

PREPARATION AND CHARACTERISATION OF PELLETS CONTAINING A NON-STEROIDAL ANTIINFLAMMATORY DRUG, COATED WITH AN ENTERIC POLYMER

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Abstract

The aim of this study was to produce and characterise pellets containing a non-steroidal antiinflammatory (NSAID) drug, coated with an enteric polymer. The drug-loaded pellets were prepared by extrusion-spheronization using microcrystalline cellulose (Avicel® PH 101) as a spheronization aid, lactose as a filler and polyvinylpyrrolidone K30 as a binder. The coating of the pellets was carried out in a top-spray fluid bed equipment using an enteric coating polymer (Acryl-EZE®). The pellets were analysed for the following physical parameters, relevant for subsequent processing of the pellets: size distribution, circularity, bulk density. A dissolution study was performed using two dissolution media with different pH values, corresponding to the pH values of the intestinal environment (pH 6.8 phosphate buffer and 7.2 phosphate buffer). The pellets have shown characteristics suitable for hard-capsule filling. The dissolution profiles revealed an enteric drug release.

Rezumat

Obiectivul acestui studiu a fost prepararea și caracterizarea unor pelete conținând un medicament antiinflamator nesteroidian, acoperite cu un polimer enteric. Peletele cu substanță activă au fost obținute prin procedeul de extrudare-sferonizare, folosind celuloză microcristalină ca agent de sferonizare, lactoza ca diluant și polivinilpirolidona (sub formă de soluție apoasă) ca liant. Pentru acoperirea enterică a peletelor s-a utilizat un polimer de acoperire enterică (Acryl-EZE®), folosind tehnica acoperirii în pat fluidizat. Au fost analizați următorii parametri fizici ai peletelor rezultate (relevanți pentru procesarea ulterioară): distribuția după mărime, circularitate și densitate aparentă. Testul de dizolvare s-a efectuat în două medii de dizolvare cu pH diferit, corespunzând valorilor de pH ale mediului intestinal (tampon fosfat pH=6,8 și tampon fosfat pH=7,2). Peletele au prezentat caracteristici adecvate pentru introducerea în capsule gelatinoase tari. Profilul de dizolvare a substanței active a relevat o eliberare enterică.

Keywords: pellets, extrusion-spheronization, enteric coating, NSAID drug, dissolution testing.

Introduction

Pellets, as multiparticulate drug delivery systems, generate an increasing interest as dosage forms, due to their numerous pharmacological and technological advantages over single-unit dosage forms, like tablets [1, 2].

Pellets can be homogenously distributed in the gastro intestinal (GI) tract, thus maximizing drug absorption and reducing peak plasma fluctuations, minimizing the risk of local gastric irritation and dose dumping, decreasing dosing frequency and increasing patient compliance, improving the safety and efficacy of the drug [3-6]. In addition, their spherical shape is ideal for coating with various films. Enteric-coated pellets are particularly suitable for the administration of drugs that are unstable in the gastric fluid, that cause the irritation of the gastric mucosa or that are absorbed at the duodenal or intestinal level [7].

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis. Its use is limited by the high incidence and severity of its adverse effects associated with long-term administration of oral immediate-release dosage forms (tablets, capsules).

Therefore, it is adequate to formulate a NSAID, respectively indomethacin, in a multiparticulate drug delivery system, such as pellets, which can be filled in hard gelatin capsules, a pharmaceutical dosage form well-accepted by the patients, with the aim of reducing its gastric adverse effects, such as erosions, ulcerations and bleeding [8, 9].

Currently, there are various technological options for the manufacture of pellets, which have many practical applications [10, 11, 14]. Among the pelletisation processes available, extrusion-spheronization is one of the widely-used and thoroughly investigated methods. It is a multistage process involving dry mixing of the powder components (drug and excipients), wet granulation, extrusion of the wet mass, spheronization of the extrudates, drying and sieving of the resulting pellets.

