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Research Article

Isoniazid Microencapsulation with HPMC HP-50 and HPMC HP-55 (2:3) Coating Using Solvent Evaporation Methods

Hestiary Ratih*, Gladdis Kamilah Pratiwi, Fikri Alatas, Mia Agustin, Bella Dewinta Saraswati

Program Studi Farmasi, Fakultas Farmasi, Universitas Jenderal Achmad Yani, Jl. Terusan Sudirman, Cimahi

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*Corresponding author: hestiary.ratih@lecture.unjani.ac.id

Abstract

The combination formulation of tuberculosis drugs may cause interactions if drugs are given simultaneously. Rifampin (RIF) decomposes in the stomach when given concurrently with isoniazid (INH), which results in a decrease in the bioavailability of RIF. The purposed is to make INH microcapsules using HPMCP HP-50 and HP-55 coatings to prevent these interactions. The process of making INH: HPMCP HP-50 and HP-55 (2:3) microcapsules was done by using solvent evaporation method. The entrapment efficiency of INH: HPMCP HP-50 and HP-55 (2:3) were 83.21% and 91.57%, respectively. The dissolution test of INH: HPMCP HP-50 and HP-55 microcapsules met the requirements of the Indonesian Pharmacopoeia Edition V. The FTIR results showed that there was no change either in the chemical composition of isoniazid or in the coating of the microencapsulation. Scanning Electron Microscopy (SEM) showed the active substance was well coated. This study resulted in a novel formula for microcapsules INH:HPMCP HP-50 and HP-55 (2:3) which can prevent the decomposition of RIF when given together with INH with a delayed release effect so that INH will be released in the intestine.

Keywords: *HPMCP HP 50, HPMCP HP-55, isoniazid, microcapsules, solvent evaporation method*.

Mikroenkapsulasi Isoniazid - Hpmcp Hp-50 dan Hpmcp Hp-55 dengan Perbandingan (2:3) Menggunakan Metode Penguapan Pelarut

Abstrak

Formulasi kombinasi obat TBC (tuberculosis) dapat menyebabkan terjadinya interaksi jika pemberian obat dilakukan secara bersamaan. Rifampisin (RIF) terurai dalam lambung jika diberikan bersama isoniazid (INH), yang mengakibatkan penurunan ketersediaan hayati RIF. Tujuannya adalah membuat mikrokapsul INH dengan penyalut HPMCP HP-50 dan HP-55 untuk mencegah terjadinya interaksi tersebut. Pembuatan mikrokapsul INH:HPMCP HP-50 dan HP-55 (2:3) dilakukan dengan metode penguapan pelarut. Efisiensi penjeratan INH:HPMCP HP-50 dan HP-55 (2:3) berturut-turut adalah 83,21% dan 91,57%. Uji disolusi mikrokapsul INH:HPMCP HP-50 dan HP-55 memenuhi persyaratan Farmakope Indonesia edisi V. Pengujian FTIR menunjukkan bahwa mikrokapsul tidak mengubah komposisi kimia isoniazid atau penyalut pada mikroenkapsulasi sehingga disimpulkan bahwa tidak ada reaksi kimia atau dekomposisi yang terjadi sebelum dan sesudah pembentukan mikrokapsul. Scanning Electron Microscopy (SEM) menunjukkan morfologi permukaan mikrokapsul bulat dan zat aktif tersalut dengan baik untuk INH:HPMCP HP-50 (2:3), sedangkan untuk INH:HPMCP HP-55 (2:3) permukaan mikrokapsul bulat tetapi berongga. Penelitian ini menghasilkan formula baru sediaan mikrokapsul INH:HPMCP HP-50 dan HP-55 (2:3) yang dapat mencegah dekomposisi RIF saat diberikan bersamaan INH dengan adanya efek pelepasan tunda sehingga INH akan dilepaskan di usus.

Kata Kunci: HPMCP HP-50, HPMCP HP-55, isoniazid, mikrokapsul, metode penguapan pelarut.

1. Introduction

Single drug therapy with isoniazid (INH) is not effective in treating tuberculosis due to the risk of developing resistance in a short time[1]. Currently, the administration of drugs recommended by WHO for the new treatment of TB cases is a combination of three or four different first-line drugs, namely rifampin (RIF), isoniazid (INH), ethambutol (ETB) and pyrazinamide (PYR). Combination formulations of tuberculosis (TB) drugs may increase the risk of drug interactions given concurrently which can affect the bioavailability of the drugs[2,3].

