Gel

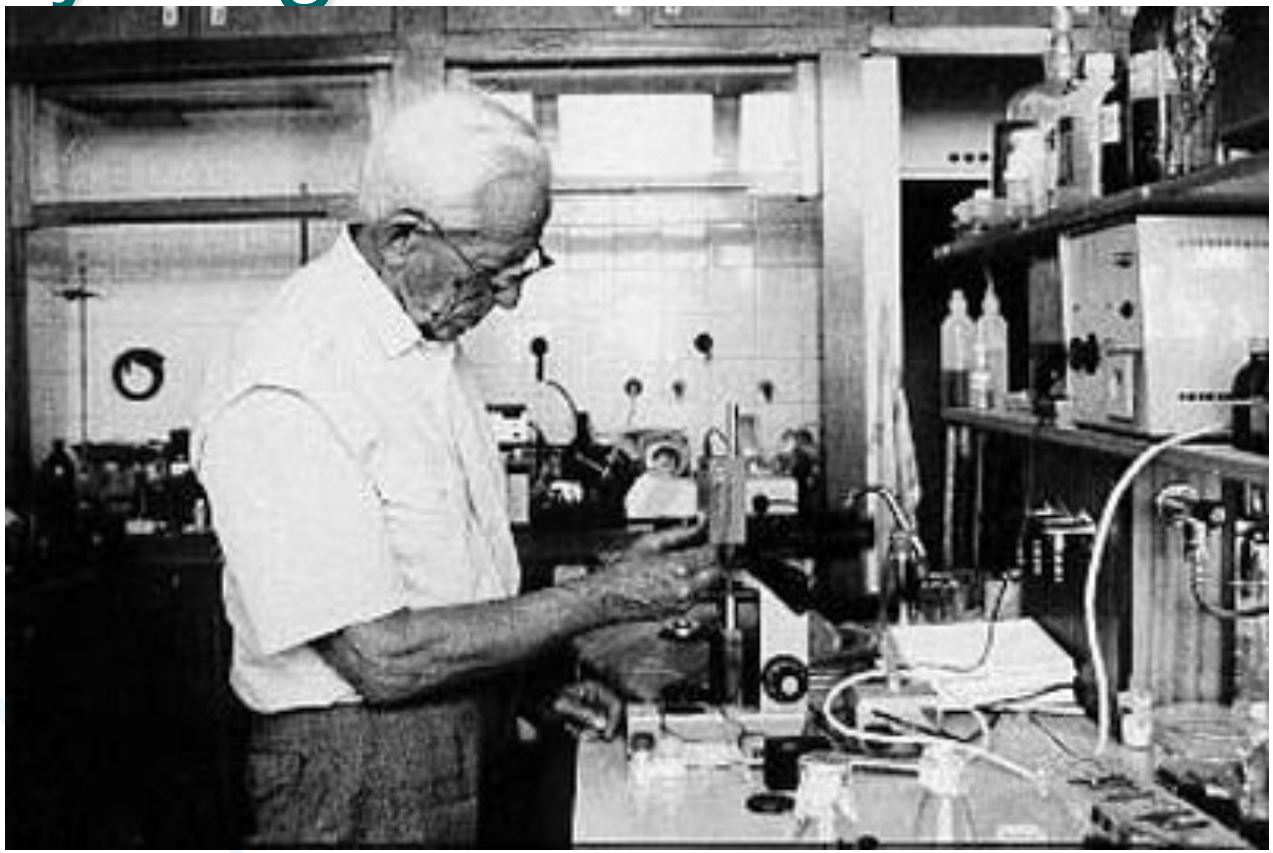
- Particolare stato della materia intermedio tra quello solido e quello liquido.
- I gel si comportano come SOLIDI o quasi solidi (solid-like behaviour), benché siano costituiti a volte da più del 99% di liquidi
- Un gel è costituito da una matrice solida reticolata (network) completamente permeata da liquido.

La consistenza di un gel varia da fluido molto viscoso a solido rigido

Idrogeli

- Strutture polimeriche
  - **reticolate e rigonfiate in acqua**
  - prodotte dalla semplice reazione di uno o più monomeri di cui almeno uno con valenza superiore a 2 (tri- , tetra- valenti)
  - o da legami di associazione fisica tra le catene, come legami idrogeno e forti interazioni di tipo Van der Waals
- Forma fisica di polimeri organici
- **Insolubili in acqua**
- Rigonfiabili in acqua fino a raggiungere un equilibrio
- Di consistenza elastica (in quanto plastificati dall'acqua),
- Memoria di forma nello stato rigonfiato

Hydrogel: A Success Story



Otto Wichterle

Otto Wichterle

- 1939: his research was interrupted when the Nazis closed the Czech universities
- 1958: he had to leave the Institute of Chemical Technology after a political purge staged by its Communist leadership
- 1968: he lost his job as head of his own research institute as a result of his participation in the Prague Spring uprising
- never gave up on his research
  - improvising equipment in his own home
  - early prototypes for his invention were made in his kitchen on machines constructed from a bicycle dynamo and an old phonograph
- Czech government sold the patent to the Americans, he did not receive any royalties for his invention
- Still used eyeglasses ☺

