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

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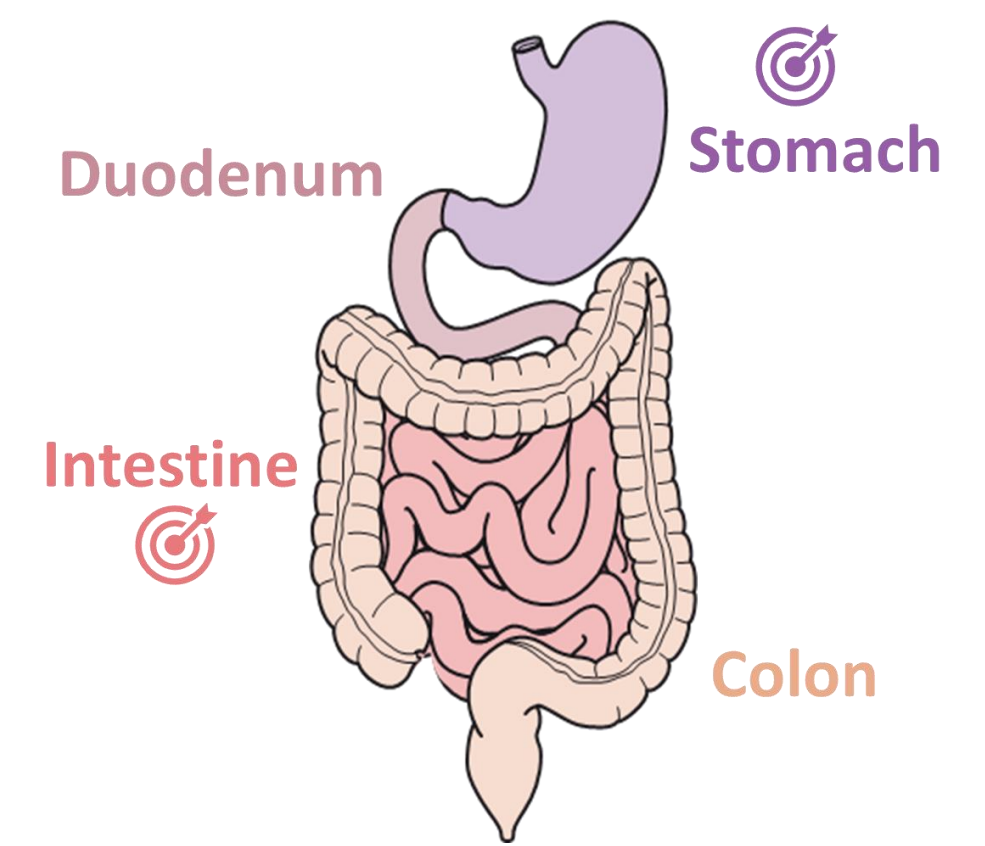
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The aim of this study is to develop mucoadhesive tablets able to target a specific region of the gastro-intestinal tract (GIT) and suitable as a drug delivery system. For this purpose, the mucoadhesive properties of tablets made of different polymers 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.



STUDIED POLYMER CHARACTERISTICS

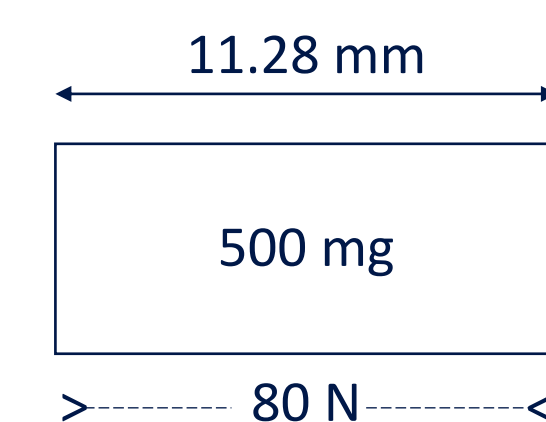
TABLET MANUFACTURING

Presence of strong functional groups that accept or donate hydrogen bonds
Hydroxyl, amine, sulfate, and carboxyl groups

Optimal molecular weight (different for each polymer)

Linear polymers: bioadhesive strength increases with molecular weight (min=100,000 g/mol)

Non-linear configuration, risk of hiding adhesive groups



Tablet formulation :
- 20% mucoadhesive polymer
- 79% dicalcium phosphate
- 1% magnesium stearate



Presence of strong cationic charges
Dependent on surrounding pH



Sufficient flexibility of the chains

An important parameter for the interpenetration and entanglement of polymers

Swelling and hydration of the polymer

The adhesive and cohesive nature of mucus increases when its water content is low: water transfer = an important factor in the mechanism of mucoadhesion

Powder
Flowability characterization

Direct compression
using the compaction simulator Styl'one Nano

Control
Weight, hardness, thickness, diameter (n=10)
Disaggregation (n=3)

→ Six polymers exhibiting one or more of the characteristics described above were selected for this study.

