MUNI PHARM

Department of Natural Drugs

Supramolecular Pharmacy

6. Gels and metallogels in pharmacy

Ondřej Jurček

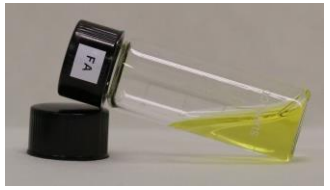
Gels around us

Gels and metallogels

- Gel are present in our everyday life, e.g., jelly, tooth-paste, contact lenses, hair gel, etc.
- Gels are formed by two or more components forming a fibrous solid-like phase (typically around 1 wt%) immobilizing large volume of liquid, gel preparation – melting point of gel
- Hydrogels and organogels
- Metallogels
- Aerogels, xerogels (supercritical or freeze drying)

aerogel

sol



T

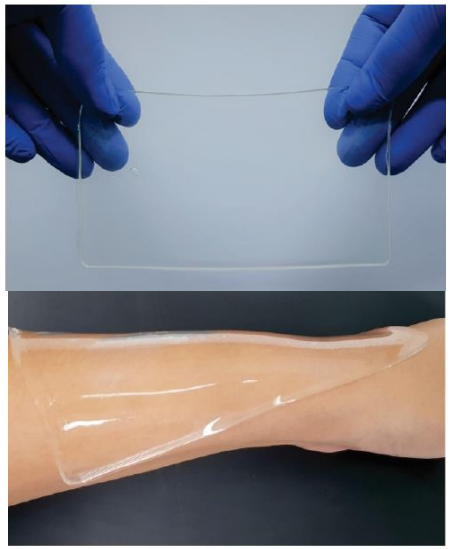
gel

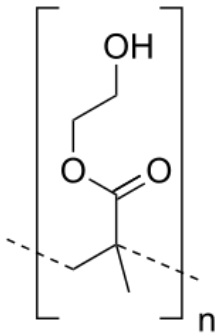
- Macroscopic proof of gel – vial inversion test
- Microscopic are often formed by bundles of fibres

- Covalent polymer or supramolecular assembly of small molecules (low molecular weight gelators (LMWG))

Polymeric gels

- pHEMA hydrogels and their use as contact lenses
- Wound dressings: (a) maintain a moist environment, (b) provide a barrier to bacterial contamination while (c) allowing oxygen access to the injured area, (d) can be removed without damage to the healing surface.
- Fat substitutes in food chemistry
- Drug delivery





pHEMA

	Matrix	Oil – solvent	Preparation	Features of emulsion gels
Fat substitutes	Locust bean gum, xanthan gum and maltodextrin	Flaxseed oil (19%)	Heat treatment	Contains omega-3 essential fatty acids, low levels of saturated fat, low levels of total fat
	Sodium alginate, quinoa protein	Olive oil (25%)	Adding GDL and $CaCl_2$	Fat substitutes in meat or non-meat products
	Whey protein, high methoxyl pectin	Soybean oil (16%-80%)	Heat treatment	Mayonnaise fat simulant
	Chia seed isolate protein	Corn oil (25%)	Heat treatment	Additive in meat products or emulsified sausages, as meat substitutes or fillers
	WPI, SPI, oil and grease, κ-carrageenan	Mixture of olive oil, linseed oil and fish oil (50%)	Heat treatment	Fat substitutes for meat products
	Sodium alginate, κ-carrageenan, collagen	Olive oil (25%)	Heat treatment	Butter alternative

Zhi et al. *Food Chem.* 2023, 424, 136399.

Polymeric gels

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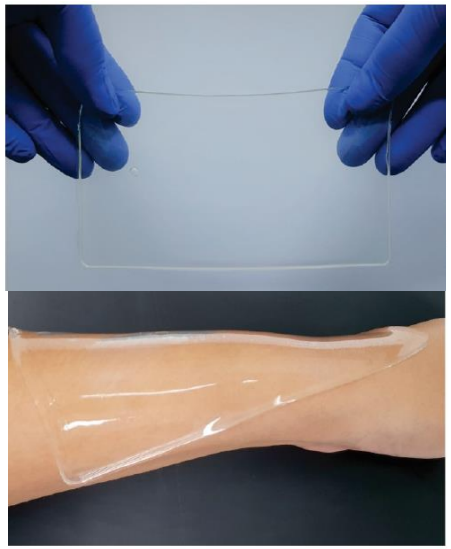

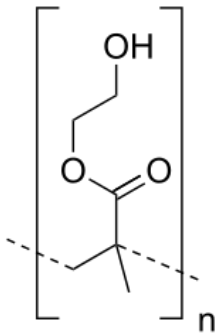

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Low molecular weight gelators (LMWG)

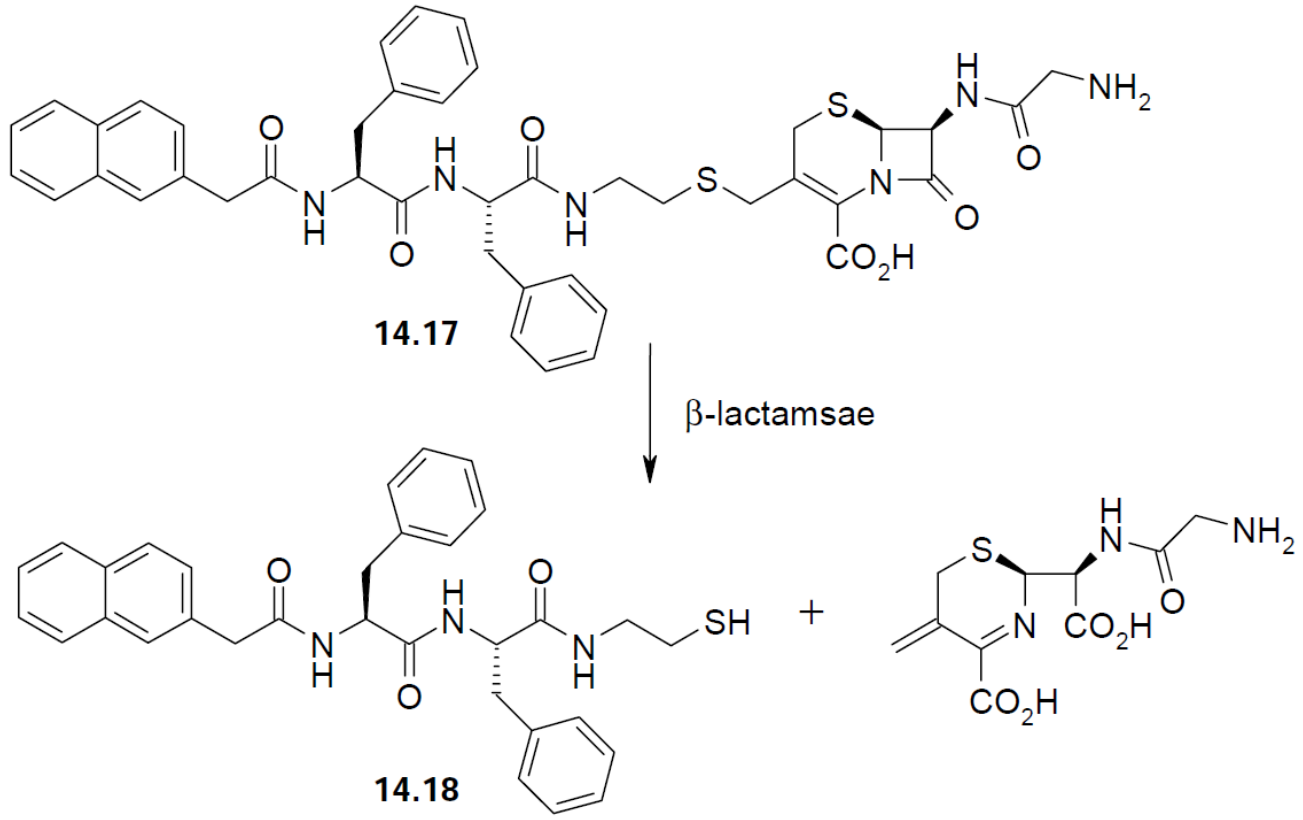
- Interesting properties of LMWG systems is the reversibility of the supramolecular interactions between the gelator molecules, suggesting the possibility of dynamic behaviour such as self-healing or slow release

