Acta Poloniae Pharmaceutica – Drug Research, Vol. 71 No. 5 pp. 833–841, 2014 ISSN 0001-6837
Polish Pharmaceutical Society

INFLUENCE OF SPRAY DRYING MANUFACTURING PARAMETERS ON QUALITY OF LOSARTAN POTASSIUM MICROSPHERES

ANDRZEJ JANKOWSKI[1]*, RADOSŁAW BALWIARZ[1], DOMINIK MARCINIAK[2], DARIUSZ ŁUKOWIEC[3] and JANUSZ PLUTA[2]

[1]Medical University of Silesia, Department of Applied Pharmacy, Institute of Pharmaceutical Technology, Kasztanowa 3, 41-200 Sosnowiec, Poland
[2]Wrocław Medical University, Department and Institute of Pharmaceutical Technology, Borowska 211A, 50-556 Wrocław, Poland
[3]Silesian University of Technology, Department of Materials Processing Technology, Management and Computer Techniques in Materials, Konarskiego 18a, 44-10 Gliwice, Poland

Abstract: A general aim of the research was to develop a technology of manufacturing microspheres with losartan potassium as an active substance, and Eudragit L30D55 as a matrix with the use of spray drying technique. During the first step of the study, optimal values of parameters in spray drying process were established (i.e., operating temperature, peristaltic pump performance, aspiration value). Those values have a crucial effect on morphological parameters, and the size and homogeneity of received particles. In the obtained microspheres, the activity of excipients, which modify morphological properties of microspheres, were tested. Additionally, we studied the impact of the type and amount of plasticizer, as well as the amount of an adopted polymer in proportion to dry matter of losartan potassium, on quality of final product. Triethyl citrate and citric acid, plasticizers tested in reported studies, were also verified. A detailed study of the influence of both plasticizers on the qualities of microspheres containing losartan potassium on Eudragit L30D55 matrix indicated a positive influence of triethyl citrate and a negative influence of citric acid on morphological properties, shape and size of particles. The application of optimal parameters of spray drying and triethyl citrate as a plasticizer in the amount of 10 to 15% allows to obtain microspheres from 1.27 to 7.24 μm.

Keywords: microspheres, losartan potassium, spray drying, spray drying parameters, influence of plasticizers

Microspheres belong to a modern multi-compartment drug formulation, used in contemporary therapy for a controlled and targeted action of medication (1). They may be treated as a drug formulation with a modified release, which should deliver the medication in a strictly specified concentration, and to a site within a given, fixed time (2). The advantages of microspheres are: biocompatibility, an extended release profile and ability to incorporate unstable substances, such as proteins and nucleic acids, into a polymer matrix (2–6). Due to the size and shape of microspheres, controlling of a polymer matrix decay rate and a medicine release rate is also possible (5, 7, 8). Morphological properties of microspheres should fulfill published parameters, which means that the final product is monolithic, smooth and porous (1, 12), has spherical shape, and its size fits into the range from 1 to 500 μm (12).

Spray drying is a closed single phase process in which we can obtain a substance in a solid form from liquid output product (solution, suspension, and rarely emulsion) (2, 9, 10–12). This method enables to generate particles smaller than 10 μm (13).

In order to obtain the end product with required properties, the parameters of the process must be carefully selected. Almost each parameter, which is modified during the spray drying process, has a smaller or bigger effect on the obtained end product (2, 14, 15). The size of dried particles depends on the nozzle shape, on the indicator of feedstock, and conditions of the process (16). The humidity content is an indicator of the end product quality in a process of spray drying (17). The efficiency is very important for the progress of a total spray drying process, and it is determined as a proportion of the mass of a substance being dried to the end product mass (10).

* Corresponding author: e-mail: ajankowski@sum.edu.pl

Active substances and excipients used in the study

Losartan potassium is an antagonist of a receptor to angiotensin II, which is applied mainly in a therapy of mild and moderate hypertension and cardiac failure (18, 19).

Polymer matrix Eudragit® and plasticizers were used as excipients, which have an influence on morphological properties, shape and size of particles, and flexibility of manufactured matrixes.

Eudragit L30D55 is a 30% hydrodispersion of polymer in water. The proportion of free ester groups to carboxylic groups is 1 : 1. It dissolves in pH over 5.5 creating salts with bases. This allows to obtain a coating which is not soluble in acidous gastric juice and it dissolves in alkaline intestinal juice (20).