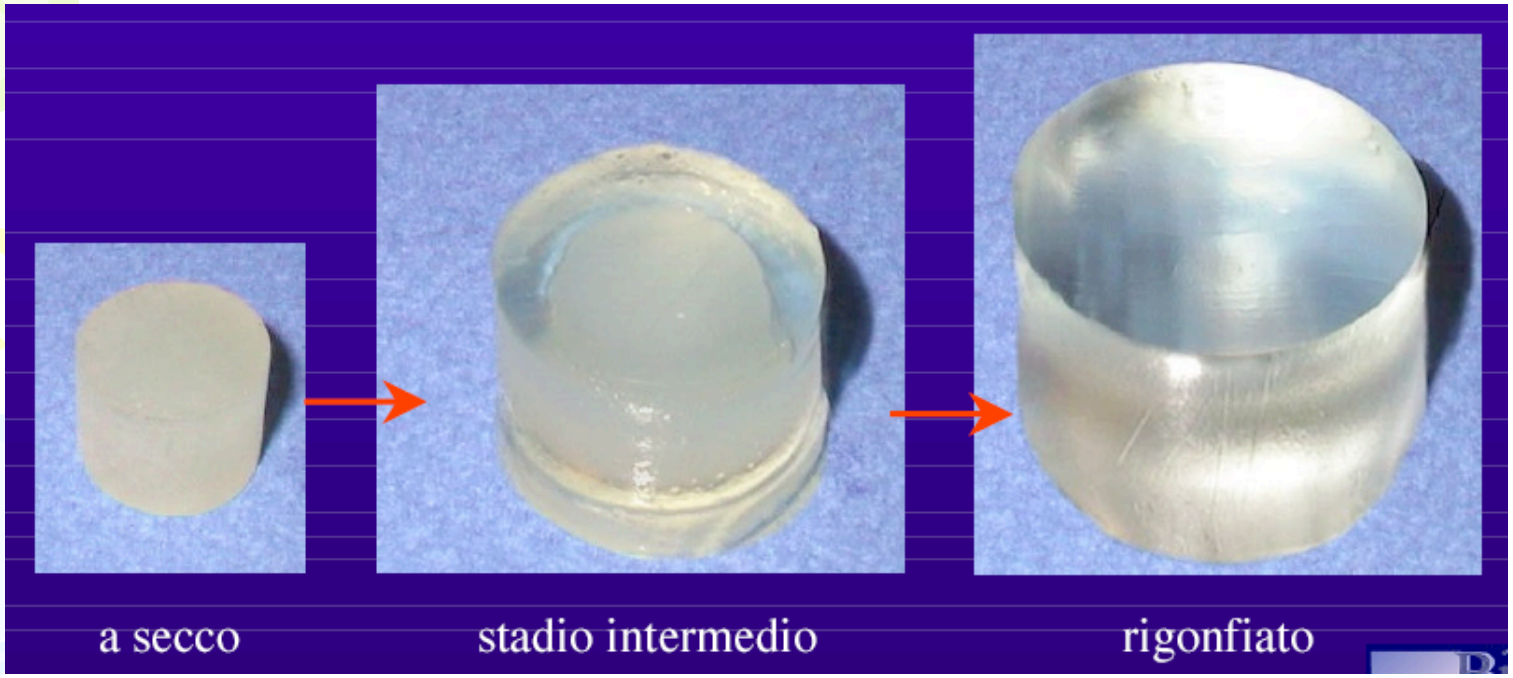
Solubilità e Gelificazione

La solubilità dei polimeri in acqua è regolata da parametri termodinamici.
Semplificando (molto) si può affermare che il simile scioglie il simile

- **idrofobicità** (sostanze apolari, ad es. olio) = insolubilità in acqua, solubilità in solventi organici non polari
- **idrofilicità** (sostanze polari, ad es. sale) = solubilità in acqua, insolubilità in solventi organici non polari

Per ottenere idrogeli (polimeri che non si sciolgono in acqua, ma che rigonfiano in acqua) occorre un giusto bilancio tra solubilità e insolubilità, idrofobicità e idrofilicità

