International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Special Issue 1, 2024

Original Article

MICROENCAPSULATION BISOPROLOL FUMARATE WITH EUDRAGIT E PO BY SOLVENT EVAPORATION METHOD

AZHOMA GUMALA[1], FEBRIYENTI[2*], FITHRIANI ARMIN[3], ZAHRAH YULINDRA[4]

[1,2,4]Pharmaceutics Department, Faculty of Pharmacy, Universitas Andalas, Padang, Indonesia. [3]Pharmaceutical Chemistry Department, Faculty of Pharmacy, Universitas Andalas, Padang, Indonesia
[*]Corresponding author: Febriyenti; [*]Email: febriyenti@phar.unand.ac.id

Received: 25 Sep 2023, Revised and Accepted: 23 Nov 2023

ABSTRACT

Objective: This study aimed to develop and optimize the microcapsule formula of bisoprolol fumarate-Eudragit EPO by double-emulsion solvent evaporation.

Methods: The preparation of bisoprolol fumarate-Eudragit EPO microcapsule was done in three different ratios 1: 3 (F1), 1: 4 (F2), and 1: 5 (F3), followed by characterization of each of the microcapsule formula using Fourier transform infrared, scanning electron microscopy, particle size analyzer. Further analysis included investigation of the drug loading, entrapment efficiency, solubility in pH 6.8, and the difference among dissolution profiles of each microcapsule using one-way ANOVA.

Results: Infra-red spectrum showed no chemical interaction between bisoprolol fumarate and Eudragit E PO in microcapsules. The morphology and structure of F1 microcapsule was irregular spheres, while F2 and F3 were regular spheres. The average particle distribution of microcapsules was 24.765±0,236 µm (F1), 28.245±0,252 µm (F2), and 40.634±0,218 µm (F3). The drug loading was 7.691±0,087 % (F1), 8.922±0,056 % (F2), and 9.012±0,133% (F3). The encapsulation efficiency was 4.980 % (F1), 5.857%(F2), and 6,285 %(F3). The average amount of bisoprolol fumarate released in pH 6.8 was 2.113±0,289 % (F1), 1.954±0,015 % (F2), and 1.619±0,020 % (F3). The dissolution profile between each formula was statistically different (p value= 0,000).

Conclusion: As the low value of drug loading and encapsulation efficiency in each formula, we concluded that the microencapsulation formula with Eudragit EPO by solvent evaporation method is not effective to entrap bisoprolol fumarate.

Keywords: Bisoprolol fumarate, Eudragit E PO, Microencapsulation, Solvent evaporation

DOI: https://dx.doi.org/10.22159/ijap.2024.v16s1.19 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Bisoprolol fumarate is a β1-adrenergic receptor blockers antihypertensive that is commonly used in the treatment of hypertension, angina, arrhythmias, and myocardial infarction [1]. This drug reduces blood pressure and heart rate in angina pectoris patients with a history of heart disease [2]. To assure the dosage accuracy in patient, compliance was necessary while taking this drug [1]. However, bisoprolol fumarate is strongly bitter. In tablet dosage form, bisoprolol fumarate was reported to have an unfavorable taste so it affects patient adherences, especially children or adult population [3, 4].

The microencapsulation technique can be used to disguise the bitter taste of the active pharmaceutical substances in dosage forms, preserve the stability of the formulation and control the delivery of the active substance. There were some therapeutic agents such as pactitaxel and insulin, microencapsulated as a promising strategy of drug delivery systems to overcome multiple challenges in drug administration. This technique can shelter the active pharmaceutical ingredients, allowing a possibility of controlled and sustained release of compounds, mask the unpleasant taste of drugs, thus increase their palatability and improving patient compliance. The ability to protect active substances, controlled drug release, and improvement in bioavailability were some advantages of microcapsule formula.

There are several methods that can be used to produce microcapsule. Emulsion solvent evaporation and phase separation are two main processes used to prepare microcapsules. The solvent evaporation procedure is an aqueous system process, while the phase separation procedure is a nonaqueous process. It follows that the solvent evaporation method is suitable for water-insoluble drugs, whereas the phase separation method is preferable for water-soluble drugs. Other methods, such as spray drying, are also used to microencapsulate solvent evaporation emulsification method. This method is simple, cheap, time-saving, and applicable to hydrophilic or hydrophobic substances [5, 6].