ADHESION CHARACTERIZATION METHODS

1) Swelling evaluation

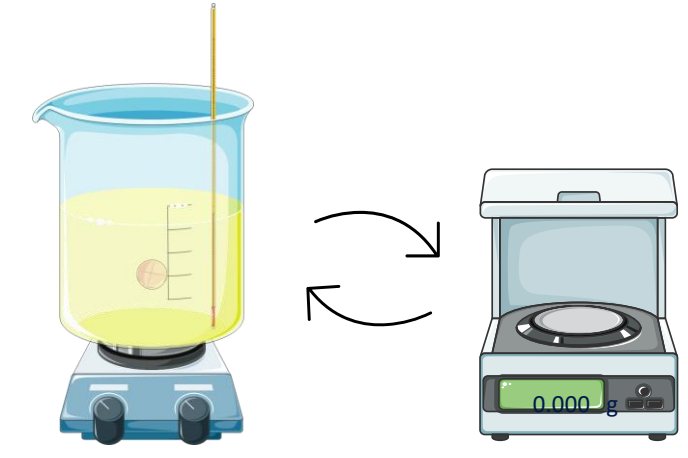
Objective : determine the hydration capacity of the formulation, the first key step in the adhesion mechanism

Assessment of swelling by mass monitoring:

The tablets are pre-weighed before being placed in the medium, then reweighed after being taken and lightly wiped with absorbent paper to remove surface water.

Swelling index: $I = \frac{w(t) - w_i}{w_i}$ With $w(t)$ the tablet weight at time t and w_i the initial weight of the tablet

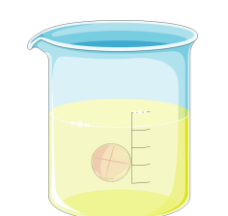
Medium: Simulated Gastric or intestinal fluid (SGF or SIF) according to the European Pharmacopeia
T = 37 ± 0.5 °C



Samplings:	
T0	45min
5min	1h
10min	1h30
20min	2h
25min	2h30
30min	3h

2) Measurement of the detachment force

Objective: Measure the tensile strength required for rupture, as well as the work of adhesion.



1- Tablet hydration:
10min in SGF or SIF

Synthetic mucosa:

Gel : 0.5% agar and 4.5% mucins¹

2- Measurement conditions:

Lowering the probe: v=0.5 mm/s

Contact: F=0.05 N et t=5 min

Detachment: v=0.5 mm/s

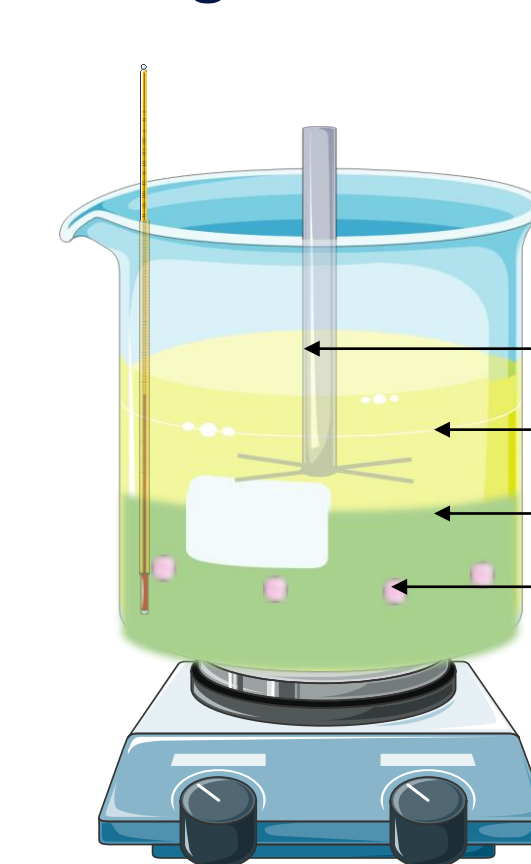
Device used:
Texture analyser TX700

Mucoadhesive tablet
Synthetic mucosa (1.0 g on a 3 cm diameter circle)
Add of 50 µL of SGF or SIF, 30 min before starting measurement

3) Adhesion time measurement

Objective: Measure the time the tablets adheres to the mucosa.