Eudragit® copolymers function as polymer carriers because they are characterized by the following required properties: they are biocompatible, do not induce toxic effects, undergo degradation in physiological conditions, and reveal low index of polydispersion that indicates the homogenous length of polymer chains (21).

Plasticizers are a separate group of additives that were used in the study. Addition of plasticizer has an influence on flexibility, strength, and adhesive properties of received polymer coatings. Plasticizers affect also the penetration of active substances through a polymer coating. The type and quantity of plasticizer that is used allow to optimize the profile of release from the drug formulation (22–24).

The aim of this work was to establish the influence of spray drying parameters on a progress in drying process of losartan potassium hydrodispersion on Eudragit L30D55, and to establish parameters for obtaining microspheres of optimal size and homogeneity. We also evaluated the additives effect**,** that is the effect of the type and quantity of used plasticizer and polymer in proportion to dry substance of losartan potassium on a size and morphology of obtained microspheres.

EXPERIMENTAL

Materials and reagents

The substances that were used in study are: losartan potassium (Valeant, ICN Polfa Rzeszów S.A.), triethyl citrate (Sigma-Aldrich Chemie GmbH), citric acid (PPH „POCH" S.A.), Eudragit® L30D55 dispersion 30% w/w (Chemical/IUPAC name: Poly(methacrylic acid-co-ethyl acrylate) 1 : 1), (Degussa).

Technology of microspheres preparation

The method of spray drying was used to prepare microspheres with losartan potassium. Thirty percent w/w hydrodispersion of methacrylic acid copolymer – Eudragit® L30D55 with losartan potassium and/or plasticizer was subjected to drying. A spray drier Büchi Mini Spray Dryer B-191 was used. Spray drying was conducted by the use of a nozzle with a diameter of 0.7 mm, with an air flow rate of 600 L/h and pressure of 4 bar. Created microspheres were separated in a cyclone and collected in a collector.

In order to obtain a product with appropriate morphology, firstly, the parameters of spray drying were determined (spray drying was conducted using variable values of pump capacity, inlet temperature and aspirator capacity). Next, we studied the influence of added plasticizer to a polymer in terms of polymer dry matter.

Experimental selection of spray drying parameters

In order to establish optimal parameters for this process, spray drying involved the use of series of water suspension of losartan potassium and Eudragit L30D55 in proportion 1 : 1. To select optimal conditions of spray drying process, the following parameters were modified: input temperature of drying gas, aspirator capacity and peristaltic pump performance.

Spray drying process of losartan potassium on Eudragit L30D55 hydrodispersion was carried out in the following input temperatures: 120, 130, 140, 150, and 160^{o}C. The flow rate through the peristaltic pump was also modified and its performance was established at the level of: 10, 15, 20, 25, 30, 40, and 50%. Another parameter that was modified during our study was aspiration capacity. During the progress of a spray drying process, the aspirator capacity was equal to 60, 70, and 80%. Each spray drying process involved collection of a product, estimation of mass, size and morphology of particles as well as the evaluation of process efficiency.

On the basis of initial experiments, the following parameters were chosen: the peristaltic pump performance at the level of 10%, the inlet temperature of 150^{o}C, and the aspirator capacity of 80%.

Size measurement and determination of microspheres morphology

Observations of sample microstructure was performed by a high resolution scanning electron microscope (SEM), SUPRA 25, ZEISS. This microscope can analyze WDS and EDS systems at 20 kV.

The analyzed materials were observed with magnification of 1 kx, 5 kx, and 10 kx. A secondary electron detector was used to analyze the image.

The size of particles was assessed with the use of image analysis software provided by the microscope manufacturer (ZEISS). The photographs of microspheres structures were taken with magnification of 1 kx, 5 kx, 10 kx. Particle size measurements were made at the magnification of 10 kx in a number of visual fields, evaluating the size of any selected 20 microspheres (10 bigger and 10 smaller particles)

Study of the influence of the amount and type of plasticizer on the particles morphology

The study assessed the influence of the type and amount of added plasticizer on the morphology and size of obtained microspheres. For plasticizers, triethyl citrate and citric acid were selected for the study. Suspensions of losartan potassium on Eudragit L30D55 in 1 : 1 ratio and plasticizer were subjected to spray drying. Triethyl citrate was added in the proportion of 2, 5, 10, and 15% to dry matter. Citric acid was added in the proportion of 0.5, 1, and 2% to dry matter. For comparison, suspensions of losartan potassium on Eudragit L30D55 in 1 : 1, 1 : 2, and 1 : 3, without plasticizer were subjected to drying. The whole process was conducted at predetermined parameters, that is with the pump performance of 10%, inlet temperature of 150°C, and aspiration of 80%.

