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Understanding the adhesion phenomena in carbohydrate-hydrogel-based systems: Water up-take, swelling and elastic detachment

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ABSTRACT

The bio-adhesion is a complex phenomenon which takes place when two materials (at least one of biological nature, the other usually is a polymeric one) are held together for extended periods of time, usually for local drug delivery purposes. Despite bio-adhesion is widely exploited in commercial pharmaceuticals such as the buccal patches, the underlying phenomena of the process are not completely clarified yet.

In this study experimental tests, in which the role of biological membranes is played by a water-rich agarose gel whereas patches are mimicked by hydrogel tablets (made of Carbopol or of Carbopol added with NaCl), have been used to analyze the behavior of the model system above described. Tablets have been forced to adhere on the agarose gel, and after a given contact time they have been detached, recording the required forces. Furthermore weight gain of the tablets (the water transported from the agarose gel toward the tablet) has been quantified.

Water transport (during the time in which the contact between tablet and agarose gel is held) and elastic part of mechanical response during the detachment are modelled to achieve a better understanding of the adhesion process. Both the two sub-models nicely reproduce, respectively, the weight gain as well as the swelling of the Carbopol tablets, and the point at which the mechanical response ceases to be purely elastic.

1. Introduction

The adhesion properties exhibited by several bio-polymers when in contact with biological surfaces and mucosas have been used to develop bio-adhesive drug delivery systems. This kind of drug dosage system has several advantages: close contact, prolonged retention at the application site, localizing of the drug delivery, an enhanced absorption at a site-specific position. All of them give an improved patient acceptance and compliance (Peppas & Sahlin, 1996). Moreover, the mucosa is relatively permeable with a rich blood supply, which makes the delivery feasible even for systemic therapies, avoiding in this way the first-pass effect and the pre-systemic elimination in the gastrointestinal tract (Bruschi & de Freitas, 2005; Friedl, Dünnhaupt, Waldner, & Bernkop-Schnürch, 2013; Xu, Strandman, Zhu, Barralet, & Cerruti, 2015).

Despite the widely application of these drug delivery systems, the mechanism behind the bio-adhesion process has not yet completely clarified. There are five general adhesion theories developed to describe the muco-adhesion process: the electronic, the wetting, the adsorption, the diffusion and the fracture theories (Donald & Chickering Ill, 1999). Each theory has its peculiar features that can describe some aspects of the process very well, but none of them alone can give a full description of the process. In the literature, the theories behind the bio-adhesion mechanisms were further rationalized, dividing into the process into the following two stages, by Smart (Smart, 1999; Smart, 2005):

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Nomenclature

General parameters

t_C	contact time [s]
ζ	moles of Carbopol monomer per mole of sodium chloride [dimensionless]
t_D	displacement time [s]
$X_{i,w}$	X generic parameter of water (w) in the domain *i*. *i* = 1 (Ω1), 2 (Ω2)

Hydration and swelling model parameters

ρ_i	density of the ith species [kg/m^3]
ρ	mixture density [kg/m^3]
$\boldsymbol{v}$	mass average velocity [m/s]
$\boldsymbol{j_i}$	diffusive flux [kg/(m^2 s)]
r_i	generation of the ith species [kg/(m^3 s)]
$\omega_i^{\Omega j}$	mass fraction of the ith species in the domain Ωj [dimensionless]
D_i^{Wj}	pseudo-diffusion coefficient of i in the domain Ωj [m^2/s]
D_i^*	diffusion coefficient of ith species in the fully swollen matrix [m^2/s]
β_i	Fujita-type coefficient [dimensionless]
$\omega_{w,eq}$	mass fraction of water in the fully swollen matrix [dimensionless]
v_R	moving front velocity due to the swelling [m/s]
K	equilibrium constant [dimensionless]
A	diffusion coefficient factor function of the NaCl concentration [dimensionless]

Elastic model parameters

$\boldsymbol{\sigma}$	stress tensor [Pa]
$\boldsymbol{\varepsilon}$	strain tensor [dimensionless]
λ_s	Lamé's first parameter [Pa]
μ_s	Lamé's second parameter [Pa]
$\boldsymbol{u}$	displacement vector
$\boldsymbol{I}$	identity matrix [dimensionless]
E_0	Young modulus [Pa]
ν	Poisson ratio [dimensionless]
r_0	average radius of the hydrated zone [m]
l_0	penetration lengths of water [m]
Δr	radial deformation respect to r_0 [m]
Δz	axial deformation respect to l_0 [m]
$I\boldsymbol{\varepsilon}$	first invariant of the strain tensor (trace) [dimensionless]

(1) the *contact* stage: in which the necessary close contact between the bio-adhesive material and the mucosas is generated
(2) the *consolidation* stage: in which the adhesive joint is consolidated and strengthen by various physicochemical interactions leading to a prolonged adhesion.

