

# ***In-vitro* characterization of the mucoadhesive properties of tablets in stomach and intestinal environments**

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## **INTRODUCTION**

Since the early 1980s, the development of mucoadhesive drug delivery systems has attracted growing interest. Mucoadhesive pharmaceutical forms can be used to target specific biological sites, to increase drug residence time at a defined release site, or to increase interactions between the pharmaceutical form and the various mucous membranes, thereby increasing the absorption of the active substance. [1] The aim of this study is to develop mucoadhesive tablets able to target a specific region of the gastro-intestinal tract (GIT) and suitable as a drug delivery system. For this purpose, the mucoadhesive properties of tablets made of different polymers have been studied in two model media mimicking stomach and intestine environments, respectively. Several tablet characterization techniques have been used and/or developed to determine their disintegration time, swelling index and interactions with mucosa by measuring a detachment strength and an adhesion time.

## **MATERIALS AND METHODS**

### **Materials**

Calcium hydrogen phosphate dihydrate (Emcompress® - JRS Pharma, Germany) was used as a diluent in all tablets. Mucines from porcine stomach Type II were purchased from Sigma Aldrich.

The various polymers tested in this study are unfortunately anonymised for reasons of confidentiality.

### **Preparation of the tablets**

A classical tablet formulation was defined with 79wt% dicalcium phosphate; 20wt% polymer and 1wt% magnesium stearate. Tablets were made by direct compression using the compaction simulator Styl'one Nano (Medelpharm, France) with a set of Euro B punches; 11.28 mm diameter (1cm<sup>2</sup> surface). The filling height and the compression force applied were determined in order to have 500 mg tablets, with a 80 N hardness. Weight, hardness, thickness, and diameter were checked on 10 tablets for each batch.

11 polymers were tested.

### **Preparation of simulated gastric and intestinal medium**

Simulated gastric (SGF) and intestinal (SIF) fluids were prepared according to the European Pharmacopoeia. SGF (pH 1.2) was made of 0.08 mol/L HCl and 0.034 mol/L NaCl. SIF (pH 6.5) was composed of 0.05 mol/L KH<sub>2</sub>PO<sub>4</sub> and 0.016 mol/L NaOH.

### **Tablet characterizations**

#### *Disintegration*

Disintegration tests were made on 3 tablets for each batch in SGF or SIF using a European Pharmacopoeia equipment (DT50, Sotax, Switzerland). Tests were stopped after 2 hours.

#### *Swelling evaluation*

Tablet swelling was measured on 3 tablets for each condition by placing weighed tablets (W1) in SGF or SIF at 37 ± 0.5°C. Sample of tablets were taken at different times, lightly wiped with paper to remove surface water, and weighed (W2).

The swelling index was determined using the following equation:  $I = \frac{W2 - W1}{W1}$ .

Swelling behavior was also evaluated regarding the tablet volume. A camera was used to measure the increase in diameter and thickness every minute during the first 15 minutes in each medium.

### **Adhesion properties**

#### *Measurement of the detachment strength of tablets contacting mucosa*

With the aim of limiting the variability associated with *ex-vivo* models and their preparation (fresh, cleaned or frozen mucosa), a synthetic mucus model was prepared by mixing 4.5wt% mucins and 2wt% agar. Such a mucus model was previously used by Müller *et al.* [2].

The texture analyzer TX-700 (Lamy Rheology Instrument, France) was used to measure the force needed to break the adhesion between a tablet and the mucins gel. The device was set to perform the following cycle: the probe was lowered at a speed of 1.0 mm.s<sup>-1</sup> until putting the tablet in contact with the mucins gel applying a compression force of 0.35 N for 180 s. The tablet was then withdrawn at a speed of 1.0 mm.s<sup>-1</sup>. The force is measured as a function of the

distance to the mucins gel surface. The measurement was carried out on 6 tablets.

