INTERNATIONAL CONFERENCE ON PHARMACEUTICAL RESEARCH AND PRACTICE
ISBN: 978-979-98417-5-9 | Universitas Islam Indonesia

Preparation And Characterization Hollow Microsphere Diclofenac Sodium

Bagus Tri Laksono, Arini Fitria Zain, Adquinta Wulandini Putri, Fitria Mayangsari, Tuhfatul Ulya, Zarin Ilafah, Lusia Oktora Ruma Kumala Sari and Eka Deddy Irawan*

Faculty of Pharmacy, University of Jember, Jember, Indonesia

Abstract. Diclofenac Sodium was a non-steroidal anti-inflammatory drug that widely used in the treatment of osteoarthritis. However, Diclofenac Sodium has low bioavailability, short half-life and side effects on the gastrointestinal. Thus a controlled release drug was prepared with a multiple unit drug delivery system to increase the effectiveness of the drug and overcome the shortages of the Diclofenac Sodium. The amount of Ethyl Cellulose, HPMC, Ethanol, Polyvinyl Alcohol (PVA), temperature, speed and duration of stirring effect on particle characteristics, drug release rate and entrapment efficiency. This study was aimed to determine the preparation of hollow microspheres Diclofenac Sodium which produces the highest EE value. The best hollow microsphere preparation was found in formula 5 with the highest EE value of 84.568 ± 0.363.

Keywords: Diclofenac Sodium, Hollow microsphere, HPMC, EC, Entrapment efficiency

1. Introduction

Diclofenac Sodium was a nonsteroidal anti-inflammatory (NSAID) that widely used in the treatment of osteoarthritis [1]. Diclofenac Sodium 99% bounded in plasma proteins and has a low enough bioavailability of 55% [2] with a short half-life of 1-3 hours [3]. The recommended daily dose as much 75-150 mg administered 3 to 4 times so it can cause fluctuations in the blood that will enlarge the side effects of Diclofenac Sodium[4]. Side effects of Diclofenac Sodium on gastrointestinal were an epigastric pain, nausea, vomiting, diarrhea, gastric irritation, and peptic ulcer[3]. Diclofenac Sodium classified into Class II Biopharmaceutics Classification System (BCS) which activated ingredient with low solubility [5], so to overcome these problems and weaknesses can be made oral preparations in the form of a controlled release dosage form, such as drug delivery system multiple units of hollow microsphere.

Preparation on Hollow microsphere Diclofenac Sodium using emulsion solvent evaporation method of oil in water (o / w) by using hydroxypropyl methylcellulose (HPMC) as a hydrophilic polymer and Ethyl Cellulose (EC) as a hydrophobic polymer[6]. HPMC was a gelling agent capable of controlling the rate of drug release [7] while EC used as a matrix to extend drug release [8]. The solvent used a mixture of solvents between Dichloromethane and Ethanol which nonpolar. The emulsifier used polyvinyl alcohol (PVA).

Many factors that influence the entrapment efficiency of hollow microspheres include polymer ratio, solvent ratio, speed and stirring time [9]. While the emulsifier concentration and the temperature of the dispersing medium may affect the particle size, yield, and buoyancy [10-12].

*Corresponding author: bagus.tri221096@gmail.com

2. Methodology

This research used the emulsion solvent evaporation method. The materials used Diclofenac Sodium (Cheng Fong Chemical Co. Ltd., Taiwan) as active ingredient, Ethyl Cellulose (PT Phapros, Tbk Indonesia) and HPMC (PT Phapros Tbk, Indonesia) as polymers, Ethanol (PT Bratachem, Indonesia) and Dichloromethane (PT Bratachem, Indonesia) as a solvent, Polyvinyl Alcohol (PT Bratachem, Indonesia) as emulsifier and distilled water (PT Bratachem, Indonesia).

