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THE POLYMERS INFLUENCE ON THE SWELLING INDEX OF NEBIVOLOL 10 MG MUCOADHESIVE BUCCAL TABLETS

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ABSTRACT: The paper presents the results of our study regarding the influence on swelling index for controlled released mucoadhesive buccal tablets of nebivolol. In this aim there were analyzed three different polymers in various ratios in order to increase the delivery of the drug: hydroxipropylmethylcelullose (HPMC) -types K4M and K15M and Carbomer 940. The profiles studied for these formulations, 4 with each of the polymers showed greater values for HPMC.

Keywords: nebivolol hydrocloride, swelling index, mucoadhesive buccal tablets, polymers.

INTRODUCTION:

Cardiovascular diseases are the leading cause of globally death. It is estimated that in 2004, 17.1 million people died, about 30% of all worldwide deaths. From these data, 7.2 million deaths were caused by coronary heart disease and 5.7 million due to strokes.

The most important risk factors of heart disease and strokes are unhealthy diet, physical inactivity and tobacco use.

Hypertension is the most powerful cardiovascular risk factor and the leading cause of cardiovascular mortality worldwide.

But Hypertension can be prevented, treated or controlled.

Currently, classes of drugs, commonly recommended for the treatment of hypertension, are diuretics, ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, beta-blockers. (Stroescu, 1989)

Nebivolol is a 3rd generation of β-blocker, which has, in addition to the characteristics of adrenergic beta-blockers also vasodilatory properties because of immediate activation of L-arginine / nitric oxide.

In optics to extend the contact time of the drug by immobilization of a desired region of the mouth, mucoadhesive formulations represent an interesting alternative to conventional pharmaceutical forms. Due to the close and prolonged contact with the oral mucosa, the formulation will release a greater amount of active substance. (Popovici *et al.*, 2008, Popovici *et al.*, 2009)

So, the aim of developing a mucobioadhesive form is to improve the absorption and bioavailability of the active substance by keeping it in close contact with the biological tissue at the site of absorption for an extended period of time. (4)

In addition, the bioadhesive transmucosal forms are an opportunity to remedy the deficiencies in traditional forms absorption. (Bottenberg *et al.*, 1991; Garcia-Gonzales *et al.*, 1992; Kellaway *et al.*, 1991; Nagai *et al.*, 1987; Smart, 1993; Wertz *et al.*, 1991)

Mucoadhesive oral formulations represent a class of modern medicines, evolving successfully and they contributes to the optimization of *in vitro* drug release.

The swelling behaviour of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The agar plate model used in this study simulates the secreting fluid around the buccal mucosa, which is required for adhesion, swelling and release of the drug from tablets. The swelling index of mucoadhesive tablets form a period of 8 hours was studied.

Referring to the swelling study, we proceed in the following mode:

The tablets of each formulation were weighed individually (w1) and placed separately in Petri dishes containing 15 ml of phosphate buffer (pH 6.8). At regular intervals (1, 2, 4 and 8 hours) the tablets were removed from Petri dishes and excess water removed carefully, using filter paper. The swollen tablets were re-weighed (w2); the swelling index of each formulation was calculated by using this formula:

Swelling index (S.I.) = W1 – W2 /W1, where

W1 = initial weight, W2 = final weight

The main feature of the bioadhesion is the attachment force of the pharmaceutical form on the biological tissue, and this is achieved by using polymers that adhere to the of epithelial mucin surface.

These polymers can be conventionally divided into three categories:

- Polymers that become sticky when they are placed in water and their bioadhesion is due to their bonding
- Polymers which adhere by non-specific interactions, noncovalently, which are primarily electrostatic (although hydrogen bonding and the hydrophobic one, can be unimportant)
- Polymers that bind on the receptor- specific sites of the cell surface

MATERIALS AND METHODS:

There were formulated and evaluated in this study controlled released mucoadhesive buccal tablets of nebivolol, 10 mg, obtained by direct compression method. This fact was the reason of choosing as preparation form the direct compression, due to its advantages compared to classic compression method after wet granulation: cancellation of the drug contact with moisture and/or high temperature, shortening of the working hours, reducing of the mechanical forces.