Study of the influence of the amount of applied polymer in proportion to losartan potassium dry matter on the size and morphology of particles

Four water solutions of losartan potassium, Eudragit L30D55 and triethyl citrate were used in spray drying. We observed a change in the amount of polymer, and the proportion of an active substance to a copolymer, namely 1 : 1, 1 : 2, 1 : 3, 1 : 4. To each solution, plasticizer was added, i.e., 10% of triethyl citrate, in relation to dry matter. The composition of formulations is presented in Table 1.

RESULTS

Optimization of spray drying parameters.

To select the optimal conditions of spray drying process, the following parameters were modified: input temperature of drying gas, aspirator capacity and peristaltic pump performance.

Each spray drying process involved collection of a product, estimation of mass, the size and morphology of particles as well as the evaluation of process efficiency. The selected results are presented in Table 2.

Figures 1 and 2 show the selected microspheres images made by a scanning microscope at magnification of 10000× dried at variable parameters of conducted process.

The experiments enabled the selection of the most optimal conditions of spray drying of losartan potassium with Eudragit L30D55. The aim of the selection was to obtain optimal efficiency of this process, but predominantly to obtain particles of optimal morphology. The following parameters were the most adequate, and were used in the further studies, input temperature of drying gas: 150°C, peristaltic pump performance: 10% and the capacity of aspirator: 80%.

Analysis of the influence of plasticizer addition

The analysis involved the verification of the influence of plasticizer addition on morphology, shape of microspheres, and efficiency of spray drying process. Triethyl citrate and citric acid were used as plasticizers for comparison. The spray drying process was conducted with addition of plasticizer (samples F4–F10) and without plasticizer addition (samples F1–F3) at previously established parameters of drying.

Table 1. The quantitative composition of the substances used in particular formulations.

Proportion drug : polymer	Losartan potassium amount [mg]	Water volume [mL]	30% w/w dispersion of Eudragit L30D55 amount [mg]	Dry matter of Eudragit L30D55 amount [mg]	Triethyl citrate volume [mL]*
1 : 1	200.00	100	666.67	200.00	35.09
1 : 2	200.00	100	1333.33	400.00	52.63
1 : 3	200.00	100	2000.00	600.00	70.18
1 : 4	200.00	100	2666.67	800.00	87.72

*Triethyl citrate density is 1.04 g/cm^3, in this part of study triethyl citrate was used in proportion of 10% in relation to the dry matter of losartan potassium and Eudragit L30D55.

Table 2. The selected, experimental parameters of spray drying of losartan potassium with Eudragit L30D55 (the proportion of active substance to copolymer is 1 : 1 in the relation to dry matter) and characteristic of the obtained product.

Input temperature [°C]	Pump efficiency [%]	Aspirator efficiency [%]	Product mass [mg]	Product efficiency [%]*	Particle size [mm]	Morphology
120	10	70	75	18.75	1.18 – 11.42	irregular particles, very few spherical structures, the size of particles very diversified
130	10	70	93	23.25	1.62 – 8.77	the presence of spherical, oval and irregular particles, size of microspheres diversified
130	20	80	123	30.75	1.58 – 9.24	presence of oval structures and particles that resemble in structure a truncated cone, size diversified, few spherical forms
140	10	70	99	24.75	1.54 – 9.14	particle structure is close to spherical with irregular edges, presence of many square forms
150	**10**	**70**	**172**	**43**	**1.52 – 7.91**	**many spherical forms and with a shape close to spherical, bigger particles with irregular shape**
150	10	80	167	41.75	1.27 – 7.24	predominance of spherical forms and forms similar in shape to spherical with slightly smudgy edge, very few forms of other shape
150	20	80	151	37.75	1.94 – 8.75	small spherical particles, bigger one with clearly irregular shapes, small number of square and truncated cone particles
160	10	80	155	38.75	1.45 – 13.86	many spherical forms and forms of shape close to spherical, bigger particles with irregular shape

*product efficienty [%] = (End product mass / (mass of losartan potassium [mg] + mass of dry matter of Eudragit L30D55) × 100%

Table 3. Drying results of losartan potassium on Eudragit L30D55 in proportion 1 : 1 with addition of plasticizer (triethyl citrate) and characteristics of generated microspheres.