The TB drug combination of rifampin (RIF) taken on an empty stomach at a pH of around 1.4–2.1 will be easily decomposition into isonicotinyl hydrazone (HYD) due to the presence of INH. This reaction is thought to be the cause of the lower RIF in vivo bioavailability of the TB drug combination. RIF is converted to 3-formylrifamysin below pH 2, which then reacts with INH to form HYD[4]. Isoniazid (INH) is soluble at pH 1.2 but has poor gastric permeability and is very well absorbed in the intestine[5].

Microcapsules contain solid or liquid active ingredients which are dispersed or dissolved in the matrix. Microcapsules are microscopic-sized reservoirs surrounded by walls that are capable of controlling the release of the active substances. Microcapsules have many advantages based on their structural and functional capabilities among others; they can be applied conveniently and administered via several routes[6,7,8].

Depending on the formulation, microcapsules can be incorporated into different pharmaceutical dosage forms such as solids (capsules, tablets, and sachets), semi-solids (gels, creams, and pastes), or liquids (solutions, suspensions, and parenterals). Another advantage of microcapsules preparations is that when compared to nanoparticles, they do not cross the interstitium as they are larger than 100 nm in size and transport does not go through lymph vessels thus it can work locally[9].

Hydroxy Propyl Methyl Cellulose Phthalate (HPMCP HP-50 and HP 55) is a cellulose-derived enteric-coated polymer that is insoluble in gastric juice but expands and dissolves in intestinal fluid. HPMCP HP-50 and 55 are commonly used as soluble coatings, respectively at pH above 5.0 and 5.5, and can withstand the release of drugs in the stomach, so it can be used as a polymer for the purpose of delayed release[10]. Microencapsulation can be made by several methods. One of the methods that are popular and often used is the solvent evaporation method[11].

This method can be done by dissolving the coating in a volatile solvent and the active substance is dissolved or dispersed in the coating solution and then the solvent evaporation is carried out[12]. This method has a short processing time and can be used for various core materials such as water-soluble or water-insoluble materials[13].

Previously, several studies have been conducted on the manufacture of INH microcapsules by using HPMCP HP-50 and HP-55 (1:1) coatings, but the results are not optimal[14 ,15]. This study aims to make INH microcapsules using HPMCP HP-50 and HP-55 (2:3) coatings to prevent interactions between INH and RIF. It is expected that INH is not released in the stomach and absorbed in the intestine after coating, preventing interaction with RIF, which could decrease its bioavailability.

2. Materials and Methods

2.1. Tools

Fourier Transform Infrared Spectroscopy (FTIR), SEM (Jeol,USA), UV-visible Spectrophotometry (Shimadzu PC-1601, Japan), orbital shaker (IKA, Germany), dissolution test equipment (Vanguard RC- 6, USA), ultrasonic/sonifier (Branson, Model 3510E-DTH, Danbury, USA), orbital shaker graded sieve (IKA, Germany), pH meter (Boeco,Germany), and analytical balance.

2.2. Materials

Isoniazid (Amsal Chem, India), HPMCP HP 50 and 55 (Shin Etsu Japan), magnesium stearate, span 80, ethanol, liquid paraffin, n-hexane, hydrochloric acid, and phosphoric buffer (Bratachem, Indonesia).

Table 1. INH Microcapsule Formulation: HPMCP HP-50 and HP-55 (2:3)

Substance	Amount of Material (% w/v)	
	HPMCP HP-50	HPMCP HP-55
Isoniazid	1	1
Coating	1,5	1,5
Acetone	30	30
Magnesium stearate	0,75	0,75
Span 80	1	1
Liquid paraffin up to	100	100

2.3. Methods

2.3.1. Manufacturing of Microcapsules with HPMCP HP-50 and HPMCP HP-55 Polymers

HPMCP HP-50 and 55 were dissolved in acetone, then stirred until dissolved (polymer solution). Isoniazid was dispersed in a polymer solution and stirred until homogeneous using a homogenizer. The isoniazid dispersion and polymer solution were further emulsified into liquid paraffin containing 1 g of span 80. The emulsion solution was stirred at 900 rpm until the solvent completely evaporated and microcapsules were formed. The formed microcapsules were then collected through the process of decantation and washed twice with n-hexane to remove the attached liquid paraffin, then dried in an oven for 2 hours. Furthermore, microcapsule evaluation was carried out[16].

