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The effect of excipients on captopril release from preparations disintegrating in the oral cavity (ODT)

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Abstract: *Captopril is often used to treat hypertension in newborns, infants and the elderly. Orodispersible tablets (ODT) may be a beneficial solution when given to this group of patients. For this purpose, tablets were made and the influence of excipients on the disintegration of tablets and the release of captopril from them was examined. The tablets were obtained by direct compression. The disintegration time was tested in water.The dissolution test was carried out in a paddle apparatus in 0.1 M HCl solution. The captopril content was determined by spectrophotometric method.In order to evaluate the process of disintegration and release of captopril, crospovidone was used in concentrations of 5% and 10%, as a superdisintegrant and mannitol, sorbitol and hypromellose as filling substances, and Avicel in a concentration of 20% and 40% as a filler and disintegrant.The optimized tablets, containing hypromellose (11.36%), glucose (11.36%), Avicel (40%) and crospovidone (5%), showed suitable disintegration time (14 s). An appropriate and complete dissolution profile within 2 minutes was also achieved for this formulation. A correlation was also observed between the disintegration time and the captopril release rate.*

Keywords: *ODTs; disintegration; release; excipients, captopril.*

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I. Introduction

Rapid disintegration of tablets, within 30 seconds and less, leads to rapid release of the active ingredient without the need to chewing or additional water.[1,2,3]. The advantage of ODTs is also the small amount of saliva necessary for their disintegration, which is extremely important in the case of older people with less saliva production.

Orally disintegrating tablets contain ingredients masking the taste of the drug substance, which can provide a pleasant cooling effect (mannitol) and give a sweet, fruity aroma, providing patients with comfort of use.[3,4,5,6]. ODTs allow rapid absorption through the mucosa of the mouth, throat and stomach. Absorption of the drug before going through the stomach can improve the bioavailability. ODT due to bypass liver first pass metabolism, in a shorter time allow to achieve therapeutic concentrations of the active substance in the body.[7].

Captopril is used to treat hypertension in newborns, young children [1] and the elderly, and in the case of congestive heart failure in children at an oral dose of 0.5-6 mg/kg.[8]. Pediatric, geriatric and dysphagia patients are special target groups in whom ODT have the greatest benefits. The size of the tablets is often an obstacle to treatment and discourages the next dose. In pediatrics, the most common form is a liquid dosage form that gives a quick effect and allows an individual dosing schedule. However, there is a problem of stability of this drug form associated with the drug substance itself (appropriate pH, frequency of opening the packaging).[9]. Captopril is most stable in a solution with pH <3.5 (mainly pH 1.2), and increasing the pH above 4 significantly accelerates its inactivation.[10]. Thabet et al tried to use in children enalapril maleate in the form of oral soluble minitablets, which were dissolved in water and other liquids immediately before administration (apple juice, orange juice). As a result of the stability test of 240 minutes from dispersing, they found that the orally disintegrating tablets were stable at this time, it is only advisable to prepare the dispersion in water due to the prolonged disintegration time in other liquids.[11].

Difficulty swallowing (dysphagia) can lead to patients abandoning therapy. Such persons often refuse to take the drug or spit it out after application.[12,13,14,15]. Dysphagia occurs in various age groups and affects approximately 1.7-11.3% of the total population.[16]. Many ODTs on the market are directed to older patients with central nervous system disorders (Alzheimer's disease, schizophrenia). Attempts were made to use ODTs obtained by lyophilization in neurogenic bladder dysfunction caused by damage to the central nervous system and resulting in urinary incontinence, including Alzheimer's disease, multiple sclerosis.[17]. The aim of the work was to obtain anorally disintegrating preparation, characterized by the shortest possible disintegration time, and

at the same time ensuring adequate mechanical resistance and pharmaceutical availability. According to the Eur. Pharm. 7.0 orodispersible tablets should disintegrate in less than 3 min. Food and Drug Administration in Guidance for Industry (FDA) recommends that this time should not exceeded 30 s (The Eur. Pharm. 7.0, 2010). The rapid dissolution effect can be achieved by using methods such as wet granulation, molding, spray drying, freeze drying and sublimation. To get an immediate disintegration of tablets in the mouth, they are made of very porous matrices, which makes the tablets fragile or brittle, often requiring special packaging. The problem also concerns high production costs.[18]. Among the technologies used to obtain ODTs, the direct compression method is of particular importance due to the numerous advantages of technology (low cost, ease and simplicity) and stability of the final form of the drug. The possibility of direct tableting is conditioned by the use of appropriate excipients.

