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Abstract: Hydrogels are hydrophilic polymer networks, able to absorb large amount of water, increasing their volume and showing a plethora of different material behaviors. Since their first practical application, dating from sixties of last century, they have been employed in several fields of biomedical sciences. After more than half a century of industrial uses, nowadays a lot of hydrogels are currently on the market for different purposes, and offering a wide spectra of features.In this review, even if it is virtually impossible to list all the commercial products based on hydrogels for biomedical applications, an extensive analysis of those materials that have reached the market has been carried out. The hydrogel-based materials used for drug delivery, wound dressing, tissue engineering, the building of contact lens, and hygiene products are enlisted and briefly described. A detailed snapshot of the set of these products that have reached the commercial maturity has been then obtained and presented. For each class of application, the basics of requirements are described, and then the materials are listed and classified on the basis of their chemical nature. For each product the commercial name, the producer, the chemical nature and the main characteristics are reported.

*Cover Letter

Università di Salerno
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Dear Editor,

Enclosed please find the manuscript entitled "**Hydrogel-based commercial products for biomedical applications: a review"** by Gaetano Lamberti and myself.

The manuscript consists of an extensive analysis of those hydrogel based products that have reached the market. The hydrogel-based materials used for drug delivery, wound dressing, tissue engineering, the building of contact lens, and hygiene products are enlisted and briefly described. A detailed snapshot of the set of these products that have reached the commercial maturity has been then obtained and presented.

In my opinion, this approach can be of great interest for readers of *International Journal of Pharmaceutics* and it is suitable for the special issue named *'Hydrogels new apps'*. It is an original work, it has not been previously published in any language anywhere and that it is not under simultaneous consideration by another journal.

Look forward to hear from you

Best Regards

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Dear Editor,

I am writing with reference to the manuscript entitled "Hydrogel-based commercial products for biomedical applications: a review" (Manuscript number: IJP-D-19-01120R1) by Gaetano Lamberti and myself, submitted for publication in International Journal of Pharmaceutics.

Attached to this letter you can find the answers and revisions we have made in response to the Reviewer 1; questions and suggestions in a point-by-point fashion (the queries are in black, the answers in red). Also, the modifications made in the manuscript are in red in the new version.

Reviewer #1:

The authors have adequately responsed to my comments. The addition of table 11 with the general overview of most applied materials and their properties have brought the manuscript to a higher level. ALso the inclusion of vaginal application has improved the overview. I was just wondering if there is no hydrogel formulation for the administration of hormones used in birth control (eg NuvaRing? Or maybe this is not based on a hydrogel...). If so, a commercial birht control hydrogel could be included in the table.

The Reviewer is absolutely right, it exists a plenty of birth control dispositive that are based on a polymeric matrix from which the active ingredients are released, usually hormones. Unfortunately, the devices used as contraceptives in vaginal delivery are usually not based on hydrogels because they have to last in the contact with body fluids for long times, not losing in terms of mechanical properties and chemical stability, that is the reason why polyolefins are usually preferred in these applications.
Concerning the mentioned Nuvaring, it is a hormones-releasing device based on Poly(ethylene vinyl acetate), with a vinyl acetate content of 28% or 9% of the total amount. Thus, it cannot be seen properly as a hydrogel, so it has not been considered in this review.
However, since Authors agree with the Reviewer that contraceptives are fundamental in drug delivery, some examples have been added to the review, in both sections of oral and vaginal delivery.

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Some spelling mistakes remain, for example

87 with final properties different respect to the initial polymers.

209 it can be used encapsulated in a hydrogel

346 It works as a fast acing and long lasting --> fast acting?

436 a very challenging tasking --> task?

444 drug transport form lacrimal fluid --> from

Corrected

All the tables in the manuscript have been re-ordered alphabetically.

Look forward to hear from you.

Best Regards
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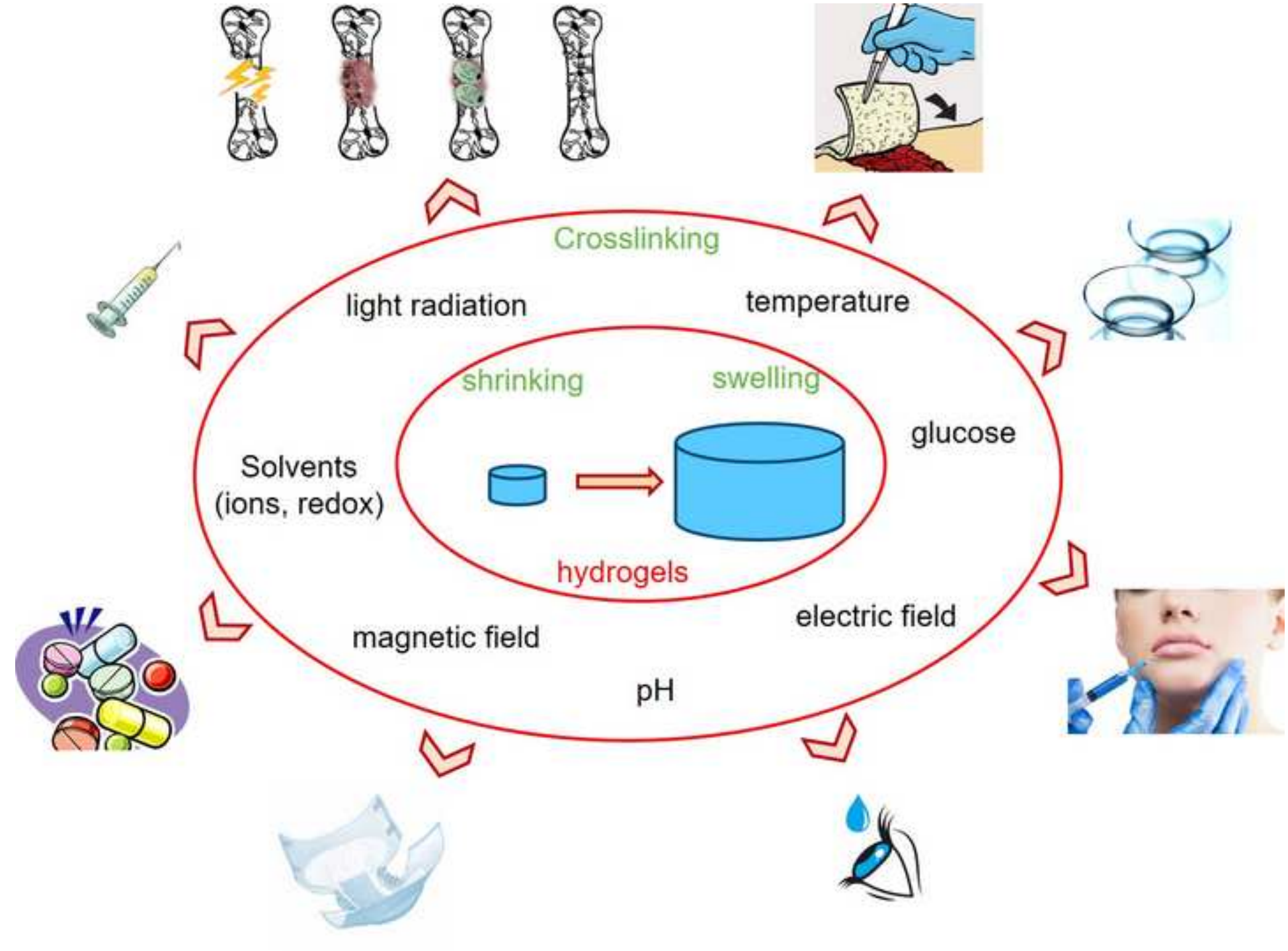
*Graphical Abstract (for review)



Hydrogel-based commercial products for biomedical applications: a review

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Abstract

Hydrogels are hydrophilic polymer networks, able to absorb large amount of water, increasing their volume and showing a plethora of different material behaviors. Since their first practical application, dating from sixties of last century, they have been employed in several fields of biomedical sciences. After more than half a century of industrial uses, nowadays a lot of hydrogels are currently on the market for different purposes, and offering a wide spectra of features. In this review, even if it is virtually impossible to list all the commercial products based on hydrogels for biomedical applications, an extensive analysis of those materials that have reached the market has been carried out. The hydrogel-based materials used for drug delivery, wound dressing, tissue engineering, the building of contact lens, and hygiene products are enlisted and briefly described. A detailed snapshot of the set of these products that have reached the commercial maturity has been then obtained and presented. For each class of application, the basics of requirements are described, and then the materials are listed and classified on the basis of their chemical nature. For each product the commercial name, the producer, the chemical nature and the main characteristics are reported.

Contents

1. Introduction

The origin of the term hydrogel goes back to 1894, when it was used to indicate colloidal gels of certain inorganic salts [1]. Nowadays, the term hydrogel is used to identify a class of material completely different from the beginning: hydrogels are three dimensional cross-linked networks of polymer chains that can absorb and hold large amounts of water in the interstitial spaces between chains. The first appearance of a hydrogel on the market is dated in 1949 with the poly(vinyl alcohol) cross-linked with formaldehyde and it was marketed with the trade name Ivalon, used for biomedical implant. However, the real turning point for the production and the use of hydrogels was the synthesis of poly(2-hydroxyethyl methacrylate) (pHEMA) gels for contact lens application in 1960, which represented the starting point for the spread and flourishing hydrogel market.

On the basis of an historical classification, hydrogels can be considered belonging to different eras: (i) first generation hydrogels (sixties onwards), which are cross-linked hydrogels with relatively high swelling and good mechanical strength; (ii) second generation hydrogels (start of seventies), which are stimuli-responsive, meaning that they are able to respond to specific stimuli such as pH, temperature, or biological molecules adapting their behavior; and (iii) third generation hydrogels comprising of stereo-complexed materials (e.g., poly(ethylene glycol)-poly(lactic acid), PEG-PLA cross-linked by cyclodextrin) [1].

The first generation of hydrogels was obtained mainly by the mechanism of chain addition reaction, usually involving vinyl monomers and an initiating free radical specie. The free radical polymerization proceeds until the recombination of two radical species or disproportionation takes place. One of the main hydrogel-forming polymer in this category was polyacrylamide (PAM), which found its place in industrial applications as an agricultural gel. Another important polymer is poly(hydroxy-alkyl methacrylate) (pHEMA) that, despite its discovery is dated 50 years ago, is still one of the key materials in the development of contact lens. Hydrophilic polymers covalently cross-linked constitute the second major category of the first generation hydrogels. Among them, polyvinyl alcohol (PVA) and polyethylene glycol (PEG) still play a major role in tissue engineering. Finally, another category in the first generation hydrogels is the cellulose-based hydrogels, which are used extensively in drug delivery application as matrix for drug dispersion [2].

During the 1960s, the scientists' attention was attracted by the possibility to transfer chemical energy into mechanical work. Moved by this aim, during the 1970s the second generation of hydrogels was introduced on the market: the stimuli responsive hydrogels [3]. The use of these hydrogels allowed the triggering of a specific event (such as the drug release or the erosion of the polymer) as a response to a change of the external environment (i.e. temperature or pH). Belonging to this generation of hydrogels, PEG-polyester block

copolymers have to be mentioned, which are commonly known under the tradename of Pluronics (by BASF) or Poloxamers (by ICI). These polymers exhibit a phase transition from the sol to the gel state at low temperatures and from the gel to the sol state at higher temperatures, feature that has been widely used in sustained and controlled release for applications in human body. The second major type of stimuli-responsive polymers are the pH – sensitive hydrogels. These polymers usually contain acidic or basic moieties that are hydrolyzed at low or high pH, respectively. Thus, using the pH variation in different zones of the body, controlled release from hydrogel can be achieved. Biomolecule – sensitive hydrogels respond to a variation of the concentration of a certain biomolecule with a conformational change. Among these biomolecules, glucose is undoubtedly the most famous one. One application involving hydrogels is based on the release of insulin incorporated in a matrix containing glucose oxidase and pH sensitive moieties. When the glucose diffuses inside the matrix, it is converted in gluconic acid, which causes a lowering of the pH and a subsequent swelling increase due e.g. protonation of amine functionalities. In these conditions, insulin can be released from the matrix, which can be considered a self-regulating system [3]. Usually, the second generation of hydrogels is characterized by the crosslinking via hydrophobic or ionic interactions.

On the contrary, the third generation of hydrogels is characterized by crosslinking methods that allow to tune the thermal, mechanical, and degradation properties of the hydrogels: stereocomplexation, inclusion complex formation, metal–ligand coordination, and peptide interactions. The first example of stereocomplexation was reported in 1953 by Pauling and Corey for a polypeptide. A polymer stereocomplex is defined as a stereoselective interaction between two complementing stereoregular polymers, with final properties different ~~respect~~ compared to the initial polymers. One of the main application of stereocomplexation to produce hydrogels concerns the employing of PLLA and PDLA (enantiomers of poly-lactic acid) blocks in amphiphilic copolymers for the preparation of injectable pharmaceutical forms. Hydrogels can be produced using the crosslinking by hydrophobic interactions, as in the case of cyclodextrins, which have a hydrophobic cavity that can host different molecules. Only a few reports on metallohydrogels, in which the reversible bonds between macromonomers are based on metal–ligand coordination, have been published: PEG, Pluronics and PEG–PLA end-functionalized with ligands such as terpyridine or bipyridine were employed as well to prepare hydrogels in the presence of transition metal ions such as Mn(II) and Ni(II) [3]. Belonging to the third generation of hydrogels are the natural building blocks that are able to naturally self-assembling in ordered structures, such as peptides. These macromolecules that assemble into hydrogels are usually designed according two different criteria: using genetically engineered copolymers or hybrid systems composed by a synthetic polymer and a peptide (or protein).

In spite of their classification or nature, it has to be highlighted that hydrogel market size nowadays is valued at USD 10.87 Billion (in 2016) and is projected to reach USD 15.33 Billion by 2022, at a CAGR (Compound Annual Growth Rate) of 6.04% from 2017 to 2022. The increase in consumption of personal care & hygiene products is one of the most significant factors driving the growth of the hydrogel market during the forecast period [4].