Table 1. Preparation of the Hollow Microsphere Diclofenac Sodium

F	DS (g)	EC (g)	HPMC (g)	E (ml)	D (ml)	PVA (g)	Stirring, Temperature
1	0.5	0.4	0.2	5	5	0.75	500 rpm, 30' , 40 °C
2	0.5	0.4	0.6	5	5	0.75	500 rpm, 30' , 40 °C
3	0.5	0.8	0.2	5	5	0.75	500 rpm, 30' , 40 °C
4	0.5	0.8	0.6	5	5	0.75	500 rpm, 30' , 40 °C
5	0.5	0.8	0.2	5	5	0.5	500 rpm, 30' , 40 °C
6	0.5	0.8	0.2	10	5	0.5	500 rpm, 30' , 40 °C
7	0.5	0.8	0.2	5	5	0.75	500 rpm, 30' , 40 °C
8	0.5	0.8	0.2	10	5	0.75	500 rpm, 30' , 40 °C
9	0.5	0.8	0.2	5	5	0.75	500 rpm, 30' ,30°C
10	0.5	0.8	0.2	5	5	1	500 rpm, 30' ,30 °C
11	0.5	0.8	0.2	5	5	0.75	500 rpm, 30' ,40 °C
12	0.5	0.8	0.2	5	5	1	500 rpm, 30' ,40 °C
13	0.5	0.8	0.2	5	5	0.75	300 rpm, 30' , 40 °C
14	0.5	0.8	0.2	5	5	0.75	500 rpm, 30' , 40 °C
15	0.5	0.8	0.2	5	5	0.75	300 rpm, 60' , 40 °C
16	0.5	0.8	0.2	5	5	0.75	500 rpm, 60' , 40 °C

Hollow microspheres Diclofenac Sodium prepared according to the formulation (F) in Table 1 by dissolving Diclofenac Sodium (DS), HPMC, and EC into a solvents mixture of ethanol (E) and dichloromethane (D). Then the solution mixture dropped into an aqueous phase containing PVA. The stirring process carried out with four-bladed propellers *(IKA Labortechnik, Germany)* with speed, time, and temperature according to Table 1. Hollow microspheres formed filtered with a vacuum filter equipped with Whatmann no filter paper. 1 and the result was washed with distilled water three times. Then the hollow microspheres dried in an oven *(Memmert, Germany)* at a temperature of 40 ° C until a constant weight obtained. Furthermore, the hollow microspheres of Diclofenac Sodium weighed with a weight equivalent to 50 mg of Diclofenac Sodium, then mashed in a mortar and dispersed with a phosphate buffer solution of pH 7.2 as much as 100 ml, then filtered and the filtrate was diluted 25 times using a phosphate buffer solution of pH 7.2. Previously the standard curve was prepared at the maximum wavelength of Sodium Diclofenac at 276 nm. The standard curve was prepared in a concentration range of 10, 15, 20, 25, 30 ppm. Then the results of this dilution were analyzing use a UV Vis spectrophotometer *(Genesys 10S, Thermo Scientific, USA)* and compared with the standard curve to determine the concentration of the drug which was further incorporated in Equation 1. In this study observed the value of EE (Entrapment efficiency) and determined the four formula that has the highest EE value.

$$\%EE = \frac{\text{the actual concentration of the drug}}{\text{concentrations og theoretical drugs}} \text{ x } 100\% \quad (1)$$

Four formulas with the highest EE values were chosen to determine buoyancy value and yield value. the process of buoyancy test by weighed hollow microspheres containing a drug 100 mg of diclofenac sodium. then put into a glass beaker containing 300 ml of 0.1 N HCl pH 1.2 and containing Tween 80 (2%) at a temperature of 37ºC. then stirred with a stirring speed of 100 rpm for ± 6 hours. hollow microspheres that float is dried in an oven at 40 ° C until the weight is constant and then weighed, Then calculated with the following equation according to equations 2. If the yield determination by comparing the actual weight of hollow microspheres with a theoretical weight of hollow microspheres. The weight of theoretical hollow microspheres is obtained from the sum of the weight of the active material and the weight of the polymer used [25]. The obtained hollow microspheres were dried in an oven at a temperature of 40 ° C to obtain the true constant weight of the hollow microspheres[26]. yield calculation was calculated following the equation 3.

$$buoyancy = \frac{\text{floating microspheres weight (Wf)}}{\text{total weight of microspheres (Wf + Ws)}} \text{ x } 100\% \quad (2)$$

$$yield = \frac{\text{actual microspheres weight (mg)}}{\text{theoretical microspheres weight (mg)}} \text{ x } 100\% \quad (3)$$

