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INFLUENCE OF CARBOPOL 971P NF ON FLOW RATE AND SWELLING PARAMETERS IN ANTIFUNGAL TABLETS

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INFLUENCE OF CARBOPOL 971P NF ON FLOW RATE AND SWELLING PARAMETERS IN ANTIFUNGAL TABLETS (Abstract): The purpose of this research laid in developing oromucosal bioadhesive tablets with miconazole nitrate based on hydrophilic bioadhesive polymers, Carbopol 971P NF, capable to form a good adhesion to prolong the duration of the active ingredient action for several hours. The aim is to observe the correlation between the disintegration time, the swelling index and the amount of polymer used in mucoadhesive tablets. **Material and methods:** The tablets were made using direct compression method, the mucoadhesive tablets differing in the amount of Carbopol 971P NF. The first proposed formula (FI) contains 40 mg polymer and the second one (FII) contains 10 mg polymer. After the formulation and development of mucoadhesive tablets using different grades of polymer, physicochemical parameters such as surface area, thickness, diameter, friability, hardness, disintegration time and swelling index were determined. **Results:** Both proposed formulas have an optimal disintegration time of 75 and 98 minutes. The swelling index for FI (18% polymer) is 0.4435 and for FII (4.5% polymer) is 1.0316. **Conclusions:** Considering that the mucoadhesive tablets imply a swelling index over 1 and a longer disintegration time, the FII formula, with 10 mg carbomer, can be considered optimal. **Keywords:** CARBOPOL 971P NF, MUCOADHESIVE TABLETS, ANTIFUNGAL TABLETS, MICONAZOLE NITRATE.

The proliferation of stressful conditions, as a result of the diversification of new activities in human society with the ap-

pearance of the corresponding noxious substances, as well as the diversification of microbial species, mainly due to the rapid

movement of large numbers of people around the globe, has led to the emergence and intensification of fungal infections.

Many fungi have low virulence and only cause superficial infections of the outer layers of the skin, where antibodies and immune cells cannot reach. Although these infections are not serious, they are very common. These infections are usually chronic or recurrent if the underlying cause has not been eliminated and can become very stressful for patients.

Increased susceptibility to infection has been reported in people whose immune systems are physiologically impaired or as a consequence of a disease or treatment, or whose natural defenses and normal microbial flora have been affected. The incidence of fungal infections in immunocompetent organisms with a severely compromised immune system has also been observed.

It is now noted that the most common fungal infections in humans are urinary, vaginal and oromucosal. In recent years, their etiology is changing. If a decade ago they were produced almost exclusively by *Candida albicans* (85-90%), today non-albicans strains of *Candida* are increasingly involved (1, 2).

Miconazole nitrate is a topical antifungal agent used for local treatment of vaginal, skin and nail infections due to yeasts and dermatophytes, being active against *Candida* spp., *Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp. However, oral administration of drugs has disadvantages, such as metabolism of the first hepatic passage and enzymatic degradation within the gastrointestinal tract. These disadvantages may limit or prevent the oral administration of certain drugs, especially peptides and proteins, when they are inserted into special colon administration sys-

tems (3). These limitations have led to the exploration of other mucous membranes as potential locations for drug absorption (4). The mucosal routes of drug administration (e.g., mucosa of the nasal, rectal, vaginal, ocular and oral cavities) offer various advantages over oral administration of drugs (5, 6). These benefits include possible alternative pathways for the first-pass effect and avoidance of presystemic elimination within the gastrointestinal tract (7, 8).

Strategies for oral administration of drugs are represented by the new oral dosage forms, which consist mainly of sustained release systems for oral administration, designed to deliver the drug over a period of time (9, 10).

Mucoadhesive tablets are widely used in the formulation and preparation of topical antifungal products for prophylactic or curative purposes in infections of the oral and pharyngeal mucosa, such as acute oral candidiasis. This oral candidiasis is a major problem for patients with long-term HIV infection, with corticosteroid, antibiotic, anti-inflammatory agents treatment (8).