This review is aimed to explore the different hydrogels' applications in biomedical field, with particular attention to the hydrogels that are used in commercial products. A list of the marketed products, their main constituent, and their producer is appended at the end of each paragraph.

2. Applications

Hydrogels are a unique class of materials: they are hydrophilic, self-supporting, three-dimensional viscoelastic networks, which allow the diffusion and the attachment of molecules and cells. These networks can be composed of homopolymers or copolymers, and their structural and physical integrity is due to the presence of crosslinks, which can be of physical (such as entanglements or crystallites) or chemical (junctions or tie-points) nature. Based on the nature and on the stability of the crosslinking, which can be achieved by different methods (i.e. using temperature, ions, or UV radiation), the final hydrogel results in a polymer with specific and peculiar characteristics.

Due the wide spectrum of both chemical and physical characteristics, hydrogels have been extensively used in pharmaceutical and biomedical applications. In Figure 1 the main methods to achieve the hydrogel's crosslinking are listed and some of the application fields covered by this review are depicted.

Figure 1. Some examples of methods to crosslink hydrogels and their biomedical applications.

2.1 Drug delivery

Hydrogels are extensively used in drug delivery and play a major role as drug vehicle. In this paragraph the commercial products for drug delivery based on hydrogels are listened on the basis of the administration route.

2.1.1 Buccal delivery

The oral cavity is covered with mucous membranes with a total surface area of 100 cm^2, consisting essentially of multilayered epithelium covered with mucus. The oral cavity can be divided in three areas: the floor of the mouth, the inside of the cheeks, and the gums. Each of these parts is suitable as site of drug administration: the sublingual route uses the floor of the mouth, the buccal route the cheeks, and the gingival route uses the gums [5]. The oral cavity can be considered an attractive site for drug delivery because of the ease of administration,

the avoiding of drug degradation in the gastrointestinal tract, and the avoiding of the first-pass metabolism effect [6]. The main advantages of the buccal administration route, besides that previously mentioned, are the patient compliance, due to the fact that it is not painful, the rapid onset of action, the very low risk of irritation or undesired side effects, the excellent accessibility, the ease of removal in emergency, the higher permeability than the skin, the fact that buccal mucosa is well vascularized [5, 7].

In general, to deliver a drug from the oral cavity, a series of resistance have to be passed: the drug has to leave the pharmaceutical form, to diffuse through the mucosa into the local blood circulation systems, and to reach the systemic blood circulation. Substances can be transported across the mucosal membrane by passive diffusion, carrier-mediated active transport or endocytosis [8].

From the viewpoint of permeability, the sublingual mucosa is more permeable than the buccal mucosa, making it particularly suitable in applications in which a rapid onset is desired, such as in cases of acute disorders. However, this advantage of the sublingual mucosa is lessened by the fact that a dosage form put on the sublingual site is affected by the movement of the tongue during speaking. On the other hand, a dosage form inserted onto the buccal mucosa receives less stress, but absorption of a drug from the gingiva does not seem promising and it is usually preferred for treatments of chronic disorders. Despite many dosage forms are suitable for delivery into the buccal mucosa, such as tablets, patches, sprays, chewing gums, or lollypop systems, a large part of these is affected of leakage into the gastrointestinal tract. Thus, in order to allow the release only across the buccal mucosa, mucoadhesive patches or tablets can be used [5]. The ideal characteristics of the polymer used for these formulations are: good spreadability, wetting, swelling, viscoelasticity, good adherence to the buccal mucosa and mechanical properties [9], bioadhesive properties both in dry and liquid state, low cost, biodegradability properties, non-toxic degradation products, and it has not to be a vehicle of secondary infection such as dental caries [10]. Hydrogel-based bioadhesive tablets can control the release rate of the drug depending on the hydration of the device, which is the driving force determining its swelling ability. Hydrogels commonly used in these applications are: hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyacrylic (PA) resins, carboxymethyl cellulose (CMC), polyvinyl alcohol (PVA), hydroxypropylmethyl cellulose (HPMC), chitosan [5, 7, 11, 12]. The use of cellulosic or acrylic polymers generally offers almost immediate, high adhesion performance for prolonged times, even with high drug content.

Concerning the commercial product that can be found on the market, they range from hydrogels for mouth care and hydration to sustained drug delivery systems to prevent angina. Some of them are listed below:

- Lubrajel™ BA (by Ashland) oral moisturizing hydrogel is a solution for mouth moisturization and it is used in mouthwashes, oral gels and sprays.

- Hydrogel 15% (by Honest O3) is an oral gel with ozone infused sunflower seed oil. This mucoadhesive hydrogel is uniquely formulated to clean and nourish the mouth for optimal health.
- Biotène® product line (by GlaxoSmithKline) has been formulated to manage a dry mouth and relieve the symptoms.
- SCHALI® Dental Care Hydrogel (by SchaliProduct) is a highly-effective universal product for everyday dental and gums care, intended to promote complete oral hygiene and regeneration. The product contributes to better oral microflora, fresher breath, and helps in healing different gingival conditions. SCHALI® Dental Care Hydrogel may be successfully used for treatment and prevention of infectious (bacterial and viral) diseases in oral cavity and larynx. Active phyto- and mineral ingredients of the product are capable of eliminating bacterial plaque on teeth surface, which causes inflammation and smell.
- Gengigel® (by Oraldent Ltd.) is a biological mouth and gum-care gel based on hyaluronan, which helps to accelerate the healing process of ulcers within the mouth.
- Nicorette® (by Johnson&Johnson) or Nicotinell® (by GlaxoSmithKline) chewing gums or spray are used to deliver nicotine in order to quit smoking gradually.
- Buccastem® M buccal tablets (by Alliance) are prochlorperazine tablets for nausea and vomiting in previously diagnosed migraine. Once placed, Buccastem M tablet dissolves slowly, letting the medication enter in blood stream without necessity of swallowing.
- Zilactin-B Gel® (by Zila Pharmaceuticals) is a buccal film used to relieve pain from minor mouth problems (such as toothache, sores) delivering a local anesthetic (benzocaine) numbing the painful area.
- Imdur® (by Key Pharmaceuticals) is used to prevent angina by delivering isosorbide mononitrate and it can be absorbed by sublingual route.

Table 1. Hydrogel-based commercial products used in buccal drug delivery.

Product	Company	Main constituent	URL
Biotène®	GlaxoSmithKline	Carbomer and hydroxyethyl cellulose	https://bit.ly/2txQDwE
Buccastem® M	Alliance	Xanthan gum	https://bit.ly/2Itqf1f
Gengigel®	Oraldent Ltd.	Hyaluronan	https://go.nature.com/2T5C5mv
Hydrogel 15%	Honest O3	Carbomer	https://bit.ly/2BM3Cze
Imdur®	Key Pharmaceuticals	Hydroxypropylcellulose and hydroxypropyl methylcellulose	https://mayocl.in/2GXHhlJ
Lubrajel™ BA	Ashland	Glyceryl acrylate and glyceryl	https://bit.ly/2NktRS1

		polyacrylate	
Nicorette®	Johnson&Johnson	hydroxypropyl methylcellulose	https://bit.ly/2NmKKeP
Nicotinell®	GlaxoSmithKline	Xanthan gum and gelatin	https://bit.ly/2XhRGP6
SCHALI®	SchaliProduct	Cellulose gum and hydrogenated starch	https://bit.ly/2U3P990
Zilactin-B Gel®	Zila Pharmaceuticals	hydroxypropylcellulose	https://wb.md/2U2uLoW

2.1.2 Oral delivery

The oral administration has been ever considered the simplest and the most comfortable administration route, which improves patient compliance and reduces costs if compared with the injection-based delivery. Thus, this seems the ideal administration route for therapeutic molecules, in particular for the treatment of chronic disease; however, the oral delivery is limited to small molecules. The main challenge in the oral drug delivery is to transport drugs into the intestine safely, since most of the drugs orally taken are absorbed in the gastrointestinal (GI) tract. Moreover, they have to face other obstacles such as the poor permeability across the GI mucosa, the acid catalyzed or proteolytic degradation of drugs, which is particularly relevant in the delivery of molecules such as peptides or proteins [1]. The oral delivery of these drugs is in fact seriously limited by low bioavailability due to enzymatic degradation and poor penetration of the intestinal membrane into the bloodstream. Beside the proteolytic degradation, a great problem in the oral delivery of macromolecules is constituted by the low bioavailability of macromolecules, since it decreases sharply when the molecular mass exceeds 500-700 Da. Moreover, the molecules need a minimum level of lipophilicity to be absorbed transcellularly through passive diffusion and, unfortunately, most interesting macromolecules are hydrophilic [13]. Thus, since from the discovery of insulin and heparin [13], one of the greatest challenges is to deliver macromolecules orally [14]. The looking for a solution to overcome these limitations has focused the attention of scientists for long time [15]. Successful delivery of these molecules requires innovative techniques, such as protection by hydrogel networks [16, 17]. In example, in order to avoid the degradation of proteins or peptides, which takes place in the acidic environment of the stomach, ~~it~~ they can be ~~used~~ encapsulated in a hydrogel that remains shrunk in the acidic environment avoiding the release of the drug. To reach this goal, natural polymers with anionic pendant groups are usually used since they remain protonated in acidic environment [18, 19]. The most common practice is to graft natural polymers with acrylic acid derivatives in order to achieve a pH sensitivity to the final polymer [1, 20-22]. These kind of hydrogels are called “stimuli-responsive hydrogels”, which are able to adapt their network structure, swelling behavior, permeability, or mechanical strength depending on the environmental changes, enabling the control of the drug release [23]. The external stimuli can be of physical (temperature, electric field, light) or chemical (pH, ionic strength, and

molecular recognition events) nature [16]. A review on the polymeric network design of hydrogels to address responsive and mechanical properties has been published by Liu et al. [24].

The drug release mechanisms from hydrogels can vary significantly depending on a series of factors, which can be related to solute characteristics, formulation composition, or polymer properties [25-27]. In general, drug release can be classified into three categories, depending on the release rate limiting step: i) diffusion controlled, which depends on the drug diffusivity across the polymeric matrix; ii) swelling controlled, which depends on the time necessary to the solvent to penetrate inside the polymeric matrix and form the gel layer; and iii) chemically controlled, which depends on reactions happening inside the polymeric matrix such as hydrolytic or enzymatic degradation of the matrix, usually called generically “erosion” of the matrix [28].

Two kinds of conventional formulations based on hydrogels are widely used in oral drug delivery: the matrix systems and the reservoir systems. Concerning the matrix systems, the drug is completely dispersed into the polymeric bulk, usually this result is obtained by mechanical mixing of dry powders. When these matrices enter in contact with biological fluids, the solvent diffuses into the matrix and causes the glass-rubber transition, the gel formation, and the polymer swelling. Through the gel layer, the dissolved drug can easily diffuse to be released into the dissolution medium. Meanwhile, the polymer chains dissolve causing the erosion of the matrix. The reservoir systems are composed by a drug core which is surrounded by a polymer shell. In these systems the drug release rate is controlled by the hydrogel properties (its composition and molecular weight), the shell thickness, the physicochemical properties of the drug (its solubility, particle size, or molecular weight) [29, 30].

Some of the commercial products based on hydrogels for oral drug delivery available on the market are listed below.

- Suprax® (by Sanofi Aventis) is an antibiotic useful to treat a number of bacterial infections. It was patented in 1979 and approved for medical use in the United States in 1989. It exerts its bactericidal effect by attaching to penicillin-binding proteins and inhibiting peptidoglycan synthesis, thus causing damage to the bacterial cell wall.
- Lopid® (by Pfizer Inc.) is a lipid regulating agent, which decreases serum triglycerides and very low density lipoprotein (VLDL) cholesterol, and increases high density lipoprotein (HDL) cholesterol.
- Advil® Film-Coated (by Pfizer Inc.) is designed for fast pain relief, in the whole Advil® products family the active ingredient is ibuprofen.
- Kaletra® (by AbbVie Ltd) is a prescription medicine that is used with other antiviral medicines to treat human immunodeficiency virus-1 (HIV-1) infection.
- Vicoprofen® (by AbbVie Ltd) combines the opioid analgesic agent, hydrocodone bitartrate, with the nonsteroidal anti-inflammatory (NSAID) agent, ibuprofen.

- Gaviscon® (by Reckitt Benckiser Group) is a sodium alginate-based pharmaceutical form used for the treatment of symptoms resulting from the reflux of acid, bile and pepsin into the esophagus such as acid regurgitation, heartburn, indigestion.
- Toviaz® (by Pfizer Inc) is indicated in adults for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur with overactive bladder syndrome.
- Belviq XR® (by Eisai Inc.) extended-release tablets of lorcaserin hydrochloride is a serotonin 2C receptor agonist for oral administration used for chronic weight management.
- Ranexa® (Gilead Sciences) is a prescription medicine used to treat angina that keeps coming back (chronic angina). In 2016, it was the 276th most prescribed medication in the United States, with more than a million prescriptions.
- Xartemis XR® (Mallinckrodt Pharmaceuticals) is an extended-release tablet for oral administration containing both immediate- and extended-release components. Xartemis XR® is formulated to immediately release a portion of its oxycodone and acetaminophen doses and it is designed to swell in gastric fluid and gradually release the remainder of oxycodone and acetaminophen to the upper gastrointestinal (GI) tract.
- Aplenzin® is bupropion hydrobromide extended-release tablet, indicated for the treatment of major depressive disorder (MDD).
- Voltaren® is available as enteric-coated tablets for oral administration of diclofenac sodium. It is indicated for relief of the symptoms of osteoarthritis or rheumatoid arthritis.
- Levora® and Portia® are oral contraceptive that delivers levonorgestrel and ethinyl estradiol, hormones that are commonly used in birth control systems. The hormones release is regulated by croscarmellose sodium, which is an internally cross-linked sodium carboxymethylcellulose, used as a disintegrant and hypromellose, respectively.
- Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane coating. Some examples are Concerta® (by Alza Corporation), extended-release tablets approved for the treatment of attention deficit hyperactivity disorder (ADHD), Jurnista® (by Janssen), prolonged release tablets with a semipermeable cellulose acetate coating, both produced using the OROS® technology, properties of Alza Corporation.