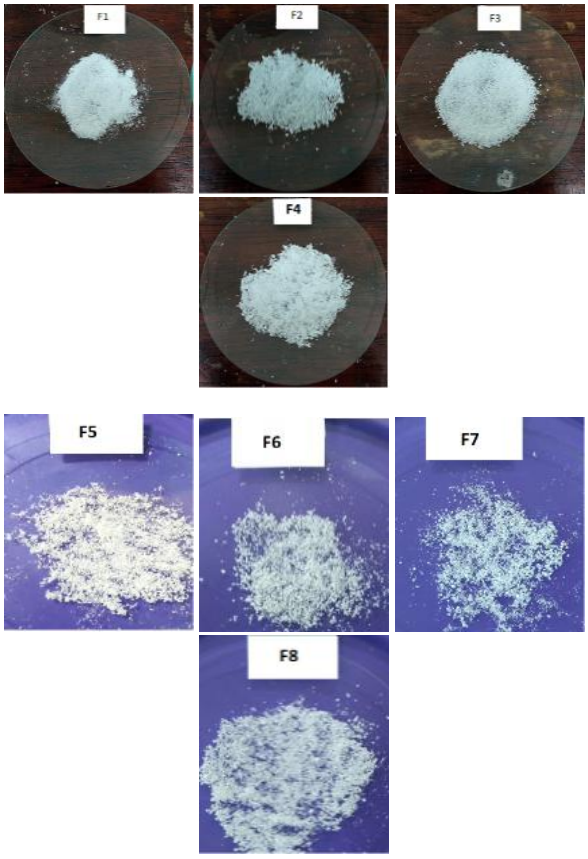
The morphology, shape, and size of the particles was analyzed using scanning electron microscope / SEM (*TM 3000 Hitachi*) with an 800 times magnification, A

*Corresponding author: bagus.tri221096@gmail.com

number of hollow microspheres were placed scattered on the glass tube and then it was placed in a Scanning Electron Microscope Chamber with a pressure chamber of 0.1 mmHg and a voltage of 20 kV. The character of its complex formation was analyzed using Fourier transform infrared / FTIR *(Genesys 10s)* with a resolution of 2 cm^{-1} and a scanning range of 400 - 4000 cm^{-1}, and compared with the results of pure diclofenac sodium.

3. Results

From the manufacture of Hollow microspheres, each formula showed similar results, which was a coarse white powder (Figure 1). Based on the results of the EE test in Table 2, there were four formulas with the highest value that was F3, F5, F11, and F14. From the four formulas determined buoyancy values, yield value (Table 3), particle shape and morphology analysis with SEM, and FTIR analysis



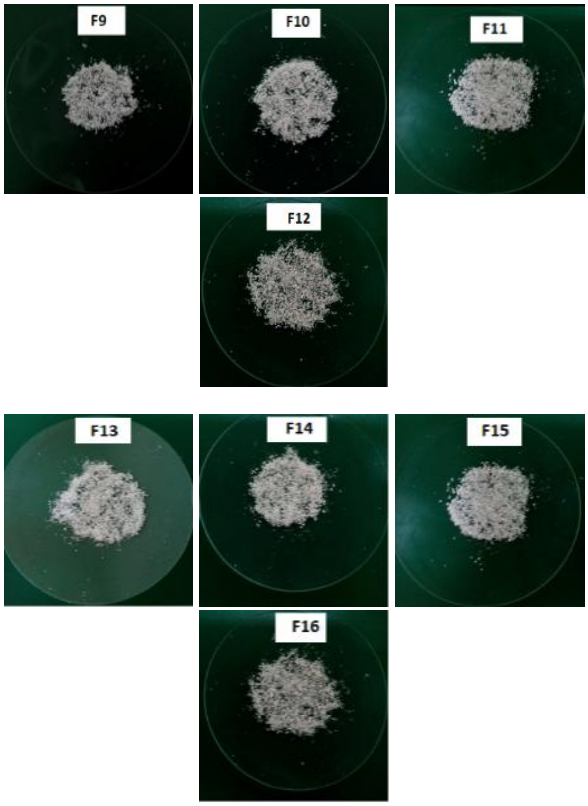


Fig. 1. Results of making hollow microspheres Diclofenac Sodium

Table 2. Entrapment Efficiency (EE) test results

Formula	EE (%)	Formula	EE (%)
1	43.34 ± 0.266	9	60.916 ± 4.955
2	74.61 ± 1.200	10	52.550 ± 4.419
3	80.48 ± 0.397	11	81.910 ± 4.300
4	69.62 ± 0.312	12	65.100 ± 5.341
5	84.568 ± 0.363	13	73.69 ± 0.648
6	74.979 ± 0.461	14	81.09 ± 0.475
7	65.543 ± 0.348	15	49.82 ± 0.269
8	57.918 ± 0.324	16	65.33 ± 2.449