2.3.2. Microcapsule Evaluation and Characterization

Microcapsule Particle Size Distribution

The size distribution of the microcapsules was evaluated using a sieve shaker. A series of two sieves (numbers 35 and 40) was arranged in succession from the size of the largest sieve hole. A total of 5 grams of microcapsules was placed in the top sieve, and then the sieving machine was run for 10 minutes. Each fraction in the sieve was weighed and carried out 3 times for each formula[17].

Entrapment Efficiency

Weighed the equivalent of 500 mg microcapsules, then dissolved in ethanol up to 100 ml. Absorption was measured at a maximum wavelength of 266 nm by UV spectrophotometry. The test was carried out 3 times for each formula[17].

Isoniazid Dissolution Test

The dissolution profile of isoniazid powder and microcapsules was determined using a type 2 dissolution apparatus (paddle) at a speed of 50 rpm at 37±0.5 ºC in a solution of hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 with a medium volume of 900 ml for 12 hours. A sampling of 5 ml was carried out during the 1st and 2nd hours. The sampling was continued in phosphate buffer medium pH 6.8 at 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours.

The samples obtained were analyzed and their absorption was measured at a wavelength of 266 nm using UV spectrophotometry. Each time a sample was taken, the volume of the medium was replaced with a new medium solution with the same volume and temperature[17].

Table 2. Microcapsule Particle Size Distribution for INH-HPMCP HP-50 (2:3) and INH-HPMCP HP-55 (2:3)

Size (µm)	Microcapsule Size (%)	
	HPMCP HP-50	HPMCP HP-55
≥500	21,11±1,13	61,53±4,65
250-500	79,24±0,47	35,35±2,19
≤250	0,01±0,01	1,47±0,92

Table 3. INH Microcapsule Formulation: HPMCP HP-50 and HP-55 (2:3)

No	Amount of Material (% w/v)	
	HPMCP HP-50	HPMCP HP-55
1	87,09	92,08
2	82,47	90,33
3	80,08	92,29
Average ±SD	83,21%±3,56	91,57%±1,07

Fourier Transform Infrared Spectroscopy (FTIR)

A total of 3 mg of the sample was put into a clean and dry sample holder, then sample analysis was conducted on a programmed FTIR device and the spectrum results would come out[17].

Microcapsule Shape and Surface Morphology

The shape and surface morphology of the microcapsules were observed using Scanning Electron Microscopy (SEM)[17].

3. Result

Microcapsule particle with a stirring speed of 900 rpm produced the most microcapsule size of INH: HPMCP HP-50 at a size of 250-500 µm with an average percentage of 79.24%, and in INH: HPMCP HP-55 produced a slightly higher percentage of microcapsules at a size above 500 µm with an average of 61.53%, as shown in Table 2.

The entrapment efficiency of microcapsules was carried out to determine the level of active substances coated in the microcapsules. The entrapment efficiency results of INH:HPMCP HP-50 and 55 (2:3) microcapsules were 83.21% and 91.57%, respectively, as can be seen in Table 3.

In this study, the results of the in vitro dissolution test of pure INH in hydrochloric acid buffer medium pH 1.2 obtained solute level after 2 hours was 111.42%. Meanwhile, in INH-HPMCP (2:3) HP-50 and HP-55 microcapsules, the solute levels were 7.64% and 5.74%, respectively, as shown in Fig. 1. In vitro dissolution test results of pure INH in phosphate buffer medium pH 6.8 obtained the solute level after 2 hours was 104.62%. Meanwhile, in INH-HPMCP (1:1) HP-50 and HP-55 microcapsules, the solute levels were 95.60 and 99.62%, respectively, as can be seen in Fig. 1.

