MICROENCAPSULATION OF DRONEDARONE HYDROCHLORIDE BY SPRAY DRYING

ORIGINAL SCIENTIFIC PAPER

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ABSTRACT:

Microencapsulation is a method often used in various industries and one of the many advantages is that controlled release of the active ingredient can be achieved. The aim of this study was to prepare microcapsules by spray drying by changing the process conditions and ratios of the used components, polymer excipient poly(vinyl alcohol) and active ingredient dronedarone hydrochloride. Dosage forms of poly(vinyl alcohol) and dronedarone hydrochloride were prepared in 1:1, 2:1 and 3:1 weight ratios and the solutions were dried in a laboratory spray dryer at four different atomization flowrates. The morphology of the obtained microcapsules was examined using a scanning electron microscope (SEM). The release kinetics of the active ingredient from the microcapsules were examined by in vitro laboratory testing and the resulting release profiles were described using the Weibull model. The results showed that the change of weight ratio has influence on the morphology of microcapsules, the efficiency of microencapsulation and drug release.

KEYWORDS: microencapsulation, spray drying, dronedarone hydrochloride, poly(vinyl alcohol), *in vitro* drug release

INTRODUCTION

In the pharmaceutical industry, coating processes of active ingredients are increasingly used to obtain controlled and prolonged drug release. A well-designed, controlled release drug delivery system can overcome some of the problems of conventional delivery of the active ingredient and improve the therapeutic efficacy of a given drug [1]. One of the methods that enables the delivery of the active ingredient to the targeted location is microencapsulation [2]. Microencapsulation is a process where very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material [3]. The primary reasons for microencapsulation are controlled drug release, improvement of the physical and chemical properties of the dosage form, protection of the active ingredient, masking of bad taste masking and easier handling of the dosage form [4]. An important step in microencapsulation process is selection of the polymer material for coating of the active ingredient. When choosing a polymer, it is important to pay attention to the following characteristics: polymer biodegradability, physical, chemical and thermal properties of polymer, compatibility between the polymer and active ingredient, etc. [5]. There are many different methods of microencapsulation and the most commonly used method is spray drying. Spray drying is a method of drying liquid and semi-liquid solutions, suspensions, emulsions and droplets, in just one production step. The principle of spray drying is to disperse the drug solution into very small droplets in the atomizer. Solvent rapidly evaporates in hot dry media to obtain a dry product in powder or granular form. In this process, a product with a high degree of purity and a narrow particle size distribution is produced [6]. The aim of this work was to prepare prolonged release dosage form. Dronedarone hydrochloride (DNR) was used as the active ingredient and poly(vinyl alcohol) (PVA) was used as a polymer for the coating of the active ingredient. Microencapsulation was performed in a spray dryer and the release kinetic of dronedarone hydrochloride was studied by *in vitro* laboratory testing.

MATERIALS AND METHODS

MATERIALS

Antiarrhythmic drug, dronedarone hydrochloride, used in the experiments is received from TAPI Pilot, PLIVA Croatia Ltd. Dronedarone hydrochloride (DNR) is fine white crystalline powder, with melting point in range of 149 – 153°C [7]. Particle size of used DNR, expressed with as $x_{90,}$ is 39.92 μm [8]. Poly(vinyl alcohol) (Acros Organic) with average molecule weight of 50000 – 85000 g mol^{-1} was used for microencapsulation.

PREPARATION OF MICROCAPSULES

Solutions with a different weight ratio of DNR and PVA (Table 1) were prepared for the spray drying process. DNR was dissolved in 100 mL of the ethanol under stirring conditions at room temperature. PVA solution was prepared in 100 mL of the distilled water preheated at 80°C. Prepared solutions were combined together and then used as a feed solution for the spray drying process in Büchi Mini Spray Dryer B-290 (Büchi Labortechnik AG, Switzerland) with 1.4 mm nozzle. The process parameters were set as follows: inlet temperature 75°C, atomization air flowrates 1.22 - 4.84 x 10^{-4} m^2 s^{-1}, feed flowrate 2.5 x 10^{-8} m^3 s^{-1}, and drying air flowrate 1.06 x 10^{-2} m^3 s^{-1}.