Table 2. Hydrogel-based commercial products used in oral drug delivery.

Product	Company	Excipients	URL
Advil®	Pfizer Inc	hydroxypropyl methylcellulose	https://bit.ly/2EWtWb0

Aplenzin®	Valeant Pharmaceuticals International, Inc.	Ethylcellulose and polyvinyl alcohol	https://bit.ly/2Cet1ln
Belviq XR®	Eisai Inc.	Polyvinyl alcohol, hydroxypropyl methylcellulose, polyethylene glycol	https://bit.ly/2VK8o82
Concerta® Jurnista®	Alza Corporation	hydroxypropyl methylcellulose (Hypromellose) and polyethylene oxide	https://bit.ly/2XRKLfy https://bit.ly/2TIrJsV
Gaviscon®	Reckitt Benckiser Healthcare Ltd.	Sodium alginate and carbomer 974P	https://bit.ly/2F4Vyfd
Kaletra®	AbbVie Ltd	Polyvinyl alcohol	https://bit.ly/2CdCwSa
Levora®	Mayne Pharma Inc.	Croscarmellose sodium	http://bit.ly/2LMq159
Lopid®	Pfizer Inc	hydroxypropyl methylcellulose	https://bit.ly/2UvsT8n
Portia®	Teva Pharmaceutical Industries Ltd.	Hypromellose	http://bit.ly/2nl1Z7U
Ranexa®	Gilead Sciences	Polyvinyl alcohol and hydroxypropyl methylcellulose	https://bit.ly/2NYIhYn
Suprax®	Sanofi Aventis	hydroxypropyl methylcellulose	https://bit.ly/2J7dZnv
Toviaz®	Pfizer Inc	Polyvinyl alcohol and hydroxypropyl methylcellulose	https://bit.ly/2O05Kso
Vicoprofen®	AbbVie Ltd	hydroxypropyl methylcellulose	https://bit.ly/2Tvt7ja
Voltaren®	GlaxoSmithKline	hydroxypropyl methylcellulose and polyethylene glycol	https://bit.ly/2XRTA9e
Xartemis XR®	Mallinckrodt Pharmaceuticals	hydroxypropyl cellulose and polyvinyl alcohol	https://bit.ly/2ERRnC1

2.1.3 Vaginal delivery

Bacteria, fungi, or viruses can easily colonize the vaginal lumen, causing various pathologies, among them the most diffused is the vaginitis. Thus the vagina has been traditionally employed as route of administration for the delivery of antimicrobial and antiviral drugs. The vagina constitutes an alternative to the parental route for the administration of propranolol (which is more available if the hepatic first-pass effect is avoided), human growth hormone, insulin, and steroids (which show reduced side effects if taken by vaginal route). Since a lack of drug interactions has been observed in vagina compared to the gastrointestinal tract, vaginal delivery offers some advantages respect to the oral delivery. Moreover, it has also great potentiality for systemic delivery due to its large surface area, highly perfusion of tissues, and high permeability to a wide range of compounds, including peptides and proteins. On the other side, vaginal delivery as administration route is underestimated

because of gender specificity and cyclic variations. In fact, the permeability of vaginal membrane is influenced by estrogen concentration, which of course affects the pharmacokinetics of an administered drug, and by the vaginal fluid amount, which changes depending from the period and the age, and can lead to the detachment of a pharmaceutical form. However, a large variety of pharmaceutical forms are currently used for vaginal delivery, they include: tablets and capsules, liquid preparations, gels, foams, vaginal films or rings, and tampons.

Thus, one of the main drawbacks of this administration route is its physiological removal mechanism, which is responsible of reduced residence times of the administered forms, that limits considerably the potentiality of this route. Two main approaches have been proposed to overcome this limitation: the use of mucoadhesive formulations to prolong the residence times onto the vaginal mucosa, and the external stimuli-sensitive gelling systems, which undergoes a sol-gel transition in the vaginal environment [31].

The formulations having mucoadhesive properties allow better contact with the vagina surface and longer residence times. The mechanism of adhesion involves a contact stage, in which three phenomena take place simultaneously: hydration, wetting, and diffusion [9]. Then, a consolidation stage, which involves the strengthening of polymer–mucin joints due to the interactions between the polymer chains and the mucus layer, mainly due to van der Waals forces, hydrogen bonds, or electrostatic interactions [31]. Usually, these properties are conferred to a formulation by excipients or polymers. The most used polymers in vaginal formulation are hydrogels: polyacrylates, which are the most investigated bioadhesive polymers for vaginal applications, chitosan, which is a natural polymer easily processable, cellulose derivatives, in particular carboxymethyl cellulose (CMC), hydroxypropylmethylcellulose (HPMC) and their mixtures, Carbopol, and hyaluronic acid, a natural polymer employed for its high hydration properties [32]. Among the others, alginate and gelatin can be used in the preparation of vaginal delivery formulations due to their properties of moisture retention and biocompatibility.

Environmentally-sensitive gels are able to undergo a sol-gel transition in the vaginal environment and, among them, the most used are undoubtedly the thermo-sensitive hydrogels. These gels change their characteristics gelling when the temperature changes from ambient to the physiological one. Thermo-gelation is a reversible mechanism that includes partial crystallization, coil-to-helix transition, hydrophobic association, and micelle packing, which serves as reversible physical cross-linking points to form a gel [33].

The most used products already available on the market are the vaginal odor control products, which are used to contain odor originating from the vaginal area, including odor during menstruation, urinary incontinence, or odor due to imbalance of bacteria. It has been estimated that only the global vaginal odor control product market will grow at a CAGR of 5.32% during the period 2018-2022.

Some of the commercial products based on hydrogels for vaginal applications available on the market are listed below.

- Replens® Long-Lasting Moisturizer contains a bioadhesive that allows it to attach to dry cells and deliver continuous moisture until those cells are naturally regenerated.
- Hyalo gyn® acts as a moisturizer due to the strong hydrating properties of HA derivative, Hydeal-D®. It adheres to the vaginal mucosa, enhancing the residence time, thus hydrating and protecting the tissue.
- ProHydrate® Complex is exclusive to Vagisil. This formulation contains a blend of moisturizers, including Hyaluronic Acid.
- Zestica Moisture™ is formulated utilizing two different lengths of HA molecules: i) shorter molecules of HA, which release water immediately for instant relief and ii) longer HA molecules, which gradually break down to deliver a second wave of moisture.
- Canesbalance Bacterial Vaginosis Gel is a triple benefit, 7-day treatment that relieves the symptoms of bacterial vaginosis infection: it helps to regulate the pH balance, which effectively relieves unpleasant odor and abnormal discharge, restricts growth of bad bacteria, and supports good bacteria (lactobacillus).
- Deligyn is indicated to combat the symptoms of irritation, dryness and itching of the vaginal mucosa with a special adhering formulation that guarantees the efficacy of the treatment.
- Elanee Intimate Hydrogel is a medical water-based lubricant with panthenol as additive. It moisturizes the skin and avoids the vagina drying out.
- SILOffGyn is a medical product in the form of a vaginal cream gel for the treatment of human papillomaviruses (HPV) or dryness. SILOffGyn creates a protective vaginal mucosa film that acts as a defense barrier and provides optimal conditions for the healing of HPV-induced epithelial micturition and dryness as a complementary therapy.
- RepHresh™ Vaginal Gel promotes the maintaining of natural pH using bioadhesive ingredients (Carbopol), staying in place for up to 3 days.
- pHemme revive Natural moisturizer using *aloe vera* extract and other natural ingredients, which help to maintain the natural moisture of the vagina such as sodium HA that penetrates the skin and gives immediate moisturizing relief.
- Vagisil® is one of the most diffused vaginal products. It works as a fast acting and long lasting treatment for the symptoms of dryness and helps to re-establish the natural moisture.

- Cervidil® (dinoprostone, 10 mg) is a vaginal insert approved to start and/or continue the ripening of the cervix in pregnant women who are at or near the time of delivery. Cervidil® should only be inserted by a trained healthcare professional in a hospital setting appropriate for childbirth.
- Metrogel Vagina® is the intravaginal dosage form of the synthetic antibacterial agent, metronidazole, at a concentration of 0.75%.
- Crinone® is a hormone delivery system to administer progesterone usually during fertility assisted procedures. When the gel is inserted into vagina, the progesterone is slowly released into the bloodstream throughout the day.
- Encare® is a vaginal contraceptive that releases nonoxynol-9 as spermicide directly in vagina.
- Conceptrol and Gynol II are two hormones-free contraceptives. They are based on the use of spermicides that act directly in the vagina.

Table 3. Hydrogel-based commercial products used in vaginal drug delivery.

Product	Company	Excipients	URL
Canesbalance BV Gel	Bayer AG	Methylhydroxypropyl cellulose	http://bit.ly/2ZhCaGG
Cervidil®	Ferring Pharmaceuticals Inc.	PolyEthylene Oxide	http://bit.ly/33OnJt0
Conceptrol® Gynol II	Caldwell Consumer Health	Sodium CarboxyMethyl Cellulose	http://bit.ly/2M6gG8p http://bit.ly/2B1NokV
Crinone®	Serono	Carbopol	http://bit.ly/2KO6dOo
Deligyn	Dermofarm S.A.	Carbomer	http://bit.ly/2YZYeGH
Elanee Intimate Hydrogel	Grünspecht Naturprodukte GMBH	Hydroxyethylcellulose	http://bit.ly/2KNyqDq
Encare®	Blairex Laboratories Inc.	Polyethylene glycol	http://bit.ly/2M7PIgA
Hyalo gyn®	Fidia pharma USA Inc.	Hyaluronic acid	http://bit.ly/2ZdTZSM
K-Y® jelly	Johnson&Johnson	hydroxyethyl cellulose	http://bit.ly/2KX6Gws
Metrogel Vaginal®	3M Pharmaceuticals	Carbopol	http://bit.ly/2Z9uffd
Miphil®	Sandoz	Hydroxyethylcellulose	http://bit.ly/2TLIjFW
pHemme® Revive	Aurium Pharma Inc.	Hydroxyethylcellulose	http://bit.ly/2KWULi9
RepHresh™ Vaginal Gel	Church & Dwight Co., Inc.	Carbopol	http://bit.ly/2ZcC5A0
Replens®	Church & Dwight Co., Inc.	Hydroxyethylcellulose	http://bit.ly/30mviVI
Vagisil®	Combe Inc.	Hyaluronic acid	http://bit.ly/2KGdteQ
Zestica Moisture™	Searchlight Pharma Inc.	Hyaluronic acid	http://bit.ly/2TIid6O

2.1.4 Transdermal delivery

During the last years, transdermal delivery has represented an attractive alternative to oral drug delivery. For a certain kind of drugs, transdermal delivery offers many advantages with respect to the most common oral administration. This route can be used when an oral administration is not feasible due to a poor absorption of the drug, or to a high first-pass effect, or enzymatic degradation in the gastrointestinal tract or liver, or when injections using hypodermic needles is not tolerated by the patients [34]. However, only a minority of drugs can be delivered by passive penetration into the skin. The skin is a very heterogeneous membrane, which has the role to impede the flux of toxins into the body and minimize the water loss. This results in a very low permeability to the penetration of foreign substance, and the stratum corneum, which is the external skin layer, is the main controller of the absorption. This layer, although it has a thickness of only 20-25 μm, is a very effective barrier toward the penetration of drugs and it constitutes the major problem to overcome in order to make this administration route effective [35]. Thus, the number of drugs that can be administrated by conventional patches is limited to those having a low molecular mass, high lipophilicity, and small required doses [36]. Even if the transdermal route of administration has been traditionally considered only for topical use to treat skin diseases, in recent years it has been considered also for systemic delivery of drugs [37]. In 1979 in the United States the first transdermal system for systemic deliver was approved. It consisted in a three-day patch for the delivery of scopolamine to treat sickness connected to motion. A decade later, the nicotine patches were launched on the market and became the first transdermal blockbuster, enhancing the visibility and the compliance of patients toward the transdermal patches. Since then, it was estimated that a new patch was approved on average every 2.2 years [38]. The most important events and dates associated to the transdermal drug delivery are reported in Prausnitz et al. [36, 38].

The conventional transdermal patches that have been marketed during the years can be divided into two main categories: the reservoir-type and the matrix type patches. The first kind are characterized by a complex design which provides the holding of the drug into a solution or a gel from which the deliver can be controlled by a membrane located between the drug reservoir and the skin. The latter kind is characterized by a simpler design in which the adhesive and mechanical properties of the formulation are combined and usually the rate of drug delivery is governed only by the skin permeability. The main advantage of the reservoir-type patches on the matrix-type is the flexibility of the formulation and the better control of the delivery rates [36]. After the success of patches on the market, it was realized that the skin enhancement permeability was necessary to enlarge the applications of transdermal delivery. This goal can be achieved by i) increasing the skin permeability by the rupture of the stratum corneum structure, or ii) providing an additional driving force for

the transport across the skin, and this has to be realized avoiding injury to the deeper living tissue [38]. These techniques can provide the use of [39]:

- **chemical enhancers:** they disrupt the highly ordered bilayer structures of the intracellular lipids in stratum corneum by inserting amphiphilic molecules or by extracting lipids using solvents and surfactants [40-42];
- **biochemical enhancers:** peptides have been examined as enhancers of skin permeability (magainin) [43] or enzymes (trypsin) [44];
- **iontophoresis:** it applies a continuous low-voltage current that provides an electrical driving force for transport [45, 46];
- **noncavitational ultrasounds:** they apply an oscillating pressure wave at high frequency that disrupt the stratum corneum lipid structure [47];
- **electroporation:** it uses short, high-voltage pulses to reversibly disrupt lipid bilayer of the skin, providing also an electrophoretic driving force that can persist for hours [48, 49];
- **cavitational ultrasound:** in this case the ultrasounds generate cavitation, which is the formation, oscillation and, in some cases, collapse of bubbles in an ultrasonic pressure field. The bubbles oscillate and collapse at the skin surface generating localized shock waves and liquid micro-jets at the stratum corneum surface enhancing the skin permeability [50];
- **microneedles and microneedle arrays:** they are minimally-invasive devices that painlessly by-pass the skin's stratum corneum. Microneedles pierce across the epidermis and increase the skin permeability creating micron-scale pathways into the skin and they can actively drive drugs into the skin using i.e. hollow microneedles [51, 52].