**Evaluation of the adhesion time of the tablet to the mucins gel**  
To carry out this test, the sides of a beaker were covered with the same type of mucins gel containing a higher proportion of agar (2wt%) than the gel used in the previous test (0.5wt%) to have a stronger gel able to be kept on the beaker's side. Then, pre-hydrated tablets (10 min in the selected medium) were placed on the mucins gel. 900 mL of the corresponding medium were added in the beaker, at 37°C. A mechanical stirring was maintained at 80 rpm until the tablet detaches from the gel. The system is monitored visually to determine the adhesion time of the tablet to the mucins gel. The measurement was carried out on 3 tablets for each condition.


## RESULTS AND DISCUSSION

### Disintegration test

One of the main objectives of mucoadhesive tablets targeting the GIT is to have a sustained release of the active pharmaceutical ingredient. Thus, disintegration test is very important to prove the tablet can resist for an extended period of time in the concerned medium. Four formulations were not further characterized because their disintegration time was less than 30 minutes.


### Results

**Table 1: Characterization of adhesion in the stomach (pH 1.2)**

 Polymer	Swelling at 10min (%)	Detachment force (N)	Work of adhesion (N/mm)	Adhesion time (h)
Without polymer	7.45%	0.26	203.5	0
Polymer A	55.57%	1.65	838.6	8.0
Polymer B	56.49%	1.73	1355.9	0.92
Polymer C	34.14%	0.47	376.2	0.03
Polymer D	32.60%	0.33	305.2	0.02
Polymer E	9.30%	0.16	125.2	0
Polymer F		1.44	1189.4	4.4

(N=3)

**Table 2: Characterization of adhesion in the intestine (pH 6.5)**

 Polymer	Swelling at 10min (%)	Detachment force (N)	Work of adhesion (N/mm)	Adhesion time (h)
Without polymer	8.16%	0.15	0	0
Polymer A	45.54%	1.46	642.2	4.7
Polymer B	45.71%	1.91	1122.7	5.0
Polymer C	31.09%	0.44	211.2	0.1
Polymer D	36.30%	0.64	258.5	0.3
Polymer E	14.04%	0.36	110.2	0
Polymer F		1.89	1450.0	6.9

(N=3)

### Swelling evaluation – discussion

Mucoadhesion mechanism can be described by the succession of two main steps. First, tablets hydrate and swell in the medium, and get in contact with the mucosa and the mucus. Secondly, the polymer contained in the tablet create

some non-covalent bonds as well as their chains diffuse and interpenetrate in the protein's chains of the mucus. [3] Thus, hydration is a key property of the polymer-based tablets to obtain satisfying adhesion properties. Swelling evaluation is one of the easiest ways to characterize hydration ability of a solid dosage form.

All of the tested polymers present a pH-independent swelling. The measurement was not possible on polymer F because of its lack of consistency, which prevented it from being transferred between the beaker and the balance.

### Adhesion properties

As mentioned above, different tests were performed: the measurement with the texture analyzer subjects the adhesion under tensile force, while the measurement of adhesion time subjects it to shear forces, more representative of the forces occurring for example in the stomach.

In the various tests carried out, 3 polymers stood out from the others, showing significant values for both tests carried out and whatever the surrounding pH conditions: polymers A, B and F. It is also interesting to note that polymers A and B have the highest swelling values. Polymers C and D show more moderate swelling (around 30% after 10 minutes), and their adhesion results are much poorer. Lastly, polymer E does not appear to have any adhesive properties. No significant difference was observed compared to the polymer-free tablet.

Finally, all the tests carried out to characterize adhesion to the gastric and intestinal mucosa appear to be satisfactory. For the polymers tested, swelling capacity appears to be an important parameter for measuring a polymer's ability to make a good mucoadhesive matrix tablet. Moreover, the two tests set up make it easy to characterize adhesion and obtain robust results.

## CONCLUSION

This study enables to highlight mucoadhesive properties of tablets made of different polymers widely used in pharmaceutical applications. It also allows to learn more on mucoadhesion mechanisms and polymers-mucins interactions, as well as the pH impact on this complex phenomenon.

## REFERENCES

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