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Method Validation of Contact and Immersion TLC-bioautography for Determination of Streptomycin Sulfate in Shrimp

Karideste Streptomisin Sülfat Tayini için Kontak ve İmmersiyon İTK-biyootografi Yönteminin Validasyonu

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ABSTRACT

Objectives: Contact and immersion thin layer chromatography (TLC)-bioautography were developed for identification and quantification of streptomycin sulfate in shrimp.

Materials and Methods: TLC of streptomycin sulfate standard solution was carried out using silica gel F₂₅₄ and 7.5% of KH₂PO₄ solution as stationary and mobile phase, respectively.

Results: The retardation factor of the streptomycin sulfate standard was 0.51 and the selectivity of streptomycin sulfate was 4.1 with the presence of kanamycin sulfate in the shrimp. The bioautography was performed with *Escherichia coli* ATCC 8739 as a test bacterium. The limit of detection of streptomycin sulfate obtained by contact and immersion TLC-bioautography was 0.24 µg and 0.16 µg, respectively. Both methods showed good linearity with an r value greater than 0.999 and a V_{x0} value less than 2%. The accuracy of the contact and immersion TLC-bioautography was tested by standard addition method and the obtained percentage recovery was 86.93±1.60% and 96.42±0.65%, respectively. The coefficient of variation of the contact and immersion TLC-bioautography was 2.39±1.79% and 0.53±0.17%, respectively.

Conclusion: The immersion TLC-bioautography was more sensitive with better recovery than the contact TLC-bioautography. In addition, immersion TLC-bioautography was successfully employed for determination of streptomycin sulfate in shrimp.

Key words: Streptomycin sulfate, contact TLC-bioautography, immersion TLC-bioautography, shrimp

ÖZ

Amaç: Kontak ve immersiyon ince tabaka kromatografisi (İTK)-biyootografi, karideslerde streptomisin sülfatın tanımlanması ve miktarının belirlenmesi için geliştirilmiştir.

Gereç ve Yöntemler: İTK, streptomisin sülfat standart çözeltisi, sabit ve hareketli faz olarak sırasıyla silika jel F₂₅₄ ve %7,5 KH₂PO₄ çözeltisi kullanılarak gerçekleştirilmiştir.

Bulgular: Streptomisin sülfat standardının alıkonma zamanı 0,51 olarak bulunmuştur ve karideste kanamisin sülfat varlığında streptomisin sülfatın seçiciliği 4,1 olarak tespit edilmiştir. Biyootografi, bir test bakterisi olan *Escherichia coli* ATCC 8739 kullanılarak yapılmıştır. Kontak ve immersiyon İTK-biyootografi ile elde edilen streptomisin sülfat tayini için sınır değerler, sırasıyla 0,24 µg ve 0,16 µg olarak bulunmuştur. Her iki yöntem de r değeri 0,999'dan büyük ve V_{x0} değeri %2'den düşük olan iyi doğrusallık göstermiştir. Kontak ve immersiyon İTK-biyootografinin doğruluğu standart ekleme yöntemi ile test edildi ve elde edilen yüzde geri kazanım sırasıyla %86,93±1,60 ve %96,42±0,65 olarak bulunmuştur. Kontak ve immersiyon İTK-biyootografinin varyasyon katsayısı sırasıyla %2,39±1,79 ve %0,53±0,17'dir.

Sonuç: İmmersiyon İTK-biyootografi, geri kazanımının daha iyi olması nedeniyle kontak İTK-biyootografiden daha hassas olduğu sonucuna varılmıştır. Ek olarak, immersiyon İTK-biyootografi, karideslerde streptomisin sülfatın belirlenmesi için başarıyla kullanılmıştır.

