https://doi.org/10.31925/farmacia.2020.5.12 **ORIGINAL ARTICLE**

EVALUATION OF THE IMPACT OF THE INLET AIR HUMIDITY DURING COATING STEP ON THE *IN VITRO* DISSOLUTION OF MODIFIED-RELEASE FILM-COATED PELLETS CONTAINING A BCS CLASS I ACTIVE SUBSTANCE

PAUL ANCU DUMITRAȘCU [1,2#], CRISTIAN FUNIERU [1#], VALENTINA ANUȚA [1]*, ALEXANDRU GEORGE COMAN [2], CARMEN ALECSANDRESCU [2], ALINA IVANCENCU [2], LĂCRĂMIOARA POPA [1], MIHAELA VIOLETA GHICA [1], CRISTINA ELENA DINU-PÎRVU [1]

[1] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2] *Zentiva S.A., Strategy and Investment Department, Bucharest, Romania*

**corresponding author: valentina.anuta@umfcd.ro*
[#] *Authors with equal contribution.*

Manuscript received: May 2020

Abstract

Present study aimed to evaluate the impact of the inlet air humidity during the coating step on the *in vitro* release profile of modified-release film-coated pellets containing a BCS class I active substance, by assessing the results obtained for 25 experimental batches. In order to ensure both the delayed and the prolonged-release mechanism, the release controlling agent (metacrylic acid - ethyl acrylate copolymer in a 1:1 ratio) was added in both matrix pellets and film-coat. The gastro-resistance of the pellets was evaluated after 2 hours in acidic media according to the in-force EMEA and FDA Guidelines. Based on the results obtained for 22 experimental batches, it can be concluded that the optimum absolute humidity of the inlet air during coating should be above 4.5 g/kg, in order to provide an acidic barrier for the pellets. A lower value for the absolute humidity of the inlet air during the coating process increase the brittleness of the coating and therefore reduces its barrier capability. Three experimental batches were manufactured by reducing the inlet air volume and the inlet temperature and by increasing the spray rate, therefore by reducing the product temperature at which the coating is form. The changes in the manufacturing process reduced the impact of a lower inlet air humidity during, but the dependency was not completely cancelled.

Rezumat

Prezentul studiu a avut ca scop evaluarea impactului umidității aerului de intrare în timpul etapei de filmare asupra profilului de cedare *in vitro* a unei substanțe active model ușor solubile, aparținând clasei I a Sistemului de Clasificare Biofarmaceutică, din peletele filmate cu eliberare modificată. Evaluarea s-a realizat prin procesarea rezultatelor obținute pentru 25 de loturi experimentale de pelete. Pentru a asigura atât caracterul enterosolubil, cât și cedarea prelungită a peletelor, a fost utilizat un amestec acid metacrilic - copolimer acrilat de etil în raport 1:1, care a fost adăugat atât în matricea peletelor cât și în filmul exterior. Gastro-rezistența a fost evaluată după 2 ore în mediu acid în conformitate cu reglementările în vigoare. Pe baza rezultatelor obținute pentru 22 de loturi experimentale, s-a putut concluziona că umiditatea absolută optimă a aerului de intrare în timpul procesului de filmare ar trebui să fie peste 4,5 g/kg. O valoare mai mică pentru umiditatea absolută a aerului crește friabilitatea filmului și, prin urmare, reduce capacitatea de barieră a acestuia. Trei serii experimentale au fost fabricate prin reducerea debitului aerului de intrare, reducerea temperaturii aerului de întrare și creșterea debitului de acoperire, lucru care a generat reducerea temperaturii în produs la care se formează filmul de acoperire. Schimbările în procesul de fabricație au redus impactul negativ al unei umidități mai mici a aerului, dar influența acestuia nu a fost complet anulată.

