

Characteristics And Release Of Gentamicin Sulphate From Sodium Alginate Microspheres Entrapped In Emulgel

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Submission date: 20-Apr-2020 11:16AM (UTC+0800)

Submission ID: 1302167573

File name: document_Characteristics_And_Release_Of_Gentamicin....pdf (460.86K)

Word count: 4756

Character count: 25352

RESEARCH ARTICLE

Characteristics And Release Of Gentamicin Sulphate From Sodium Alginate Microspheres Entrapped In Emulgel

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Received: 23th Oct, 19; Revised: 25th Nov, 19, Accepted: 15th Dec, 19; Available Online: 25th Dec, 2019

ABSTRACT

Gentamicin sulfate is a broad-spectrum aminoglycoside antibiotic that can be used for primary and secondary infections of the skin. Microspheres can be used to extend drug release on the skin; the resulting therapeutic effect is constant and has a longer duration of action. Therefore it can reduce the frequency of use and increase patient compliance. This study investigated the appropriate profile and release kinetics model of gentamicin sulfate microspheres entrapped on the emulgel base. Gentamicin-alginate microspheres were made by the ionotropic gelation method with aerosolization technique, using 2.5% Na-alginate low viscosity, CaCl₂ solution of 1.5M as a crosslinker, maltodextrin as lyoprotectant and were dried using the freeze-drying method. The result of microspheres characterization, gentamicin microsphere was spherical with smooth surface structure and had particle diameter of $3.021 \pm 0.017 \mu\text{m}$. Gentamicin microspheres had moisture content 2.89%, and maximum swelling index was $2625 \pm 21.70\%$ was achieved within 5 hours. The drug loading of microspheres was $1.75 \pm 0.11\%$, and entrapment efficiency was $10.96 \pm 0.19\%$. The release evaluation during 720 minutes showed that the amount of gentamicin release from alginate microspheres on emulgel base was $14.857 \pm 0.816\%$, and gentamicin release on emulgel conventional was $49.239 \pm 5.954\%$. The model of release kinetics of gentamicin microspheres on emulgel was Higuchi model that showed the release of the active ingredient through the diffusion process. While the model of release kinetics of gentamicin on emulgel base was first order, that showed the release of active agent depends on remaining concentration.

Keywords: Characteristics, Gentamicin-alginate microspheres, Gentamicin emulgel, Sodium alginate, Release kinetics
International Journal of Drug Delivery Technology (2019); DOI: 10.25258/ijddt.9.4.33

How to cite this article: Purwanti, T., Syamsuar, M., Hariyadi, D.M. and Erawati, T. (2019). Characteristics And Release Of Gentamicin Sulphate From Sodium Alginate Microspheres Entrapped In Emulgel. International Journal of Drug Delivery Technology, 9(4): 704-710.

Source of support: Funding from Universitas Airlangga.

Conflict of interest: None.

INTRODUCTION

Gentamicin sulfate is a broad-spectrum aminoglycoside antibiotic group, its use to treat infections caused by gram-positive bacteria and especially gram-negative bacteria.¹ Gentamicin sulfate can be given orally, parenterally and topically. Gentamicin sulfate has a short half-life; systemic use three times a day has serious side effects, and namely nephrotoxic and autotoxic.² The local use of antibiotics with extended-release can overcome the side effects that occur. Gentamicin sulfate topical use is applied 3–4 times a day on the skin to treat primary and secondary infections.³ Repeated use can reduce adherence to patients. Therefore a certain drug delivery system is needed to extend the duration of action of the drug and reduce the frequency of use.⁴

The development of drug delivery systems is carried out to overcome problems that occur in conventional delivery systems. One of the topical drug delivery systems is the microsphere. Microspheres are small spherical particles with

a diameter of 1–1000 μm .⁵ The microspheres are designed to trap active ingredients so that they can be used to prolong the release of drugs on the skin. The therapeutic effect produced is constant and has a longer duration; therefore, it can reduce the frequency of use and improve patient compliance. In addition, microspheres can protect active compounds from physical and environmental degradation.⁶