There were also chosen to be used three different polymers in various ratios in order to increase the delivery of the drug. These polymers are: HPMC of two types: K4M and K15M and Carbomer 940.

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The studied formulations, 4 with each of the polymers mentioned above, are shown in the following table:

Table 1.
Composition of formulations containing HPMC K4M, HPMC K15 and Carbomer 940 at different ratio

Formulation code	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 mg	F11 mg	F12 mg
Nebivolol	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	10	20	30	40	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	10	20	30	40	-	-	-	-
Carbomer 940	-	-	-	-	-	-	-	-	2,5	5	7,5	10
Mannitol	97	87	77	67	97	87	77	67	104.5	102	99.5	97
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Total weight (mg)	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**
Ratios	**1:1**	**1:2**	**1:3**	**1:4**	**1:1**	**1:2**	**1:3**	**1:4**	**1:0.25**	**1:0.5**	**1:0.75**	**1:1**

There were obtained 8 mm flat faced tablets with a weight of 120 mg.

The active substance is nebivolol, the lubricant is magnesium stearate, the diluent is microcrystalline cellulose, and mannitol is a sweetener.

Before going to direct compression, all the ingredients were screened through sieve no. 100. Except the lubricant, all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min.

After sufficient mixing, lubricant was added and again mixed for additional 2-3 min.

The mixture is compressed using 8 mm flat faced punch on a rotary tablet compress machine.

Referring to the swelling study, we proceed in the following mode: The tablets of each formulation were weighed individually (w1) and placed separately in Petri dishes containing 15 ml of phosphate buffer (pH 6.8). At regular intervals (1, 2, 4 and 8 hours) the tablets were removed from Petri dishes and excess water removed carefully, using filter paper. The swollen tablets were re-weighed (w2); the swelling index of each formulation was calculated by using this formula:

Swelling index (S.I.) = W1 – W2 /W1, where W1 = initial weight, W2 = final weight

RESULTS AND DISCUSSION:

The obtained results are presented in the following table and they are illustrated in the following figures:

Table 2.
Swelling index of the analysed tablets

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0,27	0,32	0,39	0,48	0,16	0,24	0,31	0,35	0,11	0,08	0,21	0,32
2	0,84	1,01	1,15	1,45	0,33	0,41	0,51	0,55	0,42	0,37	0,67	0,93
3	1,25	1,57	1,73	1,73	0,56	0,62	0,89	0,96	0,66	0,72	1,01	1,25
4	1,55	2,1	2,08	1,96	0,79	0,85	1,34	1,45	0,95	1,25	1,46	1,51
5	2,11	2,25	2,36	2,15	1,23	1,53	1,89	1,97	1,14	1,44	1,75	1,86
6	2,25	2,32	2,56	2,37	1,54	2,23	2,34	2,45	1,35	1,69	2,12	2,26
7	2,35	2,48	2,61	2,63	2,42	2,38	2,49	2,51	1,58	2,06	2,37	2,59
8	2,41	2,5	2,6	2,67	2,49	2,5	2,63	2,68	2,49	2,52	2,54	2,6