Hydrogels are being used for transdermal delivery in various forms such as patches or creams. They facilitate the skin permeation of drugs via skin hydration by a moisturizing effect and are suitable for topical applications. Furthermore, they have been studied as a means for stabilizing and improving transdermal delivery of other systems such as liposomes, micelles, and nanoparticles [53].

Some of the commercial products based on hydrogels for transdermal delivery available on the market are listed below.

- Clean & Clear® Persa-Gel® 10 Acne Medication is a unique formula that goes to work immediately, releasing the medicine deep into the pores where pimples start.
- Neutrogena® family (by Johnson & Johnson) are used to deliver several active ingredient in a cosmetic line containing hydrogels to control the delivery through the skin.

- Collagen Hydrogel Mask (by Skin Republic) is a serum mask that instantly restores moisture, elasticity and a healthy glow to the skin. The formula contains nutrient-packed sea minerals to nourish and hydrate.
- Astero® (by Gensco Pharma) is a FDA-cleared hydrogel plus topical anesthetic (containing Lidocaine HCl 4%) indicated for painful wounds such as ulcerations, pressure wounds, first and second degree burns, post-surgical incisions, cuts and abrasions.
- Voltaren Gel® and Voltadol® (by GlaxoSmithKline) and Flector® Patch (by IBSA Farmaceutici Italia) contain diclofenac, a nonsteroidal anti-inflammatory drug to reduce pain and inflammation.
- Lidoderm® (by Teikoku Pharma USA) was the first prescription, topical, hydrogel patch approved in the United States for post-herpetic neuralgia (PHN) in 1999. Lidoderm provides analgesia (without anesthesia) directly to the affected nerves delivering lidocaine.

Table 4. Hydrogel-based commercial products used in transdermal drug delivery.

Product	Company	Main constituent	URL
Astero®	Gensco Pharma	Polyethylene Glycol(PEG) 400	https://bit.ly/2GV67U8
Collagen Hydrogel Mask	Skin Republic	Collagen and Sodium Hyaluronate	https://bit.ly/2GVGoex
Flector® Patch	IBSA Farmaceutici Italia	Gelatine and carboxymethylcellulose	https://bit.ly/2NHPThJ
Lidoderm®	Teikoku Pharma USA	sodium carboxymethylcellulose	https://bit.ly/2EtPdbM
Neutrogena®	Johnson & Johnson	Hyaluronic Acid	https://bit.ly/2UjIwzH
Persa-Gel® 10	Clean & Clear	Carbomer, HPMC	https://bit.ly/2n9BfUk
Voltaren Gel®, Voltadol®	GlaxoSmithKline	Polyethylene Glycol(PEG)	https://bit.ly/2TqC8cJ

2.1.5 Ocular delivery

The eye is a very particular organ both from the anatomical and physiological point of view, since it contains several different structures, each with a highly specific function. For this reason, the design and the optimization of the ocular drug delivery systems have always been a very challenging task~~ing~~ for scientists [54]. The main obstacle that these formulations have to overcome is to bypass the protective barrier of the eye without causing permanent tissue damage [55]. The first problem to be solved is the drug loss from the ocular surface that is due to two main causes: the flow of lacrimal fluid, which removes the administered compounds from the eye surface, and the systemic absorption instead of ocular absorption, which takes place both in the conjunctival sac (due to local blood capillaries) or after the solution flow to the nasal cavity [56]. Corneal epithelium limits drug absorption from the lacrimal fluid into the eye since the most apical corneal epithelial cells form junctions that limit the drug permeation. However, trans-corneal permeation is the main mechanism of drug transport ~~form~~ from lacrimal fluid to aqueous humor. Moreover, the blood ocular barriers have to be

taken into account, both the anterior one, which is composed of the endothelial cells in the uvea that limit the transport of hydrophilic drugs into the aqueous humor, and the posterior one, between blood stream and eye that comprises the retinal pigment epithelium. An overview of the ocular barriers to anterior segment delivery and the methods to overcome these barriers using nanocarrier systems can be found in Bachu et al. [57]. Thus, factors affecting ocular bioavailability are: inflow and outflow of lacrimal fluids, absorption or interaction of drugs into lacrimal tissues, dilution with tears, and corneal barriers. Due to all these obstacles, topical application of a drug to the eye normally entails a loss of approximately 95% of the administered dose, which results in poor ophthalmic bioavailability [58-60]. Ideal properties of ophthalmic delivery systems are: good corneal penetration with prolonged contact time with corneal tissues, appropriate rheological properties, comfort and easiness of installation for the patient, and stability.

There are several possible routes of drug delivery into the ocular tissues depending on the target tissue. Usually, topical ocular and subconjunctival administrations are used for anterior targets and intra-vitreal administrations for posterior targets [56]. Topical ocular delivery is usually accomplished by eye drops or ointments, which account for approximately 90% of currently marketed ophthalmic pharmaceuticals due to their low costs, rapid drug action, ease of administration, and high acceptance by patients because they are not invasive [61]. Among their disadvantages, in addition to the scarce bioavailability, there is the short contact time on the eye surface that usually implies repeated administrations that can weaken the patient compliance [62]. The contact times can be prolonged by formulations design such as gels, gelifying formulations, hydrogels, nanoparticles, liposomes, and micelles [63]. Using the subconjunctival administration, the drug can bypass the conjunctiva–cornea barrier, giving direct access to the trans-scleral route [64]. Due to this, this route of administration has been often used clinically despite it is very invasive due to the repeated injections [62]. One of the most used devices for drug delivery into the conjunctival sac are the resorbable ones, which dissolve over the time releasing their drug content. These devices have the main advantage that they have not to be removed, even if usually they have a limited time of action (typically less than 24 h), requiring frequent administrations [61]. Concerning the drug delivery into the vitreous humor, this has the advantage to offer a direct access to the vitreous and retina, determining an immediate and increased therapeutic effect at the intended tissue. This delivery technique has been long used in therapeutics: since 1911 intravitreal injections were described to employ an intravitreal air bubble tamponading a retinal tear [65]. Moreover, being the humor itself a gel, primarily composed by hyaluronan, hydrogel-based release systems are perfect candidates for sustained intravitreal protein delivery, especially if they are designed to be biocompatible, injectable or rapidly in-situ forming, bioresorbable or biodegradable, and transparent [66]. Hydrogels have been approved for several ophthalmic applications since they offer several advantages compared to the traditional materials such as colloidal drug delivery systems or polymeric implants. Among these advantages, the mild preparation

conditions and the high water content are important features to preserve the activity of molecules such as peptides, nucleic acids, and proteins. Moreover, some kinds of hydrogels can be administered using less invasive methods compared to the use of long-term delivery implants, such as the temperature responsive or in situ crosslinked hydrogels [67]. These hydrogels can be administered in the sol-state into the human body and the gelation happens in situ.

Concerning the market of biopharmaceuticals for ophthalmic prescriptions, the global sales exceeded $8 billion in 2016 and is expected to reach $35.7 billion by 2025, with a strong growth in the next five years [68]. The global ocular drug delivery technology market was valued at 15 Billion of US dollars in 2016, and is expected to reach 25 Billion of US dollars by 2025, expanding at a CAGR of 5.81% from 2017 to 2025 [69].

Some of the commercial products available on the market are listed below.

- Hylo® Gel (by Candorpharm Inc.) ensures an intensive and lasting lubrication of the ocular surface to treat severe, chronic dry eyes. These highly viscous eye drops remain for considerably long times on the ocular surface.
- SYSTANE® Gel Drops provide lasting relief from dry eye irritation. They are a thicker eye drops formulation that creates a protective shield over the eyes.
- Clinitas Hydrate Eye Gel (by Altacor) is another formulation intended to relief the dry eye syndrome. The eye gel works to enhance the layer of your tear film, providing longer-lasting moisture throughout the day.
- Ocular Therapeutix™ is a versatile platform used to encapsulate ophthalmic pharmaceuticals within hydrogels to deliver sustained and therapeutic level of drugs to targeted ocular tissues (https://www.ocutx.com/about/hydrogel-technology/).
- Retisert® (by Bausch and Lomb) is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye for approximately 2.5 years.
- In 2014, The US Food and Drug Administration approved Iluvien® (by Alimera Sciences) for the treatment of diabetic macular edema to deliver 36 months of continuous, low-dose corticosteroid with a single injection.
- Restasis® (by Allergan) ophthalmic emulsion is indicated to increase tear production in patients whose tear production is limited due to ocular inflammation.
- Ocusert®, a pilocarpine ocular therapeutic system, is the first product marketed by Alza Corporation. It is used for glaucoma treatment and it is composed by a copolymer membrane in which the core is a drug reservoir dispersed into an alginic acid matrix.

- Lacrisert® and Vitrasert® (by Bausch and Lomb) are a prescription lubricant that is inserted into the eye to provide up to 24-hour relief from moderate to severe dry eye symptoms and the first intravitreal implant for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients, respectively.
- Ozurdex® (By Allergan) is a tiny implant for ophthalmic intravitreal injection that slowly releases corticosteroid medication over time, without the need for monthly injections. It dissolves naturally and does not need to be removed.
- Dexycu and Yutiq™ employ Verisome® technology (property of EyePoint Pharmaceuticals) to dispense a sustained-release of drugs using biodegradable formulations.
- I-vation intravitreal implant and sustained drug delivery system (by Surmodics, Inc.) have been proven to provide controlled long-term drug delivery into the posterior chamber of the eye.

Table 5. Hydrogel-based commercial products used in ocular drug delivery.

Product	Company	Main constituent	URL
Clinitas Hydrate®	Altacor	Carbomer	https://bit.ly/2GIlmz9
Hylo® Gel	Candorpharm Inc.	Sodium hyaluronate	https://bit.ly/2Gzopta
Iluvien®	Alimera Sciences	Polyvinyl alcohol and silicone adhesives	https://bit.ly/2DwpyyJ
I-vation	Surmodics, Inc.)	Poly(methyl methacrylate) (PMMA)	https://bit.ly/2GGDyc7
Ocusert®	Alza Corporation	Alginic acid	https://bit.ly/2E6y4FP
Ozurdex®	Allergan	poly (D,L-lactide-co-glycolide) (PLGA)	https://bit.ly/2GKGzbk
Restasis®	Allergan	Carbomer	https://bit.ly/2GAf44u
Retisert® Lacrisert® Vitrasert®	Bausch and Lomb	Silicone elastomer and polyvinyl alcohol membrane Hydroxypropyl cellulose Polyvinyl alcohol coating	https://bit.ly/2X4sNGy https://bit.ly/2GHVqU3 https://bit.ly/2UUZKmL
Systane®	Alcon	Polyethylene Glycol 400	https://bit.ly/2StjFfZ
Yutiq™	EyePoint Pharmaceuticals	polyvinyl alcohol	https://bit.ly/2Bz0xT3

2.2 Wound dressing

Wound healing is a complex process that includes the replacing of devitalized or missing cellular structure and tissue layers and it is strongly dynamic, since it involves several cell populations, the extracellular matrix, and the intervention of mediators (i.e. growth factors) [70]. It is a continuous process, which involves coordinated actions between different immunological and biological systems: the fact that different parts of a wound may be at different healing stage makes the wound treatment an interesting and challenging topic. Since a

complete and detailed description of the phases of wound healing and the factors affecting the process is beyond the scope of this work, the reader can refer to more specific literature [71-73]. Despite that, it is worth to mention properties that, if owned by the dressing used to treat the wound, can help during the healing process. First of all, keeping a wound moist rather than dry allows to heal more rapidly and with less chance of scarfs. Keeping away the wounds from mechanical stresses, which can cause the opening of the wound, and from the external environment, minimizing the danger of contaminations due to pathogens or foreign bodies is a common practice. Of fundamental relevance is to keep high level of oxygen tension on wound's surface, since oxygen is not only a key element in the reparative processes such as cell proliferation and synthesis of collagen, but even because it aids the generation of leukocytes, which are essential to kill bacteria [74]. An ideal wound dressing should contribute to maintain an appropriate temperature to promote the blood flow to the wound bed, it must be sterile, non-toxic, and non-allergic [75].

Due to the hydrogels' properties of maintaining a high moisture content at the wound site and simultaneously allowing the gas exchange between the wound and the external environment, of biocompatibility, of fast biological fluids absorption (i.e. of wound exudate), and of providing a cooling effect decreasing the temperature of the wound site, their applications in wound management have attracted both the academic and the industrial interests [2]. Moreover, due to hydrogels' softness and elasticity, they are easy to be applied and removed, making the dressing more comfortable and then attractive for patients. One of the main drawbacks in the use of hydrogels as wound dressing is that exudate accumulation can cause maceration and bacterial proliferation in the wound. Moreover, the low mechanical strength of hydrogels leads to a difficulty in handling [75]. When a new material is proposed to be used as wound dressing, the testing of its mechanical properties is of a fundamental relevance. It has to possess good tensile properties (tensile strength), since it has to bear the elongational stresses applied on the human skin. Tensile strength, which is defined as the ratio between the force necessary to break the sample and its cross-sectional area, and elongation at break, which is defined as the ratio between the length at breaking point and the initial one, can be easily measured using a texture analyzer. The polymer sample is held between two clamps positioned to a certain distance between them. Once the test is started, one of the clamps begins to move pulling the sample towards the top. The force and the elongation are measured at film broke [76].