Rigonfiamento in acqua

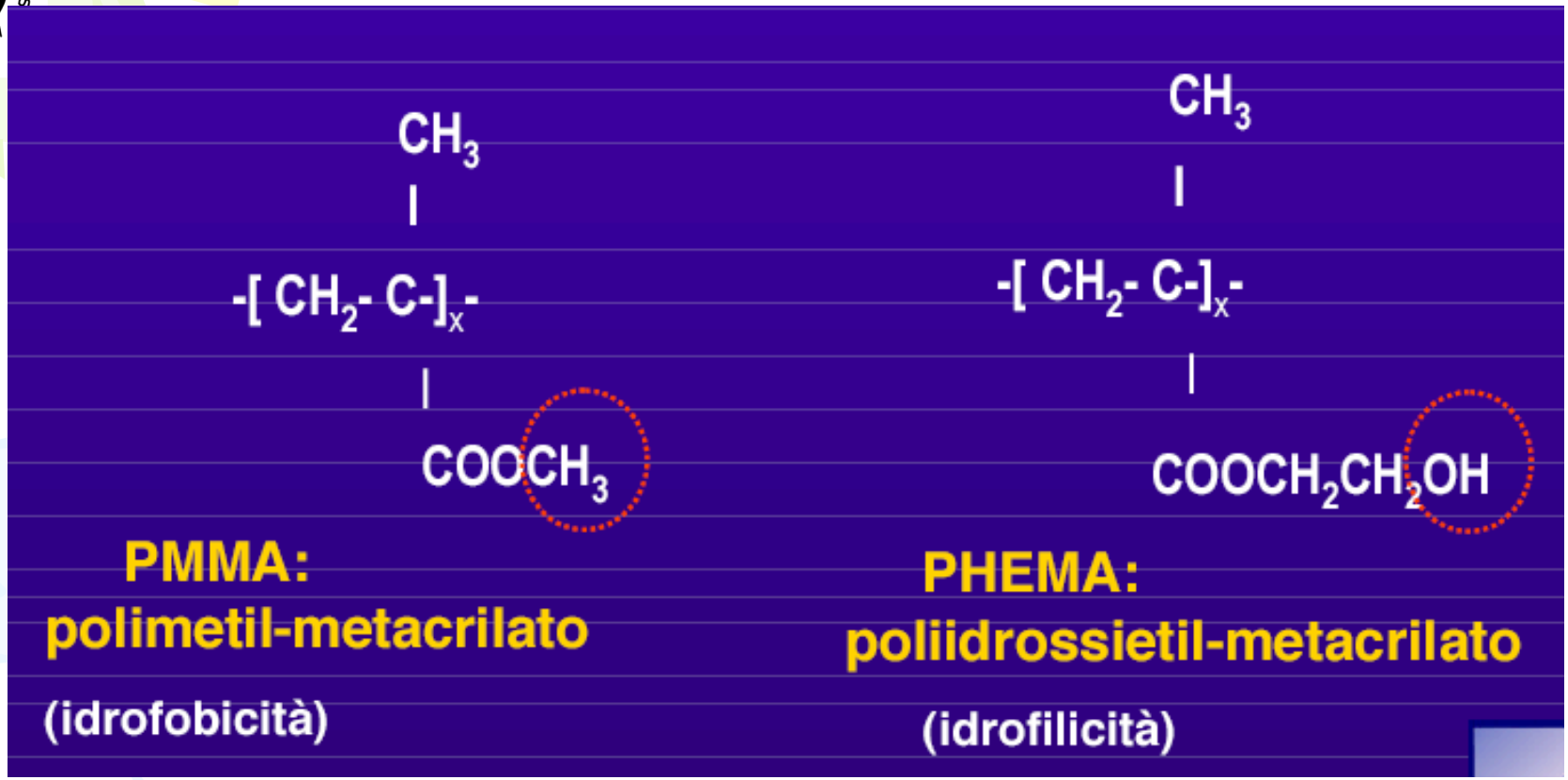


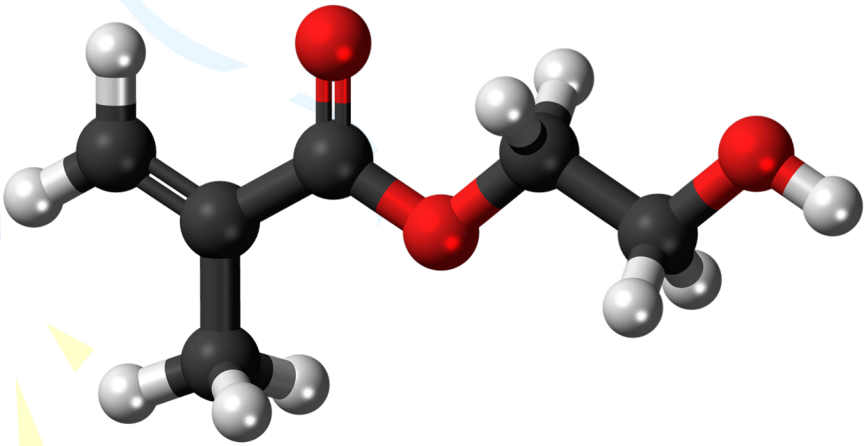
PHEMA in dry state are hard and glassy. However, when swollen, they are soft and flexible, have low surface friction, and can be easily cut with a scalpel or scissors.

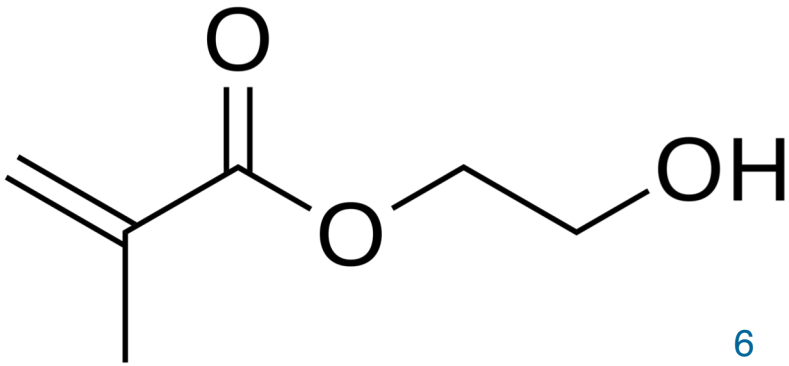
As the name "Hydrogel" suggests, water content plays important roles in PHEMA properties.
The equilibrium water content can be increased by copolymerization with a monomer more hydrophilic.

Oxygen permeability coefficient increases exponentially with the water content.

Confronto PMMA - PHEMA







PHEMA
Poly-Hydroxy Ethyl MethAcrylate

The introduction of PHEMA (Poly-Hydroxy gels) as biomaterials in 1960 was considered as the initial development of synthetic polymeric hydrogels utilized for biomedical applications.
Since then, extensive studies have been done on the structural, chemical properties, and applications of PHEMA.

With C – C backbone, PHEMA cannot be degraded enzymatically or hydrolyzed by acids or bases.
PHEMA are neutral (non-ionic) with water content of approximately 40%. The water content can be regulated by copolymerization with hydrophobic or hydrophilic monomers.
To avoid solubility, high percent conversion polymer is introduced by cross-linking with EDMA (Ethylene glycol Dimethyl Acrylate).

Hydrogels

Hydrogels have received significant attention because of their high water contents and related potential for many biomedical applications.

Hydrogels are polymeric structures held together as water-swollen gels by:

(1) **primary covalent cross-links**;
(2) **ionic forces**;
(3) **hydrogen bonds**;
4) affinity or “bio-recognition” interactions;
(5) **hydrophobic interactions**;
(6) polymer crystallites;
(7) **physical entanglements**

Or a combination of two or more of the above interactions.

Hydrogels

Water swollen crosslinked polymers

- Crosslinks may occur:
  - by reaction of one or more monomers
  - hydrogen bonds
  - van der Waals interactions
- Exceptional promises for biomedical use

Hydrogels

Classification based on preparation method

- homopolymer hydrogels (one type of hydrophilic mer)
- copolymer hydrogels (two types of mers, at least one hydrophilic)
- multipolymer hydrogels (more than three types of mers)
- interpenetrating polymeric hydrogels (swelling a network of polmer$_1$ in mer$_2$, making intermeshing network of polymer$_1$ and polymer$_2$)

Hydrogels

- Classification based on ionic charges
  - neutral hydrogels (uncharged)
  - anionic hydrogels (having negative charges only)
  - cationic hydrogels (having positive charges only)
  - ampholytic hydrogels (having both positive and negative charges). These last gels may end up with a net negative, positive or neutral charge

- Classification based on structure
  - amorphous hydrogels (chains randomly arranged)
  - semicrystalline hydrogels (dense regions of ordered macromolecules, i.e. crystallites)
  - hydrogen-bonded hydrogels

The physical properties of the gels held together by such secondary associations are critically dependent on the network density of these interactions, as well as on the many environmental conditions that can affect them. **Hydrogels may also be classified as stable or degradable, with the latter further categorized as hydrolytically or enzymatically degradable**.