Anahtar kelimeler: Streptomisin sülfat, kontak İTK-biyootografi, immersiyon İTK-biyootografi, karides

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INTRODUCTION

Shrimp is one of Indonesia's export commodities with a significant impact on its economy. High export demand sometimes results in uncontrolled cultivation because farmers generally use antibiotics to prevent fish diseases.^{1,2} As regulated by the Minister of Maritime Affairs and Fisheries in the PER regulation number 02/MEN/2007,³ fishery products must be free from drug residues, chemicals, biological materials, and other contaminants. One of the antibiotics used by farmers for disease prevention is streptomycin. Streptomycin is an aminoglycoside used for treatment of infections caused by aerobic gram-negative bacteria and is also effective against gram-positive bacteria such as *Staphylococcus aureus*.⁴ In Indonesia, streptomycin is usually used for treating bacterial diseases in shrimp and ornamental fish.⁵ According to the Codex Alimentarius, the maximum residue limit for streptomycin is 600 µg/kg.⁶ Antibiotic residues in food can be a risk to human health because they can contribute to antibiotic resistance through the food chain.⁷ Therefore, a fast and perfect analysis method is needed to detect antibiotic residues, especially streptomycin sulfate in shrimp.

Thin layer chromatography (TLC)-bioautography is used for determination of the level of antibiotics in complex samples based on microbiological activities. In TLC-bioautography, determination of antimicrobial levels is initiated by applying antimicrobial analytes to the TLC plate followed by elution with a suitable mobile phase. Contact TLC-bioautography was performed by putting the TLC chromatogram plate on the surface of the agar medium inoculated with the test bacterium and it was left in contact with the agar medium for a certain time for the diffusion process.⁸ Subsequently, the chromatogram plate was removed and incubated for 16-24 h for the growth range, but this can be reduced to 5-6 h by spraying 2,6-dichlorophenol-indofenol or 2,3,5-tetrazoliumchloride on the surface of the test medium. The antimicrobial activity was determined from the inhibitory zone around the reservoir hole on the surface agar medium or the spot position on the TLC-bioautogram plate, corresponding to the spots on the TLC chromatogram plate.⁹

Immersion bioautography is a combination of direct and contact bioautography. The chromatograms are sprayed until the plate is covered by test medium containing the test bacterium at a temperature of 45 °C. The plate is then cooled to condense and allow the diffusion process. Furthermore, the plate is incubated at a certain temperature for a certain time, and then sprayed with tetrazolium salt to visualize the inhibitory zone.

Antibiotic analysis in the shrimp matrix of kanamycin,¹⁰ oxytetracycline,¹¹ and streptomycin sulfate¹² with the TLC-bioautography contact method has been reported. However, comparison of contact and immersion TLC-bioautography methods in determining the levels of streptomycin in frozen shrimp has never been reported, and so it is necessary to conduct research to select a more effective method and provide results that meet the validation parameters.

MATERIALS AND METHODS

Chemicals

Streptomycin sulfate and kanamycin sulfate obtained from PT Meiji, shrimp obtained from a local market, *Escherichia coli* ATCC 8739, KH₂PO₄, nutrient broth and nutrient agar (Oxoid), sodium chloride p.a., methanol p.a., TLC silica gel plate GF₂₅₄ (Merck), methyl thiazole tetrazolium (Sigma Aldrich), distilled water (Otsuka), a microliter syringe (Hamilton), a chromatographic vessel (10x10x6 cm³), an incubator (Mettler), calipers (Tricle brand), an autoclave (Huxley HV-340 Speedy), a spectrophotometer (Genesis 20), and a shaker incubator (Thermo Fisher Scientific) were used in this study. Ethic committee approval and patient informed consent were not required.

Preparation of growth medium

Eighteen grams of agar, 8 g of nutrient broth powder, and 1000 mL of distilled water were mixed and heated until dissolved and homogeneous. The liquid medium was poured into a test tube (10, 15, and 20 mL) and then covered with cotton. The medium was sterilized by autoclaving at 121 °C for 15 min.¹³

Preparation of bacterial test

Escherichia coli ATCC 8739 was inoculated on agar slant medium and incubated at 35-37 °C for 24-48 h. The bacterial suspension was prepared by adding 10 mL of sterile saline (NaCl 0.9%) solution to a 24 h culture and shaking by vortex until the entire colony was removed from the surface of the agar medium. A 25% transmittance of bacteria was measured by spectrophotometer at a wavelength of 580 nm.