II. Material And Methods

II.1. Materials

As the active substance for the preparation of tablets, captopril was used; serial numer 0000007451, distributor - Polfarmex S.A. As auxiliary substances were used: lactose (Eurochem BGD Sp.zoo), anhydrous glucose (Eurochem BGD Sp.zoo), D-sorbitol, series 017K0092, Sigma, D-mannitol, series PP / 2016/06866, Lachner, hypromellose HP -55 Shin - Etsu Chemical Co., Ltd., Avicel® PH - 101 Bio Chemistry Fluka, crospovidone, A0353770 series, Acros Organics, magnesium stearate, series 0726/02/11, POCH SA, 36% hydrochloric acid; lot No. 130810, POCH S.A.
All substances were analytically pure and complied with quality standards.

II.2. Method of captopril determination

The quantitative determinations of captopril were made by spectrophotometric method using a Cecil CE 3021, 3000 Series spectrophotometer. The maximum absorbance was determined on the basis of the captopril spectrum in an aqueous solution in the range of 190 to 350 nm.Based on the obtained spectrum, a wavelength of 195 nm was chosen for further determinations. The absorbance vs. concentration curve was drawn up, which is described by the equation y=0,0616x+0,0005 and the regression coefficient $R^2 = 0,9982$; $p < 0.01$; linearity up to 20 mg /dL. The photometric accuracy of the spectrophotometer was ± 0.005 A.
For the chosen wavelength range, spectra of all the auxiliaries used in the technological process were made.It was found that none of the substances used presented maximum of absorption at 195 nm and should not affect the results of the captopril quantitative determination.

II.3. Preparation of powder mixtures

The selection of excipients was aimed at obtaining the shortest possible disintegration time of tablets (less than 30 s) and release of the entire amount of captopril in the shortest time. For the preparation of the tablet mass, single substances as a disintegrant or in combination were used, and various amounts were used: sodium alginate, microcrystalline cellulose, methylcellulose, hypromellose, carmellose sodium and crospovidone. After preliminary tests for orally disintegrating tablets, substances were selected which ensured disintegration of the drug form in a time not exceeding 30 s: microcrystalline cellulose and crospovidone.

The first step of the research was to prepare 12 formulations of powder mixtures. As the active ingredient, captopril in the amount of 12.5 mg per tablet was added to each formulation, which was 31.25% of the tablet mass. A mixture of excipients was added in portions to the powdered drug substance and mixed thoroughly.

As a filler in all formulations, microcrystalline cellulose (Avicel) was used in amount of 20 and 40% of the tablet mass. As the next filling substances were used: mannitol in F-I - F-IV formulations, sorbitol in F-V - F-VIII formulations and hypromellose in F-IX - F-XII formulations. In order to compare the effect of lactose and glucose on the disintegration time of tablets, glucose was add to the formulations marked as FI, F-III, FV, F-VII, F-IX, F-XI and lactose to the formulations F-II, F-IV, F-VI, F-VIII, FX, F-XII. Formulations containing 20% of microcrystalline cellulose (Avicel) contained 10 % crospovidone as the disintegrant, while formulations containing 40% of Avicel contained 5% of crospovidone. The composition of powder mixtures and formulations is shown in Table 1.

II.3.1. Evaluation of properties of powder mixtures

Bulk mass before and after whipping was determinated according to Polish Pharmacopoeia, 11th edition, 2017 [19]. 100 g of the dry weight was weighed and introduced into a 250 ml graduated cylinder without compacting. The apparent volume occupied by the powder for each formulation was read, and then the bulk volume for each formulation was calculated.

Subsequently, the powder mass in the cylinder was whipped in the STAV-II volume apparatus of J. Engelsmann AG for 1 minute and the powder volume was read. Next, the bulk mass and the bulk density before

and after whipping were calculated [19]. On the basis of bulk mass and bulk density, the coefficient of powder compactness and powder flow were determined – Carr's index (IC) and Hausner coefficient (IH).