Triethylcitrate relation to the dry matter [%]	Product mass [mg]	Process efficiency [%]	Average size of particles [mm]	Microspheres morphology	Sample symbol
2	163	40.75	1,17 – 8,06	spherical forms are dominant, vary few oval forms and those with irregular shapes	F4
5	181	45.25	0.95 – 7.95	clear spherical particles, presence of structure with almost spherical shape, singular oval particle	F5
10	179	44.75	0.82 – 6.97	clearly spherical particles, very few oval forms	F6
15	172	43.00	0.75 – 7.22	clearly spherical forms, few oval forms and those with irregular shape	F7

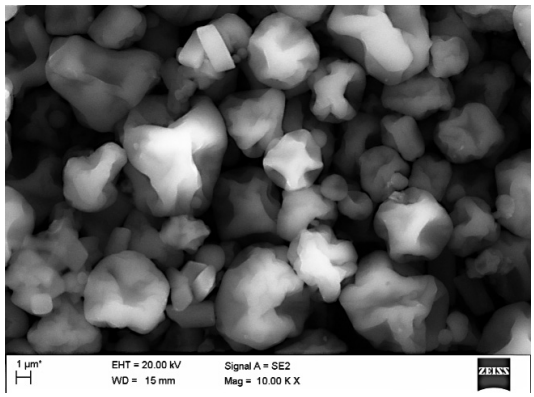

Figure 1. Photo, made by the scanning electron microscope (SEM), of microspheres in proportion losartan potassium : Eudragit L30D55 1 : 1 dried in parameters: inlet temperature 150°C, delivery of a pump 20%, aspirator capacity 70% (magnification 1000×)

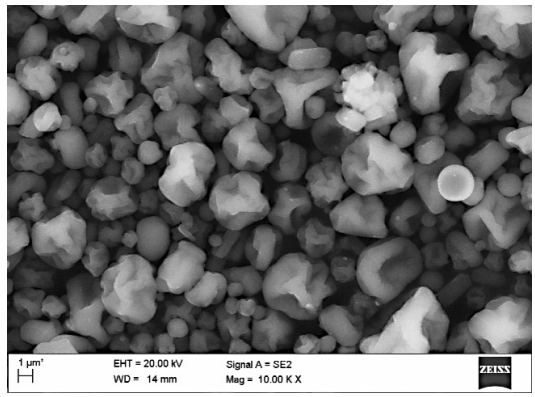

Figure 2. Photo, made by the scanning electron microscope (SEM), of microspheres in proportion losartan potassium : Eudragit L30D55 1 : 1 dried in parameters: inlet temperature 150°C, delivery of a pump 10%, aspirator capacity 80% (magnification 1000×)

Microspheres dried with addition of triethyl citrate had an optimal size and shape, which is especially clear in the case of samples where the plasticizer addition was 10% and 15%, respectively.

Triethyl citrate had also a beneficial effect on the size of microspheres, there was only a slight reduction of average particle size and improvement in a quality of microspheres. The increase of efficiency of the process was noticed in samples to which plasticizer was added in the amount of 5, 10, and 15%. The drying efficiency was improved at a level of 5%. The best effect on both, the process efficiency and morphology of achieved microspheres had an addition of plasticizer in the amount of 10% in terms of dry matter of losartan and Eudragit L30D55. The same amount of triethyl citrate was used in further studies. The detailed data on efficiency as well as the average size of particles, and a detailed description of morphological parameters of obtained microspheres after addition of triethyl citrate are shown in Table 3.

Citric acid had a negative effect on all parameters of spray drying process of losartan potassium with Eudragit L30D55. Each addition of plasticizer caused deterioration of particle morphology, and had a negative effect on process efficiency. The average size of particles increased but the quality of obtained microspheres deteriorated. The microscope image presents a great number of irregular particles and forms of non-spherical structure. The efficiency of the process after adding citric acid decreased to 25%. The detailed data on the efficiency of the process, size and morphology of particles are presented in Table 4.

