Influence of Hydroxypropyl Methylcellulose on Flowing and Swelling Parameters in Biomucoadhesive Tablets with Miconazole Nitrate

MAGDALENA BIRSAN, NELA BIBIRE, MADALINA VIERIU*, ALINA DIANA PANAINTE, ILEANA COJOCARU
Grigore T. Popa University of Medicine and Pharmacy of Iasi, Faculty of Pharmacy, 16th Universitatii Str., Iasi, Romania

Original pharmaceutical formulations have been produced as oral biomucoadhesive tablets for antifungal medication. They have been obtained through direct compression using as matrix forming polymers various sorts of hydroxypropyl methylcellulose. The main goal of the study was determining the swelling index of the new mucobioadhesive formulations with miconazole nitrate in order to correctly evaluate the time of contact with mucosa, and the prolongation of drug release. For each formulation, the flowing parameters have been determined: flowing time, friction coefficient, repose angle, Haussner ratio, Carr index, and the swelling index for 6 formulations containing various sorts of hydroxypropyl methylcellulose as matrix molders, while the formulation variables studied were time and association ratio between those polymers. Though results analysis, we noticed that the values of the swelling index depended on the type and quantity of polymer, results that could also be explained by the proportionality relationship to flowing and compressibility parameters.

Keywords: hydroxypropyl methylcellulose, swelling index, mucobioadhesive tablets, miconazole nitrate.

Mucoadhesive formulations address the adhesion to the mucosa by immobilizing the preparation on the target area, and they are a modern, booming pharmaceutical trend.

Among mucoadhesive formulations, oral mucosal bioadhesive tablets caught the attention of researchers. The motivation for choosing miconazole nitrate as a study subject was based on its importance as an antimicotic substance and due to the fact that it penetrates the stratum corneum and remains there a few days, building up a concentration that favors the treatment of various forms of candidiasis that have appeared during the last few years [1-4].

To improve the bioavailability of the active substances in the oral cavity, various systems of bioadhesive tablets have been developed these recent years, with various active substances. The buccal adhesives tablets can be applied in various places of the oral cavity, for instance on the palate, on the mucosa of the cheeks, or in between the upper lip and gingiva. They soften and adhere to the mucosal layer and they must maintain a certain position until total dissolution and/or complete release. After a short time, that patient no longer feels the tablet in his/her mouth [5-6].

Solid particles are a fundamental type of tablets in pharmaceutical technology, therefore, it is essential knowing the properties of the particles, since the majority of pharmaceutical formulations experience that state. To produce a tablet, especially a new generation one, such as buccal biomucoadhesive tablets, the substance particles must be in a crystalline state, with its granulometry adapted to the technological process of the pharmaceutical

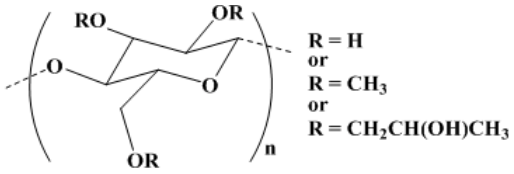

Fig. 1. Chemical structure of hydroxypropyl methylcellulose

formulation. Prior to the compression stage, we determined the flowing and compressibility parameters for each formulation [7].

The flowing properties or rheology of powders include the flow, not only in free state (fluidity, slipping), under the effect of gravity, but also under the action of a force (pressure, vibration), as it is the case inside a cohesive material [8].

The swelling index is a parameter generally studied in tablets which contain matrix – forming polymers as bioadhesion excipients.

We used hydroxypropyl methylcellulose (HPMC), due to its bioadhesion properties in all 6 formulations of bucal biomucoadhesive tablets.

Hydroxypropyl methylcellulose (fig. 1.), also known as Hypromellose, is the most frequently used polymer in adhesive formulations. Its main qualities (Table 1) are rapid hydration speed, compression properties, gelation capacity and low toxicity [9-13]. In contact with water, HPMC hydrates fast, forming a gel barrier around the tablet. The release speed of the active substance depends on the following factors: type of polymer, polymer/active

Methoxyl content (%)	26.0-30.0
Hydroxypropyl content (%)	8.0-11.0
Gelation temperature (°C)	54-75^{0}C
Loss on drying (%)	≤ 5%
Ash	≤ 2%
pH value (1% solution, 25°C)	7-8
Appearance	White powder
Particle size (mesh)	80-100
Viscosity (mPa.s, 2% solution, 25°C)	7.5 million, 10 million, 15 million, and 20 million

Table 1
PROPERTIES OF HPMC

*email: madalina.vieriu@umfiasi.ro

All authors have had equal contributions in the experiments and editing the article.

Pharmaceutical substances (mg/tablet)	F I	F II	F III	F IV	F V	F VI
Miconazole nitrate	25	25	25	25	25	25
HPMC 4K	5	10	15	-	-	-
Mannitol	182	177	172	182	177	172
HPMC 100K	-	-	-	182	177	172
Aerosil	6	6	6	6	6	6
Magnesium stearate	2	2	2	2	2	2
Total weight (mg)	220	220	220	220	220	220

Table 2
FORMULATION OF MUCOADHESIVE TABLETS WITH MICONAZOLE NITRATE

substance ratio, size of particles, and type and quantity of diluent used in formulation.