Determine the relative mucoadhesive capacities of tablets submitted to shear forces, more representative of the forces to which the tablet is submitted in the gastrointestinal tract



Agitation (70 rpm)
SGF or SIF – 37°C
Mucins gel
Mucoadhesive tablets

RESULTS AND PERSPECTIVES

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	7.5%	0.26	204	0
Polymer A	55.6%	1.65	839	8
Polymer B	56.5%	1.73	1356	0.93
Polymer C	34.1%	0.47	376	0.04
Polymer D	32.6%	0.33	305	0.03
Polymer E	9.3%	0.16	125	0
Polymer F	1.44%	1.44	1189	5.6

Results are presented as mean ± SD (n=3)

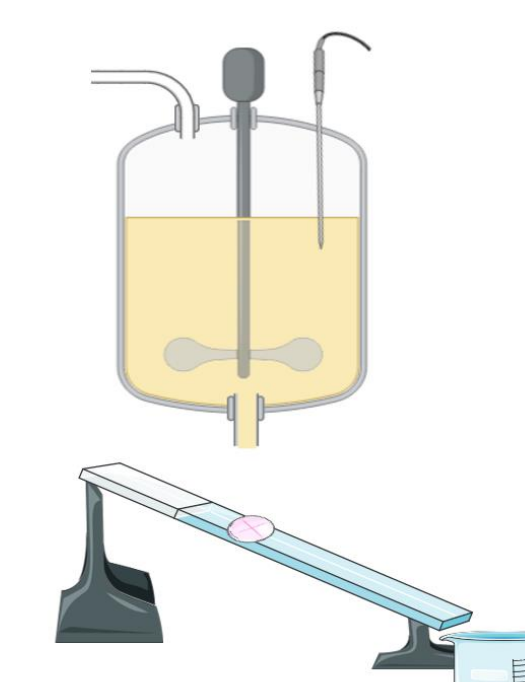
2) Characterization of adhesion in the intestine (pH 6.4)

Polymer	Swelling at 10min (%)	Detachment force (N)	Work of adhesion (N/mm)	Adhesion time (h)
Without polymer	8.2%	0.15	72	0
Polymer A	45.5%	1.46	642	5.6
Polymer B	45.7%	1.91	1123	6.0
Polymer C	31.1%	0.44	211	0.2
Polymer D	36.3%	0.64	259	0.4
Polymer E	14.0%	0.36	162	0
Polymer F	1.89%	1.89	1450	8

Results are presented as mean ± SD (n=3)

5) Prospects

Spontaneous adhesion



Implementation of a set-up to characterise spontaneous adhesion of tablets to a synthetic mucosa and after immersion in a medium representative of *in vivo* conditions

Implementation of *in vivo* characterization methods



Determining the most representative and appropriate animal model as well as the most suitable mucoadhesion identification method

Application: API introduction

Very interesting technology to:
- Target specific biological sites
- Increase drug residence time at a defined release site
- Increase interaction with the mucous membrane
For which type of API?
✓ API with a higher solubility at low pH
✓ API with a local action
✓ API with a narrow absorption window

3) Correlation

	Swelling at 10min (%)	Detachment force (N)	Work of adhesion (N/mm)	Adhesion time (h)
Swelling at 10min (%)	1.00			
Detachment force (N)	0.86	1.00		
Work of adhesion (N/mm)	0.83	0.94	1.00	
Adhesion time (h)	0.69	0.85	0.73	1.00

Critical value for Pearson's correlation coefficient, $\alpha = 5\%$: $R = 0,576$ ($n = 12$)

4) Discussion

- Good correlation between the different tests
- Crosslinked polymers present lower mucoadhesion properties
- Polymers with several functional groups that donate hydrogen bond present good mucoadhesion properties
- More than swelling, gelation seems to be a critical parameters

CONCLUSION

This study enabled the implementation of robust characterization methods to identify the mucoadhesive properties of tablets *in vitro*. Moreover, it enabled to highlight mucoadhesive properties of tablets made of different polymers widely used in pharmaceutical applications. It also allowed to learn more about the mechanism of mucoadhesion and the interactions between polymers and mucins, as well as the effect of pH on this complex phenomenon.

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