Applications

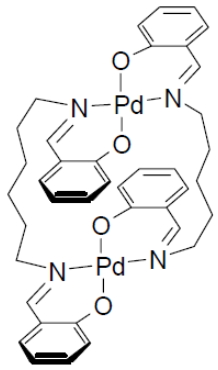
- **Tissue engineering** – gels can act as a form of nanoscaffolding encouraging the growth of slow growing tissue such as nerves through peptide-based gels
- **Drug delivery** – many drugs are already formulated as polymer gels for oral delivery. Small molecule based gels offer the possibility of slow release or a sudden burst of drug from a chemically triggered gel-sol transition
- **Templating or transcribing self-assembled morphology** – gels have been used extensively as growth regulators for the preparation of metallic nanoparticles or as templates for the formation of porous polymers
- **Napalm** – an infamous gel originally made up of the aluminium salts of napthenic and palmitic acids mixed with petrol
- **Molecular electronics** – the long, fibrillar nature of gels strongly suggests that they might find applications in the construction of molecular wires

Low molecular weight gelators (LMWG)

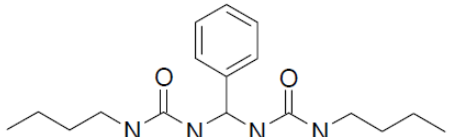
- **Sensing** – compound 14.17 is a poor gelator in itself but undergoes a reaction with *β*-lactamase enzyme to produce 14.18 which is a good gelator. Bacteria resistant to penicillin can perform such hydrolysis - way of sensing the presence of penicillin-resistant bacteria



