INSTITUTO TECNOLÓGICO Y DE ESTUDIOS SUPERIORES DE MONTERREY
CAMPUS MONTERREY

Words words words
Hydrogels

A thesis presented by

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Acknowledgements

Total Thanks.

Thank..

Dedication

To ...

To ...

Abstract

In summary: More research is needed.

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Chapter 1

Introduction

Curiosity/phenomenology Paragraph that will tell the reader that hydrogels are cool.

Applications/Market size of the applications sectors If the previous paragraph does not convince the reader, well my last hope is that money does.

Besides, because of such a wide variety of response triggers, hydrogels can serve as sensors or actuators or can be utilized in controlled drug delivery systems, biosensors, tissue engineering scaffolds, and others [20], because of their biomimetic properties and multi functionalities [21](**?**).

In particular, biomedical applications are very popular and include cell culture [5], wound dressing and healing [2,6], drug delivery [2,7,8], tissue engineering scaffolds [9], bone repair [10], and cartilage regeneration [11](**?**).

Description of the Thesis What the reader will find in each chapter and section.

Why computers and not rheometers? Explain how in silico experiments can help to understand the relation between the network and the mechanical response.

1.1 State of the art: Hydrogels

- Characteristics
- Descriptions
- Synthesis techniques
- Cross-linking (Bond breaking)

General description of a hydrogel A hydrogel is commonly describe as a material composed by a network of polymers chains that exhibits the abilitiy to swell and retain a significant fraction of water within its structure, but will not dissolve in water(**????**).[1] The water absorption capacity, network stability of hydrogels, and the conformation of the network with polymer chains are attributable to crosslinking mechanisms(**??**). Meanwhile, the polymer

[1] the main difference with the microgels, is the size. Hydrogel is bulk, and microgelgel is particle.

chains are predominantly composed with hydrophilic functional groups and can be modified to suit a variety of applications(**???**).

While the analysis of the impact of functional groups is important, the present project prioritizes the examination of mechanisms that are more pertinent to the mechanical response. The crosslinking mechanisms[2], in particular, are of particular interest, as they are responsible for resisting dissolution. This suggests that crosslinking mechanisms enable the network to undergo modification by external stimuli.

The subsequent sections will present the essential information to facilitate a comprehensive understanding of the crosslinking mechanisms, their relationship to the mechanical response, the reported mechanical response of hydrogels, and the correlation between rheology experiments and stress curves.

1.1.1 Crosslinking mechanisms

What a low hysteresis means in a hydrogel?

Intro to cross linking A crosslinker is a molecule that functions as a bridge between polymer chains, thereby facilitating the formation of an interconnected network. As previously suggested, it is pertinent to understand the mechanisms of crosslinking in order to gain insight into the correlation between these mechanisms and mechanical properties, such as elasticity, viscosity, solubility, glass transition temperature, strength, toughness, and melting point stiffness, swelling capacity, viscosity, and so forth(**?**). The elements under consideration form stable bonds, which are comonly categorized into two main types: covalent (permanent) and physical (reversible)(**?**). However, recent mechanisms, such as mechanical crosslinker mechanics, have been demostrated to form bridges due to the topology of the constituents of the hydrogel.

Difference between physical and chemical bonds Although the concept of bonding is central to comprehending chemical structures and reactions. The criteria employed to characterize a chemical bond, its physical origin, and its nature remain subjects of debate(**?**). Consequently, establishing a precise distinction between “covalent” and “non-covalent” bonds remains challenging. Therefore, the description of crosslinker mechanisms is limited to the principal interactions reported in articles and the synthesis process, rather than focusing on the classification of interactions as “covalent” or “non-covalent”, but rather as “reversible” or “irrevarsible”. Also in the recent work (**?**) it is shown a “covalent” reversible network. Nonetheless, a general consensus exists that non-covalent bonds are, as a rule, recognized as being weaker than covalent bonds and it is widely accepted that a distinguishing characteristic between covalent and noncovalent bonds is the energy of interaction and equilibrium bond distance(**??**).