Sodium Alginate is a natural polymer that is biodegradable, biocompatible and has low toxicity.⁷ This polymer is polysaccharide consisting of polyuronic acids (D manuronic acid and L-guluronic acid). Alginate can form a gel through reaction with divalent cations. A crosslinking occurred between COO⁻ group of guluronic acid and divalent cations formed egg-box structures that is forming unit of microspheres particles,^{8,9} whereas electrostatic interactions occurred between cationic gentamicin sulfate and COO⁻ group anionic in manuronics. Alginate cannot swelling at low pH (pH <4) so that active ingredients cannot be released.^{7,9}

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There are several microspheres preparation methods, including emulsion solvent evaporation technique, spray-drying technique, coarservation method, and ionic gelation method.⁵ The selected method of making microspheres in this study was the aerosolization technique of ionic gelation. Ionic gelation methods involve the interaction of ionic polymers with oppositely charged ions to produce cross-linked reactions.⁷

The aerosolization technique was chosen because of several advantages, namely simple, inexpensive, fast, non-toxic, and drug ingredients in the form of proteins can avoid denaturation. In addition, aerosolization techniques are used to produce uniform microspheres. The polymer used was 2.5% Na-Alginate with a CaCl₂ 1.5M crosslinking solution. The stirring speed was 1000 rpm in 90 minutes. Drying used freeze-drying technique.¹⁰

Characteristics are important factors because there are affected the release of the active ingredient and the stability of microspheres.⁵ The microsphere's characteristics are included the morphology, particles size, swelling index, yield value, drug loading, entrapment efficiency and moisture content.¹¹

Gentamicin microspheres were prepared in Hydroxy Propyl Methyl Cellulose (HPMC) emulgel base. Emulgel has the advantage of being able to store drugs efficiently on the skin with even distribution, can release drugs and migrate freely to the site of action, can maintain the drug at therapeutic levels in the target tissue for sufficient duration to provide pharmacological effects and have good acceptability.^{12,13}

To determine the release of gentamicin sulphate a release test was carried out on gentamicin sulfate microspheres gel and conventional gentamicin sulfate gel as a comparison. The concentration determination method is carried out by UV-Vis spectrophotometry. Because gentamicin has a weak absorption at the UV-Vis wavelength, indirect spectrophotometric methods were carried out. Ninhydrin reagent was used for colorimetric reactions at wavelengths of 200–400 nm.⁶ In this study, optimization is still needed to determine the ninhydrin level and the heating time to be used.

MATERIALS AND METHOD

Material

Sodium alginate pharmaceutical grade, CaCl₂ pharmaceutical grade, gentamicin sulphate, maltodextrin food grade, HPMC pharmaceutical grade, liquid paraffin pharmaceutical grade, propylene glycol pharmaceutical grade, ninhydrin, phosphate buffer pH 7.4 ± 0.05, aquademineralisata.

Instruments

Stirrer Plate Dragon Lab MS pro, pH meter SCHOTT glass mainz CG 842, Jasco FT-IR 5300, DTA Mettler Toledo FP-65 DTA P-900, Optical Microscope PS 1 AIR FI-31-032, Scanning Electron Microscop inspect S50 Tipe FP 2017/12, Mettler Toledo HB43 S Moisture analyzer, UV-visible spectrophotometer, Franz diffusion cell, cellophane membrane

Formula of gentamicin-alginate microspheres

Microsphere⁶ were made with the composition as mentioned in Table 1. 2.5 g of sodium alginate was dissolved in 100 mL

aquademineralisata, and were mixed on a plate stirrer with a magnetic stirrer at a speed of 1200 rpm for 15 minutes until sodium alginate dissolved. Gentamicin sulfate 500 mg was dissolved in 20 mL aquademineralisata until dissolved. CaCl₂ 1.5 M solution by weighing 16.65 g CaCl₂.2H₂O dissolved in 50 ml aqua demineralisata. Gentamicin sulfate solution and CaCl₂ solution were mixed on a plate stirrer with a magnetic stirrer at a speed of 1200 rpm for 15 minutes until homogeneous. Then aqua demineralisata was added up to 100 mL. The sodium alginate solution was sprayed at constant speed into gentamicin sulfate solution-CaCl₂ using an aerosol spray, with a 45 µm spray hole diameter, 8 cm spraying distance from the solution surface, and 40 psi pressure. The wet microspheres were stirred at 1000 rpm for 90 minutes to perfect the cross-link reaction. The suspension was filtered, then dried by the freeze-drying method.