II.4. Preparing of tablets

Magnesium stearate was added to the obtained powder mixtures (F-I-F-XII) as a lubricant directly before tableting proces. The tablet mass was compressed in an Erweka impact tablet press machine, type AR 400, using a compression force of 5kN and using punches with a diameter of 5mm. Orodispersible tablets were obtained by direct compression.

II.5. Evaluation of properties of tablets.

II.5.1. Uniformity of the mass (according to the Polish Pharm., 2017)

20 taken at random tablets were weighed individually and the average mass was determined. No more than 2 of the individual masses may deviate from the average weight by more than the percentage deviation. Polish Pharmacopoeia 11th edition predictes a deviation of ± 10% for tablets weighing ≤ 80 mg.
When the average mass is equal to or below 40 mg, preparation is not submitted to the test for uniformity of mass but to the test for uniformity of content of single-dose preparation.

II.5.2. Uniformity of content of single-dose preparation (according to the Polish Pharm., 2017)

The content was tested in each of 10 randomly selected tablets. Each tablet was crushed and dissolved in 0.1 M HCl. The content of active substance was determined spectrophotometrically. The preparation meets the requirements if the content of active substance in each tablet ranges from 85% to 115% of the average content.

II.5.3. The friability test (according to the Polish Pharm., 2017)

20 accurately weighed and dedusted tablets were placed in the friabilator drum (EF-2W, Electrolab, Mumbai, India). After 100 turns of the drum, the tablets were removed, cleaned loosy dust and weighed again. The mass loss for uncoated tablets can not be greater than 1%.

II.5.6. The hardness test (according to the Polish Pharm., 2017)

The hardness test (n = 10) was carried out using the MultiTest 50, Pharmatron Dr Schlauniger apparatus. The results were presented as the average value expressed in [N] and then the hardness coefficient P [N / m^2] was calculated.

II.6. The disintegration time (according to the Polish Pharm., 2017)

The method used to measure the disintegration time of ODTs is the same as for uncoated tablets. The pharmacopoeial test was conducted in a one liter beaker with 800 mL of distilled water The disintegration time (n = 6) was tested at 37ºC ± 2ºC using DisiTest 20, Pharmatron Dr Schlauniger.

II.7. The wetting time n=6

The measurements were carried out according to the metod described by Bi et al. [20]. The wetting test was conducted for 6 tablets of each formulation. The tablet was put on twice folded filter paper placed in the middle of a Petri dish (7 cm in diameter) containing 7 mL of 0.05% red dye aqueous solution. The time necessary to the complete wetting of the outer surface of the tablet was detected by stopwatch. Data are presented as median.

II.8. Dissolution test in vitro

The study was carried out in an Erweka DT-600 paddle apparatus (USP 2 paddle apparatus) [21, 22]. 6 tablets from each of the formulations were tested. As the acceptor fluid, 0.1M HCl was used in a volume of 900ml at 37 °C. The speed of the mixer's movements was set at 50 rpm. The test for each of the formulations lasted 10 minutes. Every minutes, 3ml of liquid was with drawn and the volume of 0.1M HCl was filled up. Absorption of each sample was measured using a spectrophotometer at 195 nm. The concentration of substances in individual time intervals was calculated based on the equation of the standard curve.

II.9. Statistical analysis

The results were analyzed using the Statistica 13.1 program. In order to check the conformity of the obtained data with the normal distribution of the amount of released active substance during the time of disintegration, the Shapiro-Wilk test was used. The obtained results did not have a normal distribution. Further

calculations were carried out using the U-Mann Whitney test. Statistically significant values were those whose significance levels (p) <0.05.

III. Results and discussion

III.1. Evaluation of powder mixtures

In order to determine the flowability of powders, parameters characterizing this property were determined by calculating the Hausner coefficient (IH) and Carr's index (Ic). The properties of powder mixtures are presented in Table 2. It was found that both marked parameters indicate very good and good flowability [23] and were respectively: Hausner coefficient from 1.04 to 1.18, and Carr's index from 4.08 to 15.09. These parameters indicated the possibility of using a direct tableting method as a method of preparation tablets. In the work of Siemiradzka et al. the orodispersible tablets parameters obtained as a result of tableting preceded by wet granulation and as a result of direct compression were compared. It was found that tablets made by direct compressing were characterized by a significantly shorter disintegration time [24].