The first stage can be quite simple in some cases, for instance by placing and holding a delivery system (e.g., a tablet) on oral cavity or vaginal mucosa. In other case, such as the drug delivery to the respiratory tract, it is not possible to directly keep in place the material to the mucosa (e.g., breathing air flow is used to bring microparticles in contact with the mucosa in the respiratory tract). The second stage is much more complex and the literature essentially reports two main theories which describe how the strengthening of the adhesive joint occurs. One is based on the macromolecular interpenetration theory, whereas the other one focuses the attention on the water transport in the system.

In the "*macromolecular interpenetration theory*" it is assumed that macromolecules of the bio-polymeric formulation and of the biological surface, respectively, migrate and interpenetrate in each other. Even if this theory is supported by theoretical description and experimental works (Jabbari, Wisniewski, & Peppas, 1993; Ponchel, Touchard, Duchêne, & Peppas, 1987), several objections could be raised. The first opposition is related to the time scale of the phenomenon: muco-adhesion arises very quickly (within few seconds) and it is unlikely that the interpenetration of macromolecules can occur on this time scale. Moreover, it has been shown that muco-adhesive materials adhere even better to solid surfaces such as wet Perspex (where the opportunity for macromolecular interpenetration and secondary interactions is clearly minimal) and the presence of mucus appears to inhibit, rather than promote, the adhesion.

The second theory is the so called "*dehydration theory*". When a material, which is able of rapid gelation in an aqueous environment, is brought into contact with a second gel/mucosa, water movement occurs until equilibrium is achieved. According to these hypotheses there will be a quick dehydration that enhances the mucosa adhesive properties (Mortazavi & Smart, 1993) and generates a suction force. This last theory has attracted the attention of several researchers that, despite enlightening different aspects and developing different techniques of analysis, have tried to quantify the water transport and to relate it to the adhesion force (Borde, Bergstrand, Gunnarsson, & Larsson, 2010; Mortazavi & Smart, 1993). One of the most frequently applied methods to quantify the adhesion force is based on the use of a Texture Analyzer (T.A.), which is a dynamometer capable of measuring the detachment force required to separate a bio-adhesive device from a biological/test surface, widely used in hydrogels-based systems characterization (Caccavo, Cascone, Lamberti, & Barba, 2015a; Cascone, Lamberti, Titomanlio, d'Amore, & Barba, 2014; Lamberti et al., 2013)

Despite water movements and bio-adhesion forces were measured and quantified in several works, to the best of our knowledge, there is still a lack in their description by a mechanistic model, in order to explain these phenomena and to link them together. Recently, computer modeling has been used as a tool to propose mechanistic models to describe the transport phenomena which take place working with other drug delivery formulations (Caccavo, Cascone, Lamberti, & Barba, 2015b; Kaunisto et al., 2010; Siepmann & Peppas, 2001). A similar approach will be adopted in this study.

Aims of this study are to investigate the effects of the contact time and the role of different excipients on the adhesion mechanism between Carbopol tablets (simulating a bio-adhesive material) and agarose gels (simulating biological mucosa); and to develop a mechanistic model able to describe the observed behaviors. In particular, this latter model will be based on a two-steps approach which encompasses: first the quantification of water transport and swelling within the delivery system, and thus the description of mechanical responses through a purely elastic model.

2. Materials and methods

2.1. Materials

In this work, as bio-adhesive model system Carbopol (or Carbopol mixed with NaCl) tablet was used, whereas the mucosa was mimicked by an aqueous agarose gel (1% (w/w)), similarly to Borde et al. who exploited this gel for its ability to be loaded with salts or varied in concentration (Borde et al., 2010). Carbopol 974-P NF containing maximum 2.5% sulfated ash was purchased from Noveon (USA). Agarose for electrophoretic routine use, ≤1% sulfated ash, was bought from Sigma-Aldrich (Germany). Sodium chloride was