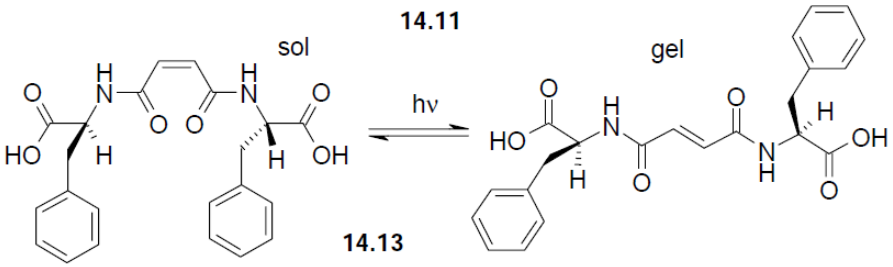
Molecules of gelator



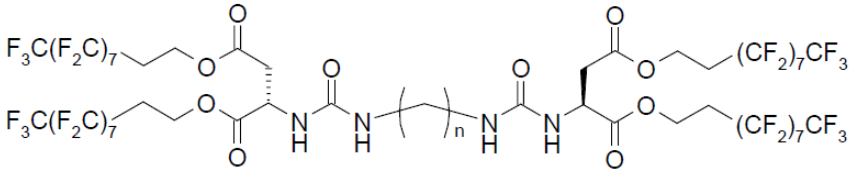
14.12



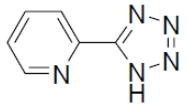
14.11



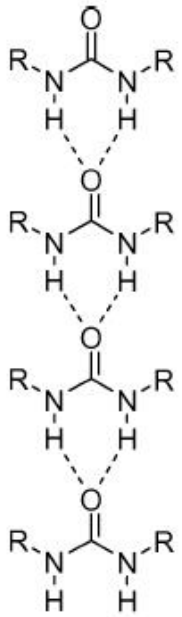
14.13

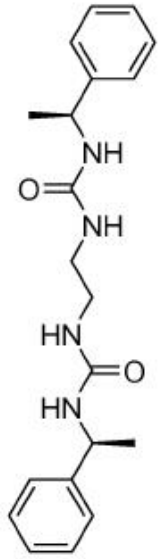


14.14

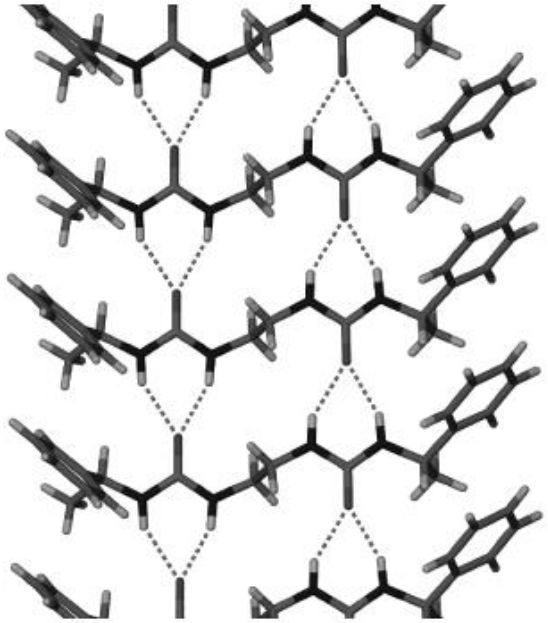


14.15

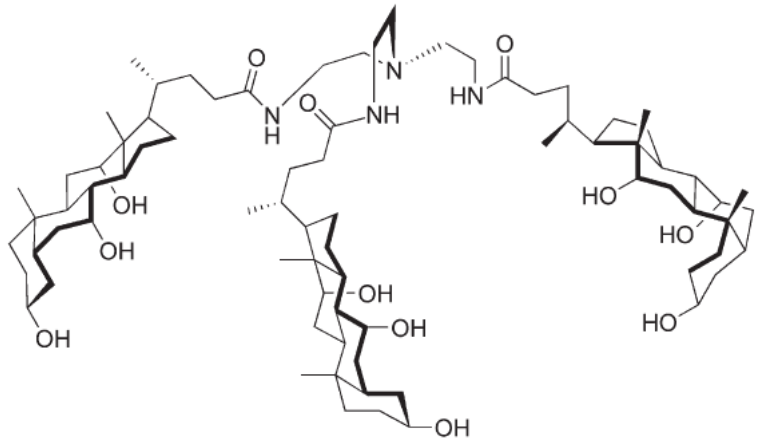


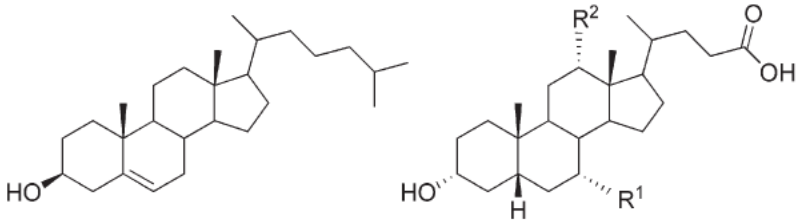


14.16

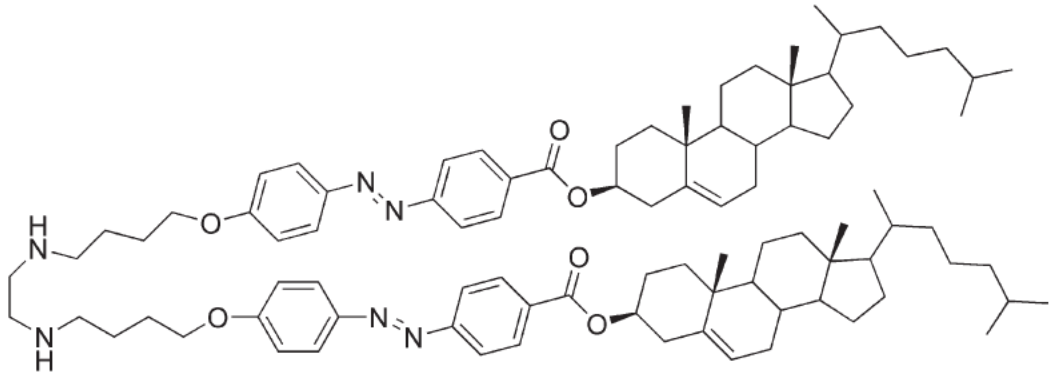


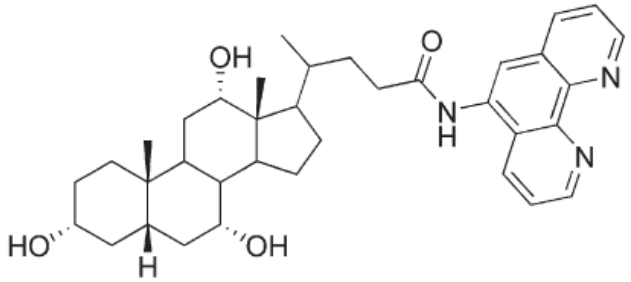
Steroidal gelators

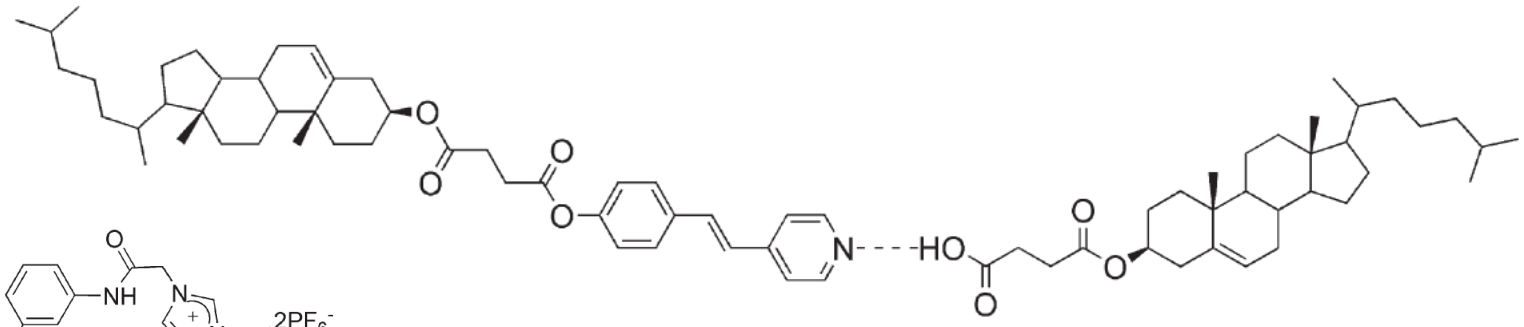


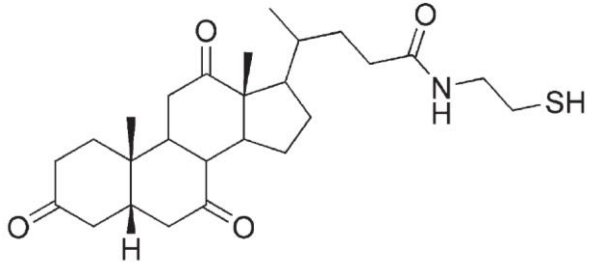


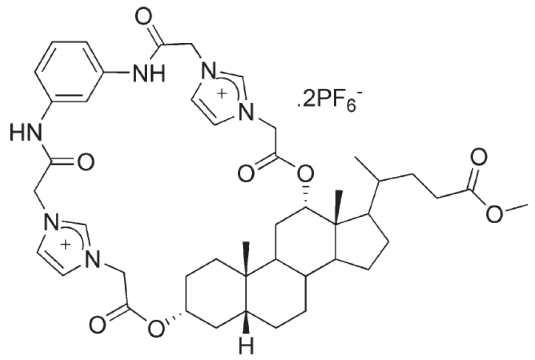
	R^1	R^2
Lithocholic acid (LCA)	H	H
Deoxycholic acid (DCA)	H	OH
Chenodeoxycholic acid (CDCA)	OH	H
Cholic acid (CA)	OH	OH







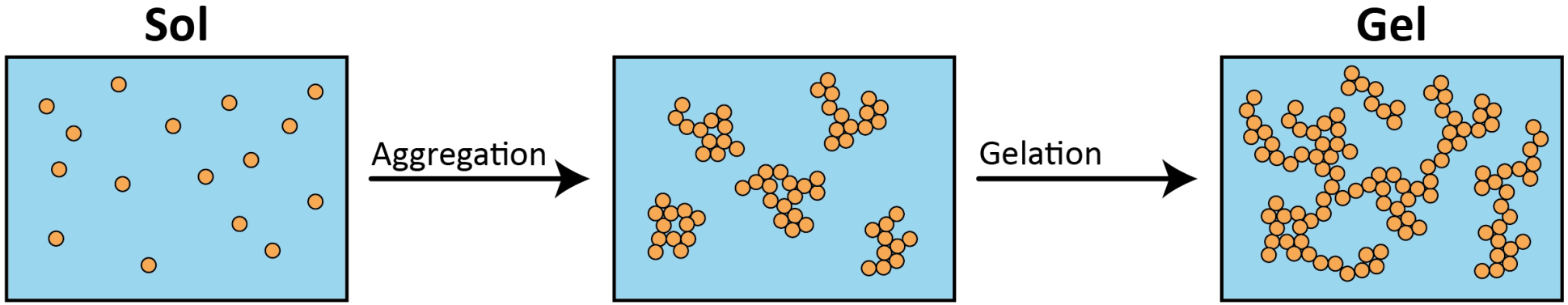




Sievänen: *RSC Adv.* 2012, 2, 4985–5007.