Coating the pellets with polymeric films of different nature or thickness is useful in controlling the drug release rate. For the enteric coating of pellets, polymers for which the solubility in water is pH-dependent, or polymers insoluble in water but permeable to it, can be used.

The aim of this study was to prepare pellets with a NSAID drug (indomethacin as a model drug) by extrusion-spheronization, to characterise the resulting pellets and investigate the influence of an enteric pH-dependent coating agent (Acryl-EZE[®]) on the *in vitro* dissolution of the drug from the pellets, as an indicator of their *in vivo* performance. The results showed that extrusion-spheronization is a feasible method to obtain pellets with

suitable characteristics and that by coating them with Acryl-EZE® (with 10% weight gain), a release of the drug at pH values, similar to those in the intestinal environment, is achieved.

Materials and Methods

Materials

Indomethacin (Terapia Ranbaxy, Romania), Microcrystalline cellulose (JRS Pharma, Germany), Lactose monohydrate (De Melkinustrie Veghel, Netherland), Polyvinylpyrrolidone K30 (Merck, Germany), Acryl-EZE® (Colorcon), hard gelatin capsules (Gelcaps, Romania).

All the materials used for the formulation and manufacture of the pellets comply with compendial or manufacturer's requirements.

Equipments

Extruder Model 25 (Caleva Process Solutions Ltd., UK), Spheronizer Model 120 (Caleva Process Solutions Ltd., UK), Caleva Minicoater/Drier 2 (Caleva Process Solutions Ltd., UK), Erweka 800 DT Apparatus 2 USP (Erweka, Germany), CISA Sieve Shaker (CISA Cedaceria Industrial, Spain), VanKel Tap Density Tester Model 50-1300 (ValKel Industries, NJ, USA), Visioscan (Courage+Khazaka Electronics GmbH, Germany), ImageJ Software, Spectrophotometer Jasco UV-Vis V-530 (Spectra Manager for Windows 95/NT vers. 1.54.03.) were used during the experiment.

Methods

The preparation of indomethacin pellets by extrusion-spheronization

The optimal formula and processing conditions were established in previous experiments [18]. Indomethacin (3.5 g) was uniformly dispersed in a microcrystalline cellulose:lactose blend (50:80).

The dry mixture was sprayed with 70 grams of a 2.5% polyvinylpyrrolidone K30 (PVP K30) aqueous solution, until a wet mass, adequate for extrusion, was obtained. The wet mass was extruded into short, cylindrical extrudates, using the extruder with screen openings of 1 mm.

The resulting extrudates were fed into the spheronizer, equipped with a cross-hatch pattern friction plate of 12 cm in diameter. The spheronization process was performed at a speed of 1000 rpm for 5 minutes. Because the pellets had a significant content of residual moisture at this stage, they were oven-dried at 40°C for 1 hour before further processing. The pellets were then sieved and the fractions larger than 1.18 mm and

smaller than 0.8 mm were discarded. The pellets with a size withing the range of 0.8-1.18 mm were subsequently coated with Acryl-EZE®.

Coating the indomethacin pellets by fluid bed technology

Acryl-EZE® is a water-dispersible, fully formulated, dry coating system. It contains Eudragit L 100-55, methacrylic acid copolymer type C respectively [12]. Acryl-EZE® is a coating material for which the solubility in water is pH-dependant. It is not affected by the acidic conditions in the stomach, but it dissolves in environments with higher pH values, such as the intestine.

Preparing the coating dispersion

The 10% Acryl-EZE® coating aqueous dispersion was prepared according to the coating polymer manufacturer's guidelines.