Table 1. PVA:DNR weight ratios, atomization air flowrates and viscosity of used in experiments

Sample	Weight ratio PVA:DNR	Atomization air flowrate, x 10^{-4} (m^3 s^{-1})	Viscosity (mPa s)
PS 1	1:1	4.84	3.7
PS 2	1:1	2.92	
PS 3	1:1	1.85	
PS 4	1:1	1.22	
PS 5	2:1	4.84	4.8
PS 6	2:1	2.92	
PS 7	2:1	1.85	
PS 8	2:1	1.22	
PS 9	3:1	4.84	6.4
PS 10	3:1	2.92	
PS 11	3:1	1.85	
PS 12	3:1	1.22	

SCANNING ELECTRON MICROSCOPY

The morphology of the microcapsules was examined by scanning electron microscopy (SEM; VEGA3, TESCAN, Czech Republic). The samples were fixed to the holder, placed in the Quorum SC7620 sputter coater and coated with a thin layer of gold and palladium in an inert argon atmosphere and a 10^{-2} mbar vacuum. The SEM was operated at an acceleration voltage of 5-10 kV.

EQUILIBRIUM MOISTURE CONTENT

The equilibrium moisture content was determined using infrared moisture analyzer Kern MLS 50-3C (KERN, Balingen, Germany). Drying was carried out at 75 °C and the equilibrium moisture content was calculated from Equation 1.

$$X_{\text{eq}} = \frac{m(\text{microcapsules}) - m(\text{dry microcapsules})}{m(\text{dry microcapsules})} \quad (1)$$

IN VITRO DRUG RELEASE

The microcapsules were filled into standard gelatin capsules, size 00, before *in vitro* studies. The weight of microcapsules was calculated according to the ration of DNR and PVA so that each gelatin capsule would contain approximately the same amount of DNR (42.75 mg). The release profiles of DNR were determined using the European Pharmacopeia method-II dissolution apparatus [9] (RC-6D, Zhengzhou Nanbei Instrument, China). Food & Drug Administration (FDA) method defined for referent drug MULTAQ® (dronedarone hydrochloride tablets) [10] was used for *in vitro* tests of prepared microcapsules. Each experiment was carried out in triplicate, using 1000 mL of a phosphate buffer with pH 4.5, at a temperature of 37 ± 0.5 °C. The paddle rotational speed was 75 rpm. The gelatin capsules were placed into Japanese sinkers, which were placed into the beakers. Sampling was performed over a 24h period. The samples were filtered using Chromafil Xtra H-PTFE-20/25 with a pore size of 0.45 μm and subsequently analyzed using a UV/Vis spectrophotometer (UV-1280, Shimadzu, Japan) to determine the concentration by monitoring the absorbance of the DNR at 289 nm.

DISSOLUTION KINETICS

The DDSolver was used for the fitting of the dissolution profile. Various mathematical models of the drug dissolution are already integrated into the DDSolver [11]. In this study, the applicability of different models was tested and the value of R^2 was used as model selection criteria. The release profiles are described by the Weibull model (Eq 2). Where, M_t is the amount of drug dissolved as a function of time and M_0 is total amount of drug being released. Parameters *a* and *b* are kinetic parameters of Weibull model.

$$\frac{M_t}{M_0} = 1 - e^{\frac{-(t)^b}{a}} \quad (2)$$

RESULTS AND DISCUSSION

The objective of this research was to obtained microcapsules of dronedarone hydrochloride to investigate the possibility of drug release control by using PVA as coating polymer. Microcapsules of different DNR:PVA ratios were successfully pre-

pared. Microencapsulation was performed by spray drying at four different atomization air flowrates. In addition, the PVA and DNR mass ratios (1:1, 2:1 and 3:1) were changed which resulted in a total of 12 experiments. Samples are labeled from PS1 to PS12, and the corresponding mass ratios and flowrates are given in Table 1. Samples PS4, PS8 and PS12 were dried at the lowest atomization flowrate 1.22 $x10^{-4}$ m^3 s^{-1}. The efficacy in experiments PS4, PS8 and PS12 was extremely low due to the huge remaining of the samples at the cyclone walls. This could be explained by low atomization flowrates that produce large droplets which, due to their size, do not completely dry at 75°C. Those samples were not used in *in vitro* study due to the low yield.