*Corresponding author: bagus.tri221096@gmail.com

Table 3. Buoyancy and yield values

Formula	*Buoyancy* Value (%)	*Yield* Value (%)
3	86.713 ± 0.607	82.907 ± 3.042
5	86.833 ± 0.602	83.439 ± 1.040
11	85.475 ± 1.103	85.776 ± 0.554
14	85.092 ± 1.564	83.082 ± 1.462

The appearance of the shape and morphology of the hollow microsphere Diclofenac Sodium which observed using SEM of the four selected formulas (Figure 2) using 800 times magnification shows the hollow microsphere has a form near the spherical (spherical) hollow on the inside and has a relatively uneven surface morphology. The result of FTIR analysis of the hollow microspheres of Diclofenac Sodium has shown in Figure 3, from the spectra has known to have a typical peak similarity with pure Diclofenac Sodium (Table 4).

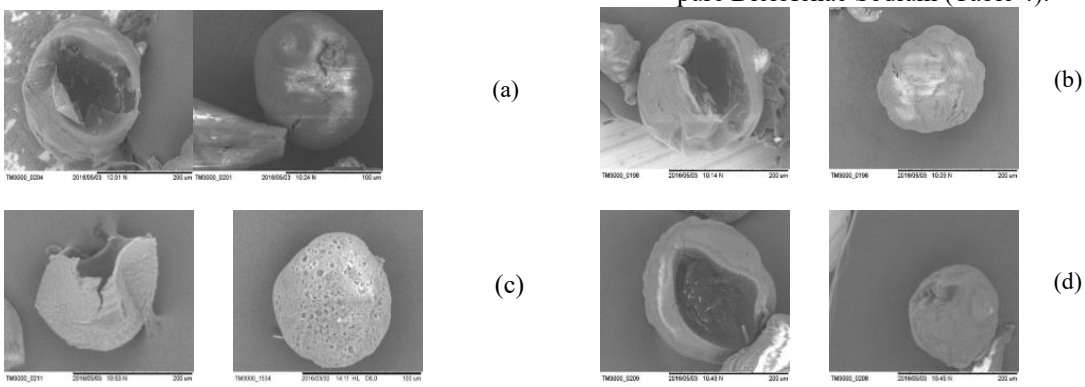


Fig. 2. Results of hollow microspheres analysis using SEM. (a) Formula 3, (b) Formula 5, (c) Formula 11, (d) Formula 14