Coating the pellets with the enteric coating dispersion

30 grams of pellets were transferred into the top-spray fluid bed minicoater and coated with the 10% aqueous dispersion of Acryl-EZE® which was continuously stirred during spraying. The pellets were coated to a 10% weight gain (based on the initial weight of the pellets). The operating conditions during the coating process were as follows:

Table I

Operating conditions in the coating stage of the pellets

<i>Operating conditions</i>	<i>Values</i>
Inlet air temperature (°C)	40°C
Pellet bed temperature (°C)	40°C
Inlet air flow rate (m/sec)	8.3
Liquid flow rate (mL/hour)	18
Atomization pressure (psi)	10
Size range of pellets (mm)	0.8 – 1.18

The characterisation of the pellets

Size and size distribution of the uncoated pellets

The pellets were sieved for 10 minutes using a CISA Electromagnetic sifter RP-09 equipped with a set of calibrated sieves (1.18, 0.8, 0.6, 0.325, 0.25 mm), fixed at an amplitude of 10 x 0.1 mm. After sieving, the fraction that remained on each sieve was weighed.

Circularity

This parameter was determined for both the uncoated and coated pellets. Photographs of 50 pellets from each type were taken using a Visioscan® VC 98 camera. The circularity of the photographed pellets was evaluated using the software ImageJ software (National Institute for Health of the USA). The software returns a value for the circularity of a photographed object.

Tap density and bulk density

The tap density and bulk density of the uncoated pellets was determined using the method described in the European Pharmacopoeia, 6th edition [13].

The compressibility index (Carr's index) and Hausner ratio were calculated as an expression of the flow characteristics of the pellets.

Dissolution test

Capsules filled with coated pellets, corresponding to 20 mg indomethacin per capsule, were used for the dissolution study, using a dissolution apparatus 2 (paddle method), according to USP 31 National Formulary 25, in the following conditions:

Table II

Conditions of the dissolution test

<i>Dissolution media</i>	- pH 6.9 phosphate buffer, respectively - pH 7.2 phosphate buffer
<i>Volume of dissolution media</i>	900 mL
<i>Temperature of dissolution media</i>	37°C
<i>Rotation speed of the paddles</i>	50 rpm

Samples of 0.5 mL were withdrawn at preset time intervals (0, 5, 10, 20, 30, 45, 60 and 90 minutes) and replaced with dissolution media to maintain a constant volume of media during the test. The samples were filtered through regenerated cellulose filters PhenexTM, Phenomenex, 0.45 µm, diameter 15 mm, not sterile, and then diluted with dissolution media. The absorbance of the diluted samples was spectrophotometrically determined against the dissolution media, at a wavelength of 315 nm.

Results and Discussion

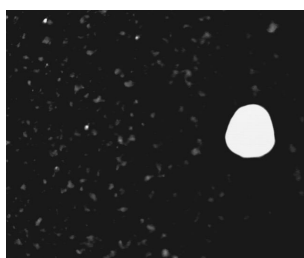
Characteristics of the pellets

The physical characteristics of the pellets are shown in table III and figures 1 and 2.

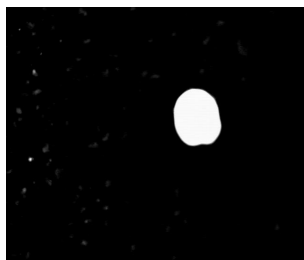
Table III

Physical characteristics of the pellets

<i>Parameter</i>	<i>Uncoated pellets</i>	<i>Pellets coated with Acryl – EZE[®]</i>
Appearance	Spherical white, slightly yellow pellets, with a slightly rough surface	Spherical white pellets, with a smooth surface
Circularity (average value for 50 pellets)	0.7891	0.8264
Carr's index	4.504	Test was performed only on the uncoated pellets
Hausner ratio	1.102	Test was performed only on the uncoated pellets
Fraction of pellets on the 0.8 mm sieve	83.49%	Test was performed only on the uncoated pellets

**Figure 1.**

Photograph of uncoated pellet (taken with Visioscan® VC 98 camera)

**Figure 2.**

Photograph of pellet coated with Acryl – EZE® (taken with Visioscan® VC 98 camera)

The results showed that the chosen formula imparts a spherical shape, strength and integrity to the pellets and excellent flow characteristics, thus they have adequate properties for a uniform filling of the capsules.

Dissolution test on the pellets coated with Acryl-EZE®

The results of the dissolution test are shown in the following tables and figures.