The polymers used in preparing the new bioadhesive formulations with miconazole nitrate, were HPMC 100K and HPMC 4K as they offered bioadhesive capacity to the tablets. The study analyzes the values of compressibility and of the swelling index, depending on the quantity and type of polymer.

Experiemntal part

Materials and methods

The materials use were: miconazole nitrate - 99% purity (Sigma Aldrich, Germany); hydroxypropyl methylcellulose HPMC 4K and HPMC 100K (Shin-Etsu Chemical Co. Ltd, Japan); mannitol (East Chemical, China), aerosil (Degussa, Germany), and magnesium stearate (Sigma Aldrich, Germany).

Miconazole nitrate was used as an antifungal active substance of oral mucobioadhesive tablets, prepared according to table 2, in 6 formulations.

For each formulation, the flowing parameters have been determined [7, 14]:

- Flowing time (t) – the time needed for 100g of formulation to flow through a funnel with a 10mm orifice;
- Friction coefficient (tg α) – dynamic method, according to the equation:

$$tg\alpha = h/r \quad (1)$$

where:

h = height and r = ray of the cone of the powder.

- Repose angle (α) – dynamic method;
- Haussner ratio (R_H) – calculated by determining the density before and after settling, according to the equation:

$$R_H = pt/pi \quad (2)$$

where:

pt = density after settling and pi = initial density.

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

$$I_C = (pt-pi/pt)\cdot 100 \quad (3)$$

Determining the swelling index of a mucoadhesive preparation is an important parameter for evaluating the prolonged release of the drug and the bucoadhesive action [15].

The swelling index of the mucoadhesive tablets has been determined by weighing one tablet of each formulation and recording the weight before placing them separately in Petri dishes. The individual initial weight was marked with (W1).

In each dish, we have added 15mL of phosphate buffer (*p*H = 6.8) and the temperature was thermostatically maintained at 37±0.5°C. At regular intervals (60, 120 min), the tablets were extracted, dried on a filter paper and weighed again (W2).

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

$$S.I. = (W2-W1)/W1 \quad (4)$$

where: W1 = the initial weight of the tablet and W2 = the weight of the tablet after 60 respectively 120 min at 37°C in phosphate buffer solution.

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

Results and discussions

The results of the determination of the flowing parameters are listed in table 3.

Through the analysis of the data obtained on the flowing and compressibility parameters of the 6 formulations, it was concluded that the density of a powder depends on the way the particles arrange so that a settled powder will have a stronger resistance, therefore a weaker flowing.

Table 3
FLOWING AND COMPRESSIBILITY PARAMETERS

Parameter		A (°)	Tg α	R_H	I_C (%)
Formulation	F I	35.59	0.71	0.7154	28.45
	F II	33.09	0.65	0.7522	24.77
	F III	38.90	0.80	0.8130	18.69
	F IV	33.61	0.66	0.7708	22.91
	F V	36.68	0.74	0.7758	22.41
	F VI	34.80	0.69	0.7560	24.40

Haussner ratio is the ratio between the density of the final settled powder bed and it is based on the friction between particles, which provides a good or poor flowability. Thus, in all 6 formulations, the result of Haussner ratio was under 1.2, which indicated an easy flowability. Formulations I, II and VI had the smallest values of the Haussner ratio, 0.7154, 0.7522, and 0.7560, respectively, which indicated that those formulations had the best flowability due to the excipients and their quantities., The smooth flowability of formulations I and II could be explained by the fact that they included low molecular weight HPMC, which eased the flowing property, and also because it was in a small proportion. The fact that formulation III had a smoother flowability, even if it included the same sort of HPMC, was explained by its triple quantity, as opposed to formulation I. For formulations IV, V and VI, the values of Haussner index were much closer, even if different quantities of polymers were used, which proved that, the parameter was influenced by the type of polymer used, in that case, the sort of HPMC.

Due to the fact that cellulose-derived polymers give the powder mixture a low flowability, we used two types of lubricants, aerosil and magnesium stearate.

Carr index, also known as compressibility index, is closely connected to Haussner index. It is another parameter that characterizes the fluidity of a powder mixture that indicates the need to add more or less of the lubricants. Compressibility is a parameter closely related to the flowing capacity, and it is defined as the capacity of a powder to instantaneously decrease in volume, under a

Name	Initial W1	W2 at 60min	W2 at 120min	S.I.
F I	0.213	0.060	0.000	-
F II	0.220	0.410	0.280	**0.8636**
F III	0.220	0.410	0.290	**0.8636**
F IV	0.213	0.270	0.040	**0.2670**
F V	0.229	0.170	0.080	-
F VI	0.230	0.280	0.050	**0.2173**