Microspheres characterization

Organoleptic

The organoleptic examination was performed on the shape, consistency and color of the preparation.

FTIR spectroscopy

Evaluation of the occurrence of crosslinking reactions was carried out by infrared spectra examination using the KBr pellet technique. The results of the examination were compared with the infrared spectrum of gentamicin sulfate, sodium alginate, and physical mixture.^{9,10}

Morphology of the microspheres

Shape and surface morphology of the microspheres examination using an optical microscope (XSZ-107 Series Microscope), sightings were taken using a camera and using a scanning electronic microscope (SEM).

Yield value

The recovery of the microspheres was determined by weighing the dry microsphere produced, then recording the results. After the weight of the dry microsphere is known, the yield value was calculated by below equation^{9,10}:

$$\text{Yield Value} = \frac{\text{weight the dry microsphere Produced}}{\text{weight of microspheres components}} \times 100\%$$

Moisture content

Moisture content analysis begins with the preparation of the moisture analyzer after that the tool lid is opened, inserted a blank pan sample into the panhandler sample on the tool, then lowered the tool cover and automatically tows to the "zero" condition. Then a number of samples were inserted above the sample pan until it shows the minimum weight for measuring the sample, then the tool cover is lowered. The tool will automatically start the measurement.

Table 1: Formula of Gentamicin-alginate Microspheres

Material	Function	Amount
Gentamicin sulfate	Active agent	0.5% w/v
Sodium Alginate	Polymer	2.5% w/v
CaCl ₂ Solution	Crosslinker	1.5M

The time has been set for 10 minutes after the measurement is complete, the measurement results will be printed on the screen. When finished, the tool lid is opened, the pan sample is taken and cleaned from the rest of the sample.^{9,10}

Particle size

Particle size measurements were carried out by microscopy with Biological Microscope Model XSZ-107 Series. Measured microspheres by placing microspheres on glass objects and measuring the diameter of the microsphere (300 particles). After that, grouping of sizes from the smallest to the largest is done and divided into several intervals and classes. Then a particle size distribution curve is made.^{9,10}

Swelling index

Measuring swelling index by weighing the microspheres weighing 50 mg is then put into 50 ml of aqua dest and then observed at 1, 2, 3, 4, 5, and 6 hours. After the time passed, the microspheres are taken dried on the filter then weighed. The value of the swelling index is calculated by the below equation.^{8,11}

$$SI = \left| \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \right| \times 100\%$$

Entrapment efficiency and drug loading

The determination of gentamicin sulfate wavelength was determined in the visible wavelength region because the gentamicin sulfate standard solution was reacted with ninhydrin reagent with a ratio of 5:1. The results of both reactions will form a purplish red solution. Then, a gentamicin sulfate standard curve was made in sodium citrate pH 8.5 ± 0.05.

The standard curve is made with five different concentrations of gentamicin sulfate solution in sodium citrate, then heated for 20 minutes at 95°C and observed using a UV-Vis spectrophotometer at a wavelength of 399 nm.

After that, the microspheres were removed using a certain amount of sodium citrate. Demolition is carried out using a stirrer at a speed of 1000 rpm and for eight hours.^{9,10}

$$\text{Entrapment Efficiency} = \frac{\text{the amount of gentamicin contained in the microsphere system}}{\text{the amount of initial gentamicin}} \times 100\%$$

$$\text{Drug Loading} = \frac{\text{gentamicin mass added to microsphere system}}{\text{microsphere total mass}} \times 100\%$$

Emulgel preparation

Emulgel preparation can be seen in Table 2.

Formula (1)

Each component was weighted with the amount as listed in Table 2. Mix gentamicin sulfate and propylenglycol stir ad homogeneous. HPMC dispersed into a number of aquadest,

which had previously been heated to 80-90°C 20 times the number of HPMC to be swelled. Stir for two hours with the stirrer until the HPMC have optimal swelling. Then mixture of gentamicin-propylenglycol was added and stirred the mixture ad homogeneous, the amount of paraffin liquid was added step by step into the gel mass, stirring homogeneously. The remaining aquadest was added and stirred the mixture ad homogeneous.