Table IV
Percentages of indomethacin released in pH 6.8 dissolution media

<i>Time (min)</i>	<i>Vessel 1</i>	<i>Vessel 2</i>	<i>Vessel 3</i>	<i>Vessel 4</i>	<i>Vessel 5</i>	<i>Vessel 6</i>
0	0	0	0	0	0	0
5	4.50	4.50	4.50	4.50	4.50	4.50
10	7.54	7.99	6.86	8.21	8.33	7.43
20	12.83	12.26	11.03	11.93	12.38	11.14
30	16.76	17.21	17.78	16.43	17.66	18.11
45	22.50	21.26	20.14	19.35	20.59	23.51
60	27.56	24.41	25.65	24.30	24.30	28.80
90	30.71	32.40	33.75	36.68	31.73	34.31

Table V
Descriptive statistics for the release of indomethacin from pellets in pH 6.8
dissolution media

Time (min)	Average	Standard Deviation	CV (%)	(+)	(-)
0	0	0	-	0	0
5	4.50	0.00	0.00	0.00	0.00
10	7.73	0.55	7.17	0.60	0.86
20	11.93	0.72	6.00	0.90	0.90
30	17.33	0.64	3.72	0.79	0.90
45	21.23	1.55	7.29	2.29	1.88
60	25.84	1.93	7.45	2.96	1.54
90	33.26	2.13	6.39	3.41	2.55

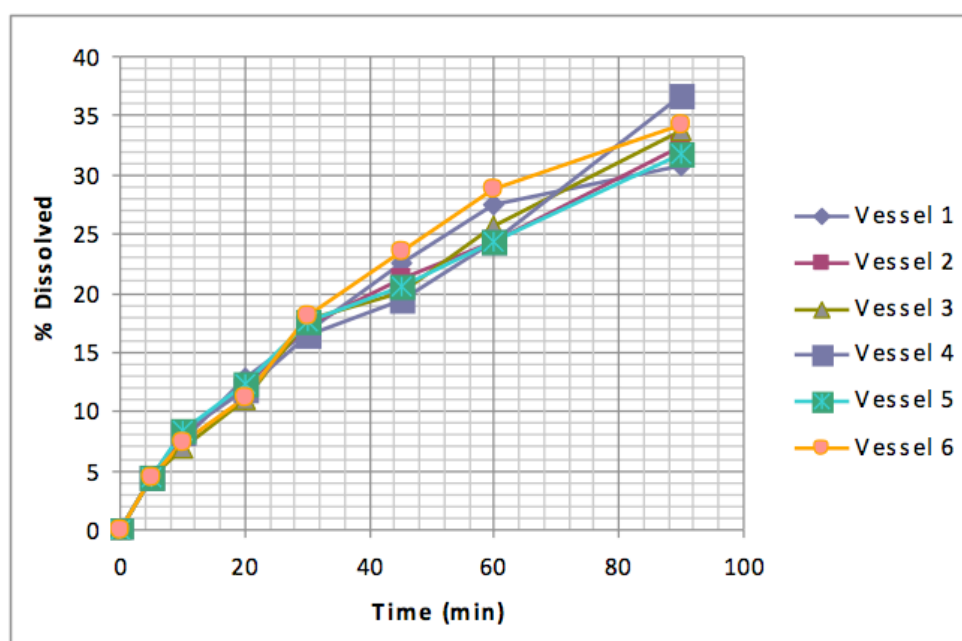
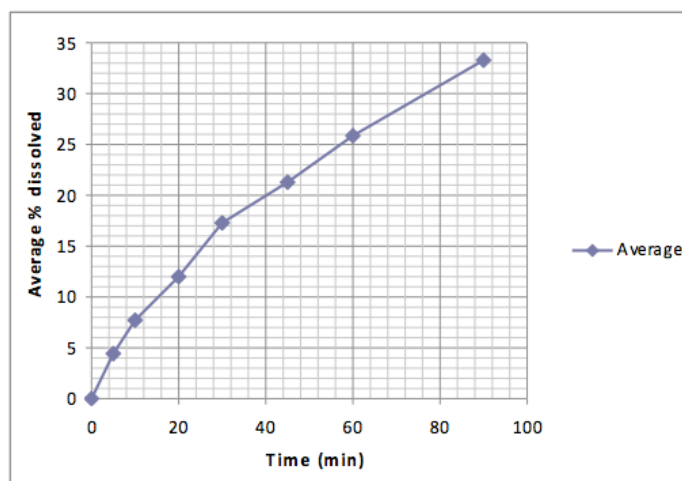


