0.66(0.224) + 0.76(0.055) + 0.49(0.721) – 0.8(0.224)(0.055) + 0.74(0.224)(0.721) + 0.02(0.055)(0.721) + 2.1(0.224)(0.055)(0.721) = 0,672 ≈ 0,67 $g.H_2O.m^{-2}.h^{-1}$

Table 4. Comparison of experiment result data with theoretical response on optimization parameters of CSW based on optimum formula using SLD method

No.	Optimization parameters	Comparison of values	
		Results of laboratory experiments	Result of theoretical response
1.	Thickness (mm)^{ns}	0.313±0.09	0.353
2.	Solubility (%)^{ns}	66.654±2.58	66.640
3.	WVTR (g.H_2O.m^{-2}.h^{-1})^{ns}	0.892±0.35	0.672

^{ns} = no-significant.

response statistically showed that the resulting equation was valid. Comparison of experimental data with theoretical responses was presented in Table 4.

Based on ANOVA the data in Table 4 shows that between experimental and theoretical value were not significant (P>0.05). These results provide an indication that the formula obtained under the SLD approach is valid and subsequently applicable. This test was very important to know the degree of validity of the formula generated based on mathematical calculations.

Prototype of hard capsule shell of optimization result

Comparison of prototype form of GsG-based capsule shell result of *filler* material optimization using SLD method with commercial capsule shell presented in Figure 3. Based on Figure 3, physically, prototype of GsG-based capsule shell from *filler* optimization using SLD method shows a shape similar to a commercial capsule shell. The prototype dimensions of the capsule shell obtained results with a length of 22 mm. This dimension is longer than the capsule dimension according to Jones (2008) (19.7 mm).

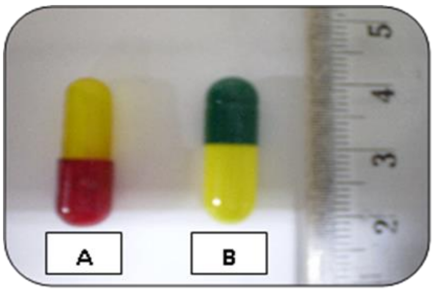

Figure 3. Comparison of prototype of GsG-based capsule shell of optimum result using SLD method (A) with commercial capsule shell (PT Kapsulindo Nusantara) No "0" (B).

Conclusions

An application of Simplex Lattice Design (SLD) as optimization method for special cubic models using 3 types of *filler* material can be applied in the preparation of hard capsule shell formulations made from goatskin gelatin. The proportion of $MgCO_3$ *filler* (0.224 part), TS (0.055 part) and SS (0.721 part) in the mixture results in better capsule shell properties.

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