The efficiency of microencapsulation, the morphology of the obtained microcapsules, as well as the equilibrium moisture content of the samples were examined. Table 2 shows the efficiency of microencapsulation expressed by the ratio of DNR weight in samples before and after drying. In addition, in Table 2 the values of equilibrium moisture content in obtained samples are presented.

Table 2. Microencapsulation efficiency and equilibrium moisture content

Sample	Mass ratio PVA:DNR	Atomization flowrate, $x10^{-4}$ (m^3 s^{-1})	Initial mass of components (g)	Mass of DNR in spray dried samples (g)	Efficiency (%)	Equilibrium moisture content (%)
PS1	1:1	4.84	2.0	0.773	77.3	6.4
PS2	1:1	2.92	2.0	0.647	64.7	7.5
PS3	1:1	1.85	2.0	0.295	29.5	6.4
PS5	2:1	4.84	3.0	0.773	77.3	7.5
PS6	2:1	2.92	3.0	0.677	67.7	8.7
PS7	2:1	1.85	3.0	0.614	61.4	8.7
PS9	3:1	4.84	4.0	0.542	54.2	8.7
PS10	3:1	2.92	4.0	0.524	52.4	9.9
PS11	3:1	1.85	4.0	0.556	55.6	8.7

Process efficiency increases with the increase of the atomization flowrate for samples with the same ratio of polymer and the active ingredient (1:1) (PS1, PS2, PS3; Table 2). On the other hand, smaller differences in the dependence of efficiency on the atomization flowrate were observed for the ratio 2:1 (samples PS5, PS6 and PS7). The effect of the atomization flowrate is insignificant for microcapsules with the highest polymer content (3:1) (samples PS9, PS10 and PS11) where the values of efficiency are similar in all three experiments. Increase of the microencapsulation efficiency can be explained through the atomization step and droplet size. Higher atomization flowrate results in droplets of smaller sizes [12] resulting in faster drying at low temperatures. Smaller particles will have enough time to complete the drying process before reaching the cyclone chamber. An increase in the polymer content leads to an increase in the viscosity of the solution, thereby reducing the microencapsulation efficiency for the samples PS9, PS10 and PS11. The formation of droplets is more influenced by viscosity than the atomization air flowrate [13]. Solution with higher viscosity will give larger droplets, which is directly related to the drying process and microencapsulation efficiency [14]. Dried microcapsules were tested for equilibrium moisture content at 75°C and the values are present in Table 2. Increased equilibrium moisture content was observed for samples with higher polymer content, which is consistent with previously described droplet size and drying conditions. The equilibrium moisture content of all samples is less than 10 %.

The samples were characterized by a scanning electron microscope (SEM) to determine their morphology. The micrographs are shown in Figures 1-4.

Figure 1 shows micrographs of the sample PS1 corresponding to an equal ratio of PVA and DNR and maximum atomization flowrate. The microcapsules are very small and due to their size agglomeration problem occurred.