Hydrogels

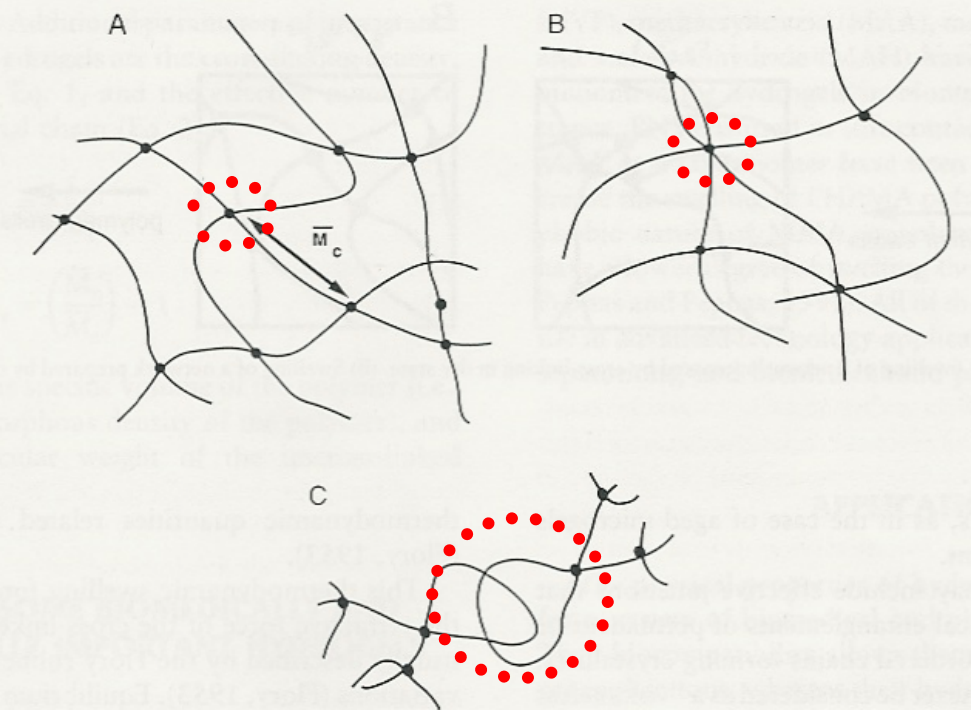
- Connection between chains called:
  crosslink or junction

- Crosslinks may be induced during polymerization or by radiation following polymerization

- Interchain connections can be:
  - a carbon atom
  - chemical bridge
  - van der Waals
  - hydrogen bonds
  - molecular entanglements

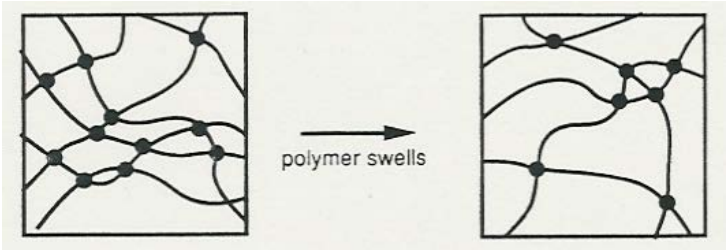
Hydrogels

- **Crosslink structure**:
  - A) ideal network with tetrafunctional covalent crosslinks (rarely observed)
  - B) multifunctional junctions
  - C) molecular entanglements (could be permanent or semi-permanent)



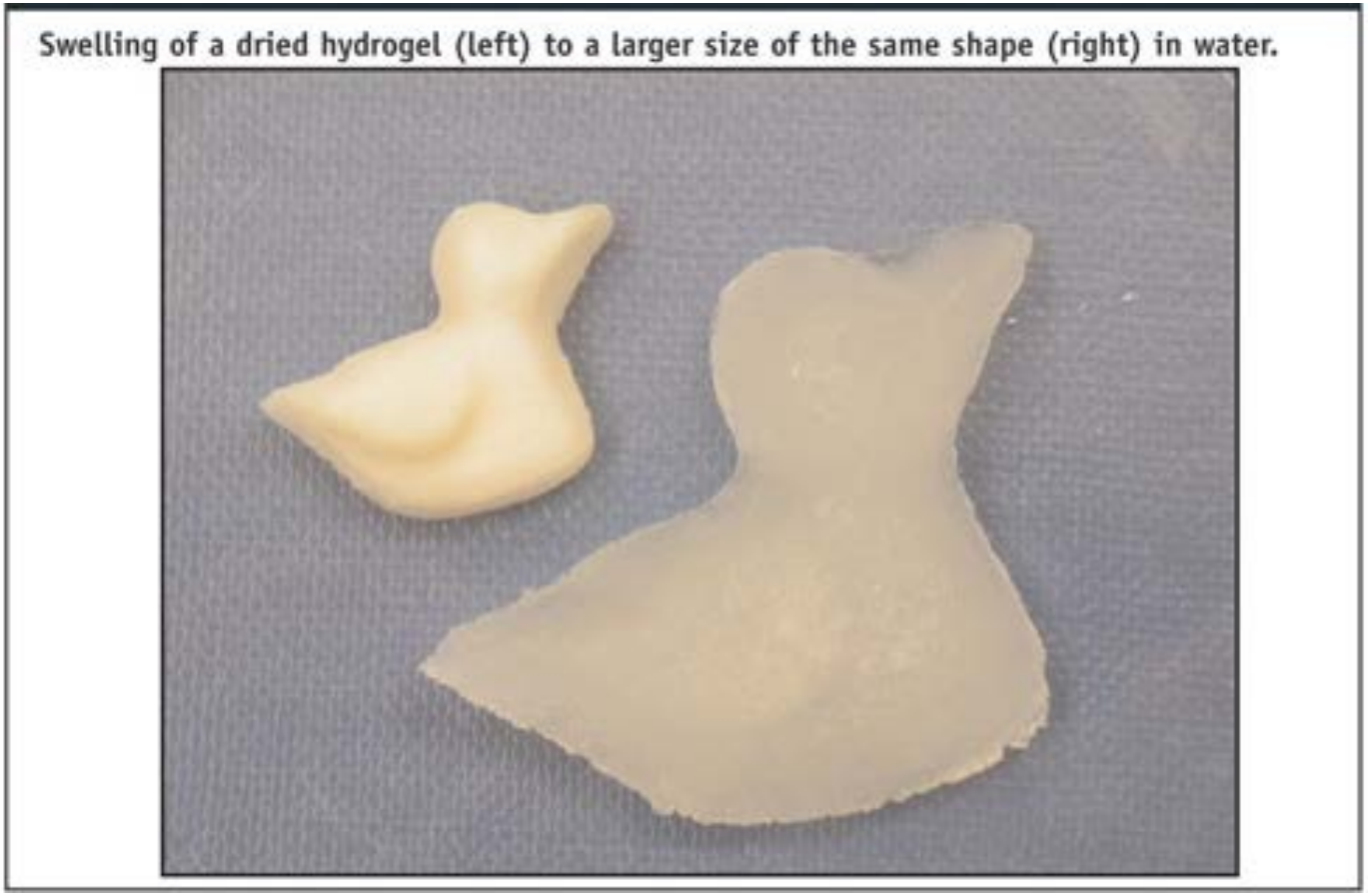
$\overline{M}_c$: Molecular weight between crosslinks

Idrogel:



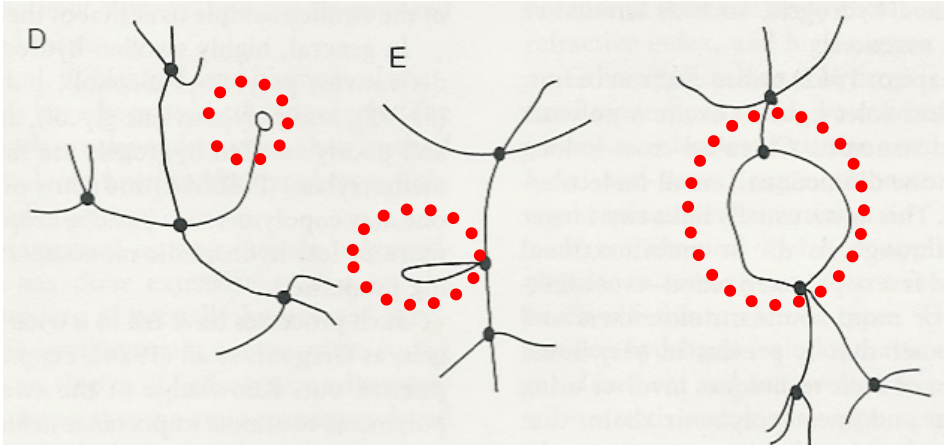
- In un idrogel reticolato chimicamente, tutte le catene polimeriche sono collegate da legami covalenti per formare una rete e, in tal modo
- può essere visto come una sola molecola di grandi dimensioni o supra-macromolecola;
- La forza di rigonfiamento è controbilanciata dalla forza retrattile della struttura reticolata;
- La proprietà unica di questi gel è la capacità di mantenere la loro forma originale durante e dopo il rigonfiamento;
- Due forze diventano uguali ad un certo punto e l'equilibrio è raggiunto.

La forma si conserva



Hydrogels

- **Defects in crosslink structure**:
  - D) unreacted functionality
  - E) chain loops



- Note that neither of the two configurations contribute to mechanical strength or physical properties of the network

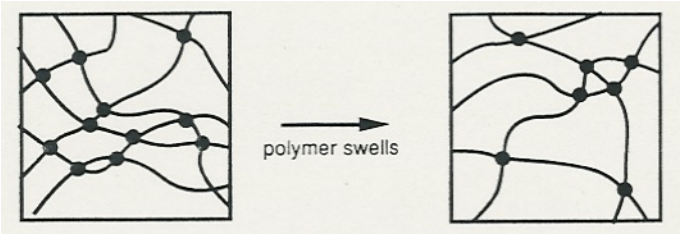
Hydrogels: Preparation

- Prepared by swelling crosslinked structures in water or in biological fluids containing water

- Crosslinks can be induced by radiation or chemical reaction
  - Radiation reactions include electron beams, gamma-rays, X-rays, or UV light
  - Chemical crosslinking
    - small molecular weight *crosslinking agents* that links two chains together through its di- or multifunctional groups
    - *copolymerization-crosslinking* reactions between the monomers and a multifunctional monomer that is present in small quantitites
    - combination of above

Hydrogels: Swelling

- After polymerization, the ***hydrophilic*** gel is brought in contact with water
- The network expands
- The thermodynamically driven swelling force is counterbalanced by the retractive force of the crosslinked structure
- ***Two forces become equal at some point and equilibrium is reached***



Hydrogels: Swelling

Why is the degree of swelling important?

- solute diffusion coefficient through the hydrogel
- surface properties and surface mobility
- optical properties (particularly for contact lens applications)
- mechanical properties

Hydrogels: Swelling

Degree of swelling can be quantified by:

- ratio of sample volume in the swollen state to volume in the dry state
- weight degree of swelling: ratio of the weight of swollen sample to that of the dry sample

Hydrogels: Swelling

- Highly swollen hydrogels:
  - cellulose derivatives
  - poly(vinyl alcohol)
  - poly(N-vinyl 2-pyrrolidone), PNVP
  - poly(ethylene glycol)

- Moderately or poorly swollen hydrogels:
  - poly(hydroxyethyl methacrylate), PHEMA and derivatives

- One may copolymerize a highly hydrophilic monomer with other less hydrophilic monomers to achieve desired swelling properties

Hydrogels: PHEMA

- The most widely used hydrogel
- water content similar to living tissues
- inert to biological processes
- shows resistance to degradation
- permeable to metabolites
- not absorbed by the body
- withstands sterilization by heat
- prepared in various shaped and forms

Hydrogels: PHEMA

- Properties depend on:
  - polymer volume fraction
  - degree of crosslinking
  - temperature
  - swelling agent
- combined with other acrylic monomers to adjust properties

Hydrogels: Applications

Biomedical use due to bio- and blood-compatibility

- Pharmaceutical use due to hydrophilicity (controlled/sustained drug release)
- Tissue engineering
- **Earliest biomedical application contact lenses**
  - good mechanical stability
  - favorable refractive index
  - high oxygen permeability
  - needs hygienic maintenance (does not apply for disposable)
- Lubricating surface coating
  - used with catheters, drainage tubes and gloves
  - non-toxic

Hydrogels: Applications

- artificial tendon and cartilage
- wound healing dressings (Vigilon®, Hydron®, Gelperm®)
  - non-antigenic, flexible wound cover
  - permeable to water and metabolites
  - low-strength
- artificial kidney membranes
- artificial skin
- maxillofacial and sexual organ reconstruction materials
- vocal cord replacement

Applicazioni degli idrogeli

Ease of purification, adjustable mechanical properties, and equilibrium water content contribute to the applications of PHEMA in as early as 1969.
It was used as a coating for surgical sutures, which was also loaded with antibiotics to increase the rate of wound healing. In the 1980s, spherical PHEMA particles were injected into pulmonary arteries to suppress hemorrhage and hemoptysis.

- lenti a contatto (PHEMA)
- rilascio controllato di farmaci
- pelle artificiale
- tendini artificiali e legamenti
- riparazione e ricostruzione di tessuti
- ricostruzione di tessuti cartilaginei
- dispositivi a contatto con il sangue
- protesi mammarie
- corde vocali artificiali

Hydrogels: Applications

- Pharmaceutical applications
  - monomer composition and relative amounts of multi-polymer hydrogels can be varied to alter the diffusion characteristic and permeability of the gel containing pharmaceutical agents
- Methods for drug delivery
  - drug gets trapped in the hydrogel during polymerization
  - drug introduced during swelling in water

Hydrogels: Applications

- Release occurs by outflow of drug from the gel and inflow of water to the gel
- Rate of diffusion is explained by Fick's law:
  - $J = -D\ (dC_m/dx)$
    - J: flux (g/cm^2sec)
    - D: diffusion coefficient
    - C_m: concentration of the diffusing material

The Cutting Edge….