Irreversible Cross-linking In irreverisble cross-linked hydrogels, polymer chains are synthesized by chain growth polymerization, graft copolymerization, addition and condensation polymerization, ezymatic method, reactive functions groups and gamma and electron beam polymerization(**??**). This types of crosslinking mechanisms exhibit a high degree of strength and stability, leading to a structural arrangement of interconnected polymer chains that is more robust and resistant to alterations in environmental conditions, such as temperature and pH(**?**).

Reversible Cross-linking In reversible cross-linked hydrogels, polymer chains are held together by molecular entanglements or physicochemical interactions, including van der Waals forces, hydrogen bonds, hydrophobic interac-

[2]The hydrogels are prepared using different methods like chemical cross-linking of monomers, physical cross-linking using temperature or pH changes, and blending of natural or synthetic polymers.

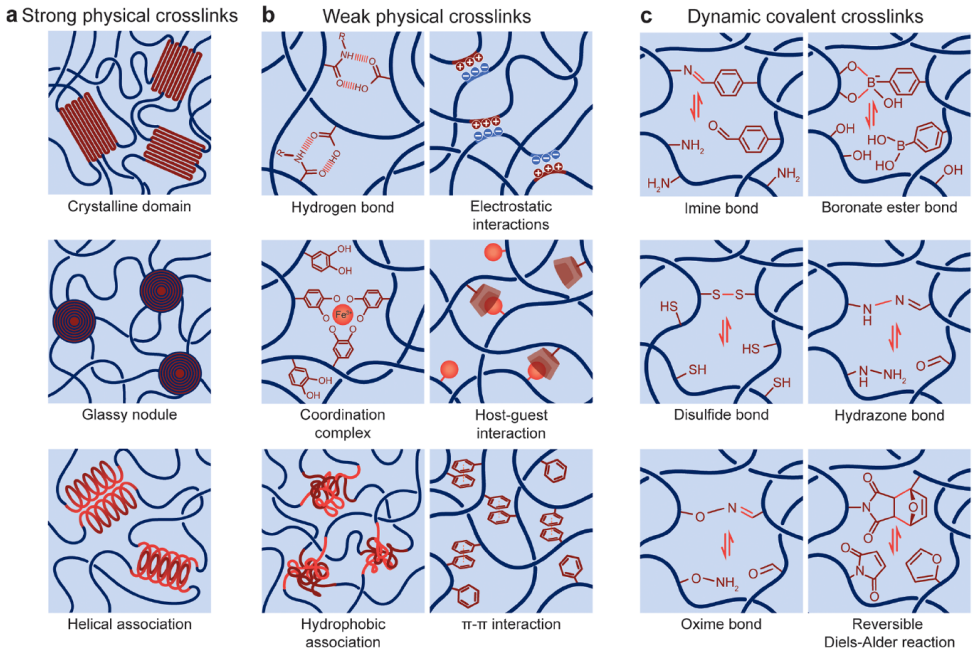

Figure 1.1: Image with the three different crosslinker mechanisms

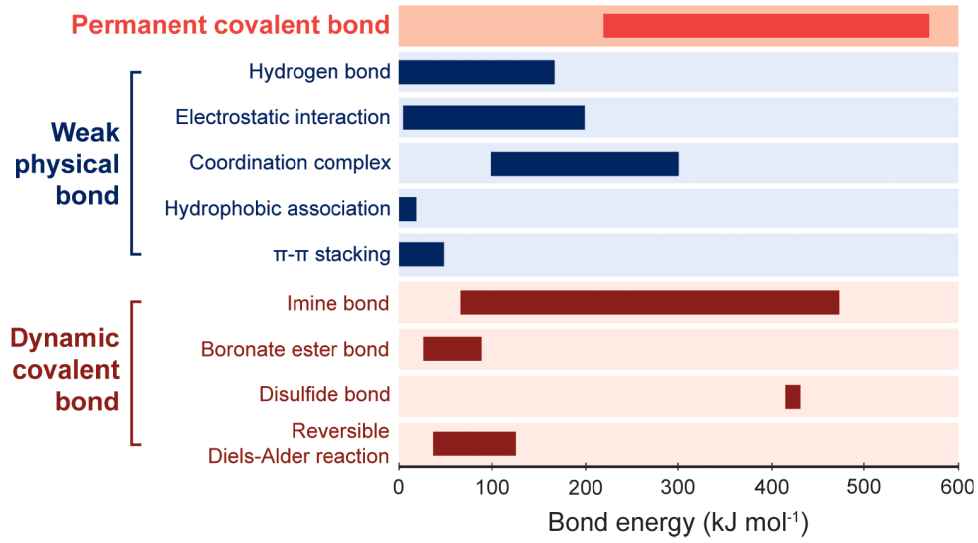

Figure 1.2: Bond energies of various types of permanent covalent crosslinks, weak physical cross-links, and dynamic covalent crosslinks.

tions, charge condensation, crystallite formation, and supramolecular chemistry(**??**). Some of the syhtesis methods for reverisble crosslinkin mechanisms are ionic interaction, crystallization, stereocomplex formation, hydrophobized polysaccharides, protein interaction, amphilic copolymers and hydrogen bond(**??**). Furthermore, molecular reversibility can be actually achieved in two different ways: either by making use of equilibrium reactions (e.g., the Diels-Alder one) or through dynamic exchange reactions (e.g., reaction of an excess amino groups with epoxide

ones)(**?**).

Mecanical bonds As previously mentioned, a novel class of polymer architecture has recently emerged within the field of polymer science kwnon as mechanically interlocked polymers (MIPs). These polymers are distinguished by the presence of a mechanical bond, that is, a constraint of two (or more) molecular components in space without the formation of covalent bonds(**?**). While these types of hydrogels exhibit substantial conformational flexibility while preserving a persistent spatial correlation between their components, their synthesis remains challenging.

1.1.2 Mechanical response of hydrogels

General mechanical properties of the croslsinking Eventhough, physical crosslinking mechanisms are weaker than chemical ones, there numerous interactions contribute to complex behaviors. Meanwhile chemical crosslinking mechanisms are easier to control than physical crosslinking mechanisms because their preparation is independent of pH(**?**) and they are very brittle due to structural inhomogeneity and lack of energy dissipation(**?**).

