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# ANALYSIS AND MODELING OF THE BEHAVIOR OF HYDROGELS-BASED SYSTEMS FOR BIOMEDICAL AND AGRO-FOOD APPLICATIONS

# Abstract

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Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. Depending on the type of polymer, number of cross-links, presence of ionic species the swelling/shrinking behavior can be greatly modified. This peculiar behavior, which has led to define this soft matter as "smart materials", makes hydrogels and hydrogel-based systems very attractive by several frontier fields, such as biomedical applications, as well as for sectors that are less demanding technology, i.e. agro-food applications.

The general aim of this Ph.D. thesis is to analyze, with ad hoc experiments, and to describe/simulate, through mathematical modeling, the behavior of hydrogels and hydrogel-based systems.

A first question to answer when approaching hydrogels is: "are they multiphasic or monophasic systems"? The answer cannot be taken for granted. Despite in most experimental cases the response is simply avoided, it become fundamental when the aim is to develop a mechanistic mathematical model of the system. The most natural approach is to consider hydrogels as single-phase matter, in which several components can coexist, like it would be indisputably done for polymeric solutions (hydrosols). Another vision is to consider hydrogels as made of different phases, i.e. the water phase is separated from the polymeric phase, and these can exchange momentum. During this work a general modeling framework has been proposed to which several models from literature, multiphasic or monophasic, can be traced back or, vice versa, depending on the chosen approach the framework can be particularized to give the multiphasic or the monophasic balance equations. In this thesis, in light of its thermodynamic and numerical robustness, the monophasic approach, which is more consistent, has been chosen.

Another important question is related to the need of modeling/analyze the full behavior, mass transport plus mechanics, or just one aspect, mass transport only. The difficulties related to the solution/analysis of the full hydrogels behavior have led many researchers to describe hydrogel-based systems with a "mass transport only" approach. This is, in example, common in drug delivery applications. During this PhD a mechanistic model based on a "mass transport only" approach for drug release from hydrogel-based system has been developed and validated against experimental data. HPMC-based tablets, loaded with Theophylline have been studied. Differently to what is normally done in dissolution tests, in this work besides the evaluation of the drug release via spectrophotometric analysis, the water and polymer residue have been determined by gravimetric analysis. This has been done on the entire tablets, as well as on portion of them, obtaining internal profiles of the components. The partially swollen tablets have been also subjected to indentation tests, which after an opportune calibration have allowed obtaining information on the water distribution inside the system. A 2D-axisymmetric model has been built on the water and drug mass transport equations; the polymer has been obtained from the mass fraction constraint. The deformations have been described with an ALE moving mesh method, whose boundaries move in relation to the amount of water and drug entering or leaving the system. The comparison between the detailed experimental results and the modeling results has shown a good agreement, in terms of masses, shape and components distribution, demonstrating that the main features had been correctly described.

Such a formulated model has been applied to describe commercial-like tablets (in which excipients were present), with two type of HPMC with different substitution pattern (i.e. different degree of cross-links) and tested in non-standard apparatus (NMR cell). Despite after a proper tuning the model has been able to describe the drug and polymer release, the shape and the water distribution inside the system (experimentally taken from MRI technique) have not been correctly described. This application demonstrated the limits of a "mass transport only" approach. In the analyzed case the forces acting on the swelling tablet (shear, centrifugal, gravitational) could have a relevant impact, but most of all the different degree of cross-links of the HPMC played the major role.

In order to consider the hydrogel mechanics, the pure hydrogel behavior has been studied. Hydrogels normally couple solvent mass transport to system deformation and vice versa. This phenomenon is generally called poroelasticity and it is characteristic also of other materials (i.e. biological tissues, soils etc.). Another peculiarity of hydrogels is that the constituent polymeric network can have viscoelastic characteristics (i.e. like polymeric melts), which eventually translate in an overall hydrogel viscoelastic behavior. Depending on the time interval of interest and on the characteristic times of relaxation and diffusion, hydrogels can behave viscoelastically, poroelastically or poroviscoelastically (when the diffusion time is comparable with the relaxation time). A 3D model describing the poroviscoelastic behavior of hydrogels, still scarcely implemented in literature, has been developed within the field of non-equilibrium thermodynamics and non-linear solid mechanics (large deformations) and implemented in a commercial FEM-based software. The results of such kind of model permit to discriminate between and to study the poroelastic and viscoelastic regime as well as

it permits to study the poroviscoelastic behavior. Experimental unconfined stress-relaxation tests have been performed on agarose-gels at different concentrations with radius and height of 1 cm, and imposing a deformation of 10%. In the time range analyzed (1200 s) the agarose-gel has shown a predominant viscoelastic behavior, releasing only little amount of water. The model, after an initial tuning of the parameters, has been able to fairly predict the experimental data. Characteristic of the developed approach is that, once the model parameters are derived, it is possible to describe the hydrogel subjected to different stimuli (mechanicals or chemicals).

The proposed poroviscoelastic model is extendable to multicomponent diffusion systems, which could be, in example, controlled release systems based on hydrogels. For the first time, to the author's knowledge, in the hydrogel-based systems modeling literature, in this thesis it has been shown how to extend the poroviscoelastic model to consider the presence of another diffusing species. The transport and constitutive model equations, opportunely modified, have been implemented in a commercial FEM-based software and, as an example, the drug release from a swelling system has been reported.