Sol-gel processes

- Sol = colloidal suspension of tiny solid particles in liquid medium (*e.g.*, blood, mud, paint…) – stable, Tyndall effect, 1-100 nm



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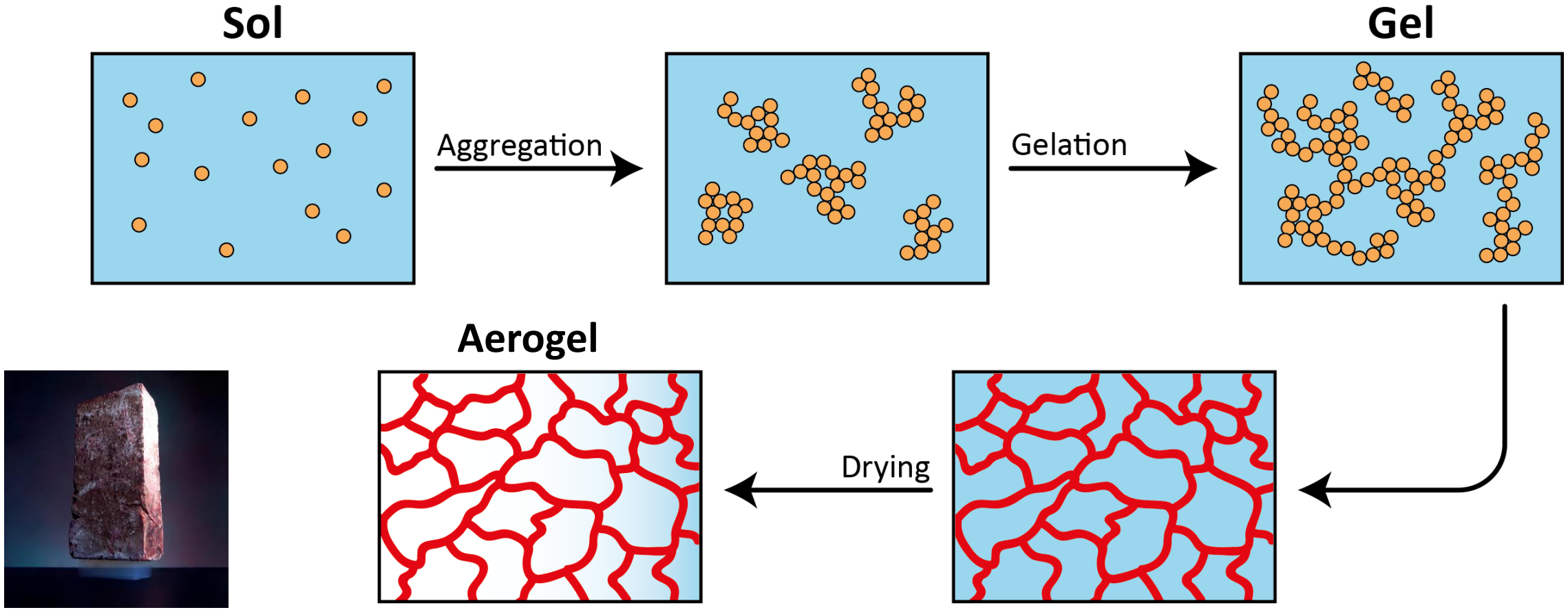
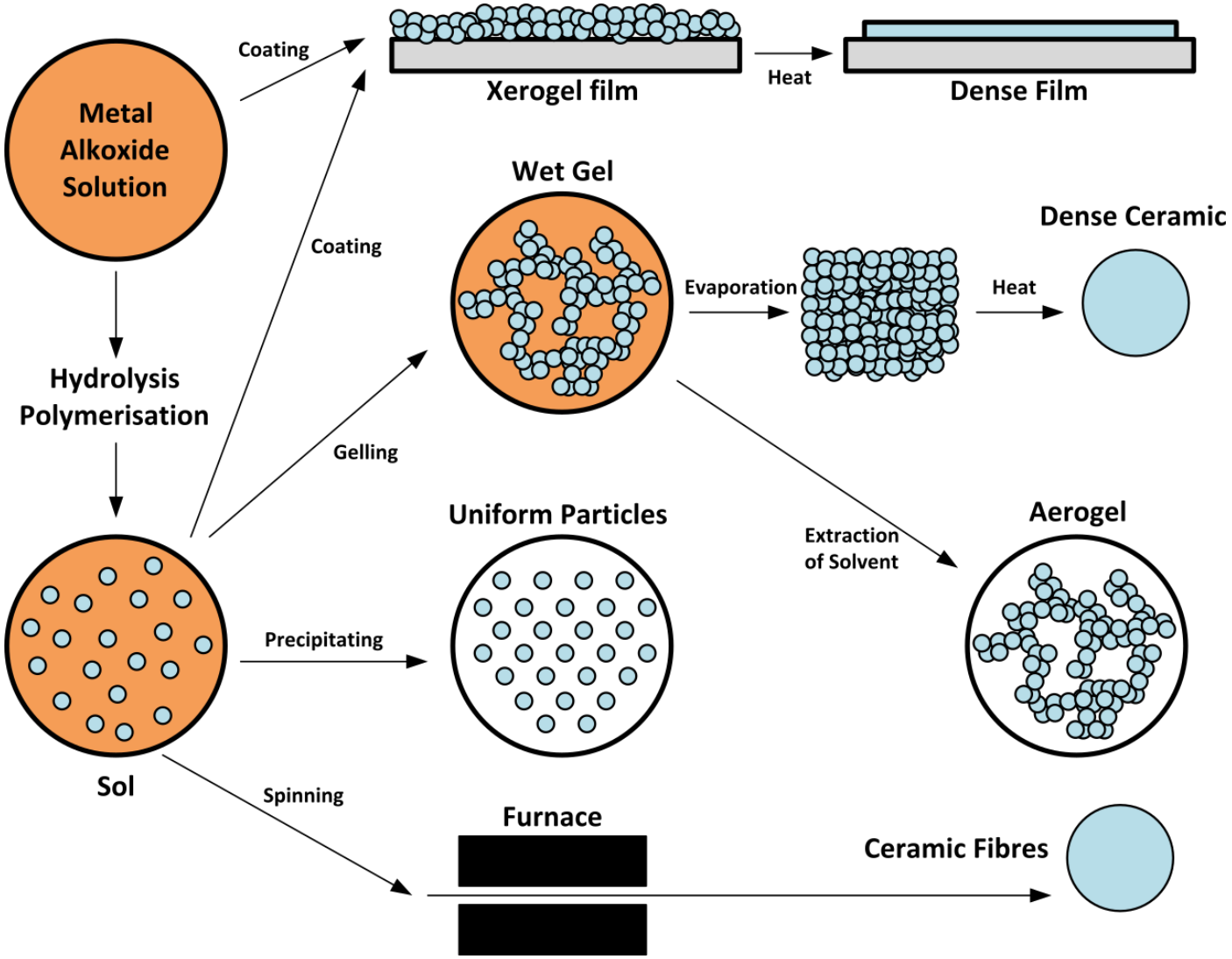
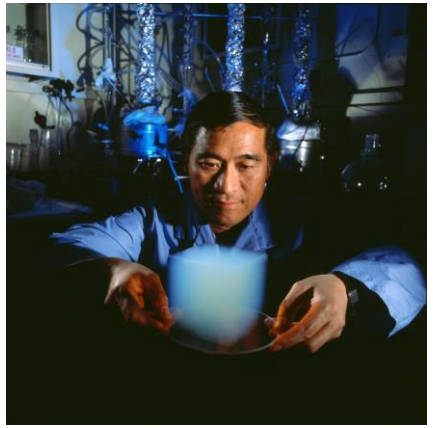