- First implantable lens for nearsightedness was approved by the Food and Drug Administration
- A surgeon slips the lens through a small incision and implants it in front of the natural lens.
- Tiny hard plastic lens works behind the scenes to help the eye create in-focus images.
- An alternative to glasses, contact lenses or Lasik surgery for people who have trouble seeing distant objects.

The Cutting Edge….

- Already in use in Europe, the lens is manufactured by Ophtec USA Inc., of Boca Raton, Fla., under the trade name Artisan, which will be distributed by American Medical Optics under the Verisyse brand name.
- Will cost $3,000 to $4,000 per eye, currently is targeted at patients who, for various reasons, can't get Lasik
- Robert K. Maloney, an ophthalmology associate professor who has corrected the vision of Cindy Crawford and Kenny G with Lasik.
  - 50 percent more accurate than Lasik.
  - better quality of vision: The vision is crisper, brighter and clearer
- 92 percent of 662 patients had 20/40 or better vision, considered standard vision necessary to obtain a driver's license, and 44 percent had 20/20 or better, the FDA said, citing Ophtec research.

The Cutting Edge….

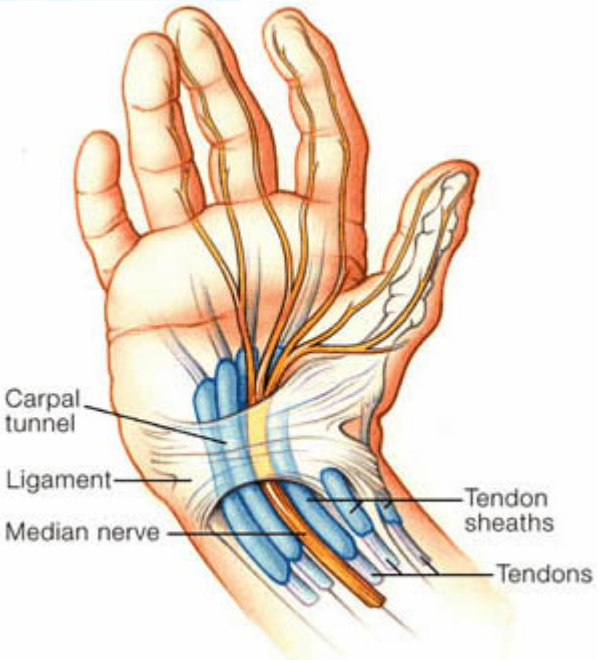
- May not eliminate the need for glasses for night driving or other activities performed in low light.
- Count Rosalia de Firmian of Santa Barbara, among the grateful.
  - Her vision began deteriorating when she was 6 years old.
  - corrective contact lenses for 40 years,
  - I can see my shoes, my slippers. Everything. I see the wall, the clock."
- others warn of the risk of patients developing cataracts or eye-destroying infections.
  - Balamurali Ambati, an ophthalmologist and corneal specialist at the Medical College of Georgia. "Anytime the eye is opened, bacteria can get in."
  - Nicholas Tarantino, vice president of global clinical research and development for Advanced Medical Optics, said no patients in the U.S. clinical trials developed cataracts.
- The FDA is requiring the company to do a follow-up, five-year study of users of the lens to determine any side effects.
  - One possible concern, FDA said, is the loss of endothelial cells in the corneas of patients who received the implants.
  - These cells form a layer on the undersurface of the cornea and are essential to keeping the cornea clear.
  - In the tests, there was a steady loss of endothelial cells of 1.8 percent a year.
  - The FDA is requiring the lens label to specify it be used only in patients with a dense enough layer of these cells to stand some loss over time.

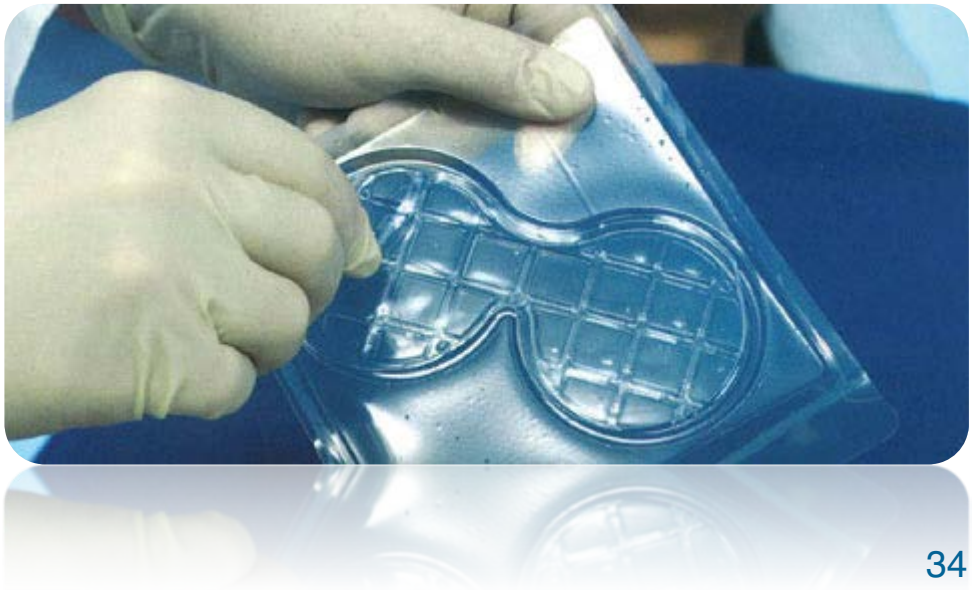
Idrogel: Applicazioni

- Medicazione per guarigione delle ferite (Vigilon®, Hydron®, Gelperm®)
  - non antigenico, copertura della ferita flessibile
  - permeabile all'acqua e ai metaboliti
  - bassa resistenza

Il gel crea un ambiente umido per il trattamento di patologie minori come lievi ustioni, lacerazioni superficiali, tagli e abrasioni.