In case of microspheres obtained without addition of triethyl citrate, we can observe the Eudragit L30D55 crystals ("broom shaped" structures that are visible on the image of sample F9), which cannot be seen in a microscope image of microspheres dried with addition of triethyl citrate.

Increased amount of polymer negatively affected the quality of obtained microspheres: the size of particle increased and the morphology deteriorated. Particular data on efficiency of the process, size and morphology of particles are shown in Table 5.

Figures 3 and 4 present the comparison of microspheres dried with addition of triethyl citrate in amount of 10% in terms of dry matter of losartan potassium and Eudragit L30D55 in proportion 1 : 1 in comparison to microspheres dried without addition of plasticizer.

Figures 3A, 4A, 3B and 4B illustrate respective microspheres with and without addition of plasticizer.

Influence of the amount of applied Eudragit on size and morphology of achieved microspheres

The process involved drying of losartan potassium suspensions on Eudragit L30D55 in the proportion of 1 : 1 to 1 : 4; to each formulation triethyl citrate was added in the amount of 10% in terms of dry matter. The obtained product was collected in a collector, weighed and its size and morphology were determined by a scanning microscopy technique. The results are presented in Table 6.

Figures 5 and 6 show selected scanning electron microscope images of microspheres, for samples presented in Table 6.

Table 4. Drying results of losartan potassium on Eudragit L30D55 in proportion 1:1 with addition of plasticizer (citric acid) and characteristics of generated microspheres.

Citric acid relation to the dry matter [%]	Product mass [mg]	Process efficiency [%]	Average size of particles [mm]	Microspheres morphology	Sample symbol
0.5	122	30.50	2.87 – 9.24	Disturbed structure of particle, many forms with irregular shape	F8
1	120	30.00	2.17 – 10.15	Presence of structures with irregular shapes, small number of spherical and oval forms, particle size diversified	F9
2	117	29.25	2.29 – 11.47	Clear irregular morphology of particles, no spherical and oval particles	F10

Table 5. Characteristic of microspheres dried with a method of spray drying without addition of plasticizer.

Proportion losartan potassium : Eudragit L30D55	Product mass [mg]	Process efficiency [%]	Average size of particles [mm]	Microspheres morphology	Sample symbol
1 : 1	165	41.25	1.27 – 7.24	Predominance of spherical forms and forms similar in shape to spherical with slightly smudgy edge, very few forms of other shape	F1
1 : 2	294	49.00	1.32 – 8.57	Domination of oval forms, very few spherical forms, presence of forms with irregular shape	F2
1 : 3	354	44.25	1.95 – 12.96	Clearly visible forms with very irregular shape, no spherical forms, big disproportion in particle size	F3

Table 6. Characteristics of microspheres spray dried of losartan potassium on Eudragit L30D55 in proportion from 1 : 1 to 1 : 4 with addition of triethyl citrate in amount of 10% in calculation to dry matter drug:polymer.

Proportion losartan potassium : Eudragit L30D55	Product mass [mg]	Process efficiency [%]	Size of particles [mm]	Morphology	Sample symbol
1 : 1	172	43.00	0.82 – 6.97	Clearly spherical particles, very few oval forms	W1
1 : 2	292	48.67	0.98 – 7.04	Spherical particles, some of them contain a pit in central part of coat, very few particles of irregular shape	W2
1 : 3	415	51.88	1.06 – 7.71	Spherical particles, some of microspheres contain a recess in central part of coat, occurrence of irregular shape particles and particles containing recess in part of coat	W3
1 : 4	523	52.30	1.26 – 10.12	Presence of spherical particles with pits in part of coat, occurrence of more numerous particles of irregular shape, presence of particles with shape resembling cone	W4