Loss on drying of shrimp samples

Loss on drying was determined according to Indonesian Pharmacope 5th edition.¹⁴ Sample containers were heated at 105 °C for 30 min. The container was weighed until it reached constant weight. One gram of each sample was weighed carefully and put into the constant container. The samples were then put in an oven with an open lid. Samples and the lid were heated at 105 °C until constant weight was obtained. Loss on drying was calculated using the equation below:

$$\text{Loss on drying} = (\text{initial sample weight} - \text{final sample weight}) / \text{initial sample weight} \times 100\%$$

Validation method of contact and immersion TLC-bioautography

The methods of analysis were validated for the parameters of selectivity, limit of detection, linearity, accuracy, and precision. The accuracy was determined using the standard addition method.

Analysis using contact TLC-bioautography

First, 8 µL of test solution was applied to the silica gel TLC plate F₂₅₄ and then it was eluted with 7.5% KH₂PO₄ solution as the mobile phase. Subsequently, the TLC plate was dried and attached to the surface of agar inoculated with *Escherichia coli* in a sterile petri dish. The TLC plate was then stored in the fridge for 1 h to allow the diffusion and stain process of the compound to the medium. Marks were made on the side of the

plate followed by incubation of the TLC plate at 37 °C for 24 h. Finally, the inhibitory zone was observed and its diameter was measured.

Analysis using immersion TLC-bioautography

First, 8 µL of test solution was applied to the silica gel TLC plate F₂₅₄ and then it was eluted with 7.5% KH₂PO₄ solution as the mobile phase, followed by drying of the TLC plate and it was coated with 15 mL of inoculated *Escherichia coli* medium until a thin layer was formed. The TLC plate was stored in a sterile petri dish and then incubated at 37 °C for 16-18 h. The plates were sprayed with methyl thiazoletetrazolium (2.5 mg/mL) and finally a white-yellow inhibitory zone was observed.¹⁵

Statistical analysis

The analytical characteristics of the TLC-bioautography were validated to ensure conformity to the analytical requirements and the reliability of the results.

All the data analysis was carried out in triplicate and standard deviation and coefficient variation values were calculated.

RESULTS AND DISCUSSION

The mobile phase, 7.5% KH₂PO₄ solution, used to eluate streptomycin sulfate was based on previous research.¹³ The (retardation factor) R_f results of the contact TLC-bioautography of streptomycin are presented in Table 1. The R_f values met the requirement range of 0.2-0.8. The loss on drying of the shrimp was 9.44±1.85% (Table 2).

The selectivity was tested by spotting of streptomycin sulfate, kanamycin sulfate standard solution, and shrimp on the F₂₅₄ silica gel TLC plate. The elution was carried out by 7.5% KH₂PO₄ solution. The selectivity test results of the contact TLC-

bioautography method are depicted in Figure 1 and Table 3. The data showed the R_f and resolution (R_s) values of streptomycin and kanamycin sulfate analyzed simultaneously using the contact TLC-bioautography method. The R_s value was 4.1 (R_s≥1.5), which means that both analytes can separate well.

The detection limit was determined by the antibiotic concentration in which activity was still seen. The minimum inhibitory concentration (MIC) of streptomycin sulfate analyzed using contact TLC-bioautography was 30.4 mg/L with 8 µL of sample solution (equivalent to 0.24 µg of streptomycin), whereas the MIC of the streptomycin analyzed by immersion TLC-bioautography was 20.3 mg/L (equivalent to 0.16 µg of streptomycin) (Table 4).

The linearity test of streptomycin in contact and immersion TLC-bioautography was carried out in the concentration range 100-250 mg/L. The linearity of the streptomycin analyzed using contact and immersion TLC-bioautography was y=14.7212x-23.2398 (r value=0.9992) and y=12.6655x-18.5557 (r value=0.9994), respectively (Figures 2 and 3).