III.2. ODT specifications

The weight of the prepared tablets was 39 mg - 41 mg and none of the tablets exceeded the deviation from the mean value of 10%. Drug content in single-dose preparations F-I – F-XII showed captopril presence in tablets in a range of 95.43 ± 1.49% (F-IX) - 101.62 ± 0.97% (F-XI). Physicochemical properties such as uniformity of captopril in tablets, friability, hardness, disintegration time and wetting time of ODTs are presented in Table 3. The friability for all tested tablets was below 1%, which is in line with the requirements of USP 31 NF 26 Supplement I [25]. All tested parameters met the requirements of Polish Parmacopoeia.

As a result of the measurement of hardness, its growth was observed in tablets containing in its composition a larger amount of Avicel (40%).

III.3. Disintegration time of ODTs

The disintegration time for tablets of all formulations containing captopril did not exceed 30 seconds, (Table 3). Taking into account the fillers included in the individual formulations, it was found that the shortest time of disintegration was noted for F-I-F-IV formulations, containing mannitol, which may result from the low compressibility of this excipient and it was in the range 6.0 - 11.0 s; $p<0.001$ The F-V - F-VIII formulations, in which sorbitol was applied, presented the longest disintegration times (22.0 - 27.0 s; $p<0.001$), which may be due to the high compressibility of sorbitol. The use of sorbitol by Alipour et al. in the amount of 23 - 75% also resulted in long disintegration times (40- 150 s) [1]. The formulations F-IX-F-X with hypromellose as a filling substance, showed an intermediate disintegration time (11.0 - 17.0 s; $p<0.001$). The use of lactose (F-II, F-IV, F-VI, F-VIII, F-X and F-XII formulations) resulted in a longer disintegration time compared to glucose (FI, F-III, F-V, F-VII, F-IX and F-XI).

The amount of microcrystalline cellulose used as filling substance also affected the disintegration time. The results of the study show that the lower Avicel content (20%) affects the reduction of disintegration times (F1, F-II, FV, F-VI, F-IX and F-X formulations) and a slight decrease in mechanical strength compared to formulations containing 40% of Avicel (formulations F-III, F-IV, F-VII, F-VIII, F-XI and F-XII), characterized by more favorable resistance parameters.

Crospovidone, as the disintegrant, was used in two different concentrations: 5% (formulations F-III, F-IV, F-VII, F-VIII, F-XI and F-XII) and 10% (formulations FI, F-II, FV, F-VI, F-IX and FX). As expected, the higher concentration of crospovidone was reported to provide more satisfying effects in decreasing disintegration time. In the work of Siemiradzka et al., ODTs with ondansetrone hydrochloride were prepared and studied. Crospovidone in amount of 10 % was reported to provide more satisfying effects in decreasing disintegration time compared to 5 % crospovidone [24].

III.4. The wetting time

The lowest values of the wetting time were noted for F-I-F-IV formulations ($p<0.001$).The intermediate wetting time values were observed for F-IX-F-XII formulations ($p<0.001$), the highest for F-V-F-VIII formulations ($p<0.001$), which correlates with the disintegration times for these formulations. Only the lactose little prolonged the disintegration time, while increasing tablet hardness, but shortening the wetting time. Anhydrous lactose can be used as a filler with substances sensitive to moisture, because it can absorb it, hence a better wettability of formulations containing lactose may be a result.

III.5. In vitro dissolution test of ODTs

The obtained formulations were tested for pharmaceutical availability. The captopril release profiles from the resulting F-I-F-VI formulations with respect to the F-XI formulation are shown in Figure 1 for the F-VII-FIX formulations with respect to F-X - F-XI, are shown in Figure 2. The average amounts of released