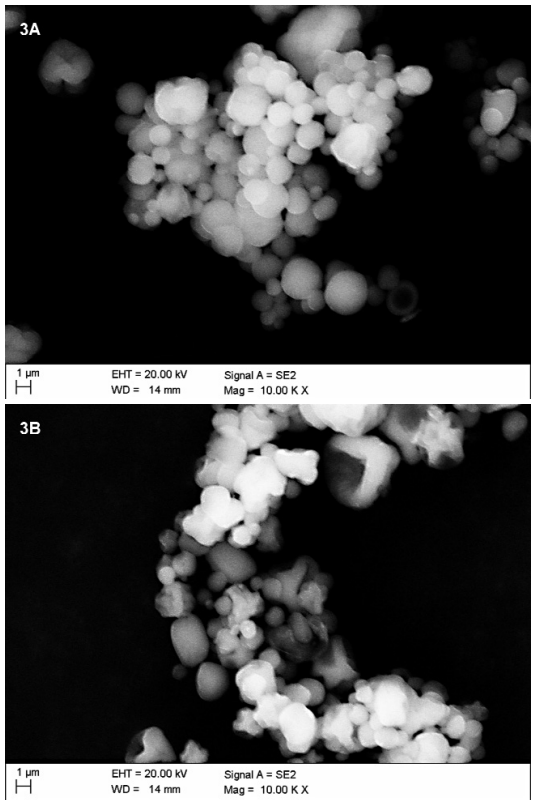

Figure 3. Photo, made by the scanning electron microscope (SEM), of microspheres in proportion losartan potassium : Eudragit L30D55 1 : 1. (3A contains the addition of triethyl citrate (sample F6 from Table 4), 3B without plasticizer (sample F1 from Table 1)

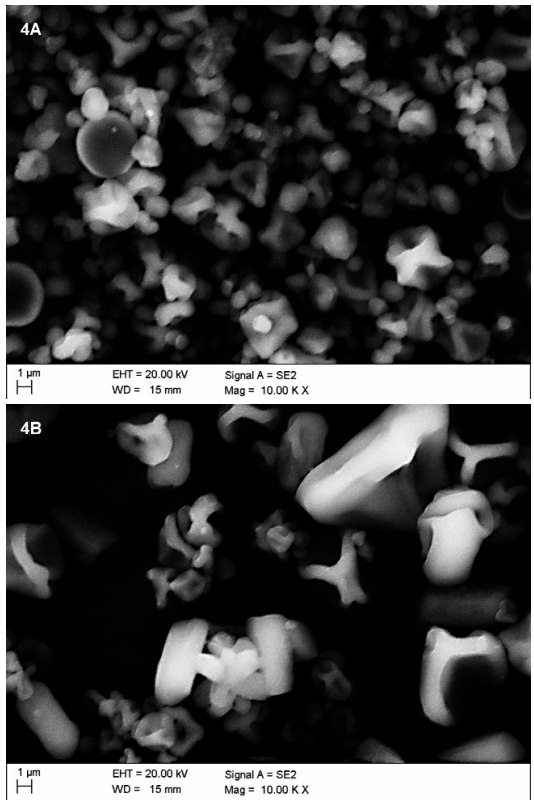

Figure 4. Photo, made by the scanning electron microscope (SEM), of losartan potassium microspheres : Eudragit L30D55. On the left side of microsphere in proportion losartan potassium : Eudragit L30D55 1 : 1 with addition of citric acid in amount of 10% of dry matter drug : polymer (sample F9 from Table 5 – Fig. 4A), on the right side without addition of plasticizer, proportion drug : polymer 1 : 3 (sample F3 from Table 6 – Fig. 4B)

DISCUSSION

The method of spray drying was used in this study to obtain microspheres with losartan potassium. Losartan potassium, the antagonist of an angiotensin II receptor, was used as a standard active substance (model substance). The medication was incorporated into the polymer matrix containing Eudragit L30D55 and plasticizer, i.e., triethyl citrate with established experimental content of 10%. The optimization of the spray drying process and determination of the optimal amount and type of used plasticizer were tested.

The research enables to evaluate the influence of peristaltic pump performance on morphology of the received end product. In all temperatures under investigation (140–160^{o}C), a disturbance in particle morphology together with the increase in peristaltic pump performance can be observed. The most spherical forms were obtained by peristaltic pump performance at 10%. The increase of the delivery of a peristaltic pump, was accompanied by the increased size of microspheres. The efficiency of this process deteriorated when values of pump performance increased.

Similar results were obtained by Esposito et al. (25). They observed that application of a flow rate of 0.5 mL/min led to creation of spherical forms with smooth surfaces, whereas, the increase of a flow rate to 5 mL/min disturbs particle morphology, resulting in the formation of particles with more irregular surfaces. At the same time, they drew the attention to depositing large quantities of the end product on the cyclone walls. Billancetti et al. (26), by decreasing the flow rate of liquid through the pump, reached a slight improvement of the pump performance, which is compatible with the experimental results of losartan potassium drying.