Reversible crosslinking The aforementioned interactions enable hydrogels to undergo structural changes without the rupture of any covalent bonds. Consequently, these materials exhibit enhance responsiveness to external stimuli, such as temperature, pH, or ionic strength. Additionally, hydrogels demonstrate high water sensitivity and thermal reversibility(**??**). These materials are known to exhibit distinctive properties, including "self-healing" behavior, where the gel can reform after being broken. The lifespan of these hydrogels is brief, ranging from a few days to a maximum of a month, when maintained within physiological media.

Ir-reversible croslsinkg Consequently, chemically cross-linked hydrogels generally exhibit greater mechanical strength and long-term stability. Furthermore, it generally contains regions of the high cross-linking density and low degree of swelling (clusters), dispersed in the regions of the low cross-linking density and high swelling index due to the hydrophobic aggregation of the cross-linking agent(**?**)..

Network-mechanical response relation Introduce the idea of how by understanding the network we can manipulate/control the mechanical response.

The research of hydrophilic polymers has been complex because the physical properties of solubility or swellability depend on different factors, such as the type of polymer, molecular weight, the ratio of polar groups, and degree of cross-linking(**?**). High molecular weight and a high degree of cross-linking will reduce the hydrophilicity of the molecule [18,19](**?**).

Tunnable mechanical response with applications Review of articles of applications

Just describe the phenomena and say that it depends on the structure and so on.

Viscoelasticity

Yield stress

Shear thinning

Transition to talk about printing hydrogels (**?**) Subsequent work developed safer cross-linking mechanisms, which began a trend toward triggering gelation in situ after injection, providing a minimally invasive way of administering hydrogels to practically any organ or tissue.29,30[3]

Unlike earlier hydrogels that relied on covalent cross-links, some of these hydrogels have self-healing properties and possess mechanical properties akin to native tissue, capable of countering natural forces and stresses of a body in motion. More recently, shear-thinning hydrogels were developed that are formed through dynamic and reversible cross-linking.34 For example, physical hydrogels use noncovalent interactions (e.g., supramolecular chemistries) between soluble building blocks in order to self-assemble into a dynamic, reversibly cross-linked network.35,36 These "dynamic hydrogels" assembled through reversible cross-links afford the unique property of being injectable even after having formed a gel, due to their shear-thinning and selfhealing behaviors. Current research on dynamic hydrogels has revealed novel and useful capabilities that have opened new frontiers for this technology.