Formula (2)

HPMC was dispersed into a number of aquadest which had previously been heated to 80-90°C 20 times the number of HPMC to be swelled. Stir for two hours with the stirrer until the HPMC have optimal swelling. Amount of paraffin liquid was added step by step into the gel mass, stirring homogeneously. The remaining aquadest was added and stirred the mixture ad homogeneous. Gentamicin sulfate microspheres was weighed equivalent to 0.6% gentamicin sulfate. HPMC emulgel base was mixed and stirred ad homogeneous.

Gentamicin sulfate release

The standard solution of gentamicin sulfate was made in the 20,50,60,70 and 80 ppm concentration by diluting gentamicin sulfate with phosphate buffer pH 7.4 to a certain volume.

Take 5.0 ml of each standard working solution of 20 ppm and 80 ppm then add 1.0 mL ninhydrin reagent 1.25%. It is then heated in a water bath at a temperature of 95°C and within 20 minutes. Then cooled and measured uptake at a wavelength of 200-700 nm. The maximum number of waves is selected based on the highest absorption value. The blank used was a mixture of 1.0 ml ninhydrin 1.25% with phosphate buffer pH 7.4.

Franz diffusion cells was prepared, filled the receptor compartment with the media. magnetic stirrer until it is full. Then attach the cellophane membrane that has been soaked in distilled water overnight and paste it with parafilm. Connect donor compartments and receptors with parafilm. The gel preparation (± 2 g) was filled into the donor compartment.

The gentamicin sulfate study, the temperature of the experiment was set at 32 ± 0.05°C, stirring speed of 600 rpm and immediately recorded as a time to zero. Take 1 ml of the sample and add the same amount of buffer solution. The sample solution was taken at the 0, 5, 10, 15, 30, 45, 60, 90, 120, 150, 240, 300, 360, 480, 600, 720 minutes.

Each sample taken was carried out in the level determination and then corrected by the Wurster equation to obtain the actual level by taking into account the dilution of 1.0 ml of the release medium.

Table 2: Formula of Gentamicin Emulgel.

<i>Gentamicin Sulphate Emulgel (1)</i>		<i>Microsphere Gentamicin Sulphate Emulgel (2)</i>	
Material	%	Material	%
Gentamicin Sulphate	0.6	Microsphere gentamicin sulphate	Equivalent to 0.6 gentamicin sulphate
HPMC	2	HPMC	2
Propylene Glicol	15	Propylene Glicol	15
Liquid Paraffin	5	Liquid Paraffin	5
Aquadest ad	Ad100	Aquadest ad	Ad100

Release kinetic determination

In vitro gentamicin sulfate release, kinetic study of the system was determined by entering the gentamicin sulfate release profile into the zero-order model equation, first-order model, and Higuchi.^{14,15}

- *Zero-order model*

The linear regression equation is made by entering the release time as the x-axis and cumulative % of the drug, which releases the y-ordinate into the release graph

- *First-order model*

The linear regression equation is made by entering the release time as the x-axis and the cumulative log percentage of the drug remaining in the y-ordinate into the release graph.

- *Higuchi's model*

The linear regression equation is made by entering the square root of the release time as the x-axis and cumulative percentage of the drug that releases the y-ordinate into the release graph.

The release rate of gentamicin sulfate can be obtained from the graph of the release profile of gentamicin sulfate in the steady-state phase. A regression equation was made in the steady-state region, the slope of the regression equation is the gentamicin sulfate release rate from the base.^{15,16}

RESULTS AND DISCUSSION

Organoleptic

The result of organoleptic, gentamicin sulfate microspheres had a white powder, odorless, and tasteless.

Infrared spectra

The physical mixture spectra of sodium alginate and gentamicin sulfate (A) had absorption in guluronic fingerprints ($900-890\text{ cm}^{-1}$) and manuronic ($850-810\text{ cm}^{-1}$). The sodium alginate spectra (B) had absorption in guluronic and manuronic fingerprints. The gentamicin sulfate microsphere hadn't absorption in guluronic and manuronic fingerprints because the guluronic in sodium alginate binds to the Ca^{2+} cation through crosslinking reactions.¹¹