Accuracy and precision were tested by spotting three different concentrations of streptomycin sulfate. The accuracy and

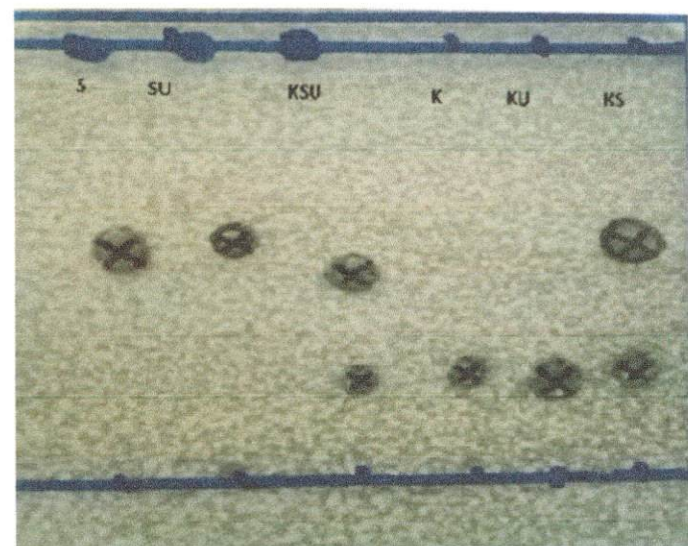


Figure 1. The retardation factor (R_f) of streptomycin sulfate (S) and kanamycin sulfate (K) in shrimp (U) for the determination of resolution (R_s) value

Table 1. Retardation factor of streptomycin sulfate standard analyzed by contact TLC-bioautography

Mobile phase	Concentration of streptomycin sulfate (mg/L)	R _f
7.5% KH ₂ PO ₄ solution	50.75	0.53
	101.50	0.51
	152.25	0.50
	203.00	0.50
	253.75	0.53
Mean of R_f		0.51

R_f: Retardation factor, TLC: Thin layer chromatography

Table 2. Loss on drying of shrimp

Sample name	Replicate	Initial weight (g)	Final weight (g)	LOD (%)	Mean of LOD (%)
Shrimp	1	1.0134	0.9187	9.34	9.44±1.85
	2	1.0187	0.9204	9.65	
	3	1.0172	0.9240	9.32	

LOD: Loss on drying

Table 3. Resolution value of streptomycin (s), kanamycin (k), and shrimp (u)

Compound name	R _f (S)	R _f (K)	R _s
Streptomycin sulfate	0.51	-	-
Streptomycin + shrimp	0.52	-	-
Kanamycin + streptomycin + shrimp (K+S+U)	0.50	0.21	4.1
Kanamycin	-	0.24	-
Kanamycin + shrimp	-	0.22	-
Kanamycin + streptomycin	0.52	0.24	3.9

R_s: Resolution, R_f: Retardation factor, S: Streptomycin sulfate, K: Kanamycin

Table 4. Detection limit of streptomycin analyzed using contact and immersion TLC-bioautography method

Method of TLC-bioautography	Concentration (mg/L)	Inhibitory zone	Diameter of inhibitory zone (mm)
Contact	20.3	-	-
	30.4 ^(a)	+	4.90
	40.6	+	6.10
	50.8	+	6.70
	60.9	+	8.10
Immersion	5.1	-	-
	10.2	-	-
	15.2	-	-
	20.3 ^(b)	+	3.50
	30.4	+	4.60

^(a): Detection limit of streptomycin sulfate in contact TLC-bioautography, ^(b): detection limit of streptomycin sulfate in immersion TLC-bioautography, TLC: Thin layer chromatography

precision results of streptomycin sulfate analyzed by the two methods of TLC-bioautography are shown in Tables 5 and 6, respectively.

The contact and immersion TLC-bioautography methods developed for the determination of streptomycin sulfate and kanamycin sulfate were precise and reliable by only using a single, cheap, and harmless solvent. Based on the TLC-bioautogram, the regression linear equation is capable of reliably predicting analyte concentration in the range of 5-100 mg/mL and 0.1-100 mg/mL for streptomycin sulfate and kanamycin sulfate, respectively.

CONCLUSION

The method was validated successfully and can be used to simultaneously determine streptomycin sulfate and kanamycin sulfate in a common market frozen shrimp. Those simple methods are recommended for monitoring antibiotic abuse in frozen foods, especially for streptomycin at the concentration of 0.16 µg in the presence of kanamycin sulfate.