To improve the bioavailability of active substances in the oral cavity, various bioadhesive tablet systems have been developed in recent years with different active substances. Oral tablets can be applied in the oral cavity, for example in the palate, the mucous membrane of the cheeks, and the upper lip and the gums. They soften and adhere to the mucosal substrate is retained in the fixed position until complete dissolution and/or complete release. After a while, the patient no longer feels the tablet in his mouth. The location of the tablet in the mouth seems to have a big impact on tolerance and retention time. Depending on the location, either palatal or gingival, the retention time varies from 20-40 minutes to

MATERIAL AND METHODS

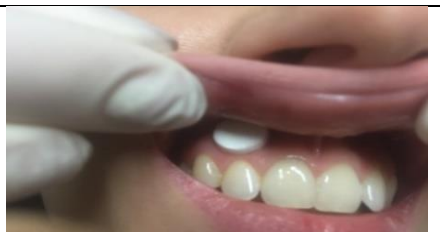
The following substances were used to develop mucoadhesive tablets: miconazole nitrate 99% (Sigma Aldrich, Germany), Carbopol 971P NF (Lubrizol, USA), mannitol (East Chemical, China), aerosil (De-

gussa, Germany), and magnesium stearate (Sigma Aldrich, Germany). Miconazole nitrate was used as an antifungal active substance of mucoadhesive tablets, which were prepared according to table II in two formulations.

TABLE II.

Formulation of mucoadhesive tablets with miconazole nitrate

Ingredients (mg/tablet)	F I	F II
Miconazole nitrate	50	50
Carbopol 971P NF	40	10
Mannitol	122	152
Aerosil	6	6
Magnesium stearate	2	2
Total weight (mg) 220		


Determining the flow rate and compressibility parameters of powder mixtures

There were monitored the typical parameters: flow rate (t), friction coefficient ($tg \alpha$), repose angle (α), Hausner ratio (HR) and Carr index (CI).

Flow rate (t) the time needed for 100 g of formulation to flow through a funnel with a 10 mm orifice;

Friction coefficient ($tg \alpha$) – dynamic method, according to the equation:

$$tg \alpha = h/r$$

where: h = height and

r = radius of the cone

Repose angle (α) – dynamic method;

Hausner ratio (HR) – calculated by determining the density before and after settling, according to the equation:

$$HR = \frac{p_t}{p_i}$$

where: p_t = density after settling and

p_i = initial density

Carr index (C_i) – identical determinations and recordings with the ones presented in Hausner ratio, but calculated according to the equation:

$$CI = \frac{p_t - p_i}{p_t} \times 100$$

Preparing the oromucosal bioadhesive tablets with miconazole nitrate

Mucoadhesive tablets were made by using the method of direct compression of the powder mixture with a Korsch tablet equipment double-sided press (size of upper punch $\phi = 9$ mm) to a compression pressure of 5 – 6 kN, for 30 seconds.

Characterization of the oromucosal bioadhesive tablets with miconazole nitrate

Dimensional characteristics. The dimensions of the tablets: diameter (d^2) in mm and height (h) in mm were determined using the automatic device PHARMA-TEST, Germany, on a number of 10 tablets and the average was calculated. The surface area of the tablets was then calculated according to the formula:

$$S = \pi \cdot d^2 / 4$$

Resistance to crushing. The resistance to crushing of mucoadhesive tablets was also automatically determined in PHARMA-TEST device.

Friability. Also called tablet wear, it is obtained after exposure to rolling the tablet. Due to the phenomenon of rolling some of

the particles of the tablet fall off. The phenomenon is also known as an abrasion and is expressed as a percentage. The friability is calculated according to the formula:

$$\text{Friability} = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100$$

Disintegration. According to USP 32 method A, the test was carried out on a number of 6 tablets of each formula. *The Pharmacopoeia* provides the determination on 6 tablets which are placed in a 500 mL conical vessel with 300 mL of water maintained at a temperature of 35-39°C. During the determination, the vessel is shaken gently twice a minute. After four hours, the contents of the vessel is filtered through a 0.8 mm mesh sieve, the vessel is washed with 300 mL of water at 37±20°C, which is brought over the remaining particles from the disintegration. It is allowed to remain on the sieve particles, which when lightly pressed with a flattened wand at one end pass through the sieve. If the result of the determination is negative, the test is repeated twice with 6 tablets each, establishing the duration of disaggregation for both determinations. The product is considered suitable if the average of these two determinations does not exceed the expected time by more than 20%. The disintegration test determines the time required to turn the tablets into fine particles or the time required to release the contents of the capsule wrapper when they are placed in a liquid medium under specific working conditions.