Shape and surface of Particles

The results of the examination of particle shape microspheres

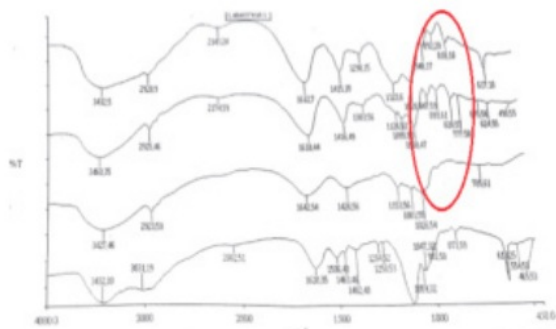


Figure 1: Comparison of infrared spectra (A) physical mixture of sodium alginate and gentamicin sulphate, (B) Sodium alginate, (C) gentamicin sulphate microspheres, (D) gentamicin sulphate.

using XSZ-107 Series Biological Microscope and Scanning Electron Microscope (SEM) showed that the microspheres had a spherical and smooth surface.

Yield

From the results of the yield, gentamicin sulfate microsphere had a yield value of more than 50% so that they had the opportunity to be developed in a large scale manufacturing process.

Moisture content

From the results of moisture content, gentamicin sulfate microspheres dried using freeze-dry for 24 hours had low water content. The results requirements are <10% (Table 4). The low results were good because higher moisture content can cause the growth of microorganisms.

Particle size distribution

Results of the particle size distribution of gentamicin sulfate microspheres had a range of 1.38-4.72 μm (Figure 4). The spherical particles can be seen in the result of the examination using optical microscope (Figure 2) and SEM (Figure 3).

The results of the average particle size, the gentamicin sulfate microspheres had a particle size of $3.01 \pm 0.02\ \mu\text{m}$ (Table 5).

Swelling index

The results showed the microspheres particles swelling gradually until the fifth hours. The swelling process depends



Figure 2: The results of the examination of particle shape of gentamicin sulfate dry microspheres using Biological Microscope Model XSZ-107 Series with 400x magnification.

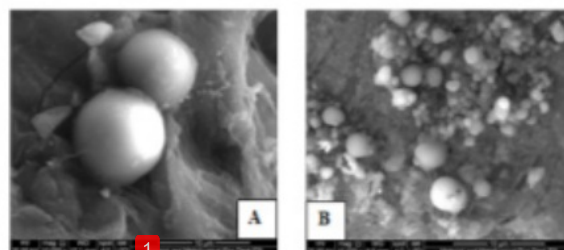


Figure 3: The results of the examination of shape and morphology particles of gentamicin sulfate microspheres using SEM at magnification (A) 10.000x and (B) 5.000x

on the ease with which water penetrates into the particles of the microspheres, the more compact the particle structure of the microspheres is the harder to penetrate water. High swelling power will cause the active ingredient to detach from the matrix easily. The swelling index and swelling profile can be seen in Table 6 and Figure 5.

Entrapment efficiency and drug loading

Results of entrapment efficiency and drug loading can be seen in Table 7 and 8.

The results of efficiency entrapment of the gentamicin sulfate microsphere, the percentage data of entrapment efficiency were 11.12 ± 0.43 %. The value of entrapment efficiency depends on the ingredients of the microspheres, polymers, and crosslinking solutions. Optimization processes are needed regarding the concentration of polymers and crosslinking solutions to increase the efficiency entrapment of active ingredients in the matrix. The higher level of the polymer used causes the viscosity to increase so the particle size increases. Increasing of particle size causes the amount of drug trapped in particles to increase, causing an increase in entrapment efficiency. An increase in the level of crosslinking solutions (eg calcium chloride) caused the particles to structure more compact so that it increases the amount of drug trapped in the microspheres.⁹

The value of drug loading is small because the reaction between the manuronic (M) in sodium alginate and NH₂ gentamicin sulphate is influenced by the ratio of mannuronic (M) : 3: guluronic (G) to sodium alginate. The use of alginate with a high M/G ratio (high viscosity) will result in a more compact microspheres conformation compared to the use of low viscosity alginates,² whereas in this study low viscosity alginates were used. In further research, optimization can be made regarding the use of high viscosity alginate polymers as an effort to increase the value of drug loading.