In the isoniazid FTIR spectrum, there is

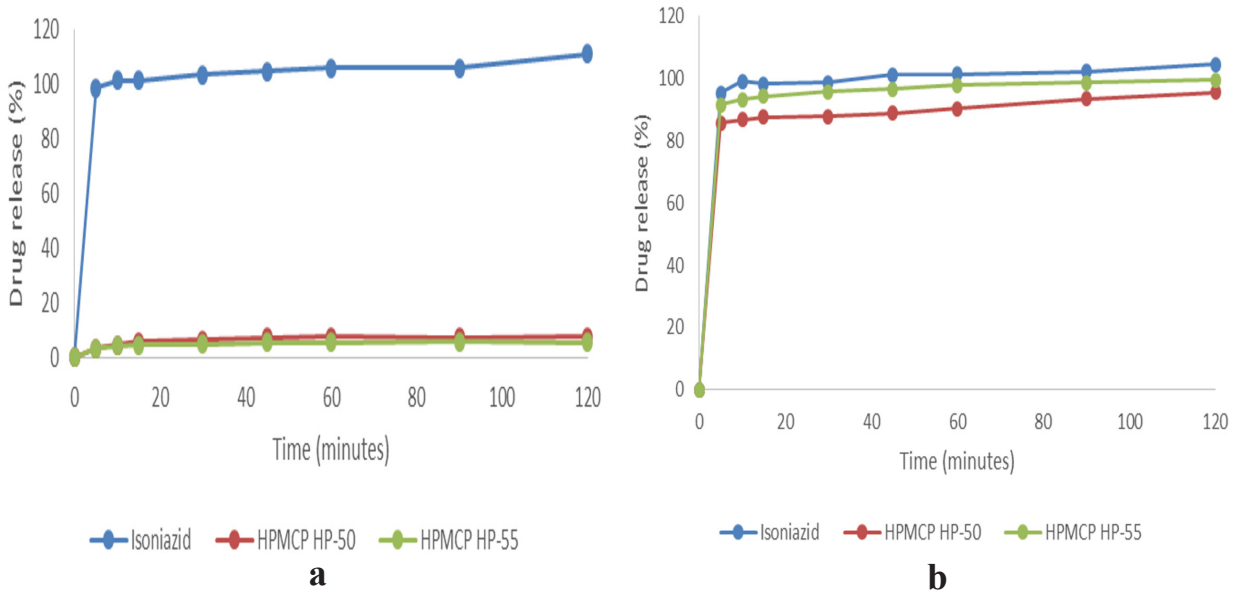


Fig.1. Dissolution profile of INH, INH-HPMCP HP-50 (2:2), INH-HPMCP HP-55 (2:3) in hydrochloric acid buffer solution pH 1.2 **(a)** Dissolution profile of INH, INH-HPMCP HP-50 (1:1), INH-HPMCP HP-55 (2:3) in phosphate buffer solution pH 6.8 **(b)**