Swelling index

The swelling index (SI) of a mucoadhesive preparation is an important parameter for evaluating the prolonged release of the drug and the adhesive action. The swelling index of the mucoadhesive tablets

has been determined by weighing only one of the two formulas and recording the weight before placing them separately in Petri dishes. The individual initial weight was marked with (W1). In each dish, we added 15 mL of phosphate buffer (pH=6.8) and the temperature was thermostatically maintained at 37±0.5°C. At regular intervals (60 minutes, 120 minutes), the tablets were extracted, and excess surface water was removed, carefully and weighed again (W2).

The swelling index was calculated for each formulation, using the formula:

$$\text{SI} = (\text{W2}-\text{W1})/\text{W1} \times 100$$

where: W1 = the initial weight of the tablet and W2 = the weight of the tablet after 60,

respectively, 120 de minutes at 37°C in phosphate buffer solution.

Statistical data analysis

Statistical analysis of the data was performed using IBM *SPPS 20* software.

RESULTS AND DISCUSION

Determining the flow rate and compressibility parameters of powder mixtures

The first parameter that was determined for the flow behavior of the powders according to the cohesive material was the value of the repose angle. If a particle is temporarily outside this limit angle, it can slide to the adjacent surface under the influence of gravitational force until the shape of gravity is balanced by the friction between the particles. The lower the repose angle value, the lower the powder flow rate. Thus, a value of the angle below 20 indicates an excellent flow and a value between 20-30 indicates a good flow and up to 40 a poor flow rate. FI formulation contains 40 mg polymer compared to 10 mg of polymer in FII, and this matrix-

forming polymer makes it difficult for the powder to flow even if it contains aerosol and magnesium stearate (tab. III).

TABLE III.
Flow rate and compressibility parameters for FI and FII formulations

Formulation	Parameter			
	α (°)	tg α	HR	CI (%)
FI	41.9	0.90	0.8800	13.99
FII	36.80	0.73	0.8300	18.65

The Haussner ratio is the ratio of the density of the final powder bed to compaction and is based on the friction between the particles which demonstrates a good or less good yield. Thus, in all formulations the result of the Haussner ratio is below 1.2 which indicates a slight flow. We can see a better flow in the FII formula with a smaller amount of polymer (tab. III).

The Carr index, also called the compressibility index, is closely related to the Haussner ratio, which is another parameter of the fluidity of the powder mixture that indicates the need to add a thinner or not. According to specialized monographs, CI with a value between 5-12 means an excellent flow of the powder and between 12-16 a good value for flow. Compressibility is the ability of a powder to decrease its volume instantly, under a pressure applied vertically (14-21).

Characterization of the oromucosal bioadhesive tablets

The macroscopic characteristics of the mucoadhesive tablets made have flat, uniform, flat-rimmed, flat-surface lenticular discs, which means that these pharmaceutical forms are suitable both in terms of Romanian Pharmacopoeia Xth edition (FRX) and optimal for administration to the oral mucosa. The diameter and thickness are suitable for mucoadhesive administration, the deviations varying within the limits of the size of the punch chosen for compres-

sion. The diameter obtained is ideal for this type of administration because the gum above the canine has a maximum size of 12-13 mm and a thickness greater than 4 mm would change compliance.

The tablets are white, uniform, without spots, without odor, slightly bitter taste diminished due to the mannitol added as a sweetener. The value of the friability test is according to the accepted parameters, a value of less than 1% for both proposed formulas (tab. IV).

All values of the mechanical strength parameter are within the corresponding limits, respectively between 30-90 N. Disintegration time is an extremely important parameter because the product must be released gradually in the oral mucosa (21). A rapid disintegration can lead to an ineffective antifungal. The longer the tablets stay in the mucous membranes, the longer the effect lasts and the longer the antifungal has time to act. The disintegration time of the proposed formulas is closely related to the amount of polymer used. In the case of the FI formula, which contains 40 mg carbopol, the disintegration time is 75 minutes and in the case of the FII formula, which contains 10 mg polymer, the disintegration time is 98 minutes. A smaller amount of polymer can soak with water forming a gel around the tablet (tab. IV). Thus, this gel slows down the disintegration of the tablet.