The study allows to select the optimal conditions for spray drying of losartan potassium with

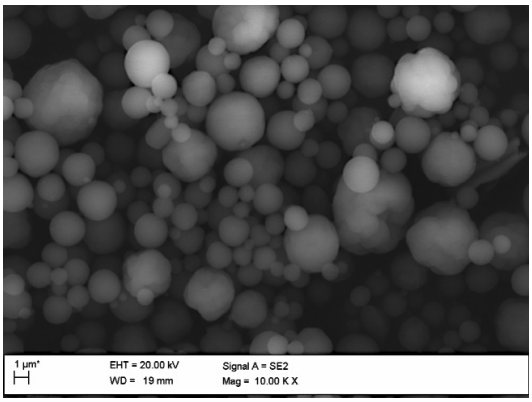

Figure 5. Photo, made by the scanning electron microscope (SEM), of microspheres in proportion losartan potassium : Eudragit L30D55 1 : 1 with addition of triethyl citrate in amount of 10% of dry matter drug : polymer (sample W1 magnification 10000×)

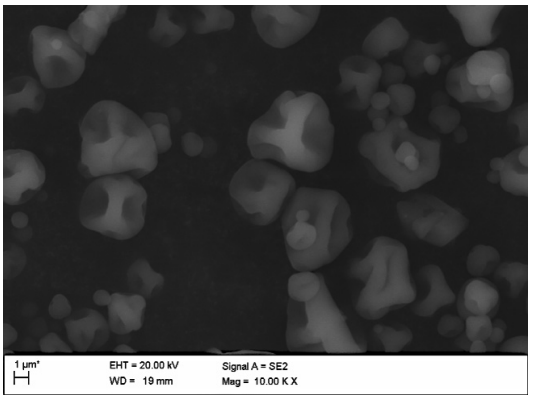

Figure 6. Photo, made by the scanning electron microscope (SEM), of microspheres in proportion losartan potassium : Eudragit L30D55 1 : 3 with addition of triethyl citrate in amount of 10% of dry matter drug : polymer (sample W3 magnification 10000×)

Eudragit L30D55. The most adequate parameters that were used for further study are: input temperature of drying gas of 150°C, peristaltic pump performance: 10%, and aspirator capacity of 80%. Application of these values enables to obtain almost 42% of end product efficiency, and ensures spherical morphology of particles.

The addition of plasticizer was also estimated in the study. The research of Rujivipat and Bodomier (27) proved that matrixes containing copolymer of metacrylic acid were not flexible enough and require the presence of plasticizer. Correspondingly to the study of Sawicki and Makulec (24), triethyl citrate was used, whereas citric acid as a plasticizer was tested in the study of Szymańska and Winnicka (2). Triethyl citrate was added in the proportion of 2, 5, 10, and 15% to dry matter of losartan potassium formulation: Eudragit L30D55 in proportion of 1 : 1. Citric acid was added in proportions of 0.5, 1, and 2% to dry matter of losartan potassium formulation: Eudragit L30D55 in proportion of 1 : 1. The morphological properties of the end product, and efficiency of reaction were accepted as the criterion of assessment.

The research has shown a positive influence of triethyl citrate on morphology and efficiency of microspheres, and a negative influence of citric acid on both parameters. The obtained microspheres dried with addition of triethyl citrate were characterized by an expected size and shape, correspondingly to the published standards. Triethyl citrate should be used in the quantity of 10 to 15%. We observed an increase in efficiency of the process in samples with added plasticizer in the amount of 5, 10, and 15%, and at these values the efficiency of drying improved approximately by 5%. Snejdowa et al. (28) suggest that added plasticizer could constitute as much as 30% of formulation. In their work, Sawicki and Makulec (24) claimed that triethyl citrate had a positive influence not only on particle morphology but also it improved the adhesive properties, and increased the flexibility of polymer matrixes.

Citric acid had a negative influence on all parameters of spray drying process of losartan potassium on Eudragit L30D55. Addition of this plasticizer resulted in deterioration of particle morphology, and had a negative influence on the efficiency of the process. The average size of particles increased but the quality of microspheres deteriorated.