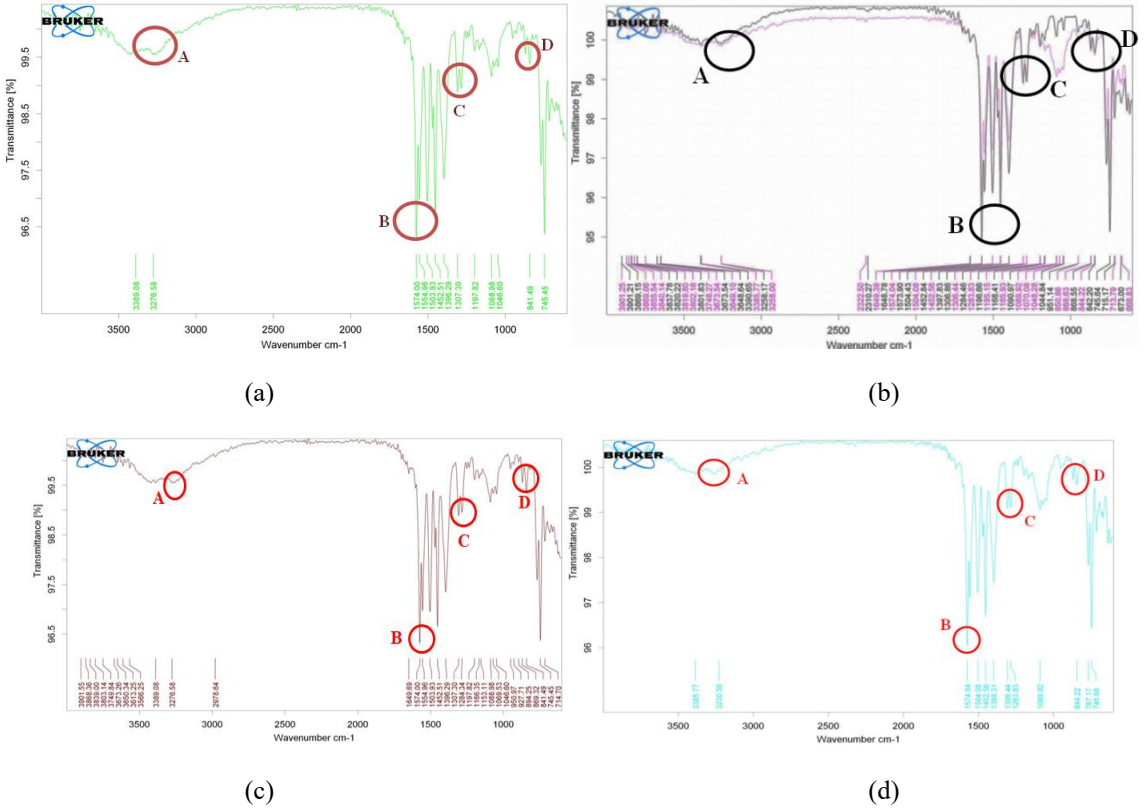


Fig. 3. FTIR spectra hollow microspheres Diclofenac Sodium. (a) Formula 3, (b) Formula 5, (c) Formula 11, (d) Formula 14

*Corresponding author: bagus.tri221096@gmail.com

Table 3. Peak range of FTIR analysis

Functional groups	Absorption Range (cm^{-1})	Formula 3 (cm^{-1})	Formula 5 (cm^{-1})	Formula 11 (cm^{-1})	Formula 14 (cm^{-1})
–NH	3600 – 3200	3276.58	3258.00	3276.58	3230.36
COO^-	1610 – 1550	1574.00	1574.04	1574.00	1574.04
C–N	1280 – 1350	1307.30	1306.44	1307.30	1306.44
C–Cl	850 – 550	841.49	844.22	841.49	844.22

4. Discussion

The success of microspheres preparation depends on the value of entrapment efficiency (EE), buoyancy and yield. If the value of EE produced was high then the amount of drug absorbed in microspheres particles was also high so the amount of drug to be released in the body was also large and can achieve the desired therapeutic effect [13,14]. The buoyancy values show the buoyancy capacity of the hollow microspheres system that has been prepared in the digestive tract [15]. While yield was a characterization of hollow microspheres that describes how efficiently the preparation method used to produce the maximum number of hollow microspheres, thus helping to determine the exact method of making hollow microspheres [16].

Based on the results of the research, the formula with the ratio of the number of EC used greater than HPMC was able to increase the value of EE, Buoyancy, and Yield. Because the EC can act as a floating enhancer that was hydrophobic [17], while EC was a water-soluble polymer that can easily trap Diclofenac Sodium. In addition, the EC was more dominant give the effect of floats compared to HPMC polymers [18,15].

While the solvent used ethanol and dichloromethane. The modified variables were ethanol, More ethanol that been used can produce droplets of small size so that the amount of drug absorbed less and the value of EE produced was small [19]. In addition, the time required for ethanol to diffuse in the aqueous phase longer, consequently, that the emulsion droplets formed stable and can prevent the droplet aggregation thus increasing the yield value [12]. while more dichloromethane solvents are used, high buoyancy will also be obtained because dichloromethane will form a larger cavity so that the density of the hollow microspheres will be smaller than the gastric fluid [20].

In this study also used Polyvinyl Alcohol as an emulsifier to be able to make hollow microspheres [10], the smallest concentration of polyvinyl alcohol will cause the formation of large particle size because it was not enough to reduce the surface charge of the particles. This causes the active ingredients were also trapped more and the amount of value EE was increasing. The large particle size will also increase the value of buoyancy[20,21]. Conversely, if the emulsifier concentration increased it can be caused a decrease in yield value[22].