Various reviews highlighted the importance of polymer used in microcapsules formula. Encapsulation will prevent the release of the active substance in the oral cavity because it is not degraded by saliva but dissolves completely in gastric juice so it does not affect absorption in the gastrointestinal tract [6]. An efficient formulation developed to allows the active substances reach the target site in the required time and for the desired time. The microcapsule formulation for drug delivery must be biocompatible, stable, safe and demonstrate predictable degradation kinetics. The amount of polymer used affects the encapsulation efficiency of the active substance, as well as the surface shape and structure of the microcapsule. Eudragit EPO is a polymer that is suitable for microencapsulation. This polymer reported was successfully disguising the taste of sildenafil citrate. The greater the ratio of polymers used, the better the ability to disguise the bitter taste of the active substance and the better the morphology and structure of the microcapsule [7].

In this study, we developed formulas of microcapsule in three different ratios between bisoprolol fumarate and Eudragit EPO by solvent evaporation method. The properties of microcapsule were characterized using FTIR, SEM, and were investigated for entrapment efficiency, solubility, and dissolution profile.

MATERIALS AND METHODS

Materials

Bisoprolol fumarate (Mehta API Pvt. Ltd, India), Eudragit EPO (Evonik Nutrition and Care GmbH, Germany), dichloromethane (Merck, Germany), acetonitrile (Merck, Germany), polyvinyl alcohol, distilled water, sodium chloride, hydrogen chloride.

Methods

Preparation of microcapsules

Bisoprolol fumarate-Eudragit EPO microcapsule was prepared in three different ratios 1: 3 (F1), 1: 4 (F2), and 1: 5 (F3). Microcapsules

were prepared by double emulsification. Bisoprolol fumarate is dissolved in distilled water meanwhile Eudragit EPO was dissolved in dichloromethane. Both solutions were mixed and homogenized to produce a water-in-oil (w/o) emulsion. The water-in-oil emulsion (w/o) was dispersed slowly into the polyvinyl alcohol solution. The process of forming microcapsules begins with the separation of the emulsion in medium and form the small grains accompanied by the slow evaporation of the dichloromethane. When the stirring is stopped, the granules will drop to the bottom of the container. The microcapsules formed were washed with distilled water and enclosed in desiccator.

Biosprolol fumarate-eudragit EPO microcapsule characterization

Morphology studies

The morphology and shape of the microcapsules was evaluated using scanning electron microscopy (SEM). The sample was placed in the sample holder and coated with gold particles using a fine coater. The morphology and structure were examined at a voltage of 20 kV. We used 100 and 500 x magnification.

FT IR analysis

The sample to be tested is placed on the ATR crystal so that it covers the entire surface of the crystal. Then, the sample was covered by applying a little pressure and the absorption spectrum for each sample was taken at wave numbers 4000-500 cm^{-1}.

Mean particle size and size distribution analysis

The particle size distribution was evaluated using a particle size analyzer (Shimadzu SALD-2300, Japan). The sample was dispersed in distilled water and the particle size distribution was recorded as volume percent in the size range from 0.01 to 2000 µm.

Drug loading amount and encapsulation efficiency

The microcapsule samples equivalent to 10 mg of bisoprolol fumarate weighed, dissolved in distilled water: acetonitrile (65:35 v/v) and filtered. The filtrate was diluted up to 10 ml with distilled water and the absorption measured at the maximum wavelength of bisoprolol fumarate (223 nm). The concentration of bisoprolol fumarate in microcapsules was calculated using linear regression from calibration curve [8].

The encapsulation efficiency calculated using the formula:

% Encapsulation efficiency = "drug level"/"theoretical drug level" x 100 %

Drug solubility in pH 6.8

This test is carried out to ensure that the microcapsules formed are completely coated with the polymer so that there are no gaps for the active substance to be released and dissolve in the saliva. The medium was prepared by dissolving sodium chloride in 100 ml distilled water and the pH of the solution was adjusted to 6.8 using hydrochloric acid. Microcapsules were weighed equivalent to the 2.5 mg bisoprolol fumarate, and the medium was added and filtered. The absorbance of the bisoprolol fumarate was determine using spectrophotometer uv-visible (Shimadzu UV-1280, Japan) and the concentration of bisoprolol fumarate in medium was calculated using linear regression from calibration curve.