Keywords: enteric coating, modified release pellets, film-coating pellets, humidity, coating process

Introduction

The enteric-coating systems use different excipients that are insoluble in the gastric media in order to prevent or to delay the release of the active pharmaceutical ingredient (API) in the stomach [12]. Generally, the gastro-resistance is needed either to protect sensitive APIs, such as proton pump inhibitors or erythromycin from degradation in acidic media [2, 13, 15] or to protect the stomach mucosa from the irritative effect of the drug [4]. In particular cases, the gastro-resistance is needed to ensure a targeted delivery of the drug [1, 9], to provide a delayed release component in the formulation [20, 21] or to prevent the interaction of the active substance with pepsin and peptones [17]. These excipients can be either ionizable polymers such as polymethacrylates [11, 18], cellulose derivatives like cellulose acetate phthalate, cellulose acetate trimellitate or other esters containing hydroxypropyl methylcellulose phthalate or hydroxypropyl methylcellulose acetate succinate [7], polyvinyl derivatives such as polyvinyl acetate phthalate [14] or excipients

that are insoluble in acidic media, but soluble at various alkaline pH such as acetyltriethyl citrate, ceresin (mineral wax), glyceryl behenate, shellac (a polyester resin), tributyl citrate and zein (aminoacidic structure) [5, 6, 10].

The evaluated formulation for this study is a low dose modified release oral dosage form containing as model drug a BCS I active pharmaceutical ingredient, namely tamsulosin hydrochloride, formulated as film-coated pellets. According to the BCS (Biopharmaceutical Classification System), a BCS Class I API is a substance with high solubility and high permeability [19]. As the selected pharmaceutical formulation was intended to present a complex release mechanism, with both a delayed release and a prolonged release component, the model drug was chosen due to its high solubility in both acidic and neutral media, in order to determine the impact of the inlet air humidity on both the gastric barrier capacity of the polymer and the release for the intestinal stage of the release profile.

Based on the results obtained for *in vitro* dissolution in acidic media, critical process parameters (CPP) were identified and the impact on critical quality attributes (CQA) of the finished product and the Quality Target Product Profile (QTPP) were assessed.

Materials and Methods

Materials

The selected release controlling agent (metacrylic acid - ethyl acrylate copolymer in a 1:1 ratio) was added in both matrix pellets and film-coating system, due to its dual role in the formulation: to act both as an acidic barrier, and to ensure a prolonged-release of the API.

Due to the fact that the metacrylic acid - ethyl acrylate copolymer (1:1) is insoluble in acid media (pH 1.2), the prolonged-release mechanism of the pellets is triggered when the pH of the media is changed to a value of 6.8. The quality of the API and the excipients were evaluated according to the current in force monographs described in the European Pharmacopoeia.

Manufacturing of film-coated pellets

During the experimental phase, the results obtained for 22 experimental batches of film-coated pellets in batches of industrial scale were evaluated and correlated to the available data for absolute inlet air humidity used during the coating step. Additionally, three experimental batches were manufactured in order to evaluate the critical process parameters and to confirm their impact on the critical quality attributes of the finished product.

The matrix pellets were manufactured by extrusion and spheronization process and coated using a solution of metacrylic acid - ethyl acrylate copolymer (1:1) in a fluid bed processor. After the coating process was performed, the pellets were sieved in order to select pellets in a defined particle size range. The input parameters, such as inlet air volume (m^3/h), the inlet air temperature (°C) and spraying rate (mL/min), as well as the output parameters, such as product temperature (°C) and outlet temperature (°C) were the same for the first 22 experimental batches. For the first 22 experimental batches, the input parameters were set in order to have an output product temperature between 28°C and 30°C.

Dissolution methodology

The *in vitro* dissolution methodology was performed using USP Apparatus II (Paddle) (PharmaTest GmbH, Germany), at 100 rpm. The gastro-resistance step of the *in vitro* dissolution was determined using 480 mL of 0.1 M HCl. The *buffer stage of the release* was performed by *in situ* changing the pH of the dissolution medium by adding a solution of K_2HPO_4 and NaOH, until the pH of the dissolution medium is changed to 6.8. Tamsulosin quantitation was performed by using a validated HPLC method with UV detection at λ = 225 nm.

The proposed acceptance criteria for the dissolution test were set according to chapter 2.9.3. *Dissolution test for solid dosage forms* of the European Pharmacopoeia [3] and to EMEA Guideline on quality of oral modified release products EMA/CHMP/QWP/428693/2013 [8]. Hence, for the gastro-resistance stage, no more than 10% of the active substance should be released within 2 hours in the acidic medium. The second point in the specification (at 2.5 hours) was set to ensure compliance with the shape of the dissolution profile (around 50% dissolved), whereas the third point (6 hours) was set to ensure that the majority of the active substance has been released (Q = 80%).

Morphology and enteric coating thickness

A scanning electron microscope (SEM, Tescan, Czech Republic) was used to study the morphology of the samples. The analytical conditions varied as follows: magnification *100x - 1500x*; energy of the electron beam 5 kV.