https://wiki.aalto.fi/

Sol-gel processes



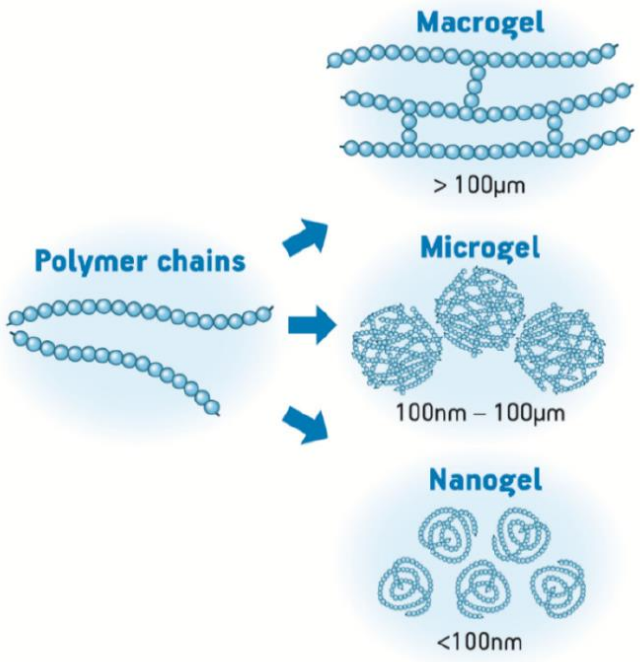


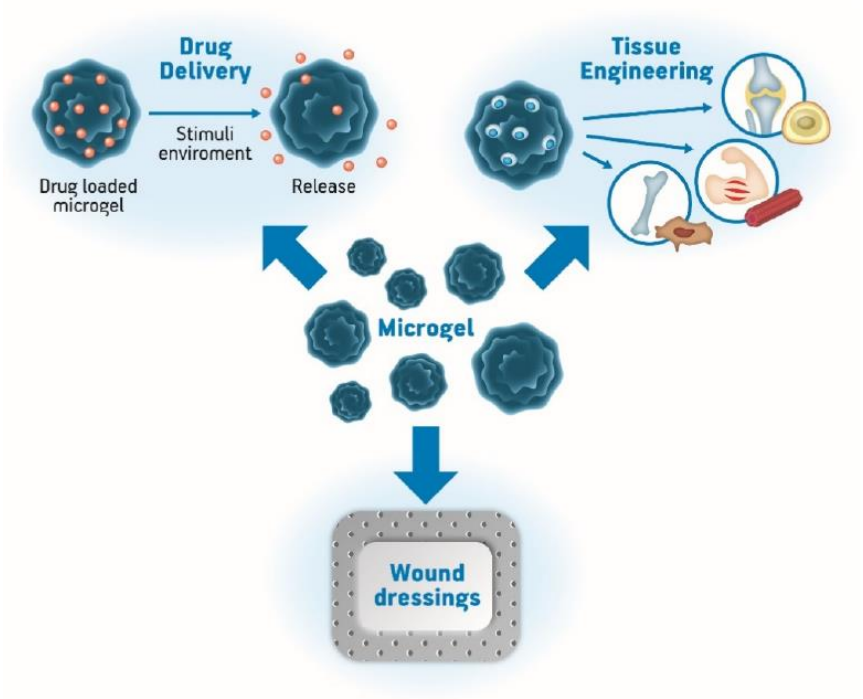
Pharmaceutical gels

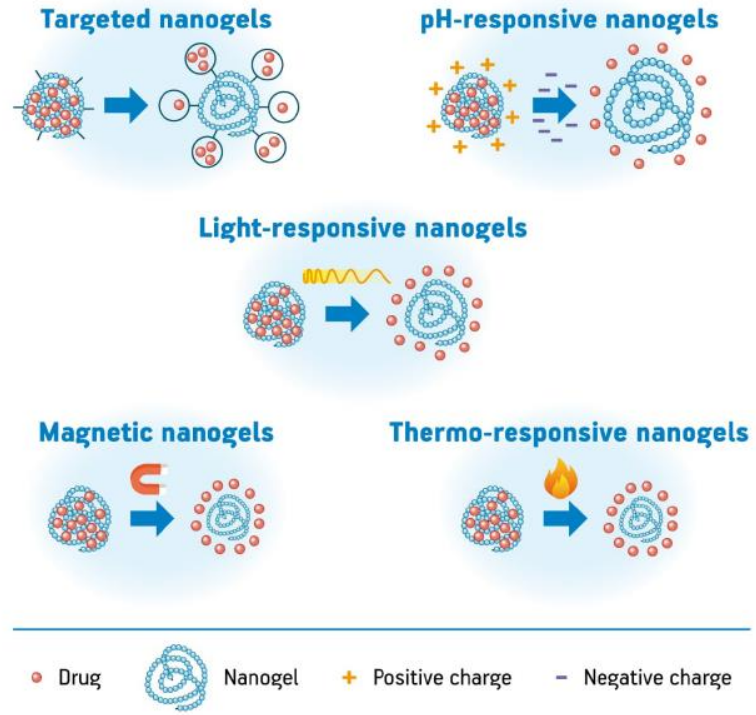
- Topical gels – topical drug delivery dosage form
- Mixture of gelator, solvent, active drug, and other excipients
- Organogels less common (lecithin gel) – occlusive layer traps moisture, allowing hydration of the skin and providing an emollient effect
- Hydrogels – biocompatible, swell to a greater volume than organogels when in contact with water and other natural liquids (less greasy, easier to remove)
- Transdermal application (largest surface area for absorption), ophthalmic, dental, intranasal, vaginal, rectal and others
- Cosmetics, which include shampoos, dentifrices, skin and hair care formulations and fragrance products, and can be used to treat scalp inflammation