- tendini artificiali e cartilagini
- pelle artificiale
- materiali per ricostruzione maxillo-facciale
- sostituzione delle corde vocali
- maschere post-blefaroplastica





- Materiali superassorbenti per pannolini
- Creme cosmetiche
- Creme per ustioni

Corning® Ultra Low Attachment

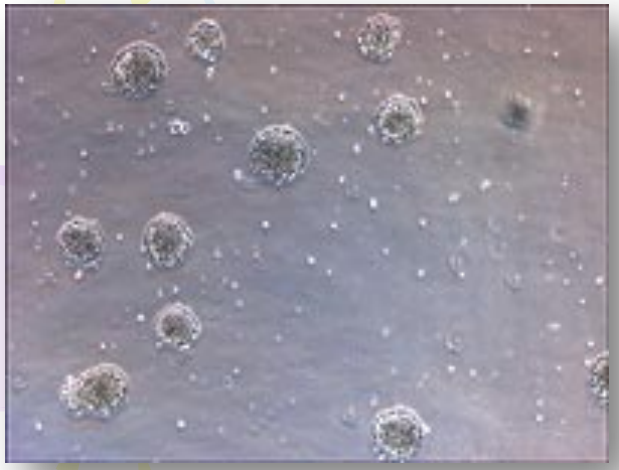
Unica superficie idrogel che inibisce l'attacco di cellule

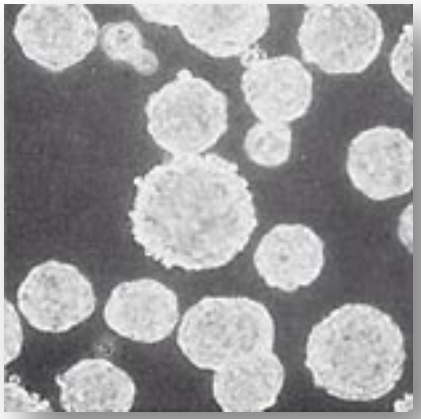
E' un idrogel idrofilo e neutro.
Poiché le proteine e le altre biomolecole si assorbono passivamente alle superfici in polistirene per interazioni idrofobiche o ioniche, uno strato di questo idrogel inibisce l'immobilizzazione aspecifica, inibendo quindi l'attaccamento di cellule.

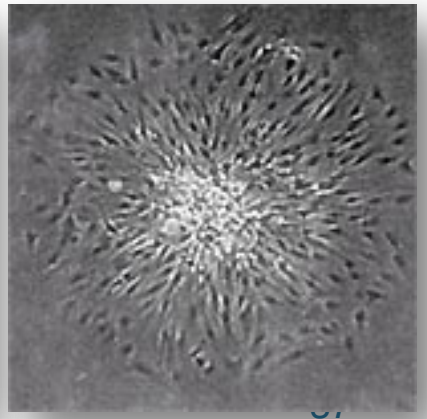
E' stabile, non citotossico, biologicamente inerte e non degradabile.

Corning® Ultra Low Attachment

- E’ utile per crescere colture primarie di di cellule tumorali o normali in forma di sferoidi
- E’ ideale per colture di cellule staminali
  - Promuove la formazione del corpo embrionale
  - Produce colonie con margini definiti
  - Morfologia più pulita
  - Rende le colonie più facili da staccare



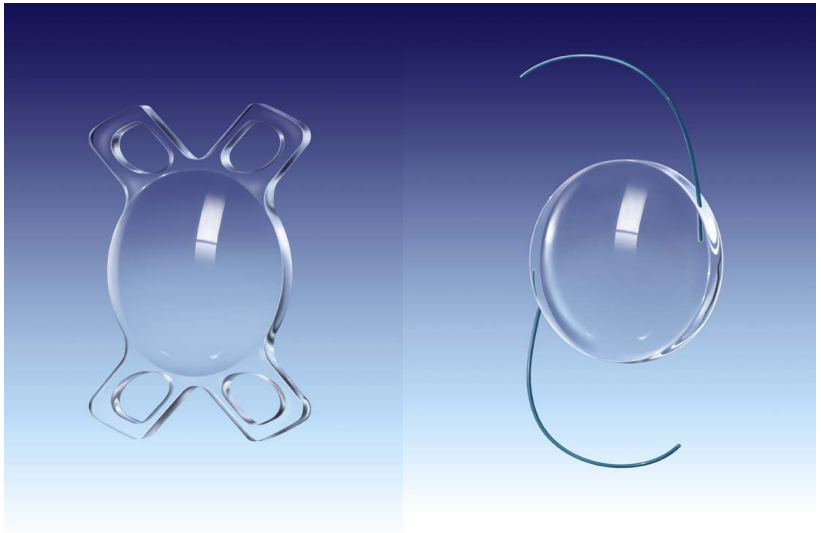




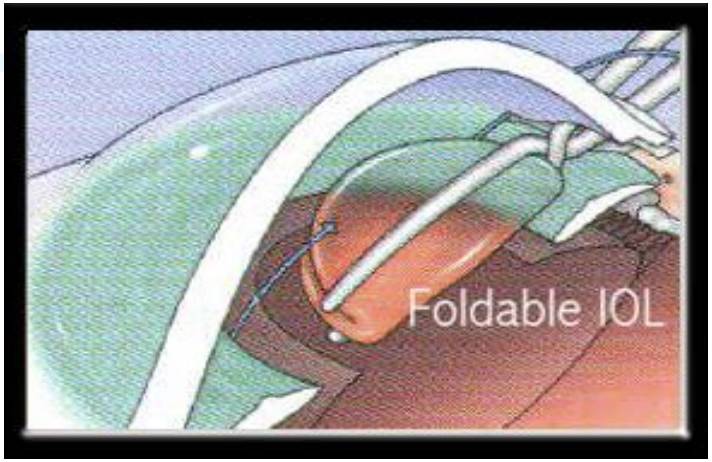
Lenti a contatto

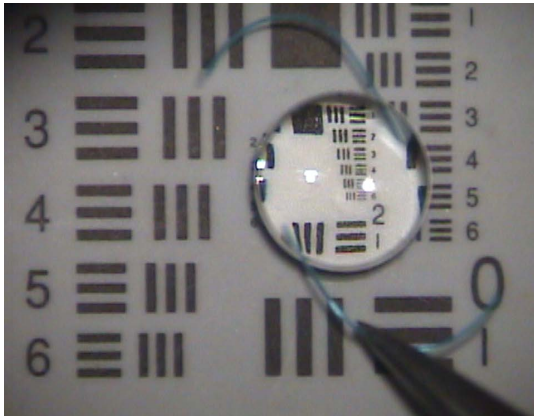
- Le lenti a contatto sono costantemente in contatto con il fluido dell'occhio: il film lacrimale
- Le lacrime sono composte non solo da acqua ma anche da proteine, grassi, sodio, calcio, bicarbonato ed enzimi
- Se un polimero è idrofobo ostacola il flusso lacrimale e ne risulta la deposizione di proteine o lipidi sulla lente (*biofilm*)
- Ciò riduce l'efficacia del contatto, causando infezioni e/o irritazione

