Stimuli-responsive liquid crystal hydrogel implants by electrospinning technique

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Biomedical applications of nanomaterials

Nanomaterials

INTRODUCTION

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**Drug Delivery System Challenges**

**Targeted drug delivery:** systems allow selective targeting of the drug to a specific tissue, organ or specific cells inside the body to achieve a targeted drug action.

**Controlled release drug delivery:** systems capable to maintain the adequate end desired release of drug over an extended period of time.

A drug-delivery system release the drug into the target and match the desired kinetics of the release.
“Smart” Drug Delivery Systems

The future of drug delivery systems will involve smart systems.

These will address the issue of keeping the drug at the desired therapeutic level in the body thus avoiding frequent administration.

The ultimate goal is to administer drugs at the right time, at the right dose anywhere in the body with specificity and efficiency.

Systems use detection of external stimuli to prompt the release of drugs.
'Intelligent' or 'Smart' materials may be defined as 'Those materials which sense any environmental change and respond to it in an optimal manner' (Roger et al.).
Smart Materials

A smart material can be described as a material that has a useful response to external stimuli.

The change in the material can also be reversible, as a change in stimulus can bring the material back to its previous state.

**Nature is Smart**

- **Clover – Shamrock flower (Koniczyna)**
- **Tulips**
- **Mimosa pudica (Mimoza wstydlwiwa)**

**Anthropogenic smart materials**

- **Piezoelectric materials**
- **Photochromic lenses**
The achievement of nanomaterials able to release therapeutic agents and change their physical properties in a controlled fashion and is a major challenge in the field of nanomedicine.

The full realization of their potential anticipates a bright future in life-science.

**Drug delivery**

**Stimulus can include:**
- Light
- Magnetic field
- pH
- Temperature
- Electrical field
- Mechanical stimuli

**Tissue engineering**

Hydrogels

- Three dimensional networks of hydrophilic polymers that are insoluble but can swell in water.
- Solid-like and liquid-like properties in one material.
- Biocompatibility.
- Controlled drug release.
Hydrogel mechanical properties

Mechanical properties are influenced by:

- Type and composition of monomers.
- Cross-linking.
- Environmental factors (e.g. temperature, pH and ionic strength).

[L.Y. Chu et al., Smart Hydrogel Functional Materials]
Liquid crystals

Freidrich Reinitzer discovers liquid crystals (1888).

Crystals: 3D long range order Molecules with both orientation and positional orders. Glasses: just short range order, positions of molecules statistically distributed.

A stable phase of matter characterized by anisotropic properties without the existence of a 3-dimensional crystal lattice. It differs from liquid that there are still some orientational order possessed by the molecules.
**Liquid crystals**

Isotropic materials: have uniform properties in all directions (liquids and gases).

Anisotropic materials: directionally dependent properties (liquid crystals).

**Molecule requirements**

The molecule must be elongated in shape—length should be significantly greater than its width.

Molecule must have some rigidity in its central region.

The ends of the molecule are somewhat flexible.
INTRODUCTION

Morphological classification

Calamitic

Discotic

Banana shape
Mechanism classification

Thermotropic Liquid Crystals
LC phase transitions resulted from temperature changes.

Lytropic Liquid Crystals
LC phase is formed when a molecule is dissolved in a suitable solvent (with specific concentration at a particular temperature).

[Diagram of Cholesteryl Myristate with temperature phase transitions: Solid 71 °C, LC 85 °C, Liquid]
Liquid crystal phases (mesophases)

- **Liquid phase**: Molecules arranged randomly.
- **Nematic liquid crystalline phase**: Long axes of molecules aligned, but ends are not aligned.
- **Smectic A liquid crystalline phase**: Molecules aligned in layers, long axes of molecules perpendicular to layer planes.
- **Smectic C liquid crystalline phase**: Molecules aligned in layers, long axes of molecules inclined with respect to layer planes.
A chiral molecule is a type of molecule that has a non-superposable mirror image. 

The feature that is most often the cause of chirality in molecules is the presence of an asymmetric sp³ carbon atom.
Chiral Nematic Phase (Cholesteric Liquid Crystal)

Molecules with intermolecular forces that favor alignment between molecules at a slight angle to one another.

The director is not fixed in space as in a nematic phase, it rotates throughout the sample.