Table 5. Accuracy of streptomycin sulfate analyzed by contact and immersion TLC-bioautography

Method	Replicate	Added amount (µg)	Inhibitory zone (mm)	Obtained amount (µg)	% Recovery	Mean of % recovery (± SD)
Contact TLC-bioautography	I	1.2992	8.50	1.1459	88.20	86.93±1.60
	II	1.4616	9.20	1.2785	87.47	
	III	1.6240	9.70	1.3825	85.13	
Immersion TLC-Bioautography	I	1.2992	9.20	1.2432	95.69	96.42±0.65
	II	1.4616	9.90	1.4119	96.60	
	III	1.6240	10.50	1.5746	96.96	

SD: Standard deviation, TLC: Thin layer chromatography

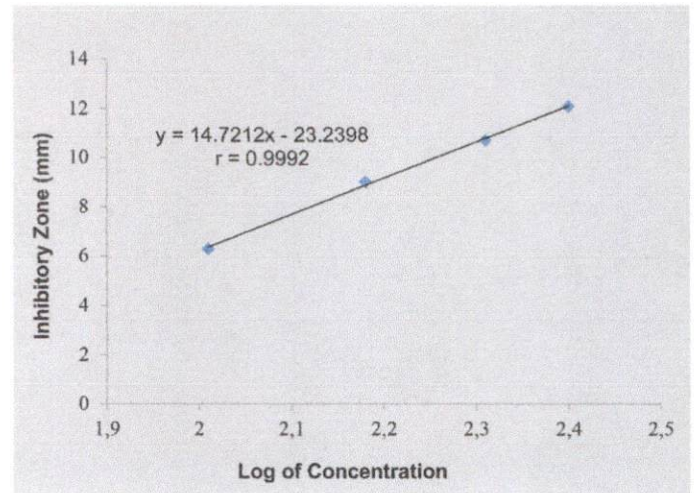


Figure 2. Linear regression of streptomycin sulfate analyzed using contact TLC-bioautography

TLC: Thin layer chromatography

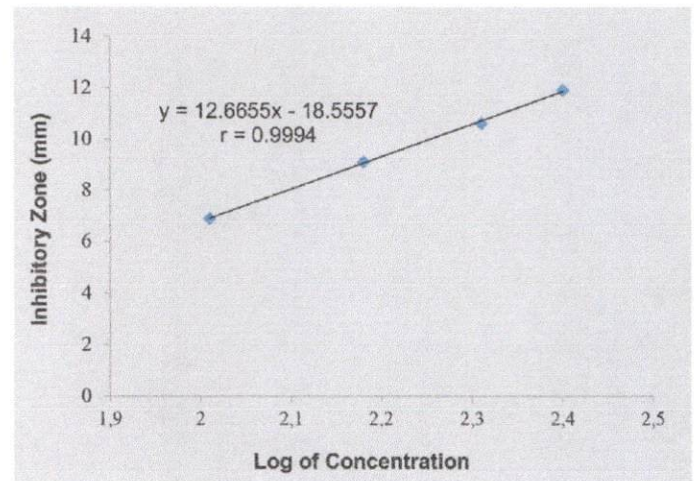


Figure 3. Linear regression of streptomycin sulfate analyzed using immersion TLC-bioautography

TLC: Thin layer chromatography

Table 6. Precision of streptomycin sulfate analyzed by contact and immersion TLC-bioautography

Method	Conc (µg)	Inhibitory zone (mm)			% CV	Mean of % CV
		I	II	III		
Contact TLC-bioautography	121.8	5.70	6.10	6.20	4.41	2.39
	162.4	8.30	8.60	8.45	1.78	
	203.0	10.10	10.30	10.20	0.98	
Immersion TLC-bioautography	160.0	8.25	8.20	8.30	1.24	0.53
	180.0	8.60	8.65	8.65	1.41	
	200.0	9.10	9.00	9.10	1.57	

% CV: Percent coefficient of variation, TLC: Thin layer chromatography

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