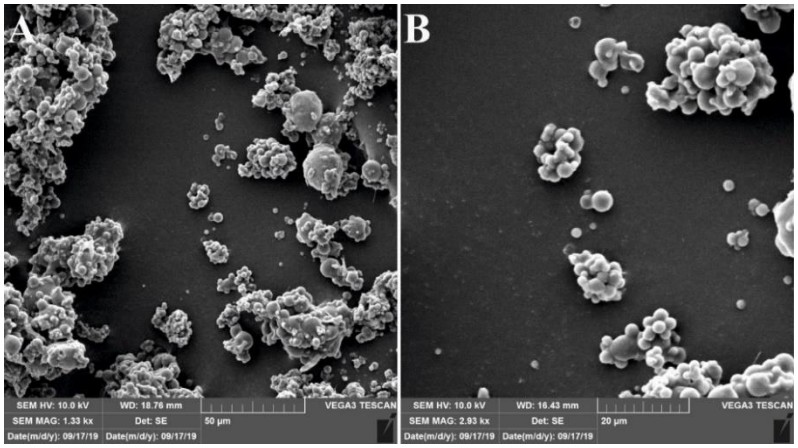

Figure 1. SEM micrographs of the sample PS1; a) 1000x, b) 2000x

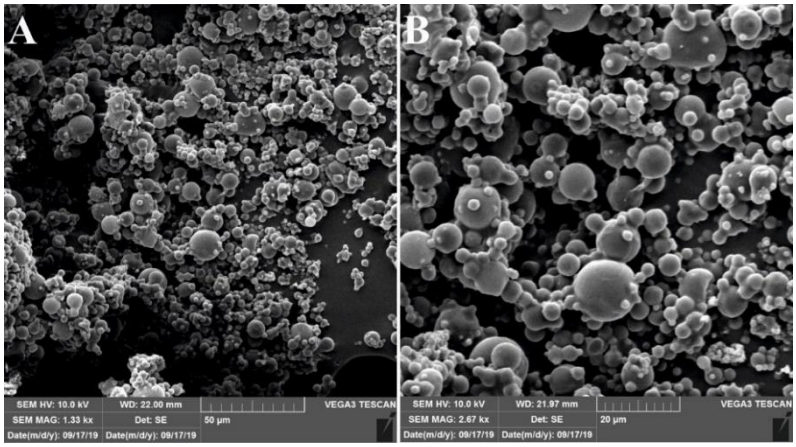

Figure 2. SEM micrographs of the sample PS5; a) 1000x, b) 2000x

Figure 2 shows micrographs of a PS5 sample containing polymer and an active ingredient in the ratio of 2:1. Both solutions (PS1 and PS5) where dried at maximal atomization flowrate resulting in small microcapsules. Same results were obtained for sample PS9 (Fig. 3).

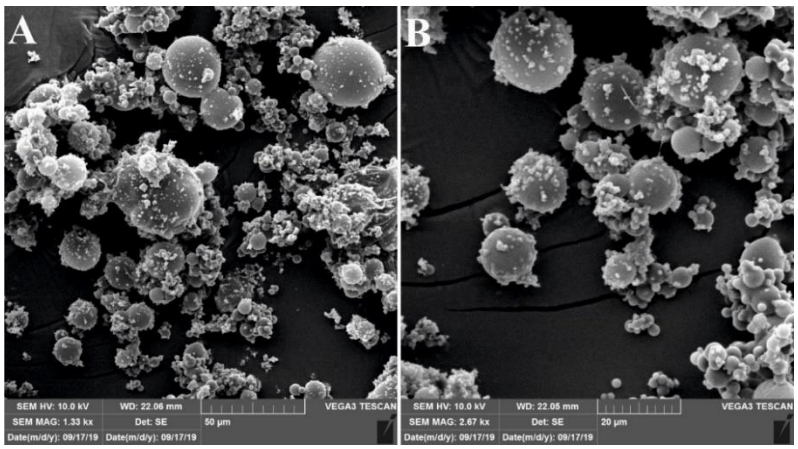

Figure 3. SEM micographs of the sample PS9; a) 1000x b) 2000x

On the other hand, if one compares polymer content in samples PS1 (1:1), PS5 (2:1) and PS9 (3:1) it can be seen from SEM micrographs that particle size increases, which is in accordance with the efficiency and equilibrium moisture content. Increasing the viscosity of the solution causes the formation of larger particles at same atomization flowrate.

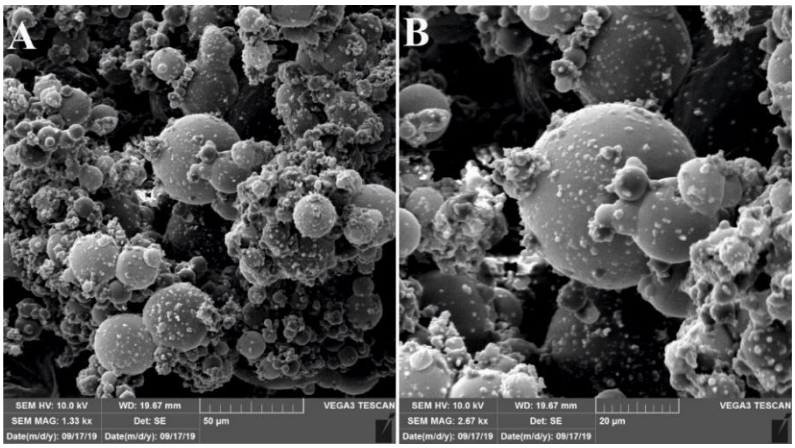

Figure 4. SEM micrographs of the sample PS10; a) 1000x b) 2000x

Figures 3 and 4 show micrographs of obtained microcapsules in which the PVA:DNR ratio is 3:1. The influence of different atomization air flowrate is considered. By reducing the flowrate of atomization air, a significant increase in particle size was seen. These samples clearly show spherical shape of microcapsules.