The existence of the temperature difference used will also affect the value of EE, enhancement of the dispersion medium temperature to 40 ° C will increase the EE value. However, the high temperature will cause the hollow microspheres to become non-hollow and the microspheres shell to be thin [10]. This causes the hollow microspheres to easily disintegrate and become finer particles in order to decrease the value of EE [16], buoyancy [10,23] and yield [6].

In the emulsification process when used 500 rpm stirring speed and longer stirring time can decrease particle size [24]. The small particle size will increase the area of the surface area so that the diffusion of the drug from microspheres will be rapid and cause the loss of the drug with the consequence of declining EE values [11]. Small particle size can also decrease the buoyancy value. The higher the stirring speed will cause the greater the value of yield obtained. it was because at low speeds, the polymer will easily form aggregates and some adhere around the stirrer blades so it can decreases that the yield value.

Based on the results of the test using SEM showed that the hollow microsphere Sodium Diclofenac has a particle size ranging from 108,667 µm ± 2,532 to 167 µm ± 2,646. This was in accordance with the microsphere size requirements of less than 200 µm [12].

In the FTIR analysis hollow microsphere Sodium Diclofenac showed no interaction between Diclofenac Sodium with changes in the amount or concentration of HPMC, EC, Ethanol, PVA, temperature, velocity and stirring time, this indicated by the appearance of four typical uptakes of N-H, COO-, C-N, and C-Cl at the hollow microsphere complex of Diclofenac Sodium.

*Corresponding author: bagus.tri221096@gmail.com

5. Conclusions

Based on several characterization results, it can be concluded that the best preparation of hollow microsphere Sodium diclofenac seen from EE value, buoyancy and yield was formula 5. The next research that needs to be developed the evaluation of bioavailability and drug release both in vitro and in vivo and the hollow microspheres of diclofenac systolic tested to ensure the quality of the preparation.

Reference

[1] V. Dhikav, S. Singh, S. Pande, A. Chawla, K.S. Anand, Non-Steroidal Drug-induced gastrointestinal toxicity: Mechanisms and management, *Journal Indian Acad Clin Med*, 4, 315-322 (2003)

[2] Aberg, Lacy, Amstrong, Goldman, Lance, Drug Information Handbook 22th edition, *Lexi-comp for the American Pharmacists Association*

[3] N. Yunarto, Optimasi Formula Tablet Salut Enterik Natrium Diklofenak dengan Bahan Penyalut Kollicoat 30 D, *Jurnal Kefarmasian Indonesia*, 4, 65-75 (2014)

[4] U.C. Oz, B. Devrim, A.Bozkir, K. Canefe, Development of reconstitutable suspensions containing Diclofenac Sodium-loaded microspheres for pediatric delivery, *Journal of Microencapsulation*, 32, 317-328 (2015)

[5] B. Chuasuwan, V. Binjesoh, J.E. Polli, H. Zhang, G.L. Amidon, H.E. Junginger, K.K. Midha, V.P. Shah, S. Stavchansky, J.B. Dressman, D.M. Barends, Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms : Diclofenac Sodium and Diclofenac Potassium, *Journal of Pharmaceutical Sciences*, 98, 1206-1219 (2009)

[6] K. Rajkumar, G.R. Sainath, S.P. Sowjanya, P. Anusha, A.S. Lavanya, E.R. Reddy, Floating Microspehere: A Novel Approach In Drug Delivery, *Journal of Drug Delivery Research*, 1 (2012)

[7] A. Siswanto, S.S. Soebagyo, Optimasi formula sediaan tablet lepas lambat teofilin dengan bahan matrik HPMC, Na CMC, dan xanthan gum, *Majalah Farmasi Indonesia*, 17, 143-148 (2006)

[8] V.S. Mastiholimath, P.M. Dandagi, A.P. Gadad, R. Mathews, A.R. Kulkarini, In vitro and in vivo evaluation of ranitidine hydrochloride ethyl cellulose floating microparticles, *Journal of Microencapsulation*, 5, 307-3014 (2008)

[9] A. Yadav, D.K. Jain, Formulation and characterization of sustained release floating microballoons of metformin hydrochloride, *Tropical Journal of Pharmaceutical Research*, 11, 561-568 (2012)