Inlet air relative humidity

For experimental batches 1 - 10, the inlet air absolute humidity could not be measured on the equipment during coating step. However, no differences between the humidity of the inlet air used during coating and the external atmospheric air were expected, due to the fact that the air was not processed in order to modify the water content, when introduced in the system, during the coating step. In this context, recorded values for the air temperature (°C) and the relative humidity (% RH) by the National Meteorology Agency [16] were evaluated for the days when the coating step was performed. Furthermore, the measured dry-bulb temperature (°C) and relative humidity (% RH) values were converted into absolute humidity (g/kg) using the Mollier diagram (Enthalpy-Humidity Mixing Ratio). For experimental batches from 11 to 22, the inlet air absolute humidity was measured on the equipment during the coating step.

Data analysis

Experimental data are expressed as mean, range and variance. *In vitro* release data are reported as mean values of 6 replicates; with the coefficient of variation (CV%; [mean value/standard deviation] * 100%) calculated for each release profile. The statistical analysis and graphical representation of the data was performed using GraphPad Prism 7 software (GraphPad Software Inc., La Jolla, CA, United States).

Results and Discussion

Based on the obtained results, out of 22 experimental batches, 10 batches (experimental batches 1 - 8 and 21 - 22) have out of specification results, according to the proposed acceptance criteria in acidic media. For all these experimental batches a burst-out effect was observed after two hours in acidic media, with results between 14 - 35% of active substance release. For the experimental batch 12, the result obtained for acidic media is borderline compliant, as the individual values are between 7.9% and 9.3%, with a RSD of 6%. Due to the high tamsulosin amount released in acidic media, the results obtained for the second time-point for the same batch was out of specification, as all the individual results are above 60% (between 61.7% and 63.5%), with a RSD of 1.4%. For the other 11 experimental batches (experimental batches 9 - 11 and 13 - 20) compliant results with the proposed specification were observed, for all the sampling points. The average results obtained for the dissolution parameters for all batches are presented in Table I.

Table I

Results obtained for study of the *in vitro* release kinetics of the experimental batches 1 - 22 (non-compliant results are depicted in red)

Batch	% released; average for 6 determinations ± SD		
	2 hours (acidic medium)	2.5 hours	6 hours
Experimental 1	**31.2 ± 1.6**	**75.7 ± 1.2**	100.4 ± 0.8
Experimental 2	**27.8 ± 2.3**	**71.8 ± 0.9**	99.2 ± 0.9
Experimental 3	**22.2 ± 0.8**	**72.5 ± 0.4**	99.3 ± 1
Experimental 4	**20.1 ± 1.2**	**69.2 ± 0.9**	102 ± 0.7
Experimental 5	**13.6 ± 0.7**	**68.5 ± 0.9**	101.3 ± 0.5
Experimental 6	**15.7 ± 1.4**	**67.7 ± 1.5**	99.3 ± 0.9
Experimental 7	**16.1 ± 1.4**	**67.9 ± 1.2**	100.2 ± 0.8
Experimental 8	**16.1 ± 1.6**	**68.9 ± 1.1**	99.4 ± 0.9
Experimental 9	1.3 ± 0.2	56 ± 1.9	99.2 ± 0.3
Experimental 10	2.7 ± 0.7	57.5 ± 1.4	100.7 ± 1.1
Experimental 11	3 ± 0.4	58 ± 1.1	98 ± 0.7
Experimental 12	8.5 ± 0.6	**62.5 ± 0.9**	99.9 ± 0.3
Experimental 13	2.4 ± 2.3	50.8 ± 2.7	95.5 ± 0.7
Experimental 14	5.5 ± 2	58.1 ± 1.1	94.1 ± 1.4
Experimental 15	0.6 ± 0.1	49.4 ± 1.9	94.2 ± 0.4
Experimental 16	0.6 ± 0.3	49.3 ± 1.5	93.3 ± 0.5
Experimental 17	0.9 ± 0.1	47.3 ± 0.7	95.3 ± 1
Experimental 18	3.6 ± 0.6	57.3 ± 1.5	94.2 ± 0.9
Experimental 19	2.6 ± 3.6	50.8 ± 2.1	95.4 ± 0.1
Experimental 20	3 ± 2.4	53.6 ± 1.7	96.2 ± 1.2
Experimental 21	**28.4 ± 1.1**	**73.7 ± 0.5**	95.1 ± 0.5
Experimental 22	**34.8 ± 0.9**	**76.9 ± 4.9**	94.6 ± 1.8

The morphology and the thickness of the coating were evaluated using Scanning Electron Microscopy for different pellets sizes. Based on the results, it can be concluded that there are no significant differences between the enteric coating thickness of the pellets from a batch with non-compliant results in acidic media *versus* the enteric thickness of the pellets from a batch with compliant results in acidic media (Figures 1 and 2). The measurement results for pellets of different sizes are presented in Table II.