Table 4
THE SWELLING INDEX (S.I.) OF ORAL MUCOSAL BIOADHESIVE TABLETS

Table 5
DESCRIPTIVE STATISTICS OF THE SWELLING INDEX FOR BIOADHESIVE TABLETS

	N	Minimum	Maximum	Mean	Std. Deviation
S.I. (n=5)	5	0.0000	0.8630	0.442000	0.3972078

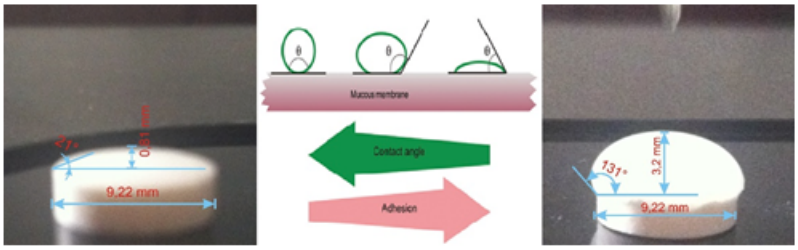

Fig. 2. Establishing the contact angle of miconazole nitrate biomucoadhesive tablets

vertically applied pressure [7]. Compressibility was satisfactory for formulation III, whereas for formulations F1, FII, FIV, FV, and FVI, it was low because in a mixture of powders there are important interactions between particles leading to a high compressibility index.

The values of the swelling index are closely related to wettability theory, probably the oldest theory for mucoadhesion. It is best applied to liquid systems or mucoadhesive pharmaceutical products which contain polymers with low viscosity [15]. It explains adhesion as an inclusion process, in which the adhesive agents penetrates the irregularities of the surface of the substrate, and it finally hardens, producing several adhesive anchors [16]. Wettability is the process of establishing a continuous contact of an adhesive with the substrate [17, 18]. A complete wettability occurs when the contact angle (fig. 2.) has 0 degrees, practically when the tablet is completely swollen.

Determining the swelling index of a mucoadhesive product is an important parameter for the evaluation of prolonged release of the drug and bucoadhesive action.

After establishing an intimate contact between adhesive and substrate, through wettability, it is believed that the adhesion is primary maintained through molecular attraction forces. The adhesion occurs only if the polymer in the pharmaceutical formulation is completely hydrated and leads to a swelling index that suits the location it has to be applied.

To produce maximum bioadhesion, there is an optimal concentration of the bioadhesive polymer. In general, a more concentrated polymer has a greater penetration because of the length of the chain, consequently a better adherence [19-25].

Both hydration and mobility of the polymers lead to an increase of mucoadhesion capacity, since they improve the interpenetration process between polymer and mucin [25, 26]. The contact time between bioadhesive mucous layer and polymer determines the swelling degree and interpenetration of bioadhesive polymer chains. More than that, the longer the initial contact time, the stronger the bioadhesive power is [27-30].

Our study proves that HPMC used as a matrix-forming polymer established a good adhesion, especially HPMC with small molecular weight, but it has to be used in 5-7% concentration. The highest swelling index showed the formulations obtained using 6% HPMC 4K. The swelling index offered by HPMC 100K were not as good, results which were also confirmed by low values of flowing and compressibility parameters.

While testing the tablet formulations for swelling, their weight changed with the swelling of polymers in aqueous medium [31-34]. The swelling index increased because the weight of the tablets increased proportional to the hydration speed, for 2 h, and then it gradually decreased as a result of disintegration in dissolution medium. That fact was owed to the erosion of the gel layer in tablets which contained small quantities of polymer. The higher the value of the swelling index is, the better adherence to buccal mucosa the tablet will have, gradually releasing the antifungal substance. The highest swelling index was found for formulations F I and F II, which was explained by the type of HPMC used. The smaller molecular weight of HPMC provided the tablet easier soaking within the dissolution medium.

It was impossible to calculate S.I. for F I, because the quantity of polymer was too small. The composition of formulations FII and FIII offered useful information regarding the capacity of the polymers to influence the value of the swelling index. For formulations that used HPMC 4K, the ideal/optimum concentration value of the polymer, was 5%, in terms of swelling index.

Formulations IV, V, and VI included HPMC 100K, which didn't allow tablets absorb water and it didn't provide a good swelling index.

Conclusions

The conducted study showed the directly proportional relationship between the quantity of HPMC 4K and the value of the swelling index. Using HPMC with a higher molecular weight did not offer a better value of the swelling index, since such a polymer would not allow the tablet to properly hydrate. The flowing and compressibility parameters were closely related to the swelling index, consequently to the type and quantity of the polymer used. The best values of the swelling index, Ic and R_H was obtained for formulation III, that included 15 mg of HPMC 4K. Formulation VI also included 15 mg of HPMC polymer, but with a different molecular weight (HPMC 100K), and the value of the swelling index, as well as those of the flowing and compressibility parameters were much smaller. We conclude that the best polymer to use while formulating such miconazole nitrate biomucoadhesive tablets is a sort of hydroxypropyl methylcellulose with a lower molecular

weight such as HPMC 4K in an optimum concentration between 5 and 7%.

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