Figure 3.
The dissolution profiles of indomethacin released in pH 6.8 dissolution media

**Figure 4.**

The average percentages of indomethacin released in pH 6.8 dissolution media

Table VI.

Percentage of indomethacin released in the pH 7.2 dissolution media

<i>Time (min)</i>	<i>Vessel 1</i>	<i>Vessel 2</i>	<i>Vessel 3</i>	<i>Vessel 4</i>	<i>Vessel 5</i>	<i>Vessel 6</i>
0	0	0	0	0	0	0
5	11.93	10.35	14.63	12.38	13.30	11.93
10	17.21	17.55	19.01	16.65	17.10	20.03
20	27.11	27.11	25.20	25.54	25.76	26.55
30	31.73	36.45	36.79	31.05	33.86	30.71
45	43.43	48.94	43.20	37.91	43.76	40.05
60	45.56	50.85	54.79	44.10	51.19	47.81
90	55.91	61.31	56.03	50.40	63.23	53.33

Table VII.

Descriptive statistics for the dissolution test in the pH 7.2 dissolution media

Time (min)	Average	Standard Deviation.	CV (%)	(+)	(-)
0	0	0	-	0	0
5	12.42	1.44	11.62	2.21	2.07
10	17.93	1.31	7.29	2.10	1.28
20	26.21	0.83	3.15	0.90	1.01
30	33.43	2.70	8.09	3.36	2.72
45	42.88	3.76	8.76	6.06	4.97
60	49.05	3.97	8.10	5.74	4.95
90	56.70	4.82	8.50	6.53	6.30

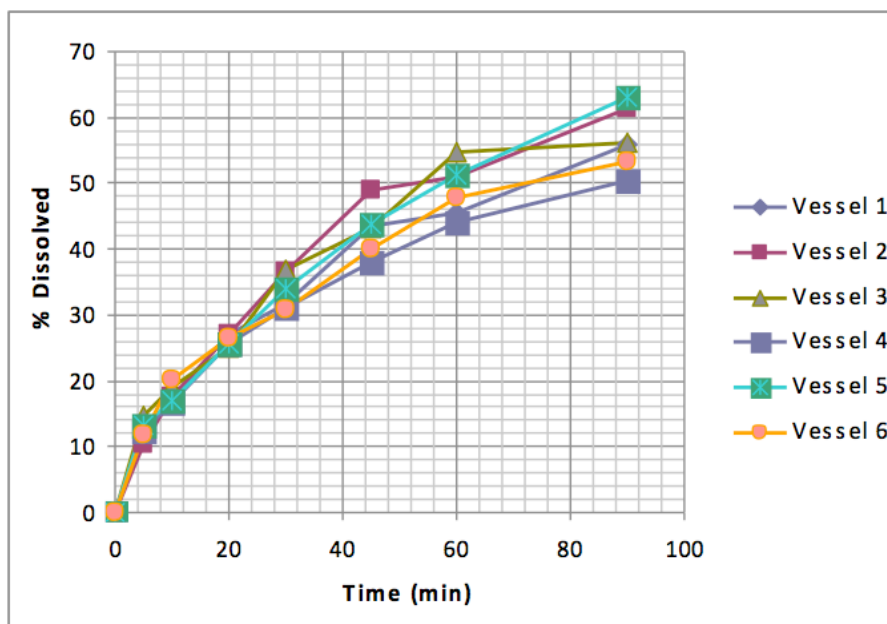


Figure 5.