Product	Manufacturer	Drug	Gelator	Use	Route
REGRANEX gel	Johnson & Johnson	Becaplermin	Sodium CMC	Treatment of diabetic neuropathic ulcers	Transdermal
Topicort Gel	Taro	Desoximetasone	Carbomer 940	Antipruritic	Transdermal
Cleocin T Topical Gel	Pfizer	Clindamycin	Carbomer 934P	Treatment of acne vulgaris	Transdermal
MetroGel Vaginal	Galderma	Metronidazole	Carbomer 934P	Treatment of bacterial vaginosis	Vaginal
Condylox Gel	Watson	Podofilox	Hydroxypropyl cellulose	Treatment of anogenital warts	Rectal

Gel division by their size







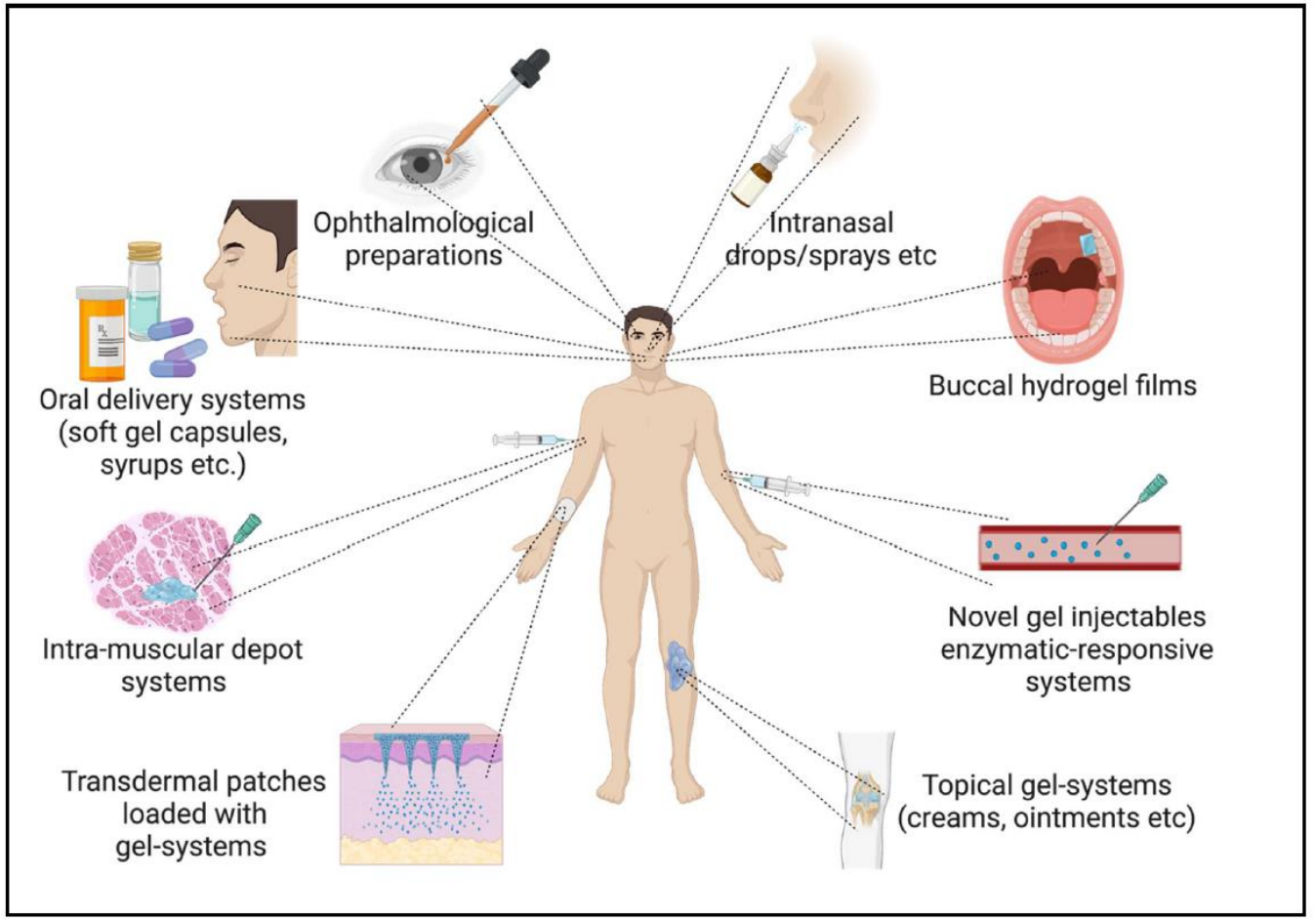
Macrogel – application *in situ* injection, *in situ* implantation, transdermal delivery

Microgel – oral delivery, pulmonary delivery, transdermal chemoembolization

Nanogel – intravenous injection, *in situ* injection

a) C. S. A. de Lima et al. *Pharmaceutics* 2020, 12, 970. b) Z. Sun et al. *Mol. Pharmaceutics* 2020, 17, 373−391.

Pharmaceutical gels



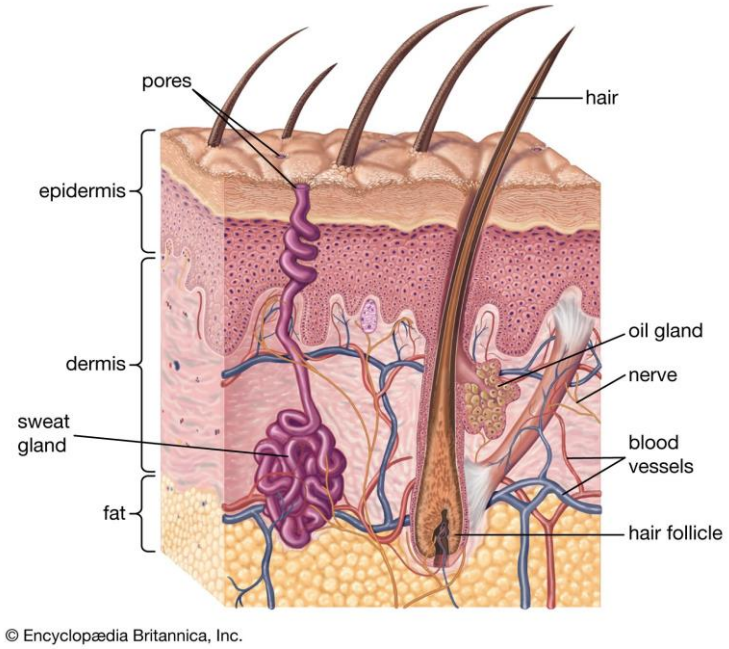
a) Trideva S. K. et al. *Gels* 2022, 8, 316. b) Al-Kinani A. A. *Adv. Drug Deliv. Rev.* 2018, 126, 113–126. c) T. Yu et al. *Expert Opin. Drug Deliv.* 2011, 8(10). d) das Neves J. *Int. J. Pharm.* 2006, 318, 1–14.