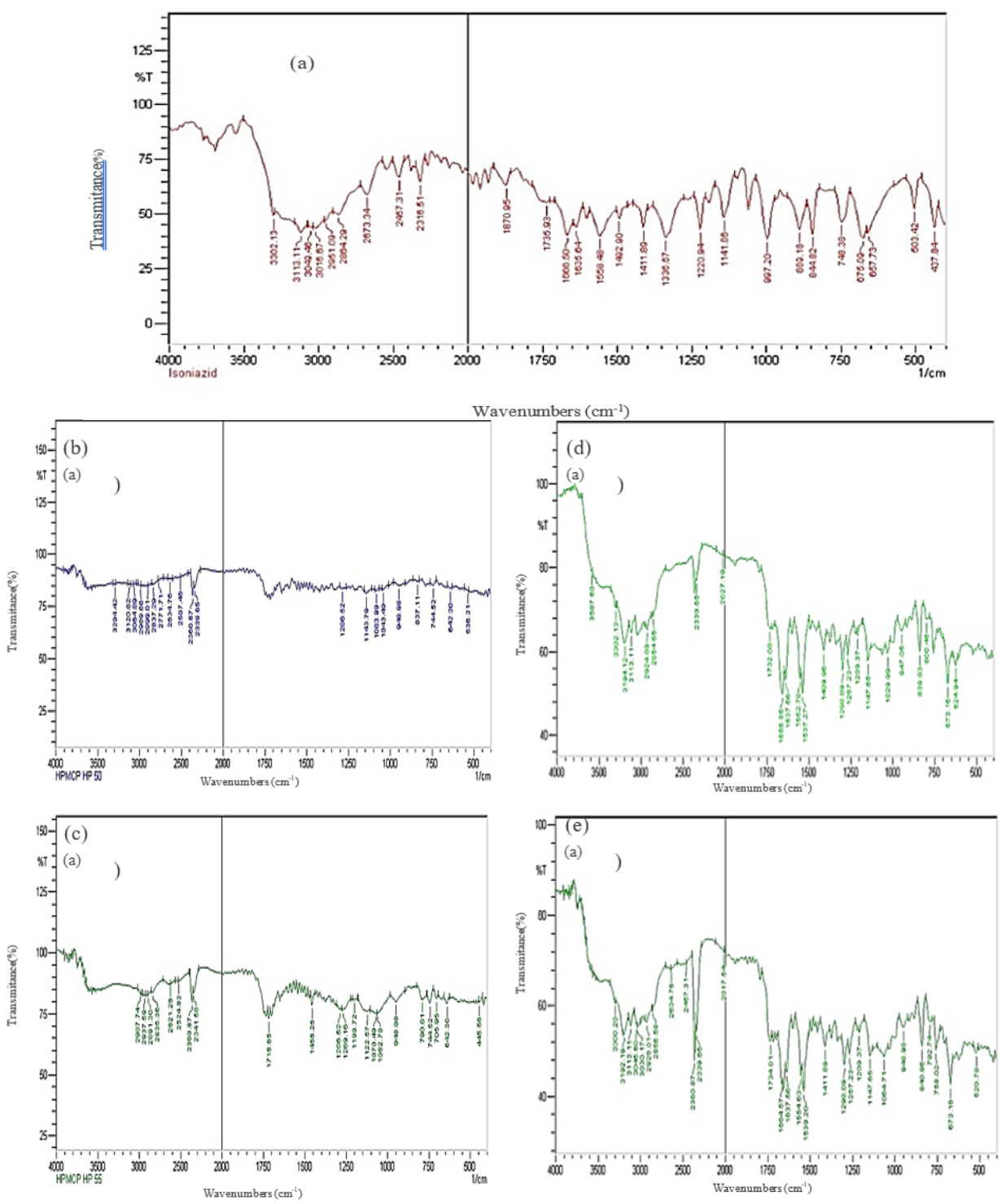
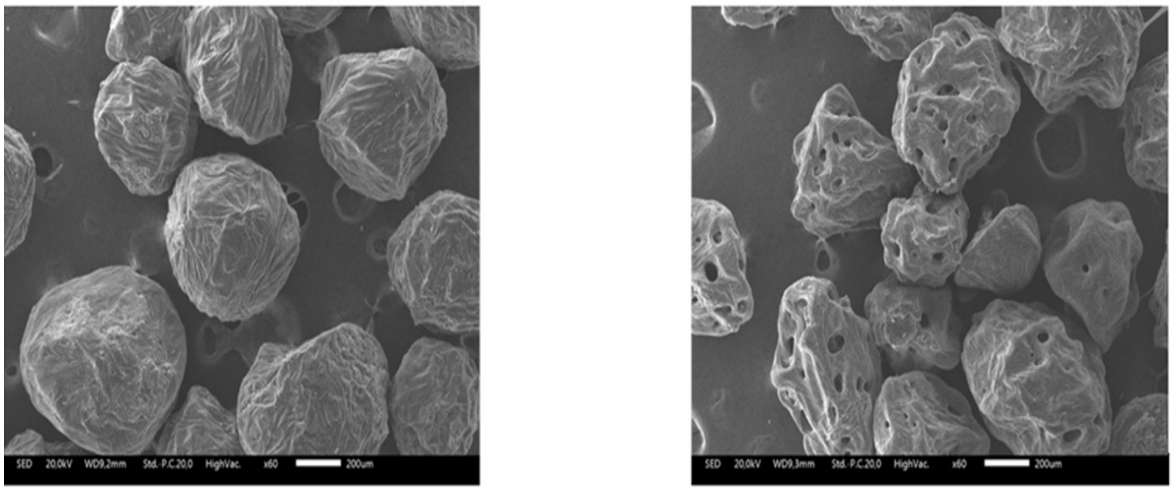


Fig.2. FTIR Spectrum (a) Isoniazid (b) HPMCP HP-50 (c) HPMCP HP-55 (d) INH-HPMCP HP-50 Microcapsule (e) INH-HPMCP HP-55 Microcapsule

absorption of the carbonyl group at a wave number of 1664 cm-1. Next, N-H strain occurs at a wave number of 1552.32 cm-1. In addition, there are many tenuous vibrational regions between 1407 and 668.53 cm-1 in the isoniazid spectrum. The carbonyl group was detected at 1716 cm-1 for HPMCP, as can be seen in Fig. 2.