For example, they can stabilize delicate protein and cellular cargoes to combat pharmaceutical cold-chain limitations,39 they can adhere strongly to tissues to form protective barriers and bandages,40 and they can be delivered through spray applications to coat complex biological geometries.41

static covalent cross-links ultimately introduced translational challenges for clinical implementation, since traditional covalent gels require invasive surgical implantation to access nonsuperficial tissues. Additionally, new manufacturing processes, such as 3D printing, require dynamic rheological properties during processing, disqualifying the use of traditional covalent hydrogels.57 Interest in further developing the translational potential of hydrogels led to innovative methods to implant them through minimally invasive means, of which the most clinically relevant is injection through a needle or catheter (Figure 3).

static covalent cross-links ultimately introduced translational challenges for clinical implementation, since traditional covalent gels require invasive surgical implantation to access nonsuperficial tissues. Additionally, new manufacturing processes, such as 3D printing, require dynamic rheological properties during processing, disqualifying the use of traditional covalent hydrogels.57

Hybrid crosslinking hydrogels consist of covalent and noncovalent crosslinking(**?**). The dynamic physical crosslinking could effectively dissipate energy via destruction and reorganization, and the chemical crosslinking could sustain skeleton construction [19,20](**?**).

The molecular reversibility can be actually achieved in two different ways: either by making use of equilibrium reactions (e.g., the Diels-Alder one) or through dynamic exchange reactions (e.g., reaction of an excess amino groups with epoxide ones)(**?**).

The general idea is that the use of dynamic covalent bonds allows the polymeric network to adjust itself as a result of an external stimulus(**?**). This can be achieved in principle through other weaker interactions, e.g., hydrogen bonding(**?**).

the use of covalent bonds displays two distinct and clear advantages [25]. In first instance, the network is still covalently linked, which renders it quite robust against small random fluctuations in environmental conditions such as temperature. Furthermore, exchange reactions such as the one of an amine with an imine are often kinetically controlled by the use of catalysts. In turn, this allows the possibility to freeze the network conformation (by slowing the kinetics) when desired(**?**). The general concept behind the use of reversible interactions for the hydrogel polymeric chains is the (reversible) network disruption with immediate release of any loading (Figure 3).

Reversible bonds can be incorporated along the backbone (red circles) or at the crosslinking point (green triangles). The network, when subjected to an appropriate external stimulus, can then break at the crosslinking point (route A) or along the backbone (route B). This generates network fragments that can be quite different in terms

[3] Why the gelation in situ after injection is important?

of chemical structure even if in both cases the loading (blue circles) will be released. As a result of the network disruption, the load is released as the polymeric chains become soluble and not able anymore to entrap the load(**?**).

1.1.3 Rheology/stress

Main review:(**??**)

Bridge of the experiments and interpretation Hysteresis curves to get the sotred energy and the dissipated energy.

Name some network structures The correlation between the structure with the hysteresis loops

Link to mechanical response Same as before.

What if we can change the structure on command and in real time? Bridge to crosslinkers.

How crosslinking affects the mechanical response Crosslinking is another essential process that can be controlled and intentionally modified using ionizing radiations(**?**).

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Curriculum Vitae

Rubén Morales-Menéndez was born in Veracruz, México. He received the degree of Bachelor of Science in Chemical Engineering and Systems (1984), the degree of Master of Science in Chemical Engineering (1986) and the degree of Master of Science in Control Engineering (1992) from Tecnológico de Monterrey, Campus Monterrey, México, where he is currently a full professor in the Mechatronics and Automation Dept. He is also a consultant specializing in the analysis and design of automatic control systems for continuous processes, and a PhD candidate. From 2000 through 2003 he has been a visiting scholar at the Laboratory of Intelligence Computer. of the University of British Columbia, Canada. His research interests include artificial intelligence techniques for control processes.