In the wound care and healing, it is crucial to identify the correct needs of the injured part in order identify the material that most appropriately has to be used. Some examples of materials that are commonly used in wound care and commercial products available on the market are listed below [77].

Hydrocolloids: it is a wide class of materials, and they are usually used on burns, necrotic wounds, or under compression wraps. They can be used as powders or pastes of gelatin, pectine, or carboxymethylcellulose.

- 3M™ Tegaderm™ Hydrocolloid Dressing (3M Health Care) is a self-adhering product used on superficial wounds and abrasions, superficial and partial-thickness burns.
- Gentell CMC Fiber Dressing (Gentell Corp.) is a carboxymethylcellulose absorptive dressing for wounds with moderate to heavy exudate since gel-like substances support the moist healing process and minimize~~s~~ the risk of leakage and maceration.
- Comfeel® Plus Contour Dressing (Coloplast Corp.) is a butterfly-shaped hydrocolloid (mainly composed by carboxymethylcellulose) dressing for better conformity and adhesion, specially designed for difficult-to-dress areas.
- CovaWound™ Hydrocolloid dressing (Covalon Technologies, Ltd.) maintains an optimal moist wound environment and provides a high rate of moisture vapor transmission. Composed of an absorbent hydrocolloid matrix that has a hydrocolloid border laminated onto a breathable polyurethane film backing. It is indicated for the management of lightly exuding wounds such as: pressure, leg and foot ulcers, superficial partial-thickness burns.
- DermaFilm® (DermaRite Industries, LLC) is a hydrocolloid protective wound dressing for minor abrasions, closed surgical wounds, superficial pressure ulcers, and skin grafts.

Alginate: this type of dressings are used for moderate to high amounts of wound drainage, venous ulcers, packing wounds and pressure ulcers in stage III or IV.

- Ca-alginate dressing (Gentell Corp.) is a sterile, comfortable, advanced fiber-structured alginate with a highly absorbent capacity. Alginate dressings absorb, collect and contain exudate while providing a moist healing environment. It is intended for application in dry form on shallow wounds including leg, pressure, and diabetic foot ulcers and surgical wounds. May also be used for minor conditions such as lacerations, abrasions, skin tears and minor burns.
- Kaltostat® (Convatec) is a soft, sterile, alginate dressing that converts to a firm gel on contact with fluid. It may be used on moderate to heavily exuding wounds chronic and acute wounds.
- Algisite M (Smith & Nephew) is a calcium-alginate dressing which forms a soft~~,~~ gel that absorbs when it comes into contact with wound exudate. Algisite M may be used for the management of minor conditions such as lacerations, abrasions, skin tears, minor burns. Alginate fibers create~~s~~ a moist wound environment at the wound surface. This helps to prevent eschar formation and promotes an optimal moist wound environment. The dressing allows wound contraction to occur, which may help to reduce scarring and also allows gaseous exchange necessary for a healthy wound bed.
- NU-GEL™ Hydrogel (Systagenix) helps to create a moist wound healing environment and is indicated for debridement and desloughing of wounds together with the management of chronic wounds

591 throughout all stages of the healing process. The gel can be used to soften and hydrate eschar by
592 facilitating rehydration of the wound.
593 • Finally, it has to be mentioned Medihoney® Adhesive Dressings (Derma Sciences Inc.), which is
594 composed of a Calcium Alginate dressing impregnated with 100% *Leptospermum* or Manuka Honey.
595 This dressing provides wound fluid absorption capabilities and continuous donation of honey to the
596 wound bed, which has an antimicrobial effect. This dressing is for partial to full thickness wounds and
597 burns that are moderately to heavily draining.
598 **Collagen**: this dressings can be used for chronic or stalled wounds, ulcers, bed sores, transplant sites, surgical
599 wounds, second degree or higher burns and wounds with large surface areas. Collagen is a fibrous protein that
600 constitutes the extracellular matrix of human tissues, among them skin, tendons, and bones and it constitutes
601 about 25% of the total body proteins.
602 • Helix3-cm® (Amerx Health Care Corp.) is composed by 100% of bovine collagen and it is a thin, semi-
603 transparent dressing used to maintain a moist wound environment allowing a better observation of the
604 wound healing process.
605 • Condress (Smith & Nephew) is a dressing composed by pure equine collagen extract from horse
606 tendons and contributes to speed up the healing process of chronic skin wounds, even acute wounds.
607 **Miscellaneous**: this type of dressing is intended for painful wounds, necrotic wounds, pressure ulcers, donor
608 sites, second degree or higher burns and infected wounds.
609 • Cutimed® Gel (Bsn Medical Gmbh) is a clear, amorphous hydrogel (Carbomer 940) for the treatment of
610 necrotic and sloughy tissues in chronic wounds.
611 • Kendall™ Hydrogel Dressing (Cardinal Health) is indicated for use on light- to moderate-draining
612 wounds, first- and second-degree burns. It is characterized by a glycerin formulation which not dry out.
613 • Sofargel (Sofar) is used in the healing of abrasions, grazes, cut, first- and second-degree burns. It is
614 mainly composed by a hydrogel (Carbopol 974P) and allows to maintain the moisture content to
615 simplify tissue regeneration.
616 • Inadine™ (Systagenix) is PVP medication dunked in Polyethylene Glycol (PEG). It is indicated for the
617 treatment of ulcers, minor burns, and chronic wounds.
618 • Finally, it has to be mentioned in this compound class Amniomatrix®4 (Derma Sciences Inc.), which is a
619 cryopreserved liquid allograft derived from the components of the amniotic membrane and amniotic
620 fluid that provides structural tissue to advance soft tissue repair, replacement and reconstruction.

621 **Table 6. Hydrogel-based commercial products used in wound dressing.**

Product	Company	Main constituent	URL

Algisite M Condress	Smith & Nephew	Alginate Collagen	https://bit.ly/2D59yU6 https://bit.ly/2Spi0Hn
Amniomatrix®4 Medihoney® Adhesive Dressings	Derma Sciences Inc.	Amniotic membrane and fluid constituents Alginate	https://bit.ly/1Y5LrJw https://bit.ly/2DS648T
Comfeel® Plus Contour Dressing	Coloplast Corp.	Carboxymethylcellulose	https://bit.ly/2MM74yn
CovaWound™ Hydrocolloid dressing	Covalon Technologies, Ltd.	Hydrocolloids	https://bit.ly/2MPPRnB
Cutimed® Gel	Bsn Medical Gmbh	Carbomer 940	https://bit.ly/2G6kTXK
DermaFilm®	DermaRite Industries, LLC	Hydrocolloids	https://bit.ly/2WFfb4d
Gentell CMC Fiber Dressing Ca-alginate dressing	Gentell Corp.	Carboxymethylcellulose Alginate	https://bit.ly/2ScM6OX https://bit.ly/2BmLjAB
Helix3-cm®	Amerx Health Care Corp.	Collagen	https://bit.ly/2HQ0fwP
Inadine™ NU-Derm™ Hydrogel	Systagenix	Polyethylene Glycol Alginate	https://bit.ly/2S5YrEJ https://bit.ly/2HZ5mem
Kaltostat®	Convatec	Alginate	https://bit.ly/2RDyrey
Kendall™ Hydrogel Dressing	Cardinal Health	Glycerin formulation	https://bit.ly/2GqY7tf
Sofargel	Sofar	Carbopol 974P	https://bit.ly/2BhPSMu
Tegaderm™ Hydrocolloid Dressing	3M Health Care	Hydrocolloids	https://bit.ly/2StNlIU

2.3 Tissue engineering & scaffolds

Tissue engineering is a relatively new field that combines the use of living cells, biocompatible materials, and growth factors to create tissue-like structures. It is aimed to restore or improve tissue functions that are defective or that have been lost because of pathological conditions. The methods used by tissue engineering can be divided into three categories: (i) implantation of isolated cells or cell substitutes into the organism, (ii) delivering of tissue-inducing substances (such as growth factors), and (iii) placing cells on or within different matrices [78]. The last strategy is based on the implantation of living cells on a natural or synthetic extracellular substrate, or scaffold, in order to be implanted in living bodies. Scaffolds are three-dimensional porous solid biomaterials that are designed to fulfill one or more function, such as: i) to promote cell attachment, migration, and cell-biomaterial interactions; ii) to allow, through adequate porosity and interconnected channels, sufficient transport of gases, nutrients, and wastes [79] in order to guarantee cell survival, proliferation, and differentiation; iii) to biodegrade at a controlled rate that usually is the same of tissue regeneration at predetermined conditions; iv) to ensure the desired mechanical characteristics; v) protect cells from possible damages via external factors; and vi) to have a minimal degree of inflammation and toxicity [78, 80, 81]. A scaffold is ideally expected to function as a temporary extracellular matrix (ECM), capable of fulfilling various

biomechanical requirements, whilst being gradually resorbed and eventually replaced by host bone [82]. The first successful tissue-engineered skin products were produced in early 1980s but most scientists agree that modern tissue engineering started around 1987. Some historical highlights related to tissue engineering and its development are reported in Berthiaume et al. [80]. Nowadays, approximately 500 different companies are involved in tissue engineering field worldwide and the global scaffold technology market has been evaluated in 879 million of US dollars in 2018 and the prevision is 1063 in 2020 [83]. Among the companies related to three-dimensional cell culture consumables and instruments, BD Biosciences is the largest with a 27% of the market share, followed by Life Technologies (16%), Corning (11%), Sigma-Aldrich (8%), Lonza (6%), Insphero (4%), 3D Biotek (4%), and Global Cell Solutions (3%) [83]. The eventual pathway from a new scaffold idea to the final clinical application is long and expensive, often taking up to 10 years with a cost ranging from 10 to over 200 million of dollars [84].

The most important characteristics that the materials chosen as scaffold must have is the biocompatibility, in order to avoid undesired body reaction to the implant, such as reject, and to facilitate the cell attachment, and the biodegradability, in order to disappear after a certain time by degradation into nontoxic products [85]. Another fundamental issue that have to be considered is the micro- and macro-structure of the materials. Highly porous materials are desirable because large surface area promotes cell attachment and growth, because the diffusion of nutrients and wastes is facilitated, as well as the vascularization, which is particularly important in tissues and organs with metabolic functions. Of course, the pore size and the pore size distribution have a fundamental role in tissue engineering [86] and they have to be adapted depending of the scaffold application [63, 85], in order to facilitate the re-vascularization of tissues. Concerning the structure of a scaffold, not only the dimensions are a critical factor, but even the continuity of pores within the matrix. In fact, if the structure is highly porous but the channels are not interconnected, the mass transport (of nutrients, wastes, and cells) is inhibited, failing the scaffold role [87]. Moreover, scaffolds necessitate to have the mechanical strength necessary to maintain its structure after the implantation, especially for application in tissues such as bones or cartilages and they have to guarantee a good processability, particularly when the final shape of the implanted scaffold has an influence on its activity [85]. Three different categories of scaffold applications can be identified: i) space filling agents; ii) bioactive molecule delivery; and III) cell/tissue delivery [88].

Hydrogels are materials commonly used in tissue engineering field because of their biocompatibility, degradability, processability under mild conditions (which facilitate the entrapment of viable cells), their mechanical and structural properties comparable with many tissues and ECM, and the possibility to be delivered in a low-invasive way [88]. Different applications of hydrogels can be found in literature related to regenerative medicine, such as scaffold for cellular organization, tissue barrier against restenosis, bioadhesives,

drug reservoir, matrix to deliver bioactive agents encouraging the natural reparative process, or to encapsulate and deliver cells [89-93]. The ECM is a complex network structure surrounding and supporting cells of natural tissues and it constitutes also a bioactive and dynamic environment that mediates cellular functions [94]. Thus, it is highly desirable to produce scaffolds that mimic both the structure and the bio-functions of the natural ECM. One of the prerequisites necessary for the cell growth process is the cell attachment to the ECM to allow cells proliferation and migration. It has to be considered that these functions last until the degradation of the polymer is complete. Thus, if the biodegradation is faster than the tissue regeneration, the scaffolds will lose their carrier function for cell growth; on the other hand, if the biodegradation is too slow compared with tissue regeneration, the scaffolds will impede tissue regeneration. Therefore, scaffolds' critical design factors are the degradation rate of the polymer and the transition of the functions between the scaffold and the emerging tissue. It has to be kept in mind that not all the tissue engineering applications require a complete degradation of the scaffold but in some cases, such as articular cartilage or corneal replacement, a permanent scaffold may be the better choice. Hydrogels have unique characteristics, such as hydrophilicity, biocompatibility, and the ability to modify the drug release rate by controlling the swelling and degradation rate with external stimuli, which make them perfect candidates to act as carriers for controlled release of bioactive molecules or drug depots. For this reason, to mimic the function of ECM as reservoir of growth factors, a class of proteins or polypeptides that contributes to cell functions such as differentiation, migration, proliferation and gene expression, they have been incorporated in hydrogel based scaffolds [94]. Using the combining of tissue engineering and drug delivery functions, the same system may be able to regulate cell response and tissue formation.

Hydrogels commonly used for scaffold production can be i) natural, such as proteins, polysaccharides; ii) synthetic, both non-biodegradable (PHEMA, PVA) and biodegradable (PEG, synthetic peptides); or iii) hybrids (complex hydrogels deriving from a combination of polymers) [94, 95].

Alginate. Alginate is a brown-algae-derived polysaccharide composed of β-D-mannuronic acid and R-L-guluronic acid units. By the addition of divalent cations, alginate solutions rapidly form ionotropical gels that have been found extremely interesting for applications in biomedical field. It is commonly used as microcarriers for cell encapsulation [96, 97]. Since alginate does not have cell-interactive properties and does not mimic the natural ECM, it can be found combined with other hydrogels, cell-interactive peptides, or growth factors that can be attached to the alginate backbone [98]. Moreover, alginate semi-interpenetrating polymer networks can be successfully used in biomedical applications, mainly due to the combination of the properties of the constituting materials that allows to overcome the disadvantages of a single polymer network, providing better thermal stability, mechanical and chemical resistance [99, 100]. Thus, alginate can be found combined with elastine and angiogenic factors for reconstruction of blood vessel, with agarose, hyaluronic acid, and growth

factor for cartilage repair applications, with chitosan for liver repair applications [98]. A review of the use of alginate hydrogels in culturing 3D cells can be found in [101], one of the most used alginate-based commercial product for 3D cell culture is AlgiMatrix® (by Thermo Fisher Scientific).