captopril are presented in Table 3. The type of excipients used was of significance for the quantity of active substance released in given time intervals. For tablets containing mannitol, the maximum amount of substance was released within 3 minutes, from the F-I (96.99%) and F-II (97.50%) formulations containing 10% crospovidone and F-III (97.47%), containing 5% crospovidone. From F-IV formulation captopril was released between the 3 and 4 minute (99.35%). The higher concentration of crospovidone caused an increased amount of released captopril in the first minute of the pharmaceutical availability study: F-I (93.47%); F-II (83.78%); F-III (79.63%); F-IV (70.58%). A smaller initial amount of released captopril was reported in tablets of formulations F-II and F-IV that contained lactose slowing down the release. F-V - F-VIII formulations containing sorbitol were characterized by a maximum release of captopril within 4 minutes. After the first minute less captopril released from these formulations: F-V (60.49%); F-VI (53.73%); F-VII (59.44%); F-VIII (53.57%) than formulations containing mannitol: F-I (93.47%); F-II (83.78%); F-III (79.63%); F-IV (70.58%). In the case of F-II and F-IV as well as F-VI and F-VIII formulations containing lactose, the release time was longer compared to the F-I and F-III and F-V and F-VII formulations, containing glucose.

In the studies of Padmaja et al. after application of lactose in the amount of 58.25% and the use of direct compression, the maximum release was recorded after a longer time, within 10 minutes [18]. The formulations F-X-F-XII, containing hypromellose, showed the maximum amount of released substance after only 2 minutes of release ($p<0.05$ in relation to formulations F-I – F-IX). The amounts of released captopril after 2 min were as follows: from the F-X - 96.36%, from F-XI - 101.62% and from F-XII - 99.13%. Captopril from F-IX was released a little longer –within 3 minutes (95.43%). The initial amount of released substance as in the above cases was also higher in the F-IX formulation tablets (88.34%) and F-X (90.15%), which contained 10% crospovidone with respect to the F-XI formulation tablets (79.86%) and F-XII (70.54%) with 5% crospovidone. Alipour et al. used two superdisintegrants in 20% each: crospovidone and Ac-Di-Sol, and as fillers Avicel and sorbitol. The best disintegration time they obtained was 40 s, while in the pharmaceutical availability study only about 30% of captopril was released after 5 min, and the entire amount was released within 30 minutes of the study's start. Perhaps this was due to the use of the tableting method preceded by wet granulation [1].

As can be seen from the above data from the fillers used, hypromellose has contributed the most to shortening the time of captopril release. Thus, the optimal disintegration time and completely dissolving of captopril within 2 minutes, provided a formulation F-X containing 10% crospovidone as a disintegrant, Avicel 20% and hypromellose 11.36% as fillers and formulations F-XI (crospovidone - 5%, Avicel 40% and hypromellose, glucose) and F-XII (crospovidone - 5%, Avicel 40% and hypromellose, lactose). Rajesh at al. used the same excipients in formulation of ODTs with ondansetrone hydrochloride (crospovidone – 10%, mannitol (50%) and microcrystalline celulose MCC-112 – ~33%). They obtained a disintegration time of 12 s and a total amount of ondansetrone released in 10 min [26]. Shahtalebi et al. successfully used a natural disintegrant - karaya gum (12% tablet weight) and mannitol and Avicel, which resulted in disintegration times of less than 30 s, similar to crospovidone, while the total amount of captopril was released longer - within 5 minutes [27]. Regardless of the sublingual forms functioning in medicine, there is a need to use ODTs preparations, because of the possibility of adapting them to individual patient's needs (form, rapid disintegration time, dose, comfort of use, stability in comparison with liquid suspensions).