CONCLUSIONS

1. Application of spray drying technique to produce microspheres with losartan potassium as an active substance on the Eudragit L30D55® matrix, allows to obtain particles with beneficial morphological parameters and a particle size.
2. The most beneficial morphological parameters of microspheres were obtained with the following parameters of spray drying: inlet temperature of 150°C, delivery of a peristaltic pump of 10%, aspiration value of 80%.
3. In order to improve the morphological properties of microspheres, plasticizers such as triethyl cit-

rate and citric acid, whose tests were reported in the literature, were verified.

A detailed study of the influence of both plasticizers on the properties of microspheres with losartan potassium on Eudragit L30D55 matrix indicated a positive effect of triethyl citrate and a negative effect of citric acid on morphological properties, shape and particle size.

4. Application of optimal parameters of spray drying and triethyl citrate as plasticizer in amount of 10 to 15% enables to obtain microspheres from 1.27 μm to 7.24 μm.

REFERENCES

1. Jachowicz R., Czech A., Jamróz W.: Farm. Pol. 65, 285 (2009).
2. Szymańska E., Winnicka K.: Farm. Pol. 65, 378 (2009).
3. Li X., Anton N., Ta T.M., Zhao M., Messaddeq N., Vandamme T.F.: Int. J. Nanomedicine 6, 1313 (2011).
4. Vasir J.K., Tambwekar K., Garg S.: Int. J. Pharm. 255, 13 (2003).
5. Sam M.T., Gayathri D.S., Prasanth V., Vinod B.: Internet J. Pharmacol. 6, 1 (2008).
6. Halkiewicz A., Janicki S.: Farm. Pol. 19, 836 (1995).
7. Szymańska E., Winnicka K.: Gazeta Farm. 10, 40 (2009).
8. Szymańska E., Winnicka K., Muśko M.: Farm. Pol. 66, 238 (2010).
9. Pattabhi K., Chowdary R., Srinivasa Rao Y.: Biol. Pharm. Bull. 27, 1717 (2004).
10. Bowey K., Neufeld R.J.: Biodrugs 24, 359 (2010).
11. Gac J., Gradoń L.: Inż. Ap. Chem. 50, 32 (2011).
12. Cal K., Sollohub K.: J. Pharm. Sci. 99, 576 (2010).
13. Sznitowska M.: Farm. Pol. 57, 962 (2001).
14. Samborska K.: Post. Tech. Przetw. Spoż. 1, 63 (2008).
15. Rizi K., Green R.J., Donaldson M., Williams A.C.: J. Pharm. Sci. 100, 566 (2011).
16. Raffin R.P., Jornada D.S., Ré M.I., Pohlmann A.R., Guterres S.S.: Int. J. Pharm. 324, 10 (2006).
17. Rattes A., Oliveira W.: Powder Tech. 171, 7 (2007).
18. Kawecka-Jaszcz K., Czarnecka D., Wojciechowska W.: Nadciśnienie Tętnicze A1 (2006).
19. Prejbisz A., Januszewicz A.: Choroby Serca i Naczyń 3, 195 (2006).
20. Ishtiaq A., Muhammad I., Habibur R.: Bangladesh Pharm. J. 13, 9 (2010).
21. Musiał W., Kubis A.: Polim. Med. 35, 39 (2005).
22. Tang E., Chan L., Heng C.: Am. J. Drug Deliv. 3, 17 (2005).
23. Csóka G., Gelencsér A., Kiss D., Pásztor E., Klebovich I., Zelkó R.: J. Term. Anal. Cal. 87, 469 (2007).
24. Sawicki W., Makulec A.: Farm. Pol. 65, 311 (2009).
25. Esposito E., Roncarati R., Cortesi R., Cervellati F., Nastruzzi C.: Pharm. Dev. Technol. 5, 267 (2000).
26. Bilancetti L., Poncelet D., Loisel C., Mazzitelli S., Nastruzzi C.: AAPS PharmSciTech. 11, 1257 (2010).
27. Rujivipat S., Bodmeier R.: Eur. J. Pharm. Biopharm. 81, 1 (2012).
28. Snejdowa E., Dittrich M.: Pharmaceutically used plasticizers. in: Recent Advances In Plasticizers. Luqman M. Ed., pp. 45–68, InTech, Rijeka 2012.

Received: 18. 12. 2013