However, SEM images (Figures 1 and 2) indicates that for the batch with non-compliant results in acidic media several fissures are observed through the enteric coating. By comparison, the aspect of the enteric coating layer of the batch with compliant results in acidic media is more dense and uniform, therefore assuring a protection in acidic media and proper dissolution profile in buffer stage.

Table II

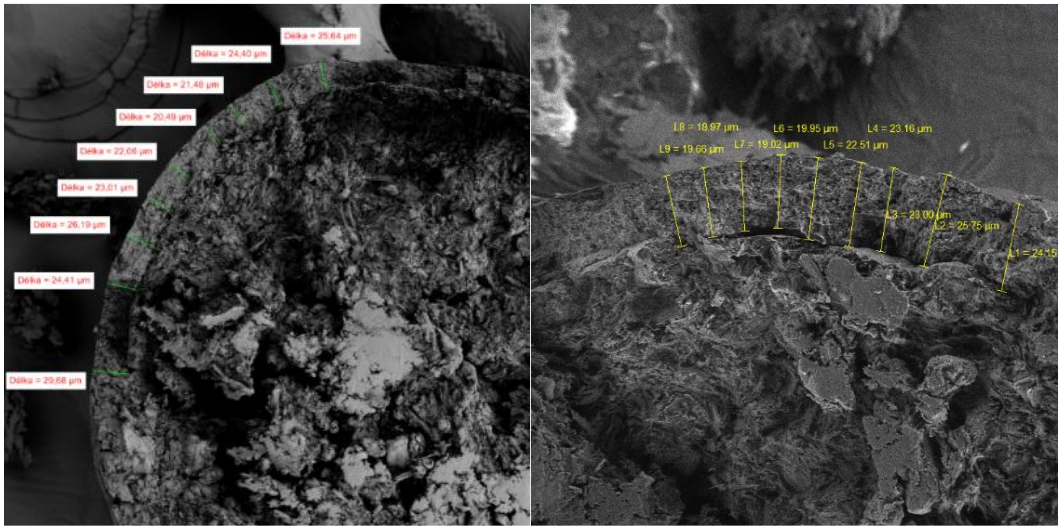
Enteric coating thickness (µm) for pellets originated from a batch with non-compliant results in acidic media and from a batch with compliant results in acidic media for dissolution parameter

Pellet size (µm)	Enteric coating thickness (µm)	
	Non-compliant batch	Compliant batch
< 500	32.3 ± 4.2	24.1 ± 5.6
500 - 600	30.6 ± 4.4	26.6 ± 5.6
600 - 710	31.3 ± 4.1	30.5 ± 6.2
710 - 850	31.5 ± 5.2	31.9 ± 5.2
850 - 1000	30.0 ± 3.5	32.9 ± 5.0

The fissures through the enteric coating can be caused by the coating process or by the mechanical stress during sectioning of the pellets when preparing them for SEM analysis. In either cases, the most probable root cause for the burst-out effect observed in acidic media is the fact that the enteric coating is too brittle.

As part of the investigation process it was determined that for the manufacturing process of all batches the same qualitative/quantitative formula was used, the same excipient sort and suppliers and the same technological process were used.