Examination of the surface morphology of INH-HPMCP HP-50 and HP-55 microcapsules was carried out using Scanning Electron Microscopy (SEM) Based on the photomicrograph results obtained, INH-HPMCP HP-50 microcapsules were well coated but not so smooth. Meanwhile, INH-HPMCP HP-55 microcapsules have less spherical shape with an uneven and hollow surface. This is thought to be caused



(a) (b)

Fig.3. Photomicrograph 60x magnification : (a) INH-HPMCP HP-50 microcapsules (b) INH-HPMCP HP-55 microcapsules

by several factors, one of which is stirring the homogenizer during the manufacture of microcapsules, with high stirring will break the microcapsule particles into smaller sizes with non-spherical shapes, as can be seen in Fig. 3.

4. Discussion

The process of forming microcapsules using the solvent evaporation method requires optimization of time and stirring speed. Optimization of time was carried out to find out how long it would take to form microcapsules. Microcapsules are formed when the acetone has evaporated completely. In addition, the stirring speed (agitation) and the type of stirrer (impeller or baffle) is one of the most critical parameters in controlling the size of microspheres, increasing the stirring speed will generally decrease the particle size[18-19]. In this study, INH microcapsules were made with a ratio of (INH: HPMCP HP-50/55) 2:3 using the solvent evaporation method. The optimum microcapsule size was obtained at the optimum stirring speed at 900 rpm. Meanwhile, at 1000 rpm, no microcapsules were formed. The principle of making microcapsules using the solvent evaporation method is to use a volatile solvent that will dissolve the microcapsule or polymer layer and not mix with other liquid carrier phases[19]. The formed microcapsules were then washed with n-hexane to remove the remaining paraffin that was still attached to the surface of the microcapsules. N-hexane has volatile criteria and cannot dissolve microcapsules that have been coated with HPMCP HP-50, its only dissolve paraffin and the remnants of magnesium stearate that are still attached to the microcapsules. In the last step, the microcapsules were vacuumed and dried at room temperature to remove the remaining n-hexane [16].

The entrapment efficiency of microcapsules was carried out to determine the level of active substances coated in the microcapsules. In this study, the entrapment efficiency results of INH: HPMCP HP-50 and 55 (2:3) microcapsules were 83.21% and 91.57%, respectively, as can be seen in Table 3. Various factors may affect the recovery results of microcapsules. HPMCP HP-50 and 55 coatings have differences in phthalate content, pH solubility and viscosity. HPMCP HP-50 and 55 viscosities were 55 and 40 cps, respectively. This indicates that the viscosity affects the adsorption of the isoniazid active substances. High viscosity which causes an increase in viscosity of the preparations will inhibit the release of isoniazid drug, so that microcapsules with HPMCP HP-50 coating will provide a lower percentage of recovery than microcapsules with HPMCP HP-55 coating. In addition to the above mentioned factors, the amount of polymer used will also affect the percentage of entrapment

efficiency. The less polymer used, the more active substance will be adsorbed during stirring. Conversely, the more polymer used, the less active substance will be adsorbed during stirring, this occurs because a strong polymer wall is formed so that it will hinder the diffusion of isoniazid [20].