IV. Figures And Tables

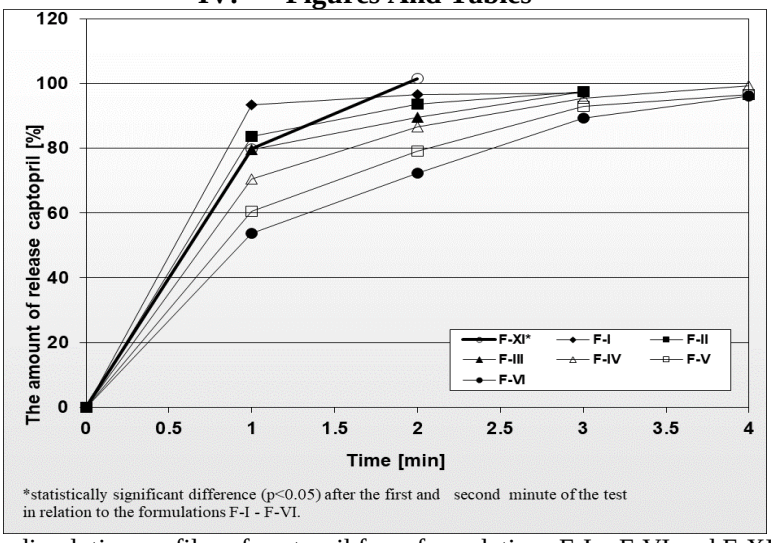

Figure 1. Mean dissolution profiles of captopril from formulations F-I – F-VI and F-XI to 0.1 M HCl.

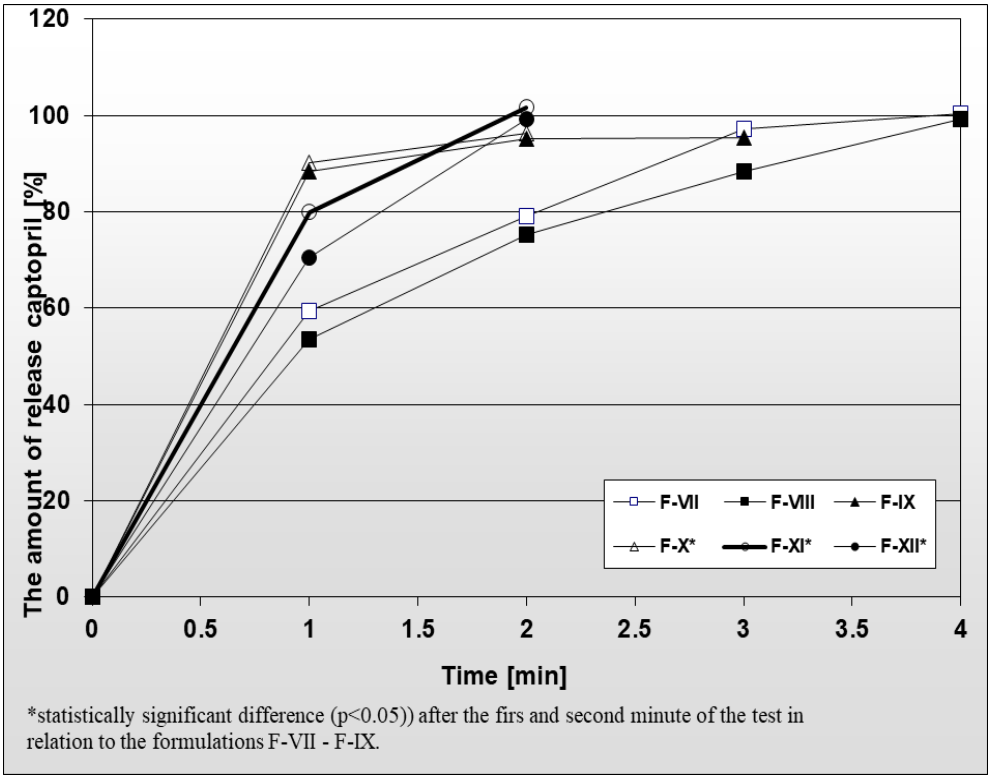

Figure 2. Mean dissolution profiles of captopril from formulations F-VII – F-XII to 0.1 M HCl.

Table No 1: Composition of manufactured ODT formulations F-I – F-XII.

Formulation	Composition of tablet mass [%]								
	Avicel	Mannitol	Sorbitol	Hypromellose	Glucose	Lactose	Crospovidone	Mg stearate	Captopril
F-I	20	18.86			18.86		10	1	31.25
F-II	20	18.86				18.86	10	1	31.25
F-III	40	11.36			11.36		5	1	31.25
F-IV	40	11.36				11.36	5	1	31.25
F-V	20		18.86		18.86		10	1	31.25
F-VI	20		18.86			18.86	10	1	31.25
F-VII	40		11.36		11.36		5	1	31.25
F-VIII	40		11.36			11.36	5	1	31.25
F-IX	20			18.86	18.86		10	1	31.25
F-X	20			18.86		18.86	10	1	31.25
F-XI	40			11.36	11.36		5	1	31.25
F-XII	40			11.36		11.36	5	1	31.25