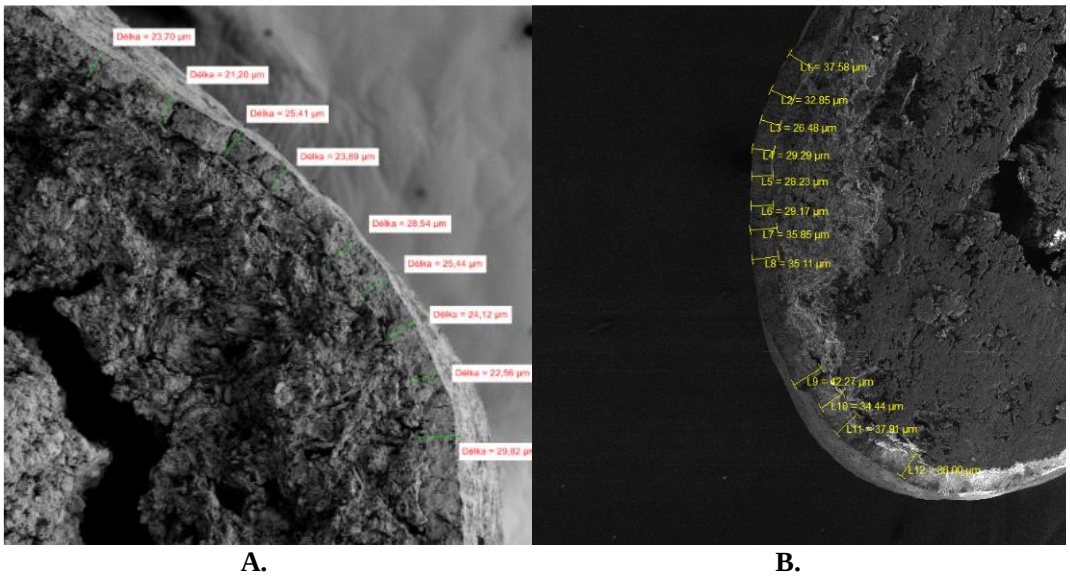
During the coating step, the input parameters, such as inlet air volume (m^3/h), the inlet air temperature (°C) and spraying rate (mL/min), as well as the output parameters, such as product temperature (°C) and outlet temperature (°C) were the same for the first 22 experimental batches. The only parameter that cannot be controlled during the coating step is the inlet air humidity, as it is directly correlated to the external air temperature and humidity.



A. **B.**

Figure 1.

SEM images of pellets with pellet size distribution (PSD) of 500 - 600 µm A. from a batch with non-compliant results in acidic media (*500x*) and B. from a batch with compliant results in acidic media (*1500x*)



A. **B.**

Figure 2.

SEM images of pellets with PSD of 710 - 850 µm from a batch with A. non-compliant results in acidic media (*500x*) and B. a batch with compliant results in acidic media (*300x*)

The calculated and/or the measured absolute humidity of the inlet air for all experimental batches are presented in Table III.

For the experimental batches 11 and 13 - 20, for which the results in acidic media were compliant, the measured absolute humidity was between 4.6 g/kg and 6.7 g/kg. For the experimental batches 9 and 10, the absolute humidity was not measured. The calculated absolute humidity obtained during the day of the coating was between 2.2 g/kg and 5.7 g/kg for batch 9 and between 3.2 g/kg and 6.1 g/kg for batch 10. However, the compliant results for acidic media are correlated with the time of the day in which the coating step was performed. For these batches the coating step was performed when the temperature was higher, and therefore the humidity was higher.

Table III

Calculated and measured absolute humidity for experimental batches 1 - 22 (non-compliant batches depicted in red)

Batch	Air temperature[a], °C		Relative humidity[a], %		Absolute humidity, g/kg			
					Calculated[a,b]		Actual value during coating step	
	Min	Max	Min	Max	Min	Max	Min	Max
Experimental 1	-1	0	90	96	3.1	3.6	na	na
Experimental 2	-1	0	90	96	3.1	3.6	na	na
Experimental 3	-3	1	92	96	2.7	3.9	na	na
Experimental 4	-3	-1	92	96	2.7	3.3	na	na
Experimental 5	-3	-1	92	96	2.7	3.3	na	na
Experimental 6	-4	2	87	98	2.3	4.2	na	na
Experimental 7	-4	2	87	98	2.3	4.2	na	na
Experimental 8	-4	6	80	98	2.2	5.7	na	na
Experimental 9	-4	6	80	98	2.2	5.7	na	na
Experimental 10	0	7	85	99	3.2	6.1	na	na
Experimental 11	3	4	95	99	4.4	5.0	4.6	5.0
Experimental 12	3	4	95	99	4.4	5.0	4.3	4.5
Experimental 13	-1	10	63	95	2.2	7.2	5.2	5.8
Experimental 14	-1	10	63	95	2.2	7.2	4.8	5.3
Experimental 15	-1	10	63	95	2.2	7.2	6.1	6.7
Experimental 16	-2	12	50	99	1.6	8.6	5.3	6.1
Experimental 17	-2	12	50	99	1.6	8.6	6.0	6.6
Experimental 18	-2	12	50	99	1.6	8.6	4.7	5.1
Experimental 19	1	19	48	98	1.9	13.5	4.6	5.0
Experimental 20	1	19	48	98	1.9	13.5	4.8	5.1
Experimental 21			na				2.5	3.6
Experimental 22							3.6	4.0

a – obtained during the whole day when coating step was performed; b – calculated using the Mollier diagram; c – the data is not available as of May, 2019; na – not available