The dissolution test was carried out in vitro to determine the dissolution profile of INH and INH microcapsules. The test was conducted in hydrochloric acid buffer medium pH 1.2 for 2 hours and in phosphate buffer medium pH 6.8 for 2 hours. Testing on these two buffer mediums carried out so that the conditions for the release of the active substance are close to in vitro conditions in the gastrointestinal tract. The results of the in vitro dissolution test of INH in hydrochloric acid buffer medium pH 1.2 obtained solute level after 2 hours was 111.42%. Meanwhile, in INH-HPMCP (2:3) HP-50 and HP-55 microcapsules, the solute levels were 7.64% and 5.74%, respectively. These results have met the requirements of the Indonesian Pharmacopoeia edition V, in which for the delayed release preparation, the percentage of the solute is not more than 10% after 2 hours in HCl buffer medium pH 1.2 as shown in Fig. 1. Coating HPMCP HP-50 and HP-55 may cause the release of the active substance in hydrochloric acid buffer medium pH 1.2 to be small as HPMCP HP-50 and HP-55 are enteric polymers that are resistant to acidic pH and will expand or dissolved in the intestines that have an alkaline pH so that their release at an acidic pH is delayed. In vitro dissolution test results of pure INH in phosphate buffer medium pH 6.8 obtained the solute level after 2 hours was 104.62%. Meanwhile, in INH-HPMCP (1:1) HP-50 and HP-55 microcapsules, the solute levels were 95.60 and 99.62%, respectively. These results have met the requirements of the Indonesian Pharmacopoeia edition V, in which for delayed release preparation, the percentage of solute is not less than 80% after 2 hours as can be seen in Fig. 1. These results indicate that the INH-HPMCP HP 50 and INH-HPMCP HP-55 microcapsules met the expected goals of producing a low level of percent dissolution in hydrochloric acid medium pH 1.2, which implies that after the microcapsules were made, the release of INH was effectively retained in the stomach compared to the pure INH, which was released 111.42% in the stomach. In previous research, it was found that the release of INH together with RIF in the stomach will cause degradation of RIF into isonicotinyl hydrazone (HYD). This reaction is thought to be the cause of the lower RIF in vivo bioavailability of the TB drug combination. The results of the microcapsule dissolution test in phosphate buffer medium pH 6.8 showed that after microcapsules were made, INH could be released and well absorbed in the intestine. The results of dissolution test also showed that INH does not interact with RIF in the stomach but is released in the intestine[4,5,21].

FTIR (Fourier Transform Infrared Spectroscopy) is a spectroscopic technique used to detect the formation of microcapsules by looking at the spectral wave numbers in certain groups. In the isoniazid spectrum, there is absorption of the carbonyl group at a wave number of 1664 cm-1. N-H strain occurs at a wave number of 1552.32 cm-1 18. In addition, there are many tenuous vibrational regions between 1407 and 668.53 cm-1 in the isoniazid spectrum. The carbonyl group was detected at 1716 cm-1 for HPMCP (19). Several characteristics of isoniazid tenuous vibrations were seen in the INH-HPMCP HP-50 and HP-55 microcapsules as can be seen in Fig. 2. The FTIR spectra of isoniazid microcapsules showed the same combined peaks as isoniazid and HPMCP. The FTIR results showed that there was no change either in the chemical composition of isoniazid or in the coating of the microencapsulation. Therefore, it was concluded that no chemical reaction or decomposition occurred before or after the microcapsules were formed[18,22,23,24].

5. Conclusion

The microcapsules INH:HPMCP HP-50 (2:3) and INH:HPMCP HP-55 (2:3) obtained microcapsules that inhibit the release of INH in the stomach and can be released well in the intestine, according to the results of the

dissolution test. From the results of this study, microcapsules INH:HPMCP HP-50 (2:3) and INH:HPMCP HP-55 (2:3) can be used as a new INH preparation to prevent interactions between INH and RIF which can cause degradation and decrease the bioavailability of RIF.

The further research needs to be verified by conducting a dissolution test on preparations containing a combination of INH:HPMCP HP-50 (2:3) and INH:HPMCP HP-55 (2:3) microcapsules with RIF.