In vitro drug release profiles of DNR are presented in Figures 5-7.

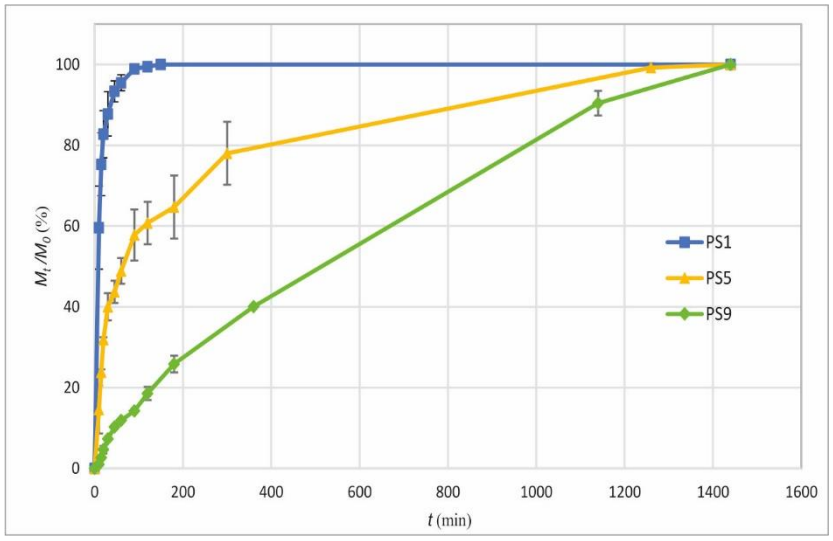

Figure 5. Dissolution profiles for different polymer content at atomization air flowrate 4.84 x 10^{-4} m^3 s^{-1}

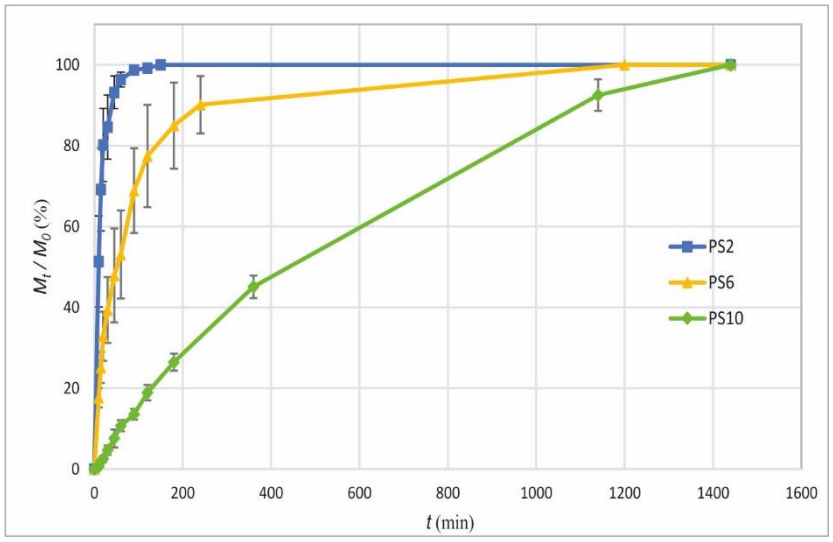

Figure 6. Dissolution profiles for different polymer content at atomization air flowrate 2.92 x 10^{-4} m^3 s^{-1}