Table 3: Results of Yield

Replication	Yield (%)	Average ± SD (%)
1	74.03	73.72±0.91
2	74.43	
3	72.69	

Table 6: The Result of Swelling Index

Time (hours)	Swelling Index (%)			Average ± SD (%)
	Replication			
	1	2	3	
1	1160.5	1150	1168	1159.5±9.04
2	1692.7	1650	1694	1678.9±25.40
3	1785	1735	1789	1769.7±30.09
4	2370	2320	2376	2355.3±30.75
5	2636	2600	2639	2625.0±21.70
6	1960	1940	1965	1955± 13.23

Table 7: Results of Entrapment efficiency

Replication	EE (%)	Average ± SD (%)
1	10.75	11.12 ± 0.43
2	11.02	
3	11.59	

Table 4: Results of Moisture Content

Replication	Moisture Content (%)	Average± SD (%)
1	2.85	
2	2.82	2.90 ± 0.11
3	3.02	

Table 5: Particle Size Analysis

Replication	Diameter (µm)	Average ± SD	CV (%)
1	3.00	3.01 ± 0.02	0.66
2	2.99		
3	3.03		

Table 8: Results of Drug Loading

Replication	Drug Loading (%)	Average ± SD (%)
1	1.63	
2	1.76	1.75 ± 0.11
3	1.85	

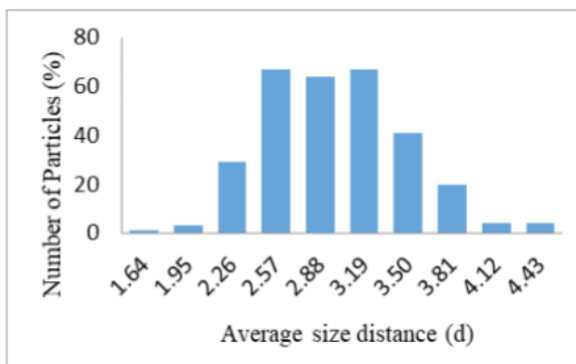


Figure 4: Particle size distribution of gentamicin sulphate microspheres.

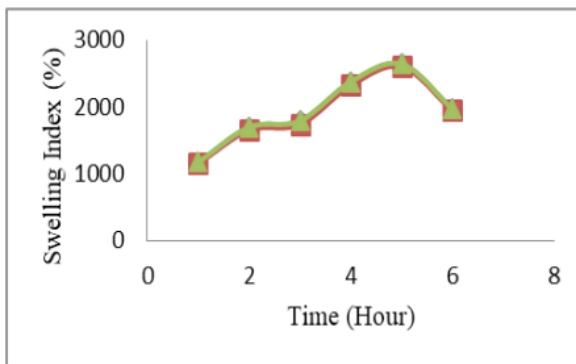


Figure 5: Swelling index profile of gentamicin sulfate microspheres for 6 hours in aqua demineralisata.

Characteristics of gentamicin sulfate emulgel

The color of droplet

From examination with an optical microscope with oil-soluble reagent (Sudan III) coloring oil droplets on the preparation. Whereas with water-soluble reagents (methylene blue) coloring the outside of the droplet. Figure 6 showed, oil droplets are found in the phase in the preparation. Because, the active ingredient (gentamicin sulfate) dissolves in water, the active ingredient in the outer phase.

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Standard curve of gentamicin sulfate in buffer solution with pH 7.4 ± 0.05

The result of absorbance standar solution can be seen in Table 9 The linear regression from the above standart curve is used to determine the level of gentamicin sulphate in phosphate buffer pH 7.4 ± 0.05 . The intercept value is (a) 0.02496, the slope value (b) is 0.0101 and the correlation coefficient value is 0.9997.

The result of release gentamicin sulfate from alginate microspheres

Until the 720th minute, gentamicin sulphare was released from gentamicin sulfate emulgel $49.239 \pm 5.954\%$ while in the emulgel gentamicin sulfate microspheres were $14.857 \pm 0.816\%$, as shown in Table 10 and Figure 7. The amount of gentamicin sulfate microspheres was smaller because the release of active ingredients depends on the swelling process and the diffusion process of the active ingredients from the matrix into the skin.

Determination of release kinetics of gentamicin sulfate from emulgels

From the result of the determination of release kinetics as shown in Table 11 obtained gentamicin sulfate in the emulgel followed the first-order release kinetics because it had a correlation coefficient of 0.840 while gentamicin sulfate microspheres in the emulgel followed the Higuchi release kinetics because it had a correlation coefficient of 0.9786.

