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Research Article

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

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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 was then molded into tablets by the direct compression method. Hence the tablets were evaluated by weight and size uniformity, hardness, friability, and disintegration time. The formulation divided into three groups, that is F1 (chitosan : PVP K-30 = 1 : 1 solid dispersion), F2 (chitosan : PVP K-30 = 1 : 3 solid dispersion), and F3 (pure chitosan). 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 with considerable potential as a producer of marine animals, which are primary natural sources of chitin, such as shrimp and crab shells[1]. 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[2]. In this study, chitin was extracted from whiteleg shrimp (*Litopenaeus vannamei*) because it was ranked first of the five 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 *L. vannamei* supplier that is 24.49%[3]. However, chitin is not soluble in water, so its use is limited. By using a strong base (deacetylation process) into chitosan, hydrolyzing chitin has better chemical properties[4]. Chitin can be transformed into chitosan, which has prospects in biomedical trends[5]. Besides being known as a drug carrier, chitosan is also known as an active agent for anticholesterol. The previous research reported that *in vitro*, chitosan could bind cholesterol by 63.5%, to prevent an increase in cholesterol levels[6]. 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[7]. 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 anticholesterol drug. Solid dispersion is a method of making a dispersion system where drugs with low solubility in water will be dispersed into a water-soluble carrier to increase the solubility and dissolution of the drug[8,9]. The carrier used in this solid dispersion formulations is PVP K-30 because its polymer is hydrophilic, has very good water solubility, and can be used as a stabilizer[10]. The results of the chitosan solid dispersion formulation hence made into direct compression tablets. The direct compression method was chosen because it is the most energy-efficient, fastest, and most economical way to produce tablets[11]. Based on this background, research will be carried out on the formulation and evaluation of the solid dispersion tablet using chitosan extract from *L. vannamei* as an active agent with PVP K-30 as a carrier in the 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 *L. vannamei* obtained from Pasuruan, East Java. The chemical reagents used include HCl (Merck's®), NaOH (Merck's®), ninhydrin solution, distilled water (Brataco®), PVP K-30, magnesium stearate, talk, and Avicel PH 102.

Methods

Chitosan synthesis

1. Pre-treatment: The shell of *L. vannamei* was washed with running water and boiled for 15 minutes. The clean shell dried in the sunlight for 2 x 24 hours or until dry. The dried shell was blended with a blender until smooth and sieved with 100 mesh[12].
2. Demineralization: 100 g of the sifted shell of *L. vannamei* powder was weighed. 1M HCl solution was added while stirring with a magnetic stirrer with a stirring speed of 200 rpm at 75°C for an 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°C for 24 hours or until it dries[12].
3. Deproteination: The dry solids demineralized were dissolved in 3.5% NaOH while stirring using a magnetic stirrer with a speed of 450 rpm at 65°C 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 65°C for 24 hours or until it dries[13].
4. Deacetylation: Chitin from the deproteination process was dissolved in 60% NaOH solution by the ratio of 1 : 20 (w/v). The solution was stirred using a magnetic stirrer with 250 rpm at 100°C for 4 hours. The mixed solution was filtered with filter paper. The residue was rinsed with distilled water until neutral pH and dried in the oven at 65°C for 24 hours or until dries[13,14].

Chitosan evaluation

Chitosan from synthesis was evaluated by organoleptic, yield, ninhydrin, and deacetylation degrees[15,16].

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 a carrier was dissolved in (1 : 5) of 2% acetic acid solvent. Both solutions were mixed and evaporated above the water bath in a fume hood at 50-60°C until a precipitate was formed. The evaporation results were dried in the oven at 50°C for 1-2 hours or until it dries. The masses were crusted and sieved with 100 mesh sieves[17].

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 ingredient was mixed until homogeneous. Hence the tablets are compressed by the direct compression method. The tablets were observed and evaluated (uniformity in weight & size, tablet hardness, tablet friability, and disintegration time)[18].

Experimental design

The dose of chitosan as an active pharmaceutical ingredient (API) is 45 mg/tab by the study of Jing *et al.*[7]. The formulas are 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 *L. vannamei* shell with PVP K-30 as a carrier of solid dispersion were started with chitosan synthesis. From these stages, the chitosan obtained was then evaluated. The results of the evaluation are presented in **Table I**, while chitosan powder appearance is presented in **Figure 1**.

Table I. Result of chitosan characterization from *L. vannamei* shell

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[19], deacetylation degree was 74.02% (>70%)[20], and ninhydrin test was positive purple[6]. The yield test is a chitosan recovery test compared to the amount of shrimp shell used, and the result is 16.21%. In previous research, the yield obtained was 15.26%[21].

Hence, the chitosan is made into a solid dispersion system to increase chitosan solubility, except for F1 that is only pristine chitosan (non-solid dispersion) as control and then formulated into tablet preparations as showed in **Table II**. The tablet formulation is carried out by the direct compression method and using additional ingredients used to formulate the direct compression tablet method to have good flow and compactibility, with the results as shown in **Figure 2**.

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	Glidant	2%	2%	2%
Avicel PH 102	Diluent	ad 350 mg	ad 350 mg	ad 350 mg

Figure 2. Solid dispersion of F2 (left) and F3 (right)

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[18]. The statistical analysis with one-way ANOVA shows that sig. 0,000. Moreover, the LSD (Least Significant Difference) shows that F2 and F3 significantly different from F1. Therefore, a solid dispersion tablet makes an impact on chitosan without solid dispersion making.

The uniformity size from F1, F2, and F3 fulfill the requirements[18], which is ⅓ T < D < 3T. T is the thickness, and D is the 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. The statistical analysis with Kruskal-Wallis from diameter shows that asymp. Sig. 0.000. Furthermore, Mann-Whitney Test shows that all the formulas have significantly different from each other. However, the Levene Test's statistical analysis from tablet thickness shows 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[22]. 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 fills requirements[22]. F3 is chitosan without made solid dispersion. Development formula from direct compression tablets is required to generate good hardness tablet quality. The statistical analysis with Kruskal-Wallis from the hardness test shows that asymp. Sig. 0.000. Moreover, 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 are <1%[23], while F1 friability is 6.05%, F2 is 46.25%, and F3 is 1.44%. Necessarily, formula development makes the tablet more compact and has a good binding, so not too weak and brittle. Wet granulation can be considered to make better compactibility because the wet granulation method makes 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[11].

The last evaluation is disintegration time. The requirement of disintegration time is no more than 15 minutes[18]. The result for F1 is 4.33 ± 0.819 s; F2 is 20.67 ± 2.33 s; and F3 is 33.17 ± 9.43 s. The tablets have so fast disintegration time because the friability is weak and does not fill the requirements. Necessarily, formula development makes the tablet more compact and has a good binding, so not too weak and brittle. The statistical analysis with Kruskal-Wallis from disintegration time shows that asymp. Sig. 0.001. Furthermore, by Mann-Whitney Test show that all the formulas have significantly different from each other. The overall results of the evaluation and characterization are presented in **Table III**.

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
Hardness (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

The manufacture of tablets in this study using the direct compression method. The 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[24]. That can also cause the evaluation of hardness and friability in this study to be unfavorable. Further method development is needed to provide better research results, such as using the wet granulation method.

CONCLUSION

In conclusion, F1, F2, and F3 formula by weight and size uniformity and disintegration time fill the requirement. F3 hardness is better than F1 and F2. Statistical analysis from weight uniformity, hardness, and disintegration time give a significant difference—obligatory formulation developing to make better tablet's compactibility.

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