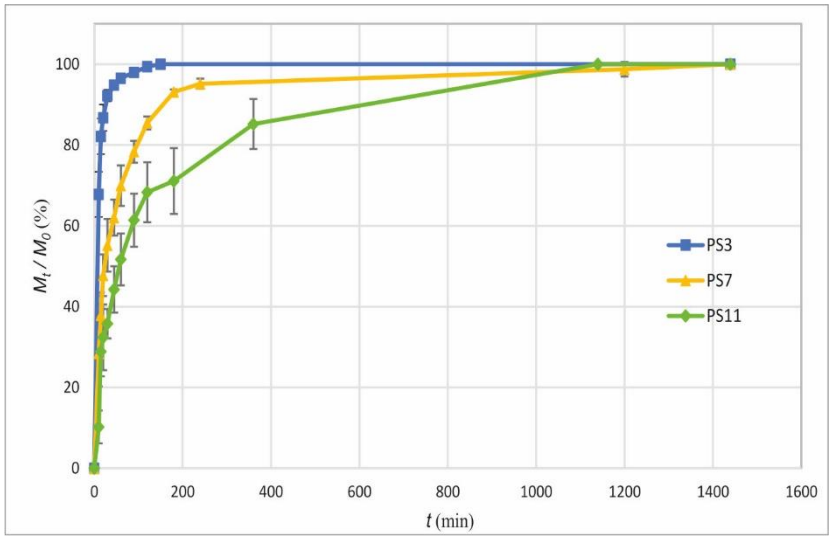

Figure 7. Dissolution profiles for different polymer content at atomization air flowrate 1.85 x 10^{-4} m^3 s^{-1}

The release profiles for the same atomization flowrate with different PVA and DNR ratios were compared. Increase in polymer content results in a prolonged release of DNR over 24h period.

Figures 8-10 provide comparisons of the *in vitro* release profiles for the samples obtained with spray drying at a different atomization air flowrate and equal PVA and DNR ratios.

Samples PS1, PS2 and PS3 have almost the same release profiles. In samples with equal PVA and DNR ratio, a large amount of DNR is released very quickly and its maximum is reached after 90 minutes. Independent of the atomization air flowrate, all samples with equal PVA and DNR ratios have the same release profile. This is explained by insufficient amount of polymer to form a shell around the DNR. The differences in the release profiles are more pronounced for different atomization flowrates by increasing the polymer content (Fig. 10 and 11).

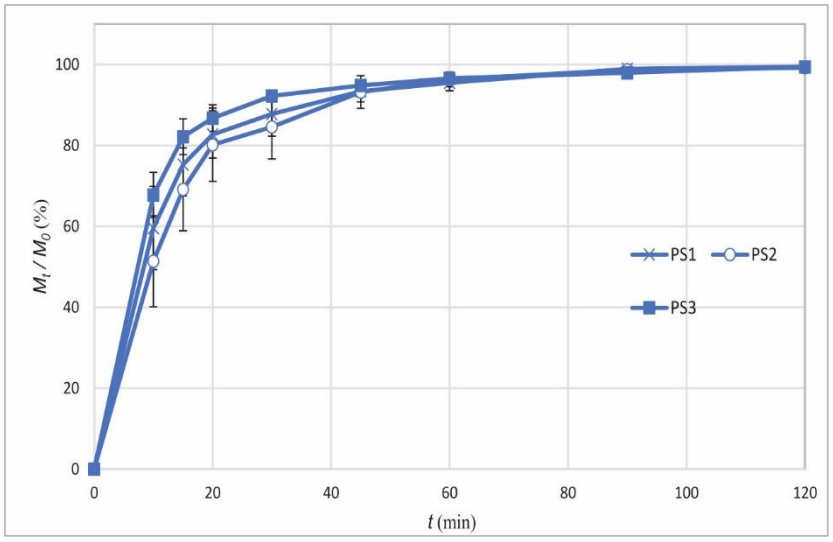

Figure 8. Dissolution profiles for different atomization air flowrate at same polymer content

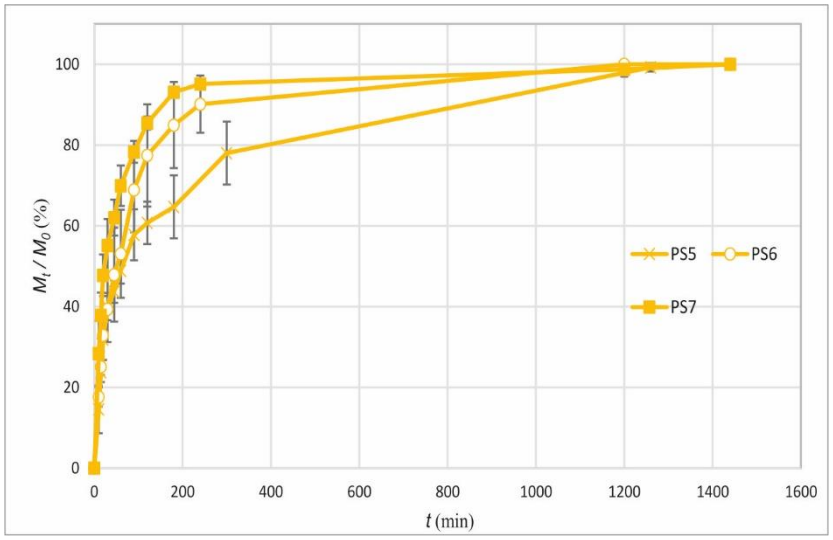

Figure 9. Dissolution profiles for different atomization air flowrate at same polymer content