Spatial diposition
Calamitic
Discotic

INTRODUCTION

Liquid crystals as stimuli-responsive materials

The seed of the project

Macroscopic contraction of a gel induced by the integrated motion of light-driven molecular motors
Q. Li, G. Fuks, E. Moulin, M. Maaloum, M. Rawiso, I. Kulic, J. T. Foy and N. Giuseppone

INTRODUCTION

Nanoscale

Tunability

Macroscopic contraction of a gel induced by the integrated motion of light-driven molecular motors
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INTRODUCTION
The final material

Soft polymer (hydrogel)

Biocompatible

External stimuli

Nanostructurated (electrospinning)

Smart drug delivery system (liquid crystals)
Macrohydrogel with chiral nematic phase

Pure Anisotropic Hydrogel with an Inherent Chiral Internal Structure Based on the Chiral Nematic Liquid Crystal Phase of Rodlike Viruses
Project plan

1. Development of the coaxial electrospinning technique.
2. Optimization of the shell removing process.
3. Structural and mechanical characterization of the developed hydrogels.
4. Analysis of the drug release properties.
5. Study of the nanostructure hydrogels external stimuli-response.
Hydrogels

Polyacrylamide

Materials:
- Acrylamide (Aam)
- N,N'-methylene bisacrylamide (BIS-Aam)
- Fluorescein-o-acrylate (FITC-acr)
- Irgacure 2959

Samples:
- EA1 mass ratio of AAm/BIS-AAm (w/w): 37.5:1
- EA2 mass ratio of AAm/BIS-AAm (w/w): 20:1
- EA3 mass ratio of AAm/BIS-AAm (w/w): 4:1

Poly(N-isopropylacrylamide)

Materials:
- N,N-isopropylacrylamide (NIPAAm),
- N,N'-methylene bisacrylamide (BIS-Aam)
- Fluorescein-o-acrylate (FITC-acr)
- Irgacure 2959

Samples:
- EN1 mass ratio of NIPAAm/BIS-AAm (w/w): 37.5:1
- EN2 mass ratio of NIPAAm/BIS-AAm (w/w): 20:1
- EN3 mass ratio of NIPAAm/BIS-AAm (w/w): 4:1
Cholesteric Liquid Crystal

Cashew

Nanercz zachodni


Tweaking the Organization of Liquid Crystallinity and Molecular Gelation in Cholesterol Tagged Cardanol by Self-Assembly

Neethu K. Sadanandhan, Sarojam Sivakala, and Sudha J. Devak[3]
INTRODUCTION

Coaxial electrospinning

- **Electrospinning**
  - **Core:** Hydrogel
  - **Shell:** Poly(L-lactide-co-caprolactone) (PLCL) (70% L-lactide and 30% caprolactone unit)

- **Post-electrospinning UV irradiation**
  - Controlled temperature (< 10 °C)

- **High Voltage Supply**
Coaxial electrospinning

- Liquid Crystal (solubility, pitch length and toxicity).
- Covalent bonding of liquid crystal into the polymer matrix.
- Nanofibers (dimension).
- Hydrogels (stiffness).
Shell removing process

Sheel dissolution and filaments extraction in N,N-dimethylformamide (DMF)
Shell removing process

Organic solvent (concentration)

Method
Structural and mechanical characterization

AFM in liquid
Structural and mechanical characterization

AFM nanoindentation in liquid

Hertz Model

\[ E = \frac{F \cdot 3 \cdot 1 - \nu^2}{4 \sqrt{r \cdot \delta^2}} \]

where \( F \) is the applied force, \( E \) is elastic modulus of the sample, \( \nu \) is the Poisson’s ratio of the sample, \( \delta \) is the indentation depth and \( r \) is the equivalent radius for a spherical indenter.

XRD analysis
Analysis of the drug release properties

- Nerve growth factor (NGF)

- Insulin-like growth factors (IFG)

Drug selection (applications, dimension, solubility, concentration, stability and detectability)
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Hydrogel external stimuli-response

Given stimuli

- Light (532 nm, 633 nm and 1064 nm wavelengths).
- Temperature (37 ± 20 °C).
- pH (7.4 ± 2).
- Electrical Field (0 - 50 V).

Detected changes

- Morphology
- Mechanical properties
- Drug release
Hydrogel biocompatibility

INTRODUCTION

Cells

- Glial cells
- Neural cells
- Chondrocytes cells (cartilage regeneration).

Techniques

- Neural tissue regeneration.
- SEM and confocal microscopy

Cells selection