Mode of action of topical gels

- Skin penetration – passive diffusion through epidermis or via hair follicles and sweat glands based on concentration gradient (active, endocytosis)
- Drug might penetrate deeper and reach capillaries – systemic circulation

Controlled by:

- *Physiological factors* such as skin properties, size of application area, frequency and force of application, hydration, temperature, etc.
- *Physicochemical properties of the drug* such as drug solubility, attraction to the skin and metabolism.
- *Gel characteristics* include stability, thermodynamic activity, and occlusive* properties.



* forms a protective film and traps moisture against the skin

Gel formulation ingredients

- Formulation of topical gels is determined by important factors such as appearance, odor, spreadability, extrudability, consistency, viscosity, pH, texture, microbial contamination potential and bioavailability
- Consistency and viscosity affect the adhesion and retention property of the gel, and are important in ensuring the gel is retained at the site of application and effective delivery of the drug

- Gelator, solvent, drug, and excipients
  - ***Gelator*** – stabilizer and thickener
    - natural gelators include tragacanth, gelatin, collagen, and guar gum; semi-synthetic gelators include methylcellulose and other cellulose derivatives; while synthetic gelators include carbomers, polyvinyl alcohol, polyethylene and its copolymers
  - ***Solvent*** – based on application – hydrophilic, lipophilic, or organic (e.g., purified water, glycerin, glycols, alcohols, sucrose, toluene, and mineral oils)
  - ***Drug*** – typically used for drugs which are easily degraded in the GI tract or susceptible to hepatic first pass effect
    - the drug should be smaller than 500 Da, be reasonably lipophilic, have pH 5-9 in saturated aqueous solution, it should not be irritant or allergenic, under constant delivery no tolerance
    - drug permeability and concentration

Gel formulation ingredients

- ***Excipients*** – components inert to the drug, which are added into dosage forms to improve its overall quality, *i.e.*, antioxidants (sodium metabisulphite and sodium formaldehyde sulfoxylate), sweetening agents (sucrose, glycerol, sorbitol and liquid glucose), stabilizers, dispersing agents, penetration enhancers (glycerin, sulfoxides and related analogues, pyrrolidines, fatty acids, ethanol, or surfactants), buffers (phosphate, citrate) and preservatives (parabens, phenolics)

Gel preparation methods

- Increasing the concentration of gelator leads to gelation at gelling point, increasing the gelator concentration increases gel viscosity (stiffness)

Gel evaluation

- pH
- Drug content
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- *In vitro* release
- *In vivo* study
- Stability (time, temperature)

Gel advantages

- Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH.
- Gels are having property to avoid enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when the route is unsuitable.
- They can avoid the first pass effect, that is, the initial pass of drug substance through the human body.
- They avoid systemic and portal circulation following gastrointestinal absorption.
- They are non-invasive and have patient compliance.
- They are applied over skin for slow and prolonged absorption.
- They have localized effect with minimum side effects.
- Excellent spreading property and cooling effect due to solvent evaporation.
- They can be washed off easily.
- Increased bioavailability, faster drug release from gels than from creams and ointments.

Gel disadvantages

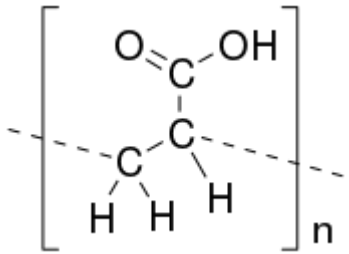
- Additives of gels might cause allergic reactions.
- Drugs of larger size do not absorb through the skin.
- Poor permeability of some drugs through the skin.
- Water content increases chances for microbial or fungal contamination.
- Possible flocculation, salting out, syneresis, changes in rheology due to temperature, humidity changes – more strict storing requirements

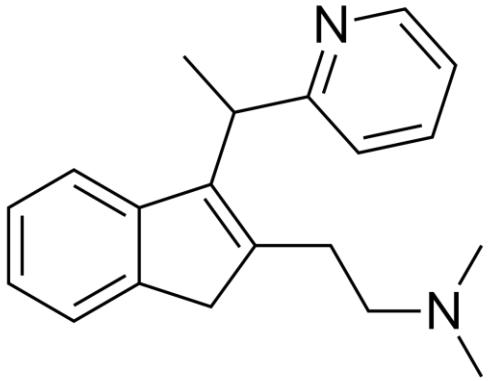
Fenistil gel

- 1 gram of gel contains dimetindeni maleate 1 mg, other excipients: benzalkonium chloride (antimicrobial preservative), dihydrate dinatrium-edetate (stabilizing effect on gelator, effects skin penetration), carbomer 974 P (gelator!), solution of sodium hydroxide 300 g/l (keeps gelator in the form of salt), propylenglycol (caution, possible irritant), purified water (hydrogel!).

- Key features of **carbomer 974 P**: suspension and emulsion stabilizer, taste masking agent
  - Additional features: extended release agent, thickener/rheology modifier, bioadhesion agent, tablet binder
  - Recommended for use in the following dosage forms: semisolids & gels, solutions & suspensions, extended release oral solid doses
  - Recommended for use in the following markets / routes of administration: oral drug delivery, topical drug delivery, ophthalmic drug delivery, oral care

Polyacrylic acid

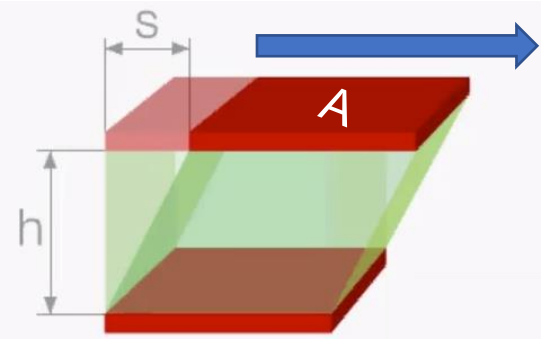




Rheology studies

- Rheology is the science of the flow and deformation of materials
- Gels exhibit different rheological properties. Do not flow at low shear stresses but undergo reversible deformation like elastic solids.
- When a characteristic shear stress, called the yield value or yield stress, is exceeded, they flow like liquids (plastic behavior rather than elastic).