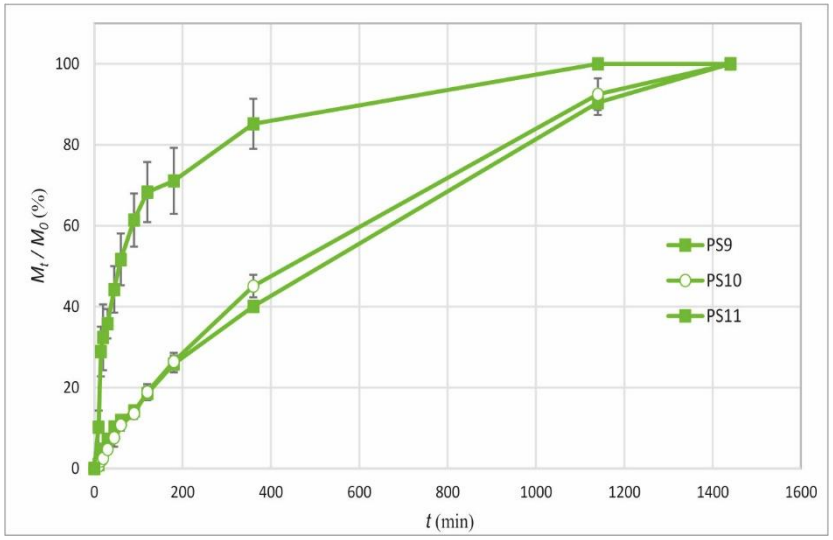

Figure 10. Dissolution profiles for different atomization air flowrate at same polymer content

The release kinetics of the active ingredient was described by the Weibull model (Eq. 2), which was selected based on the high R^2 values. The Weibull model is often used for comparison of the release profiles of an active ingredient from matrix dosage form [15]. Table 3 shows the parameter values of the selected kinetic model.

Table 3. Weibull model parameters

Sample	a, min^b	b	R^2
PS1	5.218	0.666	0.994
PS2	9.572	0.754	0.989
PS3	2.880	0.536	0.994
PS5	21.279	0.622	0.972
PS6	32.009	0.805	0.994
PS7	11.756	0.650	0.988
PS9	656.62	1.021	0.986
PS10	1277.7	1.144	0.994
PS11	29.185	0.706	0.971

Parameter *b* is related to the curve type. When the value of parameter *b* is less than 1, curve is parabolic with high initial slope and a consistent exponential character. That corresponds to the rapid release of a large amount of the active ingredient from the dosage form. When *b* is greater than 1, curve is sigmoidal with inflection point. Such curves indicate slower drug release [16]. Samples with the highest polymer content (3:1) (PS9, PS10 and PS11) show the highest values of parameter *b*, as expected, since the increase of polymer content will prolong drug release. Parameter *a* defines the release process timescale [16]. Higher values of this parameter indicate longer process time, which is, in this case, prolonged drug release. The highest values were observed for the samples with PVA and DNR ratio of 3:1, which was confirmed by parameter *b*. The only discrepancy was observed for sample PS11. We can attribute this to the lowest R^2 value and inadequate model fit for obtained experimental data.

CONCLUSION

Microcapsules of dronedarone hydrochloride coated with poly(vinyl alcohol), with different polymer content and different process conditions of spray drying, were prepared. Selected process conditions (polymer content and atomization air flowrate) affect the rate of the drug release. Atomization air flowrate has direct influence on the microcapsules size, where smaller microcapsules were obtained by increasing the atomization air flowrate. The microencapsulation efficiency is greater than 50% for all samples. SEM micrographs confirmed that the finer particles were obtained at a higher atomization air flowrate. In addition, by increasing the polymer content, the larger particles were obtained. Microcapsules with the highest polymer content showed the prolonged release of the dronedarone hydrochloride over 24h period.

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