Hyaluronic Acid. Hyaluronic acid (HA) is naturally occurring as glycosaminoglycan (GAG) and it is present in all the vertebrates. It is a major constituent of the ECM, in example it can be found in the vitreous humor of the human eye, in skin, in cartilage, in synovial joint fluid, and in the matrix produced by the cumulus cells around the oocyte prior to ovulation [102]. However, high molecular weight HA is a natural barrier for angiogenesis and proliferation, thus, to allow cellular infiltration and remodeling of the material by cells, HA can be crosslinked with protease-degradable peptides and modified with cell adhesion ligands [103]. HA-based polymers has been used as cell carriers for tissue engineered repair of bone and cartilage or their regeneration, in central neural tissues engineering for nerve and brain repair, in soft tissue repair and smooth muscles engineering [102].

- Hyalograft® (Anika Therapeutics, Inc.) is a minimally invasive tissue engineering approach, consisting in the implantation of expanded autologous chondrocytes grown on a three-dimensional HA-based scaffold, useful in treatment of acute cartilage lesions [104]. This technology has been recently resumed to produce solid HA-based treatments, including Hyaloglide®, a transparent, highly viscous barrier gel used to prevent or reduce adhesions after various surgical procedures; Hyalonect®, a bio-resorbable knitted mesh used in orthopedic and trauma reconstructive surgeries composed of Hyaff® (HA crosslinked by esterification with benzyl alcohol); and Orthovisc-T®, an ultra-pure, high molecular weight injectable hyaluronic acid (HA) designed to relieve pain and restore function to tendons damaged by chronic tennis elbow.
- Gel-One® Hyaluronate (by Zimmer Biomet) is an injectable hyaluronate gel approved for the treatment of osteoarthritis of the knee.

Collagen. Collagen is the most abundant protein in the human body, nearly 30% of all proteins. During tendons and ligaments healing, cells that usually produce collagen of normal intact tissues are induced to synthesize different types of collagen at the repair site [105]. Since the role of collagen is of fundamental relevance during the natural healing processes, this has been extensively used as support material, particularly for tendon and ligament repair [106]. Concerning the commercial products used in this area, the most famous are:

- Graftjacket™ (by Wright Medical), which is derived from human dermal collagen matrix and it is freeze-dried with a proprietary process that prevents the formation of ice crystals to preserve the intact matrix including vascular channels.

- The Restore™ Orthobiologic Soft Tissue Implant (by DePuy, Inc.) is a round device, manufactured from 10 layers of Small Intestine Submucosa (SIS), a biomaterial derived from porcine small intestine and it is composed mainly of water and collagen.
- The Zimmer® Collagen Repair Patch (by Zimmer) is a biological implant consisting of an acellular scaffold of collagen and elastin, derived from porcine dermal tissue. In tensile tests, the Zimmer Collagen Repair Patch was shown to withstand a significantly larger load than SIS patches.
- Permacol™ (by Tissue Science Laboratories) surgical implant is a porcine dermal collagen implant from which cells, cell debris, DNA and RNA are removed in a gentle process that is not damaging to the 3D collagen matrix. The resulting acellular collagen matrix is then cross-linked for enhanced durability.
- TissueMend™ Soft Tissue Repair Matrix (by Stryker Orthopaedics) is an acellular, collagen membrane used to repair and reinforce soft tissues where weakness exists. It is composed of native collagen, non-denatured, from fetal bovine dermis.
- The OrthADAPT™ Bioimplant is a biocompatible, stabilized, terminally sterilized collagen scaffold launched from Pegasus Biologics, Inc., in order to improve the repair and reconstruction of soft tissue in musculoskeletal procedures.
- Alloderm® Regenerative Tissue Matrix (RTM) (by BioHorizons) is an acellular dermal matrix for soft tissue applications, containing undamaged collagen and elastin matrices.
- Apligraf® (by Organogenesis) consists of living cells and structural proteins. The lower dermal layer combines bovine type 1 collagen and human fibroblasts (dermal cells), which produce additional matrix proteins.

Other polymers commonly used as scaffolds are:

- poly(glycolic acid) (PGA) that can be used in applications such as synthetic suture (Dexon™ by Medtronic) or bone internal fixation devices due to its good mechanical properties.
- Poly(lactic acid) (PLLA) is used in orthopedic fixation device, such as SmartPin® and Bio Mini-Revo® (by Conmed), which are resorbable orthopedic pin and screw-in implants, respectively, Bio-Anchor® (by Conmed) for shoulder repair intervention; Biocryl® and Milagro Advance Interference screw (by De Puy) used in cruciate ligament reconstruction.
- Poly(lactide-co-glycolide) (PLGA) is used for resorbable sutures (Vicryl® by Ethicon Inc.) due to its high degradation kinetics.
- Polyethylene glycol (PEG) can be used in surgical procedures, such as Veriset™ Hemostatic patch by Medtronic; a PEG ester solution and a trilysine amine solution are constituent of DuraSeal®, a synthetic absorbable surgical sealant by Integra.

766 **Table 7. Hydrogel-based commercial products used in tissue engineering applications.**

Product	Company	Main constituent	Application	URL
AlgiMatrix®	Thermo Fisher Scientific	Alginate	Cell culture	https://bit.ly/2UF71Hg
Alloderm® Regenerative Tissue Matrix	BioHorizons	Collagen and elastine	soft tissue applications	https://bit.ly/2SqFPhP
Apligraf®	Organogenesis	Collagen and fibroblast	Living cells and structural proteins to produce matrices	https://bit.ly/2TuaHvd
Biocryl® Milagro Advance	De Puy	Poly(lactic acid)	cruciate ligament reconstruction	https://bit.ly/2HZbUts https://bit.ly/2t6Icbw
Dexon™ Veriset™ Hemostatic patch DuraSeal®	Medtronic	poly(glycolic acid) Polyethylene glycol Polyethylene glycol	synthetic suture or bone internal fixation devices Hemostatic patch absorbable surgical sealant	https://bit.ly/2t6KJTc https://bit.ly/2RAH7lX https://bit.ly/2MQFOhX
Gel-One® Hyaluronate	Zimmer Biomet	Hyaluronic acid	Osteoarthritis of the knee	https://bit.ly/2Sq79Nm
Graftjacket™	Wright Medical	Collagen	preserve the intact matrix including vascular channels	https://bit.ly/2HRXvyT
Hyaloglide® Hyalonect® Orthovisc-T®	Anika Therapeutics, Inc.	Hyaluronic acid	Cartilage lesions Reduce adhesions after surgery Restore function of tendons	https://bit.ly/2G9pEQy https://bit.ly/2GbWAaQ https://bit.ly/2DUkmGh
OrthADAPT™ Bioimplant	Pegasus Biologics, Inc.	Collagen	Repair of soft tissue in musculoskeletal procedures	https://bit.ly/2SmtVWv
Permacol™	Tissue Science Laboratories	Collagen		https://bit.ly/2GlxPbD
Restore™ Orthobiologic Soft Tissue Implant	DePuy, Inc.	Collagen and water	Orthopedic tissue	https://bit.ly/2SpE7gJ
SmartPin® Mini-Revo® Bio-Anchor®	Conmed	Poly(lactic acid)	resorbable orthopedic pins shoulder repair intervention	https://bit.ly/2BfIO2Y https://bit.ly/2BjFfIW https://bit.ly/2t0YBye
TissueMend™	Stryker Orthopaedics	Collagen	Soft Tissue Repair Matrix	https://bit.ly/2UGETDQ
Vicryl®	Ethicon Inc.	Poly(lactide-co-glycolide)	resorbable sutures	https://bit.ly/2MOh4Hl
Zimmer® Collagen Repair	Zimmer	Collagen and	Rotator Cuff Tendon	https://bit.ly/2HM0LMe

Patch		elastine	Repair	

2.4 Contact lens

The first time that a corneal lens (or rigid lens) was developed dates back to 1948, when, starting from a laboratory error, an optical technician tried to wear in his own eye only the corneal portion of a PMMA scleral lens and he found that the lens could be tolerated by his eye. This discovery led to the first patent in the same year [107]. The attempts to improve the wearability and the performances of contact lenses grew during the years, but the turning point was achieved by Otto Wichterle, who produced, although discouraged by his superiors, soft lenses composed of hydroxyethyl methacrylate (HEMA). The patent [108] to produce commercially soft contact lenses was acquired by Bausch&Lomb in 1972. Since then, the market of contact lenses started to proliferate. Since the first uses of contact lenses, it appeared evident that the physiological response of the eye would have been improved by using materials more permeable to oxygen and with a reduced absorption of proteins, lipids, or other teats' constituents. The following turning point in the improvement of contact lenses was the incorporation of silicone into the basic PMMA structure, which led to the birth of a new family of polymers for contact lens applications, the so called silicone acrylates (1974). Actually, the most significant advance in contact lenses development since the introduction of HEMA has been attributed to the launch on the market of two spherical-design silicone hydrogel lenses by CIBA Vision (with the product Focus Night & Day®) and Baush & Lomb (with the product Purevision®) in 1998. In 2001 lenses manufactured from silicone hydrogel materials were introduced into the US market and, since then, their prescribing has reached a peak of 73% of all soft lenses, remaining at this level up to 2014 [109].

Being the ocular environment very sensitive to the external stimuli, the hydrogel based biomaterials used to produce contact lenses must have specific properties, such as: be permeable to oxygen and to ions, in order to ensure the corneal metabolism and the on-eye movement, respectively, be comfortable, hydrolytically stable, biologically inert, and allow a clear and stable vision maintaining a continuous tear film on the eye [110]. In order to obtain a high visual performance, the hydrogel selected as contact lens material needs to be transparent. This characteristic is usually expressed as the percentage of transmission of the visible electromagnetic spectrum. Thus, hydrogels suitable to be used as contact lens materials have to transmit at least 90% of visible light. The loss of transparency of a hydrogel is usually due to a phase separation of water that can be caused in example by temperature, thus the storage and handling of these products should be accurate. The mechanical properties of contact lens materials are fundamental since they determine the comfort, the durability, and the handleability of the product. It has to be highlighted that the mechanical properties of hydrogels are not easy to be measured, due to the hydrophilic nature of the polymers and to the

large amount of water contained in their network [23]. In fact, any deformation applied to a hydrogel involves the redistribution of water inside the network affecting the characteristics of the sample, which could result different from those of the material used during the final application [111]. In general, the strength of a hydrogel is measured in order to evaluate its resistance during handling and the elastic modulus in order to evaluate the deformability of lenses and their fitting characteristics in human eyes. Surface characteristics of contact lens materials directly affect the interaction with eyes and the surrounding tear films, which means that affect the biocompatibility with the ocular environment. Surface properties include friction, wettability, and surface water contact. Friction happens when two surfaces slide against each other, and this sliding causes the wear of one or both the surfaces. In order to prevent the wear of the surfaces, it can be provided a lubrification process. Wettability is a characteristic of a fluid that is spread on a solid surface. To enhance the comfort of contact lens, materials have been modified in order to reduce friction by increasing lubricity of the surface (i.e. adding wetting agents) [112]. Studies suggested that hydrogels having lower modulus, higher oxygen transmissibility to the cornea, and higher equilibrium water content were preferred by patients in terms of comfort [113-115]; even if it has to be considered that *in vivo* hydration levels can be influenced by lens thickness, osmolarity, size of the palpebral aperture, or environmental conditions [116]. Thus these properties are fundamental, since the first reason leading patients to the discontinuation of the use of contact lens is discomfort (about 50%), followed by vision problems (about 10%) and difficulty of handling (about 5%) [117]. In order to combine the characteristics of softness, wettability, and comfort of the conventional hydrogels with the high oxygen transmission of siloxanes and fluorosiloxane, a new class of materials, called siloxane hydrogels, have been introduced [118, 119].

Concerning the commercial products currently available on the market, they have been proliferated during the years. Among them, it can be found:

- Avaira® and Biofinity® (Coopervision Inc.) are both composed of N-vinylpyrrolidone (NPV) with viscosity modifying admixture (VMA) in order to increase comfort and stability to the lens.
- Coopervison launched in the market the MyDay® contact lenses, with the Smart Silicone™ technology, which allows to deliver oxygen to the eyes much more efficiently using less silicone. This results in softer lens and allows more room in the lenses for other components to improve the hydration of eyes.
- Based on the use of silicone hydrogel are the PremiO lenses (by Menicon), product of Japanese research to optimize the delivery of oxygen to the eye using very permeable materials.

As mentioned above, the siloxane-based materials are extensively used to produce contact lenses, some examples are:

- Dailies Total1 (by Alcon), having a water content that ranges from 33% at the core to over 80% at the surface, and at the outer surface reaches almost 100%, nearly the same as the surface of the

cornea. Moreover these lenses allow oxygen to freely flow resulting in the highest oxygen transmissibility of any daily contact lens on the market.

- Moreover, Alcon produces Air Optix® Aqua contact lenses, characterized by SmartShield Technology, which is a surface technology for moisture retention and consistent comfort, based on plasma iconicity modification. This allows to retain moisture and to limit cholesterol sorption and deposits to increase the lenses comfort.
- Finally, it has to be mentioned the first selling contact lenses brand in the world: Acuvue Oasys®, produced by Johnson & Johnson. It is characterized by the wetting technology called Hydraclear® Plus technology, which stabilizes the tear film promoting comfortable wear.

Table 8. Hydrogel-based commercial contact lens.