Dissolution profile

The dissolution test was carried out using type 2 dissolution method (paddle) in 900 ml water with hydrochloric acid addition to obtain pH=1.2 at 75 rpm for 45 min. The temperature was maintained at 37±0.5 °C. The amount of drug dissolved was determined at given interval using a spectrophotometer UV-visible (Shimadzu UV-1280, Japan). Within 20 min bisoprolol fumarate must not dissolve less than 80%. The dissolution profiles of drug released between formulas was analyzed by one-way ANOVA.

RESULTS

The SEM evaluation showed that the surface of the F1 microcapsule looks rough and has many indentations or holes Meanwhile, the F2 and F3 microcapsules showed a regular round shape but the surface still looked rough and there were many indentations or holes (fig. 1).

The particle size, drug loading, encapsulation efficiency, drug solubility in pH 6.8 and the drug dissolution after 20 min were shown in table 1.

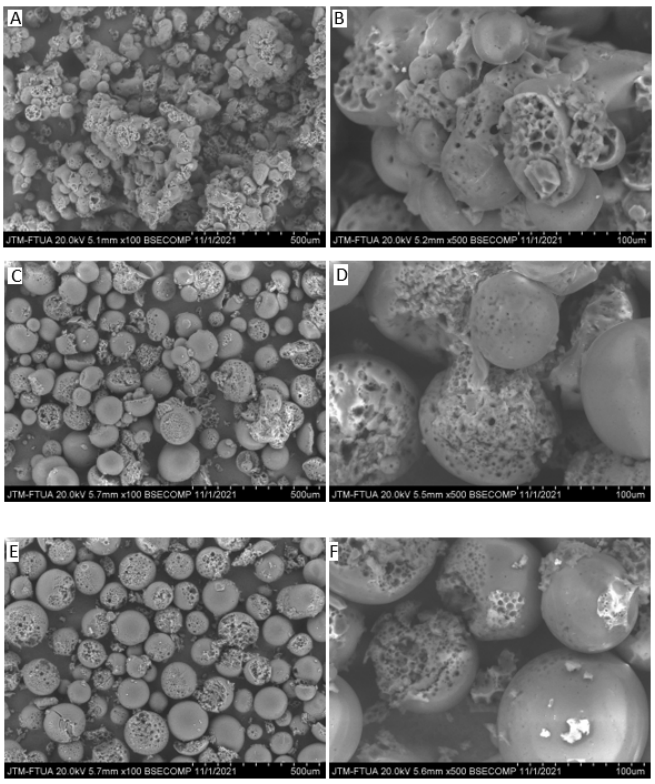

Fig. 1: Image of bisoprolol fumarate-Eudragit EPO microcapsule from SEM of F1 with magnifying 100 x (A) and magnifying 500 x (B), F2 magnifying 100 x (C) and magnifying 500 x (D), F3 magnifying 100 x (E) and magnifying 500 x (F)

Table 1: Particle size, drug loading, encapsulation efficiency, solubility in pH 6.8 and drug release in 20 min

Parameter	F1	F2	F3
Particle Size (µm)	24.8±0.2	28.2±0.3	40.6±0.2
Drug Loading (%)	7.7±0.1	8.9±0.1	9.0±0.1
Encapsulation Efficiency (%)	5	5.9	6.3
Drug Solubility in pH 6.8 (%)	2.1±0.29	1.9±0.01	1.6±0.02
Drug Released in 20 min/Q20 (%)	92.7±1.2	90.19±0.8	83.60±1.3

Data is expressed as mean±SD of triplicate sampling

Fourier transform infrared spectroscopy (FTIR) was conducted to determine whether there was any interaction between Bisoprolol Fumarate and Eudragit EPO. The results shown no indication of new group formation (fig. 2).

Measurements of 0.001% (w/v) Bisoprolol Fumarate in dissolution medium by UV Spectrophotometer shown maximum wavelength at 222.4 nm. The equation for the linear plot was y = 0,0374x+0,0216 with a correlation coefficient 0,999. This concentration of bisoprolol fumarate was calculated from the sample UV absorption at 222.4 nm and the dissolution profile was shown in fig. 3.