Table No 2: Properties of the powder mixtures (n=3)

Formulation	Bulk density (g/ml); mean ±SD	Tapped density (g/ml); mean ±SD	Carr's index (%); mean ±SD	Hausner ratio; mean ±SD
F-I	0.48±0.008	0.56±0.003	14.29±0.012	1.17±0.003
F-II	0.48±0.002	0.53±0.002	9.43±0.008	1.10±0.012
F-III	0.45±0.001	0.53±0.002	15.09±0.005	1.18±0.008
F-IV	0.43±0.001	0.50±0.002	14.00±0.037	1.16±0.005
F-V	0.49±0.002	0.56±0.001	12.50±0.021	1.14±0.005
F-VI	0.49±0.004	0.53±0.001	7.55±0.017	1.08±0.021
F-VII	0.47±0.003	0.51±0.002	7.84±0.008	1.09±0.005
F-VIII	0.47±0.002	0.49±0.003	4.08±0.021	1.04±0.009
F-IX	0.42±0.001	0.48±0.004	12.50±0.017	1.14±0.008
F-X	0.42±0.002	0.45±0.001	6.67±0.021	1.07±0.014
F-XI	0.40±0.002	0.45±0.001	11.11±0.029	1.13±0.012
F-XII	0.40±0.002	0.43±0.002	6.98±0.012	1.08±0.016

Table No 3: Physicochemical characteristics of prepared ODTs.

Formulation	The amount of captopril dissolved during the dissolution assay (%) n = 10; mean ±SD	Hardness (N/m^2) n = 10	Friability (%) n = 20	Wetting time (s) n=6	Disintegration time of ODT (s) in water n = 6
F-I	96.99±0.30	6.19×10^5	0.94	8.0	6.0
F-II	97.50±0.60	6.60×10^5	0.52	7.0	7.0
F-III	97.47±0.82	1.81×10^6	0.46	12.0	11.0
F-IV	99.35±1.38	1.97×10^6	0.42	9.0	11.0
F-V	96.65±0.59	1.71×10^6	0.21	31.0*	22.0*
F-VI	96.27±1.21	1.87×10^6	0.26	23.0*	24.0*
F-VII	100.24±1.92	2.41×10^6	0.34	59.0*	26.0*
F-VIII	99.15±3.07	2.56×10^6	0.37	46.0*	27.0*
F-IX	95.43±1.49	9.54×10^5	0.61	11.0**	11.0**
F-X	96.36±1.25	1.09×10^6	0.82	11.0**	11.0**
F-XI	101.62±0.97	1.65×10^6	0.47	21.0**	14.0**
F-XII	99.13±1.76	1.90×10^6	0.42	18.0**	17.0**

* - statistically significant difference in relation to the formulation F-I – F-IV; $p<0.001$
**- statistically significant difference in relation to the formulations F-I - F-IV and F-V - F-VIII; $p <0.001$

V. Conclusion

The Avicel and crospovidone as the superdisintegrants used in the technology of orally disintegrating tablets, allowed to obtain preparations disintegrating in less than 30 seconds. The shortest disintegration time (6.0 - 11.0 s) was noticed for tablets containing mannitol as a filling substance, while the longest time of disintegration was shown by tablets containing sorbitol (22.0 - 27.0 s), intermediate values of disintegration time were noticed for preparations containing hypromellose (11.0 – 17.0 s). Increasing the concentration of Avicel from 20% to 40% increased the mechanical strength of the obtained tablets by about 1.5 up to 3 times, but at the same time prolonged the disintegration time, to the greatest extent - about 1.5 times in the case of tablets containing mannitol as a filling substance. Increasing the crospovidone concentration from 5% to 10% resulted in a shortened tablet disintegration time. The shortest release time of captopril was observed for formulation containing hypromellose as a filling substance. The total amount of captopril was released within 2 minutes.

Tablets disintegrating in the mouth in less than 20 seconds and releasing captopril within 2 minutes can be a promising form of administration for young children and the elderly. At the same time, in addition to the rapid therapeutic effect, they are provided with adequate durability. From a technological point of view, a significant benefit is the small production costs of ODTs by direct compression compared to the technology of obtaining lyophilisates.

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