Product	Company	Main constituent	
Acuvue Oasys®	Johnson & Johnson	siloxane-based materials	https://bit.ly/2UIEBMs
Avaira® Biofinity® MyDay®	Coopervision Inc.	N-vinylpyrrolidone and viscosity modifying admixture silicone hydrogel	https://bit.ly/2GcYgkq https://bit.ly/2tFtsDy https://bit.ly/2GwSnOi
Dailies Total1 Air Optix® Aqua	Alcon	siloxane-based materials	https://bit.ly/2HV9UlN https://bit.ly/2GeAlRA
Focus Night & Day®	CIBA Vision	silicone hydrogel	https://bit.ly/2HYUZqK
PremiO lenses	Menicon	silicone hydrogel	https://bit.ly/2SwGxKC
Purevision®	Baush & Lomb	silicone hydrogel	https://bit.ly/2t6ArCx

2.5 Hygiene

Hygiene products based on hydrogels include disposable diapers, sanitary pads, and adult protective underwear for incontinence. Among the different products, disposable diaper is the largest consumer of superabsorbent polymers (SAP), which are extensively used to absorb fluids. Superabsorbent materials are three-dimensional cross-linked polymers (linear or branched) able to absorb and retain heavy amounts of liquids due to their excellent hydrophilic properties. They are characterized by a high swelling capacity, and they are capable to absorb water (or biological fluids) up to 1000 times their weight [120]. The main advantages in the use of these polymers are that they are able to hold moisture away from the skin, promoting its health, preventing diaper rush and colonization of germs, and reducing the risk of fecal contaminations, and potential spread of gastrointestinal infections [121].

Since the 1970s, diaper technology has been of great commercial interest, and about 1000 patents have been published for last 25 years on the construction and design of diapers. Japan started the first commercial

production of hydrogels in 1978 for use in feminine napkins, and later in 1980, Germany and France started using them in baby diaper [122]. The use of SAP in diaper industry was proposed in 1982 in Japan reducing the size of diapers (of about 50%) and improving the retention performances, reducing the leakage values below 2% [123]. Nowadays, the most common polymers used as superabsorbent materials are based on cross-linked synthetic polymers, such as acrylic acid and its copolymers with acrylamide. On the market of the hygiene products cellulose-derived materials containing polymeric particles, which can be synthetic, such as polyacrylates, sulfonated polystyrene, poly(vinyl alcohol, or natural, such as carboxy-alkyl cellulose, gum, carboxy-alkyl starch, or cellulose sulfate, are very common. The final characteristics of the superabsorbent polymer can vary significantly depending on its composition: i.e. the maximum absorbency of natural materials (such as cellulose or protein based materials [124, 125]) ranges from 10 to 100 g water /g material, which is far less than that of commercial synthetic polymers (∼1000 g/g) [120].

One of the major drawbacks in the use of diapers is the production of solid wastes. In fact, it has been reported [122] that a child till the age of 30 months using disposable diaper creates about 1092 m^3 of garbage per year. Disposable diapers are the third largest single consumer item in landfills, and represent about 4% of solid waste. In a house with a child in diapers, disposables make up 50% of household waste [126]. Thus, many attempts have been taken to make reuse of the items like disposable diapers, napkins, hospital bedsheets, sanitary towels, and other similar products. The recycling of such complex products is performed separating ingredients for further uses, in fact the cellulosic part is recyclable and biodegradable. This process is tedious and not efficient, thus it made scientists to think alternatively, using ingredients completely biodegradable. Novel types of hydrogels, containing sodium carboxymethylcellulose (NaCMC) and hydroxyethyl cellulose (HEC) cross-linked with divinyl sulfone (DVS), can swell like SAPs, and exhibit high water retention as a result of the capillary effects [127].

Concerning the commercial products containing SAPs, it has to be considered that Pampers (owned by Procter&Gamble) and Huggies (from Kimberly–Clark) are the two most widely used disposable diaper brands, with about 35% and 22% global market share, respectively [123]. Moreover, the global feminine hygiene products market, forecasted to be worth 38,000 million of US dollars by 2026 end, is expected to increase at a CAGR of 6.9% during the period 2018-2026.

- Aqua Keep (Sumimoto Seika Chemicals Co. LTD.) is a superabsorbent polymer which holds water within molecular chains and retain the water even under pressure. It is composed mainly of sodium polyacrylate with high content of COO^- and Na^+ ions. The difference between the ionic content inside the polymer and the external environment determines the intensity of the osmotic pressure and, consequently, of the amount of water absorbable.

- HySorb® (Basf) portfolio offers different kinds of products, among them it has to be mentioned HySorb® Biomass Balanced, superabsorbent obtained from renewable feedstock like biogas or bio-naphtha that can be derived from organic waste or vegetable oils, and Saviva®, obtained by a new technology of droplet polymerization, which forms a pathway for a quick liquid distribution thanks to a system of fine capillaries that allows an homogeneous swelling behavior.
- Ultrasorbs™ AP Premium Drypad (Medline Industries Inc.) are air-permeable drypads that feature a patented, SuperCore® absorbent that draws in moisture, locks it away from the skin and feels dry to the touch in just minutes.
- Sanwet (Sanyo Chemical Industries Ltd.) is the evolution of the first SAP appeared on the Japanese market for hygiene applications and it is characterized by two features: the controlled absorption speed and the improved-permeability of swollen gel.
- HI-SWELL™ (Songwon Industrial Co. Ltd) exhibits quick and high water absorbency and an excellent stability to heat and light.

Table 9. Hydrogel-based commercial products used in hygiene applications.

Product	Company	Main constituent	URL
Aqua Keep	Sumimoto Seika Chemicals Co. LTD.	sodium polyacrylate	https://bit.ly/2t7tAJ1
HI-SWELL™	Songwon Industrial Co. Ltd	SAPs	https://bit.ly/2Ge9S6K
Huggies	Kimberly–Clark	SAPs	https://bit.ly/2DbtVPe
HySorb® Saviva®	Basf	superabsorbent obtained from renewable feedstock	https://bit.ly/2BkN3u8 https://bit.ly/2WHlVyF
Pampers	Procter&Gamble	SAPs	https://bit.ly/2MRYsGs
Sanwet	Sanyo Chemical Industries Ltd.	SAPs	https://bit.ly/2SyWX5b
Ultrasorbs™ AP Premium Drypad SuperCore®	Medline Industries Inc.	SAPs	https://bit.ly/2UNXxtr

2.6 Fillers

Although the concept of filler injections to adjust facial soft tissue defects has been introduced since the 19th century (Neuber in 1893 was the first physician who transplanted fat from arms into facial defects [128]), it has been only 30 years since the introduction of the first Food and Drug Administration-approved filler material, the bovine collagen [129]. After that, the researches and studies in this field have been proliferated and, nowadays, there are over 35 major filler producer companies worldwide. It has been

evaluated that global dermal filler market will surpass USD 8.5 billion by 2024 and is set to 5.8% of CAGR in 2017 according to a new research report by Global Market Insights Inc., probably due to world population aging looking for anti-aging and wrinkle treatments [130]. According to the International Society of Aesthetic Plastic Surgery (ISAPS), the number of non-surgical cosmetic procedures has increased by around 9% annually in 2017. Biodegradable fillers segment held largest market part (around 88%) in 2017 due to safety offered by this type of fillers and to the fact that complications related with their use disappears spontaneously, since they are biodegradable substances that are eventually metabolized by the body, usually in a period ranging from months up to one year. Biodegradable fillers can be divided into two main classes, according with their duration into the human body: the nonpermanent fillers, such as collagen or hyaluronic acid, and the semipermanent fillers, such as polylactic acid and calcium hydroxylapatite [131]. Among hydrogels, the most used as filler in cosmetic industry are, undoubtedly, bovine collagen and hyaluronic acid, both belonging to the biodegradable fillers category, and polyacrylamide hydrogel filler, which is a non-biodegradable filler with long lasting effects. The physical properties of fillers determine their unique characteristics and, then, they define the potential application in cosmetic soft tissue and dermal correction. Among these properties, it has to be evaluated the gel hardness or, in general, the rheological behavior of the filler since this property affects the flow of the gel passing through a syringe and, when it is released and restored, it gains its viscoelastic state. Thus, the gel hardness influences both the structure and the stiffness of the filler. Gels with higher stiffness can provide a better support in facial muscles and they better resist to the dynamic forces acting during their movements. On the other side, gel with low modulus better suits the use in areas with static and superficial wrinkles, where the mechanical resistance is not a critical factor. The particle size within the gel determines the volume filling once it is injected, which means, from a clinical point of view, the degree of correction that can be realized. Moreover, this parameter has to be checked after the production because the particles size has to be able to pass through the syringe's needle during the intervention avoiding pain, bleeding, or edemas. The hydrogel concentration in the filler determines the longevity and the stability of the correction intervention [132]. Usually, the filler concentration provided by the manufactures includes both cross-linked gels and a fluid component of the hydrogel. This latter one is easily metabolized by the human body and does not contribute to the duration and effectiveness of the product [133]. The swelling degree of a filler depends on whether the filler has reached the equilibrium state for bound water, and this depends on the gel characteristics. Thus, hydrated and equilibrium gels have already reached their hydration capacity and they do not swell when injected, non-equilibrium gels, on the contrary, tends to swell post injection, thus this behavior has to be considered before the application.

Collagen. Bovine collagen was the first kind of filler approved by FDA for the use in aesthetic treatments. Bovine collagen is resorbable, and it has been used in soft tissue augmentation with a duration effect of less

than 6 months. It has to be considered that collagen is the major structural component of the dermis and it has a fundamental role in providing strength and support to human skin [128]. However, the possibility to develop an allergic reaction to the use of collagen involves many people, since the injected collagen material can be detected by body as a foreign substance and degraded by collagenases and inflammatory cells [134]. In 2003, FDA approved human-derived bioengineered collagen implants [135]. These implants are composed by collagen derived from bioengineered human fibroblasts cultured in a bioreactor simulating the human body and screened for viral and bacterial pathogens. Thus, since the collagen source is human and does not contain animal-derived products, allergy test before using these implants are not necessary. Other two types of collagen have to be considered: the collagen fibers (and extracellular matrix) derived from human cadaveric tissues and the autologous collagen, which is produced from a patient's own skin. These products have lost interest in the market once the bioengineered collagen was launched.

The most famous collagen types available are:

- Zyderm® I and II (by Collagen Corporation), and Zyplast®, both of bovine-origin, are usually the less expensive but the risk of allergic reaction is higher.
- Cross-linked porcine collagen is on the market under the name of Evolence® and Evolence Breeze® (by Johnson & Johnson). These were used in the treatment of acne scars but the manufacturer company announced the products' retirement.
- CosmoDerm® and CosmoPlast® (by Allergan) are both human-derived collagen products, and they are used for the treatments for smoothing wrinkles, filling furrows (deep wrinkles) and restoring the border of the lip.
- Isolagen® (by Isolagen Europe Ltd.) is an autologous cell therapy that uses the patient's own fibroblasts to correct defects, including wrinkles and scarring.
- Autologen® (by Autogenous Technologies) is made of human dermis from skin using a laborious process for harvesting.
- To avoid complex procedures, Dermologen® (by Collagenessis Inc.) was developed. This is identical in structure and substance to the previous one, but it is obtained, rather than using autologous skin, from a cadaveric source [136].

Obtained from a cadaveric source are:

- Cymetra® (AlloDerm, LifeCell Corporation), composed by micronized human cadaveric dermis,
- Fascian® (by Biosystem), composed by human cadaveric fascia [137].

An hybrid product, Artefill® (known in Europe as Artecoll®), is a mixture of bovine collagen and homogeneous polymethylmethacrylate microspheres, which not only help to maintain the desired results much longer, but also to stimulate natural collagen production.

Hyaluronic acid. Hyaluronic acid (HA) segment accounted over USD 4.5 billion in 2017. It is commonly adopted by elderly people to correct facial lines and reduce wrinkling. After Botox, hyaluronic acid is the most common non-surgical cosmetic procedure in the U.S. because of the large number of approved products, and the low risk of complications. Moreover, HA fillers have the advantage over collagen of being instantly reversible by the application of hyaluronidase. HA was discovered by Karl Meyer and his assistant John Palmer in 1934 [138].It is a glycosaminoglycan disaccharide, which exists naturally in the body. HA fillers can be derived both from animal or bacteria sources. HA products differ from the collagen products since they do not contain local anesthetic. This, combined with their increased viscosity compared to collagen, can result in more discomfort with injection [134]. Although its properties well fit the necessities of a dermal filler, at the beginning its use was seriously limited because of its rapid degradation in biological tissues. Later, its performances have been highly improved by the cross-linking procedure that stabilizes and prolongs its duration over the time, making HA competitive on the market. Each company uses different cross-linking chemicals to obtain its product but all of them have in common the fact that they can be irritating or toxic for the skin, thus one of the fundamental step of the filler production process is the purification [138].

- Restylane® and Perlane® products (by Q-Med and distributed by Medicis Aesthetics) are non-animal stabilized hyaluronic acids (NASHAs), or rather, of bacterial origin (they are derived from cultures of *Streptococcus equi*). Both of them are cross-linked with butanediol diglycidyl ether (BDDE). Restylane® was the first non-animal stabilized HA approved in the United States in 2003 [132], Perlane® was approved later, in 2007. The only difference between these two products is the particle size: the largest fraction of gel particles for Perlane is between 940 and 1090 μm, whereas the largest fraction for Restylane® is between 250 and 500 μm [138].
- Juvéderm™ family products are manufactured by Corneal and distributed by Allergan. They are non-particulate forms of NASHAs, cross-linked with BDDE and they were approved by FDA in 2006. According to the producer, these products feature a crosslinking process called Hylacross®, which produces a softer, more viscous gel which is intended to enhance durability, in fact is has been demonstrated that this fillers last up to 12 months [131].
- Elevess® (by Anika Therapeutics) is cross-linked with biscarbodiimide (BCDI) and was approved by FDA in 2006. It is based on chemically modified non-animal HA proprietary technology which incorporates 0.3% lidocaine and the concentration of HA in this product is the highest available on the market.
- Captique™, Prevelle Silk®, and the Hylaform® family are all manufactured by Genzyme and use divinyl sulfone (DVS) as cross-linking agent. Hylaform® was the first HA developed for dermal filling: released in Europe in 1996, it was FDA approved in the United States in 2004. Despite Captique™ and Prevelle

Silk® are bacterial-based HA, Hylaform® and Hylaform Plus® are avian-derived, from the body of rooster combs. The duration is estimated to be 4-5 months [136].