For the experimental batches 1 - 7, for which the results in acidic media are out of specification, the calculated absolute humidity was between 2.2 g/kg and 4.2 g/kg. For experimental batches 21 and 22, for which the results in acidic media are out of specification, the measured absolute humidity during coating was between 2.5 g/kg and 4.0 g/kg. For the experimental batch 12, for which the results in acidic media were borderline compliant, but out of specification for the second sampling point, the measured absolute humidity during coating was between 4.3 g/kg and 4.5 g/kg.

For experimental batch 8, for which the results in acidic media were not compliant in acidic media, the calculated humidity obtained during the day of the coating was between 2.2 g/kg and 5.7 g/kg. However, the out of specification results can be correlated with the time of the day in which the coating step was performed. For this batch, the coating step was performed in the morning when the temperature was lower, and therefore the humidity was lower.

Based on the above results it can be concluded that the optimum absolute humidity of the inlet air should be above 4.5 g/kg, in order to provide an acidic barrier for the pellets.

Taking into consideration the fact that the enteric coating was too brittle due to high drying of the film-coating, the technological parameters were re-evaluated in order to determine if the influence of the inlet air humidity can be reduced. The air volume (m^3/h) and the inlet temperature were decreased in order to form the film-coating at 23 - 25°C (product temperature). Five spraying stages were implemented – for the first four stages the spraying volume (mL/min) was low and increased incrementally between the stages. The duration of the stages were between 5 minutes and 10 minutes and the aim of these coating stages was to form an initial coating layer. The spraying volume (mL/min) for the last spraying stage was maintained constant during the duration of the coating. In this context, three experimental batches were manufactured for which the absolute humidity of the inlet air varied during the coating step (Table IV).

Table IV

Absolute humidity measured during coating process of experimental batches 23 - 25 (Average value ± SD)

Coating step	Duration (min)	Batch		
		Experimental 23	Experimental 24	Experimental 25
Charging (1)	**10**	5.72 ± 0.10	4.92 ± 0.12	3.08 ± 0.04
Heating (2)	**60**	5.87 ± 0.11	4.61 ± 0.21	3.29 ± 0.07
Cooling (3)	**10**	5.7 ± 0.08	4.27 ± 0.14	2.95 ± 0.06
Spraying 1 (4)	**10**	5.7 ± 0.05	4.12 ± 0.09	2.82 ± 0.04
Spraying 2 (5)	**5**	5.56 ± 0.05	3.97 ± 0.10	2.80 ± 0.00
Spraying 3 (6)	**5**	5.55 ± 0.07	3.93 ± 0.08	2.80 ± 0.00
Spraying 4 (7)	**10**	5.62 ± 0.07	4.02 ± 0.12	2.80 ± 0.00
Spraying 5 (8)	**180**	5.67 ± 0.07	3.46 ± 0.39	2.82 ± 0.1
Drying (9)	**90**	5.62 ± 0.07	2.94 ± 0.1	3.2 ± 0.14
Cooling (10)	**20**	5.63 ± 0.08	2.88 ± 0.07	3.24 ± 0.07
Discharging (11)	**40**	5.62 ± 0.06	2.96 ± 0.09	3.19 ± 0.07

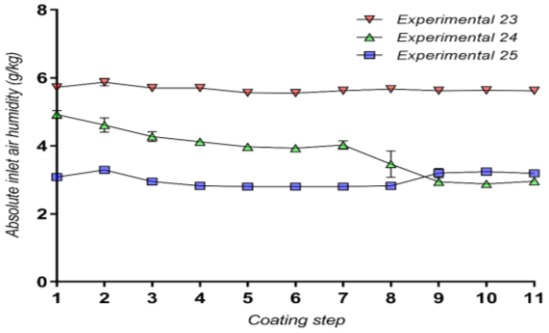


Figure 3.
Evolution of inlet air humidity (%) during coating steps for experimental batches 23 - 25

Individual and average values obtained for experimental batches 23 - 25 are presented in the Table V. For the experimental batch 23, for which the inlet air humidity was constant during all the coating steps and around 5.5 g/kg, the results are compliant for all sampling points.