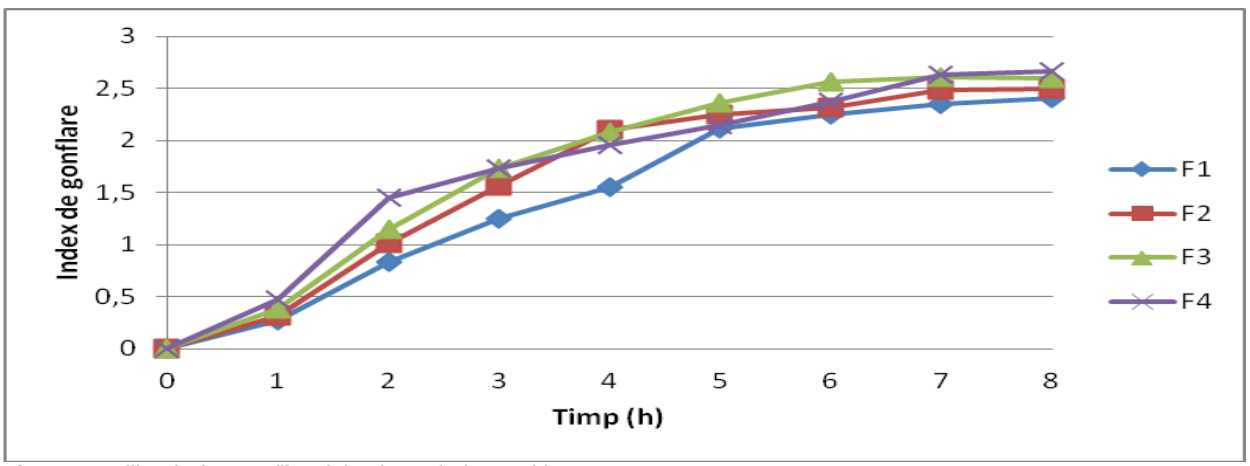

Fig. 1 Swelling index profile of the formulations with HPMC K4M

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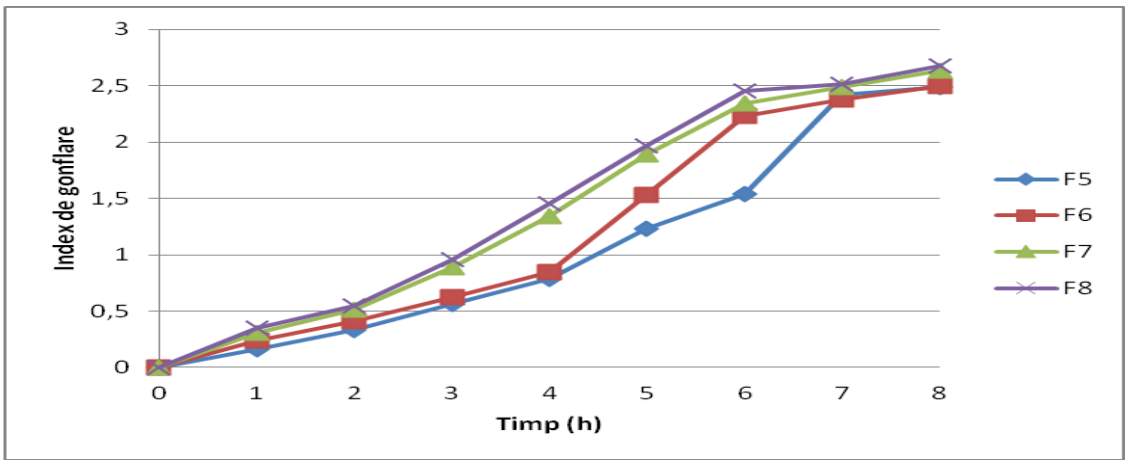