TABLE IV.
Physical properties of mucoadhesive tablets with miconazole nitrate


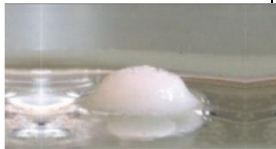
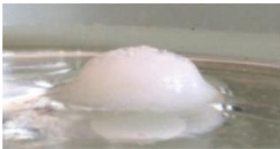

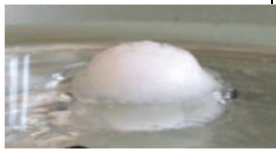
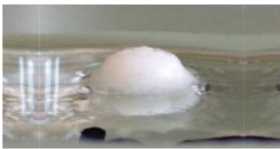
Formulation	Thickness (h) (mm)	Diameter (mm)	Surface area mm ²	Hardness (N)	Friability %	Disintegration time (min)
FI	3.280	9.260	66.75	50.29	0.8965	75
FI-SD	±0.057	±0.174	±3.376	±7.601	±0.515	±4.393
FII	4.109	9.398	71.67	61.10	0.9100	98
FII-SD	±1.02	±0.981	±2.342	±10.245	±3.456	±5.601

Swelling index

The swelling index was calculated according to time (tab. V). When performing this test on sample for swelling, the weight changed with the swelling of the polymers in an aqueous solution. The swelling rate increased as the weight of these tablets increased in proportion to the rate of hydration up to two hours and then gradually decreased as a result of disinte-

gration in the dissolution medium. It has been observed that total release is achieved when a lower concentration of polymer is added to the formula. The reason for this is the erosion of the gel layer in tablets containing smaller amounts of polymer. The higher the swelling index, the better the tablet will adhere to the oral mucosa, gradually releasing the amount of antifungal.

TABLE V.
Swelling index of mucoadhesive tablets

Formula	W1 initial (g)	W2 at 60 minutes (g)	W2 at 120 minutes (g)
FI			
	0.2390	0.3450	0.4700
	SI (%)	0.4435	0.9665
FII			
	0.2210	0.4490g	0.3200
	SI (%)	1.0316	0.4479

A swelling index at 60 min is 1.0316% for formula FII, which contains 10 mg polymer. The amount of polymer used in the FI

formula swelled in the presence of water, greatly increasing its volume. The swelling index is 55% lower, 0.4435% in the formula

FI, which contains 40 mg polymer. For prolonged-release tablets, the swelling index needs to be greater than 1 and a higher concentration of the polymer leads to a longer soaking time with an aqueous solution. A film is needed that is made on the outside of the tablet when it is positioned at the level of the oral mucosa. The higher the swelling index, the more effective the mucoadhesive tablet can be. A large amount of polymer in formula FI, 40 mg, did not have enough surface contact with water to have higher SI results. The polymer, being a network-type structure, needs time and large contact surface with water to be able to soak water. The proposed mucoadhesive tablets have a small contact surface, 9 mm, and large amount of polymer does not allow interpenetration between the upper layers. A smaller amount of polymer, FII formula, evenly dispersed in the tablet may develop a higher SI.

In the case of SI at 120 minutes, the values differ a lot. For FI formula, the SI at 120 minutes is 0.9665%, about 50% more than the SI value at 60 minutes. In this case the large amount of carbopol had enough time to come into contact with water and to swell the polymer network. In the case of FII formula, the SI value at 120 minutes is 57% lower than the SI value at 60 minutes. If the polymer is in a lower concentration, it will be dispersed uniformly in 60 minutes, which conducts to a maximum water-soaked network structure. At 120 minutes the SI value

of FII decreases because the gel formed around the tablet is gradually released.

CONCLUSIONS

Given that the antifungal active substance should be released gradually, FII formula with 4.5% carbopol may be proposed for future studies. The value of the swelling index and the disintegration time are important parameters for oral antifungal drugs in the form of mucoadhesive tablets. For FI formula, with 18% polymer, the swelling index is very small, being 132% lower than the FII formula with 4.5% polymer. Also, the disintegration time for FI formula is 30% shorter than the FII formula. The swelling index provides information about the ability of the new pharmaceutical form to stand on the oral mucosa. By disintegrating the tablet, the bioadhesive polymer in the aqueous medium forms a gel as it disintegrates. Thus, the longer this gel stays on the oral mucosa, the more active substance is gradually released from the pharmaceutical form and the contact time between the mucosa and the active substance will increase, which can provide a better action of the pharmaceutical product.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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