The dissolution profiles of indomethacin released in the pH 7.2 dissolution media

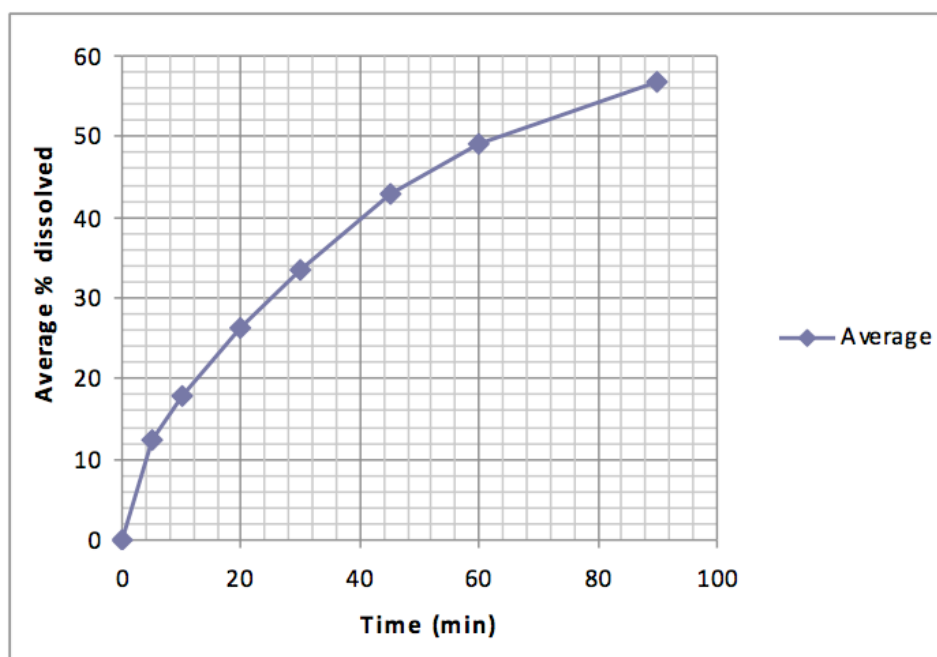


Figure 6.

The average percentages of indomethacin released in the pH 7.2 dissolution media

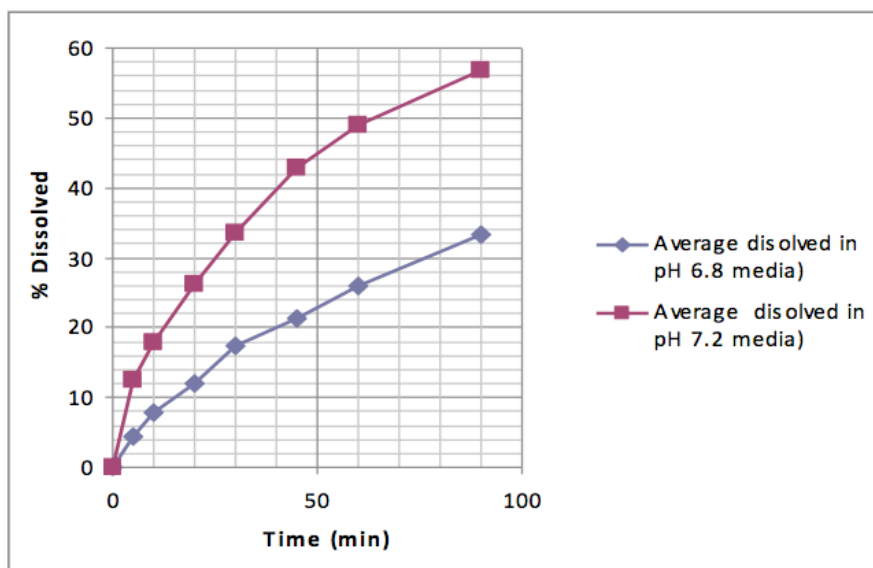


Figure 7.