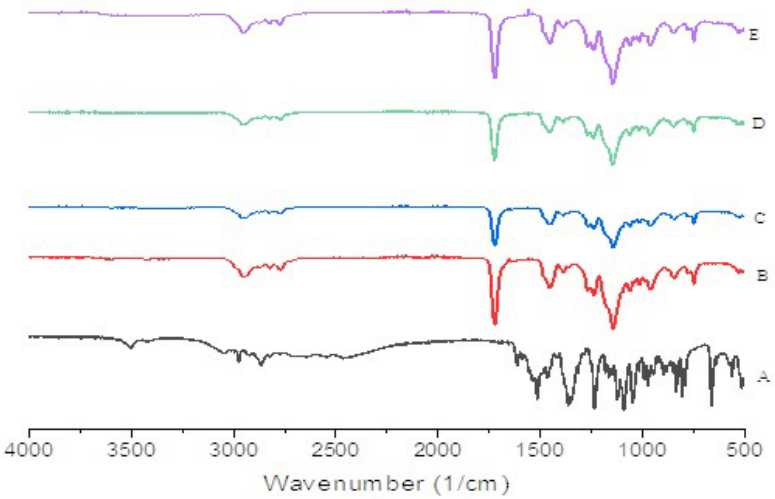

Fig. 2: FTIR spectrum of bisoprolol fumarate (A), Eudragit EPO (B), Bisoprolol fumarate-Eudragit EPO F1 microcapsule (C), Bisoprolol fumarate-Eudragit EPO F2 microcapsule (D), Bisoprolol fumarate-Eudragit EPO F3 microcapsule (E)

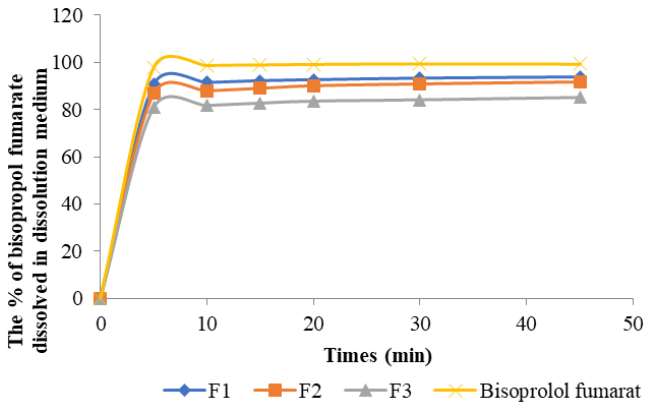

Fig. 3: Dissolution profile bisoprolol fumarate-eudragit EPO F2 microcapsule

The results of the dissolution test profiles of the F1, F2, and F3 microcapsules were statistically processed using one-way ANOVA with p value = 0.000 (<0.05). This value indicates the average percent dissolution between F1, F2, and F3 was significantly different.

DISCUSSION

The microcapsule weighing results obtained showed that the microcapsule weight produced by the three formulas was reduced from the actual weight so that the recovery did not reach 100%. This can be caused by an incomplete coating process where some of the active substance is outside the microcapsule and carried along with the washer. In addition, there is also the possibility that the size of the microcapsule particles produced is too small so that they are carried away during the filtering and washing process [9].

The variation of particle sizes of the three formulas met the recommended particles that ranged from 5-5,000 µm [10]. The average microcapsule particle size in each formula will increase with the greater concentration of polymer used. Increasing polymer concentration will significantly increase the solution viscosity, thereby reducing the homogenization process by stirring. The faster

the stirring, the smaller the resulting droplet size, and vice versa [11].

SEM images shown microcapsule particles can be seen stacked and attached to one another. This can be caused by polyvinyl alcohol which has not been completely carried away by the washer, causing the microcapsule particles to stick to one another and harden upon drying. However, the original shape of the F1 particle can still be seen, which was spherical. The surface of the F1 microcapsule looks rough and has many indentations or holes. Meanwhile the microcapsules F2 and F3 showed a regular round shape but the surface still looked rough and there were many indentations or holes. This indicates that in this variation of the formula Bisoprolol-Eudragit EPO produced spherical and regular shaped particles, but the morphology of the surface of the microcapsule particles is not covered smoothly by Eudragit EPO [5, 12].