Two plates model



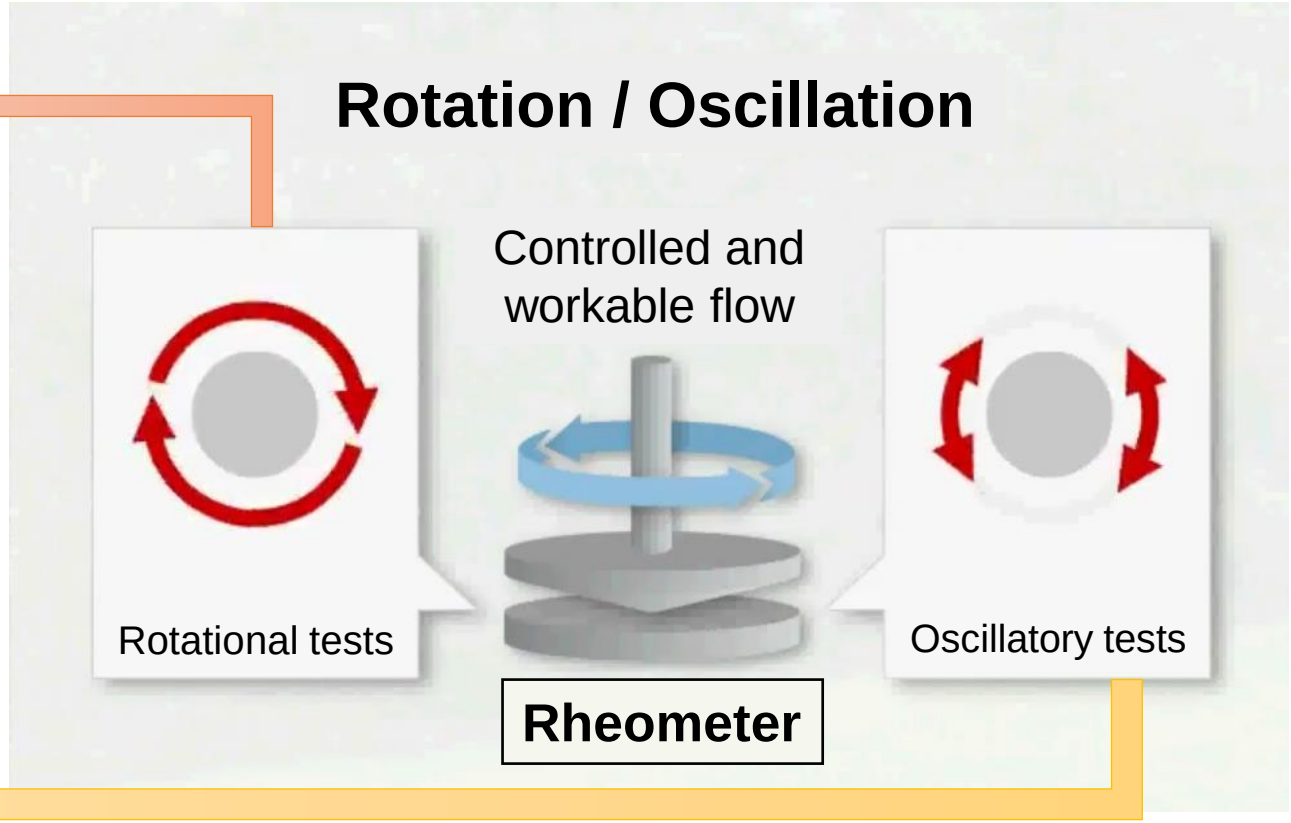
F Shear force

Budai L. *Gels* 2023, 9, 469

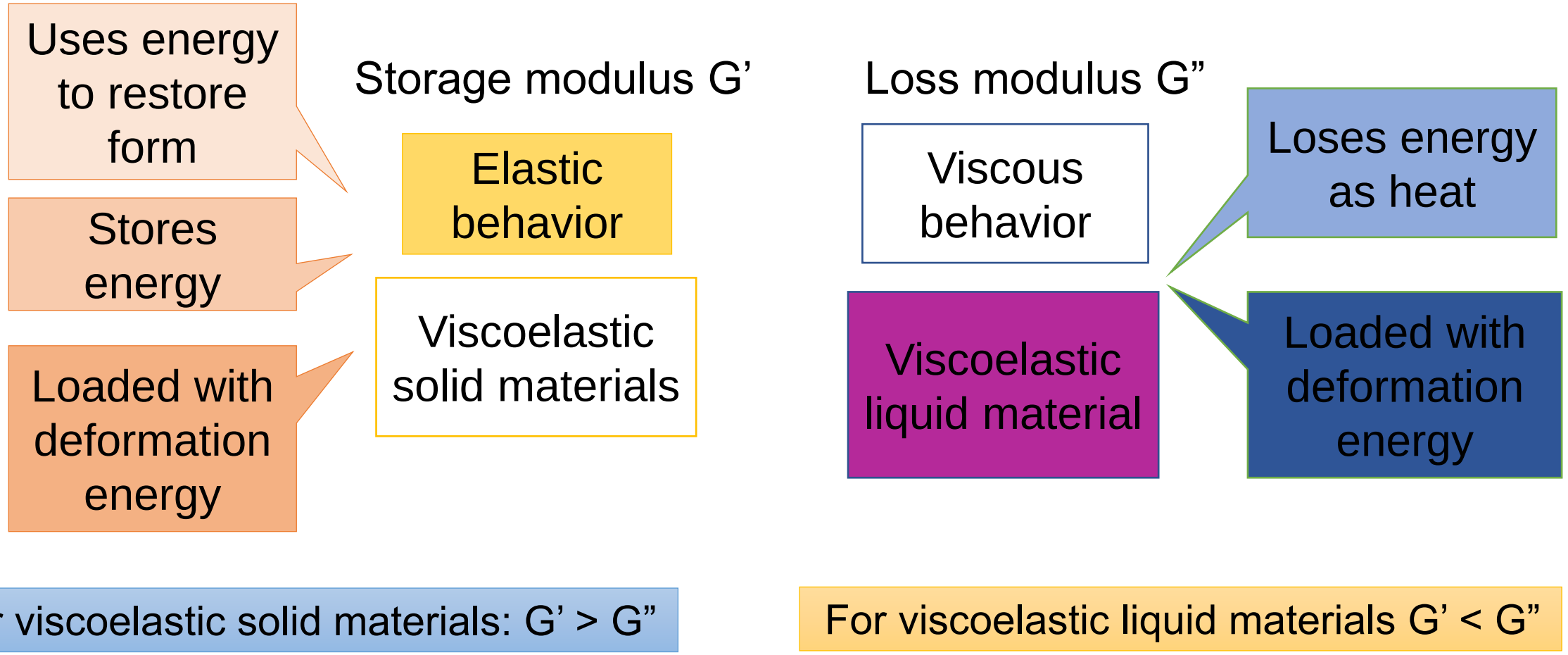
Rheology studies

Rotational tests: uses to measure liquids / detects the viscosity function of the liquid

Oscillatory tests: Covers the entire range of materials from viscous end to the elastic / detects viscoelastic behavior of materials



Energy storage and loss



For viscoelastic solid materials: G' > G"

For viscoelastic liquid materials G' < G"

In the next class…

Nanoparticles

Thank you for your attention!

With thanks to Jonathan W. Steed, Jerry L. Atwood for Supramolecular Chemistry, ISBN: 978-1-119-58251-9 and Wikipedia for several lovely images.