Formulation and Evaluation of Solid Dispersion Chitosan Tablet from Whiteleg Shrimp (Litopenaeus vannamaei) Using PVP K-30 As a Carriers-UMSIDA

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Whiteleg Shrimp
PVP K-30

Abstract

Whiteleg shrimp (*Litopenaeus vannamei*) on the market are processed or sold only to take part in the meat. The head, shell, and tail are thrown away without any prior processing. Underutilized waste causes environmental problems. An alternative to overcome this environmental disturbance phenomenon is to utilize shrimp shells containing chitin and subsequently transformed into chitosan that can be applied in various fields. Chitosan has poor solubility in water but high permeability, so to improve bioavailability is by making solid dispersions. Chitosan solid dispersion made by the solvent evaporation technique used PVP K-30 as the carriers. The result of chitosan solid dispersion then compressed into tablets by direct compression method. Hence the tablets are evaluated by weight and size uniformity, hardness, friability, and disintegration time. The formulation divided into 3 groups, that is F1 (pristine chitosan), F2 (chitosan : PVP K-30 = 1 : 1 solid dispersion) and F3 (chitosan : PVP K-30 = 1 : 3 solid dispersion). All the formulas by weight and size uniformity and disintegration time fulfill the requirements. F3 hardness is 4,275 kg is the best from F1 and F2. By statistic analytical from weight uniformity, hardness and disintegration time give significant difference with sig. < 0,05.

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INTRODUCTION

Indonesia is a maritime country that has considerable potential as a producer of marine animals which is main natural sources of chitin such as shrimp and crab shells (Elieh-Ali-Komi & Hamblin R, 2016). Shrimp shell contains 25-40% protein, 45-50% calcium carbonate, and 15-30% chitin, but the amount of the content depends on the type of shrimp (Khoushab & Yamabhai, 2010). In this study, chitin was extracted from whiteleg shrimp because it was ranked first of the 5 main commodities trafficked in the country (between provinces) as much as 72.81%. This means that a lot of shrimp production has been distributed to regions between provinces. East Java is the second highest province after Bengkulu (37.84%) as a supplier of this whiteleg shrimp that is 24.49% (BKIPM, 2018). However, chitin is not soluble in water so its use is limited. Hydrolyzing chitin by using a strong base (deacetylation process) into chitosan, it has better chemical properties (Srijanto, 2005). Chitin can be transformed into chitosan which has prospects in biomedical trends (Kurakula & Naveen, 2020). Besides being known as a drug carrier, chitosan also known as an active agent for anticholesterol . The results of research from Sanusi (2004) stated that in vitro, chitosan can bind cholesterol by 63.5%, to prevent an increase in cholesterol levels. A study stated that administering 30 chitosan tablets at a dose of 45 mg of chitosan/tablet three times a day can reduced cholesterol levels (Jing *et al.*, 1997).

However, chitosan has poor solubility in water but the permeability is high, so efforts are needed to increase the solubility so that chitosan can be used as an anti-cholesterol drug. Solid dispersion is a method of making a dispersion system where drugs that have low solubility in water will be dispersed into a water-soluble carrier to increase the solubility and dissolution of the drug (Vasconcelos *et al.*, 2007; Wardiyah *et al.*, 2012). The carriers used in this solid dispersion formulations is PVP K-30 because its polymer is hydrophilic and has very good water solubility and can be used as a stabilizer (Rowe *et al.*, 2009). The results of the chitosan solid dispersion formulation hence made into direct compression tablets. Direct compression method was chosen because this method is the most energy-efficient, fastest, and most economical way to produce tablets (Siregar *et al.*, 2016). Based on this background, research will be carried out on the formulation and evaluation of the solid dispersion tablet using chitosan extract from white leg (*Litopenaeus vannamei*) as an active agent with PVP K-30 as a carriers a in ratio of 1 : 1 and 1 : 3 (Chitosan : PVP K-30). Evaluation of solid dispersion tablets are weight and size uniformity, hardness, friability and disintegration time.

MATERIALS AND METHODS

Materials

The material used in this study were whiteleg shrimp (*Litopenaeus Vannamei*) from Pasuruan, HCl ((Mercks®) (pharmaceutical grade)), NaOH ((Mercks®) (pharmaceutical grade)), ninhydrin solution, Aquades ((Brataco®) pharmaceutical grade)), PVP K-30 (pharmaceutical grade), Magnesium Stearate (technical grade), Talk (technical grade) and Avicel PH 102 (technical grade).

Chitosan Synthesis

1. Pre-treatment

The shell of whiteleg shrimp (*Litopenaeus vannamei*) was washed with running water and boiled for 15 minutes. The clean shell dried in the sunlight for 2x24 hours or until dry. The dried shell was blended with a blender until smooth and sieved with a 100 mesh (Agustina *et al.*, 2015).