Fourier transform infrared spectroscopy (FTIR) was conducted to determine whether there was any interaction between bisoprolol fumarate and Eudragit EPO in the formulation of conjugates. Bisoprolol fumarate showed an absorption band of C=O stretching at 1100-1500 cm-1, C=C stretching of aromatic ring 1400-1600 cm-1. The FTIR spectrum confirmed there was no interference between individual components, FTIR spectrum between three formulas were identical that we attributed to Eudragit EPO spectrum.

The microcapsule drug loading in three formula requirements in compendia should fall between 90-105% and the three formulas did not meet this requirement. The three formulas also show small encapsulation efficiency (below 60 %). Incomplete coating may promote the release of bisoprolol fumarate into the external medium and carried the substances during washing process. F1 microcapsules showed the smallest drug loading and encapsulation efficiency of the active substance while F3 showed the greatest drug loading and encapsulation efficiency. The less amount of polymer used, the less bisoprolol fumarate that can be entrapped in microcapsules. Vice versa, the greater amount of Eudragit EPO would contribute to larger encapsulation efficiency. The process itself could also contribute to this low value of drug loading and encapsulation efficiency. The low boiling point of dichloromethane (40 °C) allows this solvent to evaporate quickly during stirring, but this is not accompanied by the speed of coating the active substance so that the remaining uncoated substance remains in the external phase of the emulsion and carried out during washing process [12]. Of the 400 mg of bisoprolol fumarate used in the microcapsule formulation, 355-3605 mg were detected in the external phase and washing water mixture.

The solubility test of the microcapsules in pH 6.8 (equivalent to saliva acidity) shows that there was bisoprolol fumarate released from the microcapsule. Assuming that the bisoprolol fumarate was not completely encapsulated by Eudragit EPO, the microcapsule was going to taste bitter due to its contact with saliva. There should be no active substance dissolved in the saliva if Eudragit EPO completely entrapped bisoprolol fumarate in microcapsule because Eudragit EPO is resistant to saliva [12].

Dissolution testing was carried out in medium pH 1.2 because microcapsule was expected to release bisoprolol fumarate in the stomach. The higher Eudragit EPO concentration in formula, the longer it takes to release Bisoprolol Fumarate in the formula as the percentage. The F1, F2, and F3 experienced a slowdown in the release of the active substance along with the increasing concentration of the polymer used. The more Eudragit EPO used, the thicker the microcapsule wall will be, so that it takes longer to disintegrate and release the active substance [13].

The results of the dissolution test profiles of the F1, F2, and F3 microcapsules were statistically processed using one-way ANOVA. With p value 0.05, indicates that the average percent dissolution between F1, F2, and F3 was significantly different. Microcapsules with the smallest amount of polymer (F1) showed a greater % dissolution than those with a larger amount of polymer (F3). However, formula with greater percentage of dissolution has the smaller amount of encapsulation efficiency, whereas among those formula were subpar below the dissolution specification (<90%) and ideal encapsulation efficiency (<45%).

The poor entrapment of the active compound and other characteristics of bisoprolol microcapsule can be affected by many parameters: properties of materials, formulation parameters and operating conditions. The main properties affected are microparticles mean size, particle size distributions, surface morphology and product yield. The poor entrapment efficiency in this formula can be caused because the coating is not able to completely shelter the active substance. There was also the possibility that the active substances carried away with the washing and the particle size of the microcapsules produced is too small so that they are carried away during the filtering and washing process. Particle size increases linear with the amount of eudragit EPO. Similar patterns were also shown with drug loading. Increasing amount of eudragit PO also increases the drug loading and thus leads to larger encapsulation efficiency. However, the drug solubility and dissolution are going to decrease with the increasing amount of polymer used in formula. Like other microcapsule formulation, it was found that the drug release rates of the microcapsules were significantly increased with adding of polymer, which explained by increasing hydrophilic groups [14, 15].

CONCLUSION

Formulation of bisoprolol fumarate-Eudragit EPO microcapsule in three different ratios 1: 3 (F1), 1: 4 (F2), and 1: 5 (F3) by solvent evaporation method (w/o) produced low drug loading and encapsulation efficiency. The drug entrapped in microcapsule also released in undesirable pH (6.8). We conclude that the microencapsulation formula with Eudragit EPO by solvent evaporation method is not effective to entrap bisoprolol fumarate, while commercially available bisoprolol tablet might overcome the hurdle.