For the experimental batch 24, for which the inlet air humidity started around 5 g/kg during charging of the matrix pellets in the fluid bed processor and dropped during the coating process to around 3 g/kg, the results are out of specification for the second time point for which their individual results are above 60%.

For the experimental batch 25, for which the inlet air humidity was constant during all the coating steps and around 3 g/kg, the results are borderline compliant for the acidic media and out of specification for the second sampling point for which all the individual results are above 60%.

Table V

Results obtained for study of the *in vitro* release kinetics of the experimental batches 23 - 25 (individual and average values)

		Batch		
		Experimental 23	Experimental 24	Experimental 25
2 hours (acidic medium), % dissolved	P1	1.1	3.7	9.7
	P2	1.4	2.3	9.9
	P3	1.4	3.8	9.6
	P4	1.8	2.9	9.5
	P5	1.7	3.9	9.4
	P6	1.4	2.8	8.6
	Average	**1.4**	**3.2**	**9.5**
2.5 hours % dissolved	P1	47.9	61.5	66.7
	P2	46.3	58.3	62.6
	P3	48.4	61.5	65.1
	P4	47.6	59.5	65.1
	P5	48.6	61.4	66.6
	P6	46.4	58.2	64.3
	Average	**47.5**	**60.1**	**65.1**
6 hours % dissolved	P1	94.3	101.1	101.8
	P2	95.0	100.6	101.8
	P3	95.2	101.0	100.8
	P4	93.2	100.5	101.4
	P5	95.0	101.6	101.2
	P6	94.8	100.5	102.0
	Average	**94.6**	**100.9**	**101.5**

Although the influence of the inlet air humidity on the *in vitro* release of the pellets is still present, the changes of the technological parameters reduced the impact on the *in vitro* dissolution parameter. For example, for experimental batches 21 and 25 having similar inlet air humidity during coating step (around 3 g/kg) significant differences were observed for the acid resistance of the film-coat – for experimental batch 21 a release of 28% active substances was observed after 2 hours in acidic media *versus* 9.5% release of active substance obtained for batch 25.
Further changes of the manufacturing process in order to form the film coat below 23°C (product temperature) cannot be implemented due to the fact that that sticking of the pellets was observed.

Conclusions

Based on the results obtained for 25 experimental batches, it can be concluded that the forming of the coating is highly influenced by the inlet air humidity during coating step, due to the fact that a low humidity determines a brittle coating. The impact is most visible for the gastro-resistance step of the *in vitro* dissolution, where a burst-out effect was observed for pellets with brittle coating layer.
Based on the experimental results, the optimum absolute humidity of the inlet air should be above 4.5 g/kg, in order to provide an optimum acidic barrier for the pellets.
Values of absolute humidity of the inlet air during coating step between 4.0 g/kg and 4.5 g/kg, generates a product with borderline compliant results in acidic media according to the in-force MEA and FDA requirements for gastro-resistance and out of specification results for the second point, when the film is formed at 28 - 30°C (product temperature).
For values of the inlet air during coating step below 4.0 g/kg a burst out effect was observed in acidic media, with an *in vitro* release of active substance between 14 and 35%, when the film is formed at 28 - 30°C (product temperature).
The optimization of the process parameter in order to form the film-coating at 23 - 25°C (product temperature) reduces the impact of the inlet air humidity.
Further changes of the manufacturing process in order to form the film coat below 23°C (product temperature) cannot be implemented due to the fact that that sticking of the pellets was observed.
In this context, it can be concluded that the inlet air humidity during spraying step is a critical process parameter for the *in vitro* release of modified release pellets.

Acknowledgement

This paper was financially supported by "Carol Davila" University of Medicine and Pharmacy through Contract No. CNFIS-FDI-2020-0604 (MEDEX-III) funded by the Ministry of Education and Research, Romania, from the Institutional Development Fund for Public Universities - FDI 2020.

Conflict of interest

The authors declare no conflict of interest.