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References

1. Silva AM, Carmo FA, Amaral LH. Segregated Delivery of Rifampicin and Isoniazid from Fixed Dose Combination Bilayer Tablets for the Treatment of Tuberculosis. Journal of Pharmaceutical Research International. 2014;4(14):1781–801.
2. Sanz-Ruiz P, Carbó-Laso E, Del Real-Romero JC, Arán-Ais F, Ballesteros-Iglesias Y, Paz-Jiménez E, et al. Microencapsulation of rifampicin: A technique to preserve the mechanical properties of bone cement. J Orthop Res. 2018;36(1):459–66.
3. Shrikhande S., Bajaj A, Pinto B. Rifampicin and Isoniazid Microcapsules for Treatment of Tuberculosis. Int J Pharm Sci Res. 2012;3(1):281–7.
4. Mwila C, Walker RB. Improved Stability of Rifampicin in the Presence of Gastric-Resistant Isoniazid Microspheres in Acidic Media. Pharmaceutics. 2020;12(3):234.
5. Junior ED, Almeida JMF, Silva IDN, Assis MLM, Santos LM, Dias EF, et al. pH-Responsive Release System of Isoniazid using Palygorskite as a Nanocarrier. Journal of Drug Delivery Science and Technology. 2020;55.
6. Bale S, Khurana A, Reddy ASS, Singh M, Godugu C. Overview on therapeutic applications of microparticulate drug delivery systems. Crit Rev Ther Drug Carrier Syst. 2016;33(4):309–61.
7. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. Sci Pharm. 2019;87(3).
8. Khode PD, Katre TB. Review of Micrencapsulation: A Review A Novel Approach in Drug Delivery. Res J Pharm Dos Forms Technol. 2019;11(3):191.–7.
9. Khan AA, Mudassir J, Mohtar N, Darwis Y. Advanced drug delivery to the lymphatic system: Lipid-based nanoformulations. Int J Nanomedicine. 2013;8:2733–44.
10. Debnath SK, Sarkar S, Janakiraman K, Chakraborty S. Formulation and evaluation of Microsphere of Aceclofenac. J Adv Pharmacol. 2020;1(1):65–70.
11. Belali NG, Chaerunisaa AY. Solvent Evaporation as an Efficient Microencapsulating Technique for Taste Masking in Fast Disintegrating Oral Tablets. Indones J Pharm. 2019;1(3).
12. Noviendri D. Microencapsulation Of Fucoxanthin By Water-In-Oil-In-Water (W / O / W) Double Emulsion Solvent Evaporation Method : A Review. 2014;9(3):137–50.
13. Noviza D, Harliana T, Rasyad A. Mikroenkapsulasi Metformin Hidroklorida dengan Penyalut Etilsellulosa Menggunakan Metoda Penguapan Pelarut. J Sains dan Teknol Farm. 2013;18:75–9.
14. Hanifah H. Mikroenkapsulasi Isoniazid dengan Penyalut HPMCP HP-50 Menggunakan Metode Penguapan Pelarut. Universitas Jenderal Achmad Yani; 2020.
15. Oktaviany AL. Mikroenkapsulasi Isoniazid dengan Penyalut HPMCP HP-55 Menggunakan Metode Penguapan Pelarut. Universitas Jenderal Achmad Yani; 2020.
16. Urbaniak T, Musiał W. Influence of solvent evaporation technique parameters on diameter of submicron lamivudine-poly-ε-caprolactone conjugate particles. Nanomaterials. 2019;9(9).
17. Maji R, Ray S, Das B, Nayak AK. Ethyl Cellulose Microparticles Containing

Metformin HCl by Emulsification-Solvent Evaporation Technique: Effect of Formulation Variables. ISRN Polym Sci. 2012;2012:1–7.
18. Mei Q, Luo P, Zuo Y, Li J, Zou Q, Li Y, et al. Formulation and in vitro characterization of rifampicin-loaded porous poly (ε-caprolactone) microspheres for sustained skeletal delivery. Drug Des Devel Ther. 2018;12:1533–44.
19. Gupta A, Dey B. Microencapsulation for controlled drug delivery: a comprehensive review. Sunsari Tech Coll J. 2013;1(1):48–54.
20. Kumar D, Thipparaboina R, Modi SR, Bansal AK, Shastri NR. Effect of HPMC concentration on crystal habit of nifedipine. CrystEngComm. 2015;17(7):1615-24.
21. Marzolini C, Gibbons S, van Oosterhout JJ, Khoo S. Drug-Drug Interaction Potential with Once-Weekly Isoniazid/Rifapentine (3HP) for the Treatment of Latent Tuberculosis Infection. Clin Pharmacokinet. 2022;61(3):339-346. doi: 10.1007/s40262-021-01098-8.
22. Mooranian A, Negrulj R, Chen-Tan N, Al-Sallami HS, Fang Z, Mukkur TK, et al. Microencapsulation as a novel delivery method for the potential antidiabetic drug, Probucol. Drug Des Devel Ther. 2014;8:1221–30.
23. Albadarin AB, Potter CB, Iqbal J, Korde S, Pagire S, Walker G. Development of Stability-Enhanced Ternary Solid Dispersions via Combinations of HPMCP and Soluplus® Processed by Hot Melt Extrusion. Int J Pharm. 2017;532(1):603-611.
24. Mohan B, Meshram S, Mishra A, Pathak A. Formulation and Evaluation of Microsphere of Rebiprazole Sodium. Int J Adv Pharm. 2016;5(76–83).