2. Demineralization

100 grams of sifted shell of whiteleg shrimp (*Litopenaeus vannamei*) powder was weighed. 1M HCl solution was added while stirring with a magnetic stirrer with a stirring speed of 200 rpm at 75 ºC for 1 hour. The solution was filtered with filter paper and rinse the residue with distilled water until neutral pH. The residue was dried in the oven at 60 ºC for 24 hours or until it dries (Agustina *et al.*, 2015).

3. Deproteination

The dry solids demineralized was dissolved in 3.5% NaOH while stirring using a magnetic stirrer with a speed of 450 rpm at 65 ºC for 2 hours. The mixed solution was filtered with filter paper and the residue was rinsed with distilled water until neutral pH. The residue was dried in the oven at 65ºC for 24 hours or until it dries (Harjanti, 2014).

4. Deacetylation

Chitin from deproteination process was dissolved in 60% NaOH solution by ratio of 1:20 (w/v). The solution was stirred using a magnetic stirrer with a speed of 250 rpm at 100 ºC for 4 hours. The mixed solution was filtered with filter paper. The residue was rinsed with distilled water until neutral pH and dried in oven at 65 ºC for 24 hours or until dries (Harjanti, 2014; Khan *et al.*, 2002).

Chitosan Evaluation

Chitosan from synthesis was evaluated by organoleptic, yield, ninhydrin, and deacetylation degrees (Tokatlı & Demirdöven, 2018; Hossain & Iqbal, 2014)

Solid Dispersion Procedure

Chitosan and PVP K-30 be prepared in a ratio of 1 : 1 and 1 : 3 (w/w). Chitosan was dissolved in 2% acetic acid (1 : 50), and stirred until it dissolves. PVP K-30 as carrier was dissolved in (1:5) of 2% acetic acid solvent. Both of solution was mixed and evaporated above the water bath in a fume hood at 50-60 °C until a precipitate was formed. The evaporation results was dried in the oven at 50 °C for 1-2 hours or until it dries. The masses was crusted and shieved with 100 mesh sieves (Zaini *et al*., 2017).

Tablets Formulation

Chitosan and PVP K-30 solid dispersion be prepared also weighed Magnesium Stearate, Talk and Avicel PH 102 that was sieved with a mesh 100 sieve. That ingredients was mixed until homogeneous. Hence the tablets compressed by direct compression method. The tablets was observed and evaluated (uniformity in weight & size, tablet hardness, tablet friability and disintegration time) (Depkes RI, 1995).

Experimental Design

The dose of chitosan as API is 45 mg/tab in accordance with the (Jing *et al*., 1997) study. The formulas divided into three groups (n=3). The division of groups is done based on different materials as follows :

1. F1 (control) : Pristine Chitosan as active agent
2. F2 : Chitosan : PVP K-30 solid dispersion (1 : 1) (w/w).
3. F3 : Chitosan : PVP K-30 solid dispersion (1 : 3) (w/w).

RESULTS AND DISCUSSION

The stages of the formulation of solid dispersion tablets of chitosan extract from whiteleg shrimp shell (*Litopenaeus vannamei*) with PVP K-30 as a carrier of solid dispersion were started with the synthesis of chitosan. From these stages the chitosan obtained was then evaluated. The results of the evaluation are as follows:

Table I. Result Of Chitosan Characterization from Whiteleg Shrimp Shell (*Litopenaeus vannamei*)

Parameter	Chitosan Characterization	Result	Interpretation
Shape	Flakes to powder	Powder	Good
Color	Light Brown to white	Creamy White	Good
Deacetylation Degree	<70%	74,02%	Good
Ninhydrin	(+) Changes to purple	(+) Changes to purple	Good
Yield	-	16,21 %	-

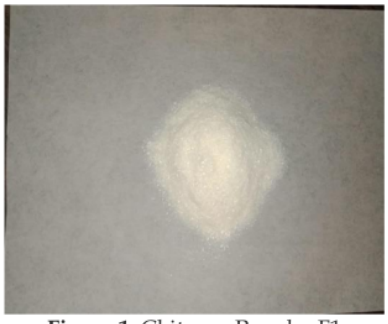

Figure 1. Chitosan Powder F1

From the evaluation of chitosan, it can be stated that chitosan has fulfilled all the evaluation requirements that exist from organoleptic (shape and color) was creamy white (Yanti *et al*., 2018), deacetylation degree was 74,02% (> 70%) (Dompeipen *et al*., 2016), and ninhydrin test was positive purple (Ylitalo *et al*., 2002). The yield test is a chitosan recovery test compared to the amount of shrimp shell used and the result is 16.21%. From the previous research activities, the yield producing was 15,26% (Zahiruddin *et al*., 2008).

Hence the chitosan made into a solid dispersion system to increase the solubility of chitosan except F1 that is only pristine chitosan (non solid dispersion) as control and then formulated into tablet preparations with the following formulation :

Table II. Formulation of Solid Dispersion Tablet Chitosan.