Table 9: Results of Absorbance of Standart Solutions at a Wavelength of 401 nm

Concentration	Absorbance
20.0 ppm	0.231
50.0 ppm	0.520
60.0 ppm	0.630
70.0 ppm	0.733
80.0 ppm	0.836

Table 11: Results of the Regression Equation and Release Kinetic Model.

Sample	Orde 0	Orde 1	Higuchi
GS Emulgel	$y = 0.0443x - 18.443$ $r = 0.9726$	$y = 0.0003x - 1.932$ $r = 0.9840$	$y = 1.9755x - 3.0374$ $r = 0.9827$
Micros-phere GS emulgel	$y = 0.0103x - 7.9108$ $r = 0.9660$	$y = 0.0005x - 1.9648$ $r = 0.9672$	$y = 0.459 - 2.9056$ $r = 0.9786$

Table 12: Results of the Detemination of Gentamicin Sulphate Release Rate.

Sample	Average Slope \pm SD
GS Emulgel	2.088
Microspheres GS emulgel	0.004

this data is based on replication average data 3 times

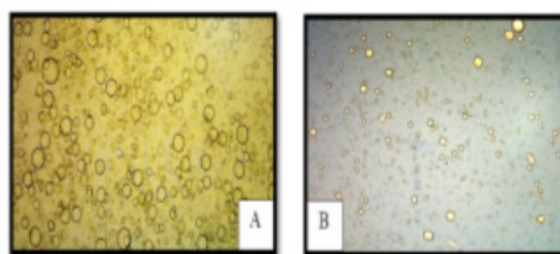


Figure 6: The color of droplet with (A) coloring with Sudan III reagents; (B) coloring with methylene blue reagents.

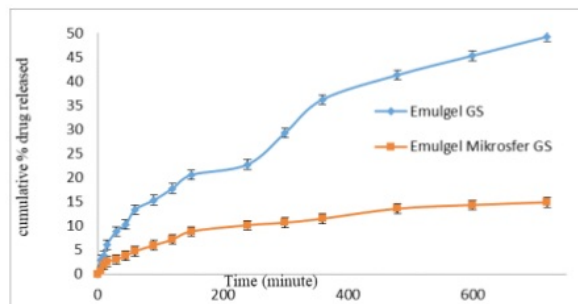


Figure 7: The release profile of gentamicin sulphate microsphere in emulgel base.

Table 10: Gentamicin Sulphate Release Test Results from the Microspheres

Sampling time (minutes)	Amount of release Gentamicin Sulphate (%) \pm SD	
	Emulgel gentamicin sulphate	Emulgel loaded with gentamicin sulphate microspheres
0	0.000 ± 0.000	0.000 ± 0.000
5	2.885 ± 1.178	0.544 ± 0.943
10	3.744 ± 1.028	1.850 ± 1.501
15	6.076 ± 3.622	2.585 ± 1.653
30	8.832 ± 3.062	3.032 ± 1.820
45	10.235 ± 3.311	3.764 ± 2.288
60	13.339 ± 2.476	4.707 ± 2.384
90	15.287 ± 2.940	5.961 ± 3.049
120	17.723 ± 3.395	7.137 ± 2.115
150	20.522 ± 4.423	8.832 ± 0.793
240	22.688 ± 5.252	10.110 ± 0.201
300	29.234 ± 6.404	10.640 ± 0.280
360	36.186 ± 4.313	11.467 ± 0.584
480	41.265 ± 4.470	13.547 ± 0.679
600	45.271 ± 5.166	14.293 ± 0.782
720	49.239 ± 5.954	14.857 ± 0.816

Determination of release rate of gentamicin sulfate on emulgel.

From the results of the determination of the release rate as shown in Table 12, the value of the flux (slope) of gentamicin emulgel was greater than the value of the flux (slope) of the gentamicin sulfate microspheres emulgel.

CONCLUSION

Gentamicin sulfate microspheres entrapped in sodium alginate matrix at a concentration of 2.5% alginate was found to have good characteristics. The release of gentamicin after 12 hours from microspheres were slower than from emulgel conventional, and the release kinetics of microspheres followed Higuchi model. This optimum formula can be further tested for the stability study.

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