References

1. Akanny E, Bourgeois S, Bonhomme A, Commun C, Doleans-Jordheim A, Bessueille F, Development of enteric polymer-based microspheres by spray-drying for colonic delivery of *Lactobacillus rhamnosus* GG. *Int J Pharmaceut.*, 2020; 584: 119414: 1-12.
2. Bendas ER, Abdelbary AA, Instantaneous enteric nano-encapsulation of omeprazole: Pharmaceutical and pharmacological evaluation. *Int J Pharmaceut.*, 2014; 468(1-2): 97-104.
3. Council of Europe. European Pharmacopoeia, 8th edition. Council of Europe, Strasbourg, France, 2014.
4. Cruz L, Assumpção E, Andrade SF, Conrado DJ, Guterres SS, Pohlmann AR, Microencapsulation of sodium alendronate reduces drug mucosal damage in rats. *Drug Deliv.*, 2010; 17(4): 231-237.
5. Dukić-Ott A, De Beer T, Remon JP, Baeyens W, Foreman P, Vervaet C, *In-vitro* and *in-vivo* evaluation of enteric-coated starch-based pellets prepared *via* extrusion/spheronisation. *Eur J Pharmaceut Biopharmaceut.*, 2008; 70(1): 302-312.
6. Dumitrașcu PA, Stecoza CG, Gavrilescu M, Alecsandrescu C, Ivancencu A, Anuța V, Popa L, Ghica MV, Dinu-Pîrvu CE, The impact of the lubrication step with magnesium stearate on the Quality Target Product Profile of a modified release oral dosage form containing a BCS class II active pharmaceutical ingredient. *Farmacia*, 2020; 68(3): 526-531.
7. Edgar KJ, Cellulose esters in drug delivery. *Cellulose*, 2007; 14(1): 49-64.
8. European Medicines Agency. Guideline on quality of oral modified release products EMA/CHMP/QWP/ 428693/2013, 2014, www.ema.europa.eu.
9. Gou J, Liang Y, Miao L, Chao Y, Zhang Y, Yin T, He H, Tang X, The promoting effect of enteric materials on the oral absorption of larotaxel-loaded polymer-lipid hybrid nanoparticles. *Eur J Pharmaceut Sci.*, 2018; 124: 288-294.
10. Hîrjău M, Miron DS, Anuța V, Lupuliasa D, Ghica MV, Jinga V, Dinu-Pîrvu CE, Evaluation of experimental multi-particulate polymer-coated drug delivery systems with meloxicam. *Coatings*, 2020; 10(5): 490: 1-22.
11. Holmes PF, Bohrer M, Kohn J, Exploration of polymethacrylate structure–property correlations: Advances towards combinatorial and high-throughput methods for biomaterials discovery. *Progress in Polymer Sci.*, 2008; 33(8): 787-796.
12. Maderuelo C, Lanao JM, Zarzuelo A, Enteric coating of oral solid dosage forms as a tool to improve drug bioavailability. *Eur J Pharmaceut Sci.*, 2019; 138: 1-15.
13. Nair AB, Gupta R, Kumria R, Jacob S, Attimarad M, Formulation and evaluation of enteric coated tablets of proton pump inhibitor. *J Basic Clin Pharm.*, 2010; 1(4): 215-221.

14. Nesbitt RU, Goodhart FW, Gordon RH, Evaluation of polyvinyl acetate phthalate as an enteric coating material. *Int J Pharmaceut.*, 1985, 26(3): 215-226.
15. Ogwal S, Xide T, Biovailability and stability of erythromycin delayed release tablets. *Afr Health Sci.*, 2001; 1(2): 90-96.
16. Romanian National Meteorology Agency, Statistical data on temperature and relative humidity, www.meteo romania.ro.
17. Rowe RC, Sheskey P, Quinn M, Handbook of pharmaceutical excipients, 6th edition. Pharmaceutical Press, London, UK, 2009.
18. Thakral S, Thakral NK, Majumdar DK, Eudragit®: a technology evaluation. *Exp Opin Drug Deliv.*, 2013; 10(1): 131-149.
19. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry, 2017, www.fda.gov.
20. Vasincu IM, Profire L, Apotrosoaei M, Petrovici AR, Pinteală M, Jităreanu A, Constantin S, Optimization and influence of some physico-chemical parameters on the synthesis of chitosan-tripolyphosphate nanoparticles. *Farmacia*, 2019; 67(6): 986-993.
21. Wen H, Park K, Oral controlled release formulation design and drug delivery: theory to practice. John Wiley & Sons, Hoboken, New Jersey, USA, 2011.