Material	Use	F1 (control)	F2 (1:1)	F3 (1:3)
Chitosan	Active agent	45 mg	45 mg	45 mg
PVP K-30	Carrier	-	45 mg	135 mg
Mg Stearate	Lubricant	1 %	1 %	1 %
Talk	Glidan	2 %	2 %	2 %
Avicel PH102	Diluent	ad 350 mg	ad 350 mg	ad 350 mg

The tablet formulation above is carried out by the direct compression method and using additional ingredients which are usually used in the formulation of the direct compression tablet method to have good flow and compactibility.

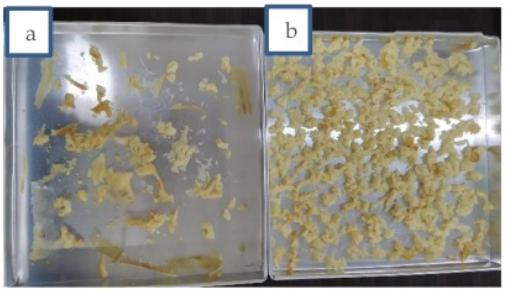

Figure 2. (a) Solid Dispersion F2 and (b) Solid Dispersion F3

Table III. Result of solid dispersion chitosan tablet characterization

Characteristic tablet	F 1	F2	F3
Diameter (mm)	11.14 ± 0.046	11.29 ± 0.255	11.09 ± 0.040
Thickness (mm)	3.75 ± 0.415	3.80 ± 0.474	3.80 ± 0.394
Weight variation (g)	0.3575 ± 0.010	0.3435 ± 0.007	0.3480 ± 0.006
Hardess (kg)	1.98 ± 0.44	1.18 ± 0.49	4.28 ± 1.48
Friability (%)	6.05	46.26	1.44
Disintegration time (s)	4.33 ± 0.82	20.67 ± 2.34	33.17 ± 9.43

Evaluation of dispersion tablet started with weight uniformity. The result from this evaluation is all three formulas have good uniformity and no one of tablet out from A and B column (Depkes RI, 1995). From the statistical analysis with one way ANOVA shows that sig. 0,000. And from the LSD (Least Significant Difference) show that F2 and F3 significantly different from F1. Therefore, solid dispersion tablet makes impact on chitosan without solid dispersion making.

The uniformity size from F1, F2, and F3 fulfill the requirements from Depkes RI 1995, which is $\frac{1}{3} T < D < 3T$. T is thick and D is diameter. F1 is 1.25 < 11.14 < 11.25, F2 is 1.27 < 11.29 < 11.40 and F3 is 1.27 < 11.09 < 11.40. From the statistical analysis with Kruskall Wallis from diameter show that asymp. sig. 0.000. And by Mann Whitney Test show that all the formulas have significantly different from each other. However, statistical analysis from tablet thicks by Levene Test show that the result is not significantly different from each other.

The tablets were also tested by the hardness tester. The requirement for tablet hardness is 4-8 kg (Lachman *et al.*, 2008). The average hardness from F1 is 1.975 ± 0.444 kg, F2 is 1.175 ± 0.494 kg, and F3 is 4.275 ± 1.482 kg. It shows that F3 is the best hardness character and the one hardness that fill the requirements from Lachman. F3 is chitosan without made solid dispersion. Development formula from direct compression tablets is required to generate the good hardness tablet quality. From the statistical analysis with Kruskall Wallis from the hardness test show that asymp. sig. 0.000. And by Mann Whitney Test show that all the formulas have significantly different from each other.

The tablet friability from all formulas is not too good. The requirements is <1% (Ansel *et al.*, 2005), while F1 friability is 6.05%, F2 is 46.25%, and F3 is 1.44%. Necessarily formula developing to make the tablet more compact

and have good binding so not too weak and brittle. Wet granulation can be considered to make better compactibility because wet granulation method make intragranular bonding (formed during granule drying) that does not break during compression, the cohesion of particles and binders, and carrier-binding adhesion is a type of bond that contributes to the strength of the tablet (Siregar *et al*., 2016).

The last evaluation is disintegration time. The requirement of disintegration time is no more than 15 minutes (Depkes RI, 1995). The result are F1 : 4.33 ± 0.819 second, F2 : 20.67 ± 2.33 second, and F3 : 33.17 ± 9.43 second. The tablets have so fast disintegration time because the friability is so weak and does not fill the requirements. Necessarily formula developing to make the tablet more compact and have good binding so not too weak and brittle. From the statistical analysis with Kruskall Wallis from disintegration time show that asymp. sig. 0.001. And by Mann Whitney Test show that all the formulas have significantly different from each other.

The manufacture of tablets in this study using the direct compression method. Direct compression method has the limitation that can ensue segregation and poor compressibility compared to the wet granulation method. Segregation can be caused by differences in density between materials (Iqubal *et al*., 2018). That can also cause the results of the evaluation of hardness and friabilility in this study to be unfavorable. Further method development is needed to provide better research results such as using the wet granulation method.

CONCLUSION

F1, F2, and F3 by weight and size uniformity and disintegration time fill the requirement. F3 hardness is better than F1 and F2. By statistic analytical from weight uniformity, hardness, and disintegration time give significant difference. Obligatory formulation developing to make better compactibility tablet.

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