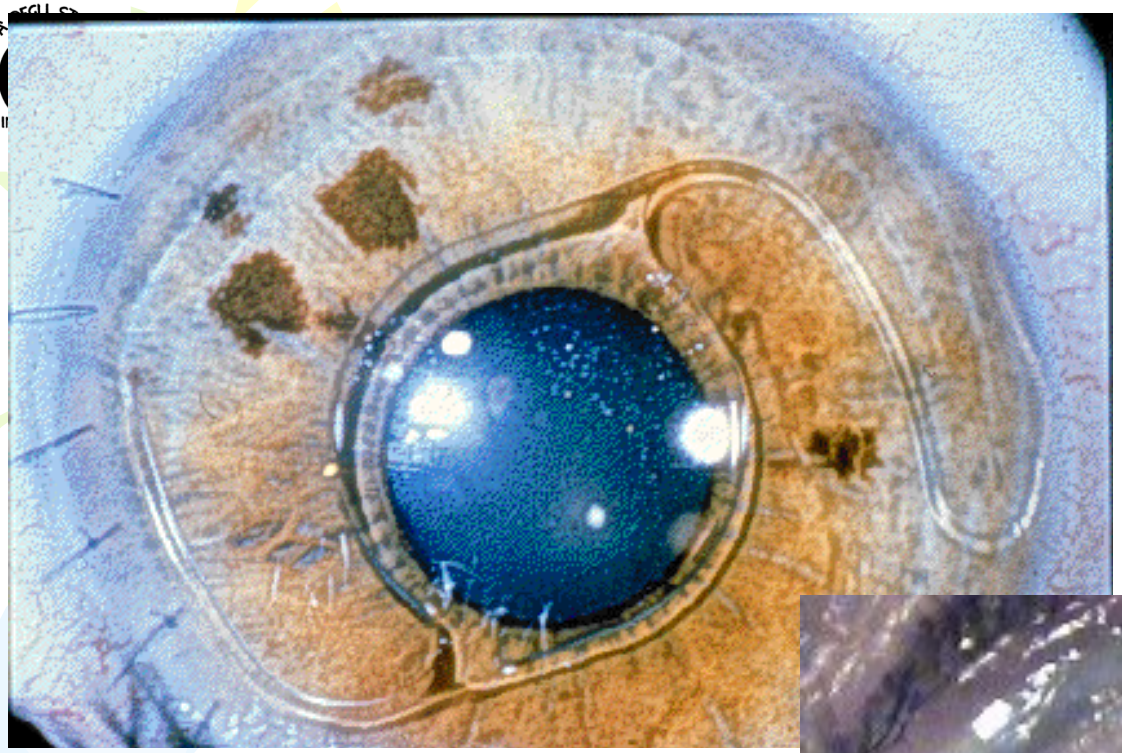
Lenti intraoculari
Intraocular lens (IOL)

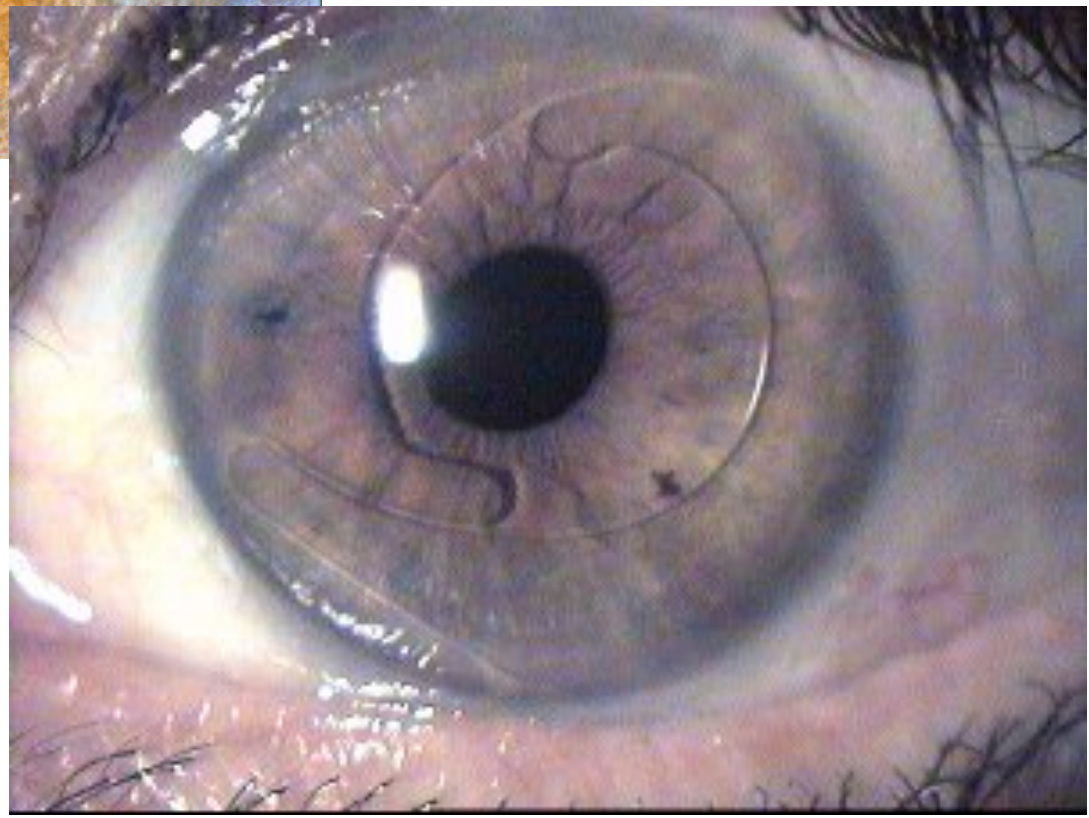


- PMMA
- PHEMA
- Polymer backbone – miscela di PMMA e PHEMA
- Si può modificare il contenuto di acqua
- Si possono aggiungere additivi come UV bloccanti









IOL Opacizzazione ottica

- Opacizzazione di superficie
- Opacizzazione nella sostanza
- L'analisi delle opacizzazioni rivela spesso la presenza di calcio