Fig. 2 Swelling index profile of the formulations with HPMC K15M

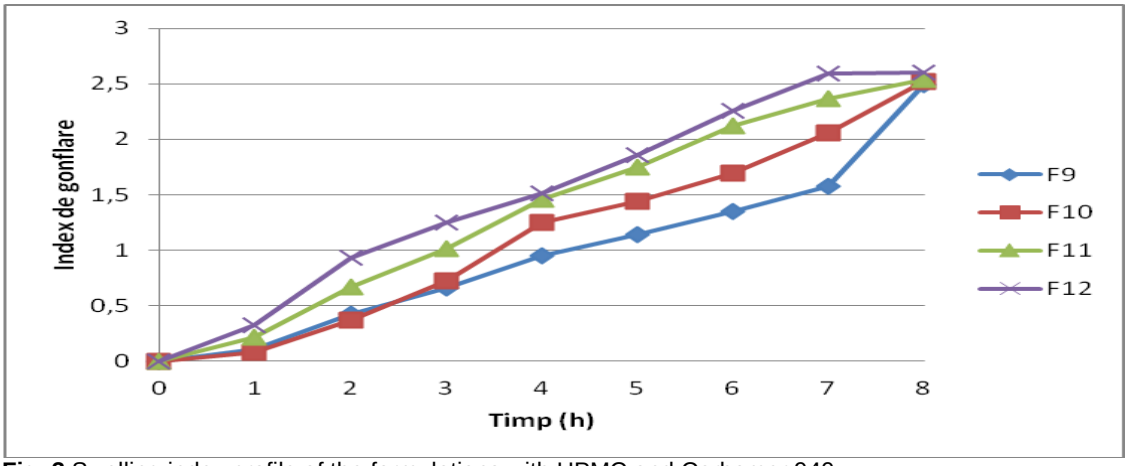

Fig. 3 Swelling index profile of the formulations with HPMC and Carbomer 940

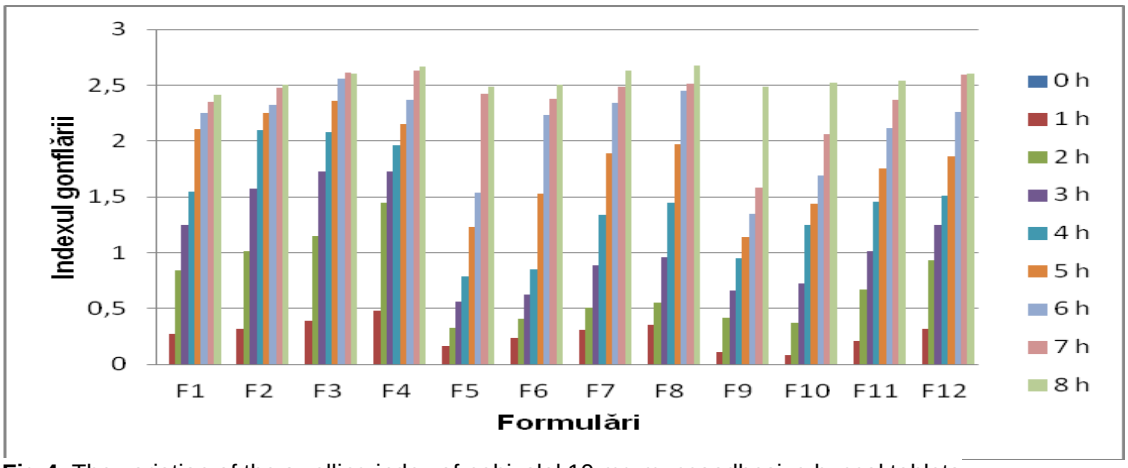

Fig 4. The variation of the swelling index of nebivolol 10 mg muccoadhesive buccal tablets

After analysing the results obtained by assessing the swelling index, we can conclude the following:

- After the first hour, the lowest swelling index was recorded for F10 formula (0.08%) which was 6 times smaller than the F4 formula (0.48%);
- After two hours, the lowest swelling index registered was for F5 formula (0.33%) and the highest one for F4 formula (1.45%);
- The trend continued for the next 3-7 hours. After 8 hours the swelling index equalised for all 12 formulations. The highest indexes were registered for the F8 formulation (2.68%) and F4 (2.67%) and the smallest for F1 (2.41%), F5 and F9 (both at 2.49%).

As a general conclusion, it can be observed that the swelling index rises in time and has greater values when hydroxipropylmethylcelullose (HPMC - K4M) is used as mucoadhesive polymer, yielding higher values for F2-F4 2.5, F6, F8 and F10-F12.

This confirms the hypothesis that the swelling behaviour certainly provides us with a uniform and prolonged release and bio-adhesion of the new formulas with nebivolol.

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