Comparative dissolution profiles of indomethacin from pellets in both dissolution media

The dissolution profiles of indomethacin from the Acryl – EZE[®]-coated pellets confirm the dependency of the release on the pH value of the dissolution media. The percentage of dissolved drug after 90 minutes was of about 33% in the pH 6.8 phosphate buffer, respectively of about 58% in the pH 7.2 phosphate buffer. This can be attributed to the higher solubility of indomethacin as the pH value increased.

Conclusions

This study describes the preparation by extrusion-spheronization, characterisation and *in vitro* dissolution study of indomethacin pellets coated with Acryl-EZE[®] in a fluid-bed minicoater.

The results of the tests showed the feasibility of the preparation of enteric-coated pellets containing a NSAID and that by coating the multiparticulate system with Acryl-EZE[®] to a 10% weight gain, an enteric release of the drug from the pellets can be obtained.

Acknowledgements

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References

1. Ghebre-Sellasie I., Knock A., Pelletization Techniques, in J. Swabrick (Ed.), *Encyclopedia of Pharmaceutical Technology*, 3rd ed. 2007, Informa Healthcare, New York, London, 2651 – 2662;
2. Bechgaard H., Hagerman N.G., Controlled-release multi-units and single-unit doses. A literature review, *Drug Dev. Ind. Pharm.* 1978, 4, 53 – 67;
3. Bashaiwoldu F., Abraham B., Podczek F., Newton J.M., The application of non-contact laser profilometry to the determination of permanent structural change induced by compaction of pellets. II. Pellets dried by different techniques, *Eur. J. Pharm. Sci.* 2004, 22, 55 – 61;
4. Chopra R., Podczek F., Newton J.M., Alderborn G., The influence of pellet shape and film coating on the filling of pellet hard shell capsules, *Eur. J. Pharm. Biopharm.* 2002, 53, 327 – 333;
5. Hu L., Lui J., Tang X., Zhan Q., Preparation and *in vitro/in vivo* evaluation of sustained-release metformin hydrochloride pellets, *Eur. J. Pharm. Biopharm.* 2006, 64, 185 – 192;
6. Gopal V.S., Multiparticulate Drug Delivery System of Accelofenac: Development and *in vitro* studies, *Drug Dev Ind. Pharm.* 2009, 35, 252 – 258;
7. Erkoboni K. A., Extrusion/spheronization for granulation, in Parikh D. (Ed.), *Handbook of Pharmaceutical Technology*, Marcel Dekker Inc., New York, 1997, 277-322;
8. Rădulescu F.Ş., Dumitrescu I.B., Miron D.S., Lupuliasa D., Andrieş A., Drăgănescu D., The *in vitro* release profiles of nimesulide from oral solid dosage forms, in compendial and modified physiological media, *Farmacia*, 2010, 58(4);
9. Elchidana P.A., Deshpande S.G., Microporous membrane drug delivery system for indomethacin, *Journal of Controlled Release*, 59, 1999, 279 – 285.
10. Balasz C., Leucuța S.E., Influența Kollicoat SR 30D asupra dizolvării clorhidratului de diltiazem din forme farmaceutice solide experimentale multiparticulate acoperite, *Farmacia*, 2004, vol. LII, 2, 5 – 13;
11. Andreea Stanescu, Lacramioara Ochiuz, Ileana Cojocaru, Iuliana Popovici, Dumitru Lupuleasa, The influence of different polymers on the pharmaco-technological characteristics of propiconazole nitrate bioadhesive oromucosal tablets., *Farmacia*, 2010, 58(3), 279-289.
12. *** Colorcon Acryl-EZE® Technical specification, http://www.colorcon.com/literature/marketing/mr/Delayed%20Release/Acryl-EZE/English/77364_Colorcon_20Acryl-EZE_20PIB_final.pdf
13. *** European Pharmacopoeia, 6th edition, 2008, Strassbourg.
14. I. Tomuta, L. Vlase, Adina Popa, S.E. Leucuta, *In vitro - in vivo* evaluation of a novel drug delivery system for colonic targeting, *Farmacia*, 2010, 58(3), 368-377.

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