[10] G. Ekta, J. Rahul, J. Aviral, Preparation and characterization of gastro-retentive floating microballoons of acrycoat S-100 bearing carvediol, *Asian Journal of Pharmaceutics*, 9, 120-124 (2015)

[11] N.S. Gandhi, S.V. Shirolkar, M.G. Tawar, Development and evaluation of microballoons of pioglitazone hydrochloride using eudragit S-100, *International Journal of Pharmaceutical Sciences*, 3, 201-212 (2012)

[12] V. Ganesan, V.S.V.S.P.K. Kanth, Preparation and In-vitro Evaluation of Microballoon Drug Delivery System of Telmisartan, *Int J Pharm Sci Drug Res*, 5, 141-145 (2013)

[13] P.B. O'Donnell, J.W. McGinity, Preparation of microspheres by the solvent evaporation technique, *Adv Drug Deliv Rev*, 28, 25-42 (1997)

[14] N.N. Hire, D.V. Derle, Microsphere as drug carrier : a review, *Int J Adv Res*, 2, 901-913 (2014)

[15] N.S. Raut, S. Somvanshi, A.B. Jumde, H.M. Khandelwal, M.J. Umekar, N.R. Kotagale, Ethyl cellulose and hydroxypropyl methyl cellulose buoyant microspheres of metoprolol succinate: Influence of pH modifiers, *Int J Pharm Investig*, 3, 163-170 (2013)

[16] P.K. Perumandla, S. Priya, Formulation and in vitro evaluation of floating microspheres of Dextromethorphan hydrobromide, *Int J Pharm Pharm Sci*, 6, 206-210 (2014)

[17] G.C. Devi, K.P.R. Chowdary, Reclinical pharmacokinetic evaluation of Pioglitazone floating tablets formulated employing cross-linked starch-urea, *Int J Pharm Pharm Sci*, 4, 104-106 (2012)

[18] V.K. Pawar, S. Asthana, N. Misrha, M. Chaurasia, M.K. Chourasia, Chitosan coated hydroxypropyl methylcellulose-ethylcellulose shel based gastropretentive dual working system to improve the bioavailability of norfloxacin, *RSC Adv*, 3, 19144-19153 (2013)

[19] K. Patel, P.K. Jain, R. Baghel, P. Tagde, A. Patil, Preparation and in vitro evaluation of a microballoon delivery system for domperidone, *Der Pharm Lettre*, 3, 131-141 (2011)

[20] P. Bhardwaj, H. Chaurasia, D. Chaurasia, S.K. Prajapati, S. Singh, Formulation and in vitro evaluation of floating microballoons of

*Corresponding author: bagus.tri221096@gmail.com

Indomethacin, *Acta Pol Pharm – Drug Res*, 67, 291-298 (2010)

[21] B.P. Kumar, V.P. Raj, D. Datta, M.N. Babu, Formulation and evaluation of Metoprolol Tartarate floating microspheres, *World J Pharm Res*, 4, 1083-1093 (2014)

[22] G.B. Avanco, M.L. Bruschi, Preparation and characterization of ethylcellulose microparticles containing propolis, *Rev Cienc Farm Basica Apl*, 29, 129-135 (2008)

[23] Y. Sato, Y. Kawa shima, H. Takeuchi, H. Yamamoto, Physcochemical properties to determine the buoyancy of hollow microspheres, *Eur J Pharm Biopharm*, 55, 297-304 (2003)

[24] S.L. He, Z.H. Zhou, C. Peng, H.H. Huang, L.J. Xiang, D.F. Cao, H. Zhou, J. Chen, B.L. Ou, Q.Q. Liu, W.N. Zeng, L.H. Liu, Morphology and size control of gelatin/hyaluronic acid composite microsphere for drug delivery, *Material Technology* (2016)

[25] A.V. Pande, P.D. Vaidya, A. Arora, M.V. Dhoka, In vitro and in vivo evaluation of ethyl cellulose based floating microsphere of cefpodoxime proxetil, *Int J Pharm and Biomed Res*, 1, 122-128 (2010)

[26] B.V. Basavaraj, R. Deveswaran, S. Bharath, S. Abraham, S. Furtado, V. Madhavan, Hollow Microsphere of Diclofenac Sodium a Gastropretentive Controlled Delivery System, *Pak J Pharm Sci*, 21, 451-454 (2008)

*Corresponding author: bagus.tri221096@gmail.com