ACKNOWLEDGEMENT

This article received no specific grant from any funding agency in the public, commercial or not-for-profit sectors There is no conflict of interest associated with this work. We declare that this work was done by the authors named in this article, with all authors approved this manuscript to be published, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Telrandhe R. Formulation and evaluation of oral fast dissolving film of bisoprolol fumarate formulation and evaluation of oral fast dissolving film of bisoprolol fumarate. J Pharm Investig. 2018;6(2):105-15.
2. Charoo NA, Shamsher AAA, Lian LY, Abrahamsson B, Cristofoletti R, Groot DW. Biowaiver monograph for immediate-release solid oral dosage forms: bisoprolol fumarate. J Pharm Sci. 2014;103(2):378-91. doi: 10.1002/jps.23817, PMID 24382794.
3. Panainte AD, Gafitanu C, Stoleriu I, Tartau LM, Popescu M, Lisa G. New modified release tablets of bisoprolol fumarate for the treatment of hypertension: characterization and *in vitro* evaluation. J Drug Deliv Sci Technol. 2019;50:402-9. doi: 10.1016/j.jddst.2018.11.011.
4. Sudhamani. Development of fast dissolving tablets of bisoprolol fumarate and statistical optimization. Erode College of Pharmacy and Research Institute; 2012.
5. Chiappetta DA, Carcaboso AM, Bregni C, Rubio M, Bramuglia G, Sosnik A. Indinavir-loaded pH-sensitive microparticles for taste

masking: toward extemporaneous pediatric anti-HIV/AIDS liquid formulations with improved patient compliance. AAPS PharmSciTech. 2009;10(1):1-6. doi: 10.1208/s12249-008-9168-z.

6. Sandile MK, Natalie P, Tsitsi N, Hendrina H, Roderick BW. The evaluation of eudragit microcapsules using USP apparatus 1. Diss Technol. 2009;5:15-22.
7. Yi EJ, Kim JY, Rhee YS, Kim SH, Lee HJ, Park CW. Preparation of sildenafil citrate microcapsules and *in vitro*/*in vivo* evaluation of taste masking efficiency. Int J Pharm. 2014;466(1-2):286-95. doi: 10.1016/j.ijpharm.2014.03.001, PMID 24607218.
8. Shahinaz AM, Mohammed EA, Shaza WS. Development and validation of uv spectrophotometric method for determination of bisoprolol fumarate in bulk and pharmaceutical dosage forms. Mediterranean Journal of Chemistry. 2017;6(5):196-9.
9. Rizky F. Mikroenkapsulasi lansoprazole dengan penyalut Eudragit rs po menggunakan metode emulsifikasi penguapan pelarut. Univeritas Andalas. 2016.
10. Leon L, Herbert AL, Joseph LK. The theory and practice of pharmaceutical industry. 3rd ed. Lea & Febiger; 1987. p. 412-6.
11. Sahoo SK, Mallick AA, Barik BB, Senapati PC. Formulation and *in vitro* evaluation of eudragit® microspheres of stavudine. Trop J Pharm Res 2005;4(1):369-75. doi: 10.4314/tjpr.v4i1.14622.
12. Bogataj M, Mrhar A, Kristl A, Kozjek F. Preparation and evaluation of eudragit e microspheres containing bacampicillin. Drug Dev Ind Pharm. 1989;15(14-16):2295-313. doi: 10.3109/03639048909052532.
13. Georgieva YG, Kassarova MK, Kokova VK, Apostolova EA, Pilicheva BP. Taste masking of enalapril maleate by microencapsulation in Eudragit EPO® microparticles. Pharmazie. 2020;75(2):61-9. doi: 10.1691/ph.2020.9123, PMID 32213236.
14. Ruan G, Feng SS. Preparation and characterization of poly(lactic acid)–poly(ethylene glycol)–poly(lactic acid) (PLA–PEG–PLA) microspheres for controlled release of paclitaxel. Biomaterials. 2003;24(27):5037-44. doi: 10.1016/s0142-9612(03)00419-8, PMID 14559017.
15. Park SJ, Kim SH. Preparation and characterization of biodegradable poly(l-lactide)/poly(ethylene glycol) microcapsules containing erythromycin by emulsion solvent evaporation technique. J Colloid Interface Sci. 2004;271(2):336-41. doi: 10.1016/j.jcis.2003.08.067, PMID 14972610.