Since the market demonstrated repulsion towards the animal-based products, NASHAs are currently the most used as fillers worldwide. Most products are cross-linked with single ether bonds, only Puragen™ family (by Mentor Corporation) subjects a two-stage double cross-linking process with 1,2,7,8-diepoxyoctane (DEO) using a proprietary DXL™ technology, which increases stability and duration over time.

Table 10. Hydrogel-based commercial fillers.

Product	Company	Main constituent	URL
Artefill®	Suneva Medical	bovine collagen and homogeneous polymethylmethacrylate microspheres	https://bit.ly/2WNkMWb
Autologen®	Autogenous Technologies	Collagen from human dermis	https://bit.ly/2TAYTaN
Captique™	Genzyme	bacterial-based hyaluronic acids	https://bit.ly/2GcZ4Wx
Prevelle Silk®			https://bit.ly/2DXsQw0
Hylaform®		avian-derived hyaluronic acids	https://bit.ly/2BonGHU
Hylaform Plus®			https://bit.ly/2DiTjTl
CosmoDerm®	Allergan	human-derived collagen	https://bit.ly/2GtwY8T
CosmoPlast®		human-derived collagen	
Juvéderm™		non-animal stabilized hyaluronic acids	https://bit.ly/2jCYoxw
Cymetra®	AlloDerm, LifeCell Corporation	micronized human cadaveric dermis	https://bit.ly/2taBtxq
Dermologen®	Collagenessis Inc.	Collagen from cadaveric source	https://bit.ly/2RM5gpM
Elevess®	Anika Therapeutics	chemically modified non-animal hyaluronic acids	https://bit.ly/2BqYAbg
Evolence®	Johnson & Johnson	Cross-linked porcine collagen	https://bit.ly/2Bmhgcs
Evolence Breeze®			
Fascian®	Biosystem	Collagen from human cadaveric fascia	https://bit.ly/2I71bwK
Isolagen®	Isolagen Europe Ltd.	Collagen with autologous cell therapy	https://bit.ly/2StKQGJ
Restylane®	Q-Med	non-animal stabilized hyaluronic acids	https://bit.ly/2mnOgJu
Perlane®			https://bit.ly/2Rqsl1g
Zyderm®	Collagen Corporation	bovine-origin collagen	https://bit.ly/2GrRNS5
Zyplast®			https://bit.ly/2Ge7ahQ

3. Conclusions

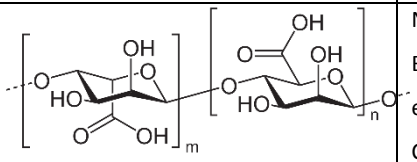
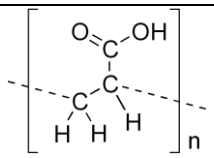
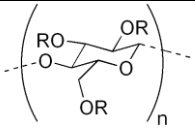
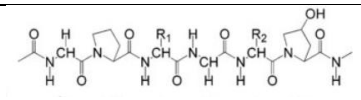
Despite hydrogels have existed for more than half century, their charm is still unquestioned. Due to their fascinating properties, hydrogels have attracted the attention of both scientific and industrial communities but,

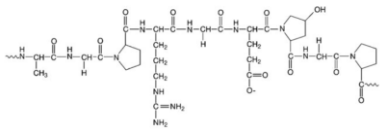
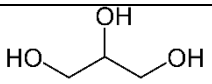
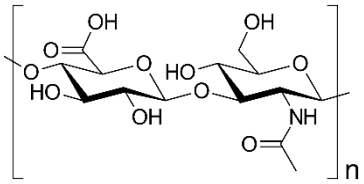
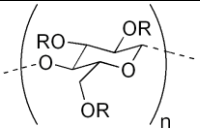
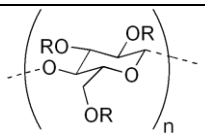
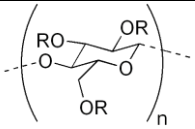
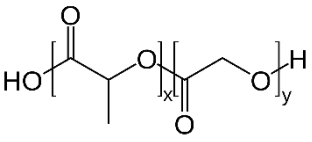
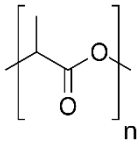
even if the studies concerning their potentiality are spread diffused, not all the formulations developed have reached the market. Focusing only on the biomedical applications, hydrogels have been used in different forms and amounts, in several fields, such as the drug delivery, wound healing, or tissue engineering.

The studies devolved to the development of new hydrogels' formulations or to the improvement of their properties are still attracting a lot of attention from scientists, but only a small part of them will result in the invention of a new product for people's daily life.

The main intent of this review is to give to the readers an overview of the hydrogels that have reached the market over the time, listing same of the commercial products that have been launched. However, the authors are aware that a complete and comprehensive review of all the commercial products is not possible, thus in the following a list of the main hydrogels that have resulted in a commercial product and the properties that characterize their use in specific application fields is reported.

Table 11. Chemical structure and properties of the main hydrogels used in biomedical applications.

Hydrogel	Chemical structure	Main properties	Applications
Alginate		Natural water-soluble polymer; Biocompatible and structured as extracellular matrix; Crosslinkable ionically or covalently.	Wound healing, drug delivery, and tissue engineering applications.
Carbomer (Poly(acrylic acid))		Weak anionic polyelectrolyte; Degree of ionization depends on solution pH; Mucoadhesive properties.	Disposable diapers, buccal delivery, gels for skin care.
Carboxymethyl cellulose	 R = H or CH_2CO_2H	Ionic cellulose-derivative; Solubility pH-dependent; Viscosity-increasing properties; Mucoadhesive properties.	Matrix for transdermal delivery and wound dressing, constituent of SAPs for hygienic applications.
Collagen		Main structural protein in the extracellular space; Biodegradable, biocompatible, and weak antigenic; Obtainable from different sources (animal and human); Cell attachment capability; Adhesive properties.	Cardiac applications, cosmetic surgery, filler, bone graft, tissue engineering, wound healing.

Gelatin		Film forming properties; Foam stabilizer; Adhesive properties as warm solution; Gelling properties.	Suspending agent, encapsulating agent, and tablet binder in pharmaceuticals
Glycerin		Smoothness improver and lubricant; Humectant properties; Plasticizer; High solvent power.	Rectal administrations, jellies and creams for topical uses, wound dressing.
Hyaluronic Acid		Natural water-soluble polymer; Biocompatible and structured as extracellular matrix.	Wound and skin healing, filler, cosmetics, tissue engineering, injectable gel.
Hydroxyethyl cellulose	 R = H or CH_2CH_2OH	Non-ionic cellulose derivative; Gelling and thickening agent; Bubble-forming; High hydrophilicity and maximum erodibility.	Excipient in pharmaceutical formulations, cream for topical medications, ointments, eye drops.
Hydroxypropyl methylcellulose	 R = H or CH_3 or $CH_2CH(OH)CH_3$	Non-ionic cellulose derivative; Thermal gelation properties; Film-forming properties; High hydrophilicity.	Excipient in pharmaceutical formulations, matrix for controlled delivery tablets, emulsifier, eye drops.
Hydroxypropyl cellulose	 R = H or $CH_2CH(OH)CH_3$	Non-ionic cellulose derivative; Fully soluble in water and polar organic solvents; Solubility in water temperature-dependent.	Topical ophthalmic protectant and lubricant, excipient for controlled delivery tablets.
poly (D,L-lactide-co-glycolide)		Biodegradable and biocompatible copolymer; FDA approved; Soluble in a wide range of organic solvents; Crystallinity and melting point tunable with the molecular weight.	Optical delivery, resorbable sutures, carrier for controlled delivery, tissue engineering applications.
Poly(lactic acid)		Biocompatibility and biodegradability; Good mechanical properties: Thermal plasticity.	Tissue engineering, wound healing, matrix for drug delivery systems.

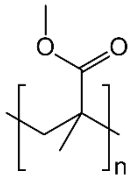
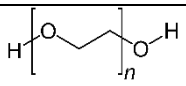
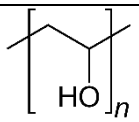
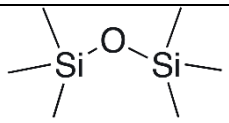
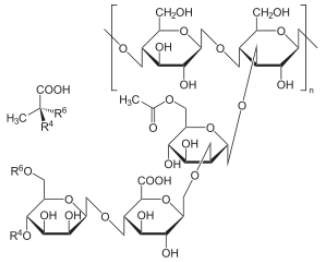
Poly(methyl methacrylate)		Non-degradable polyacrylate; Excellent optical properties; Mechanical p[roperties are tunable depending on the ratio of monomer and initiator during the polymerization	Intraocular lenses, orthopedic surgery, screws in bone fixation, cosmetic surgery, dentistry.
Polyethylene glycol		Water-soluble linear polymer; Absorbing and binding properties; Do not readily penetrate the skin.	Parenteral, topical, ophthalmic, oral and rectal preparations, base of ointments, wound dressing.
Polyvinyl alcohol		Water-soluble synthetic polymer; Film-forming, emulsifying, and adhesive properties; High oxygen barrier properties.	Excipient in sustained-release formulations, matrix for capsules, coating material for eye drops.
siloxane		Siloxane-hydrogels improve gas permeability of contact lenses, comfort of lenses and easiness of implantation.	Ocular drug delivery and contact lenses.
Xanthan gum		Natural polysaccharide; Highly soluble in hot and cold water; Stable in acidic and alkaline environments; Approved by FDA and compatible with foods.	Creams and suspensions as emulsion stabilizer, in cosmetics as thickener and stabilizer, buccal delivery.

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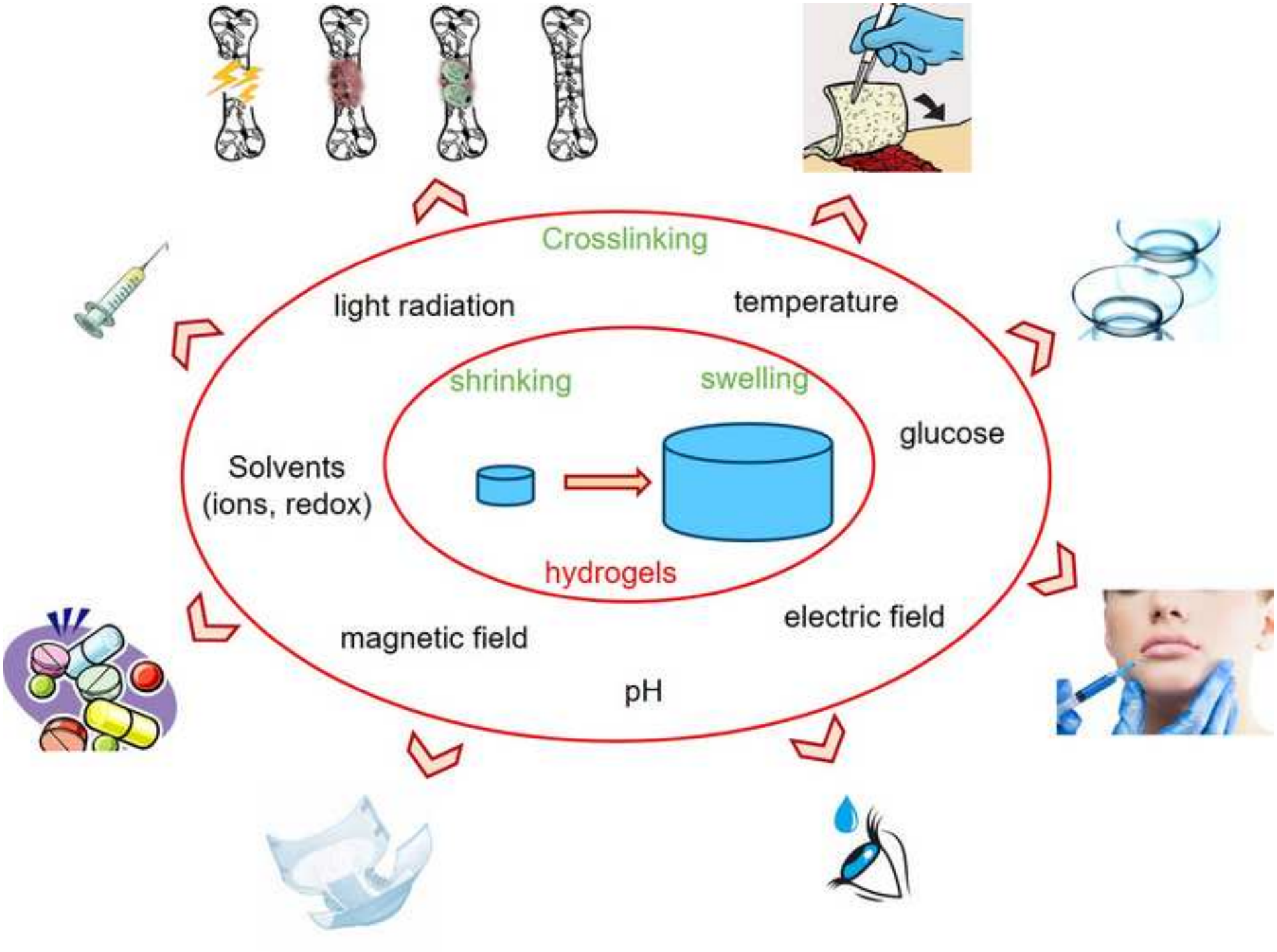
Figure 1


Crosslinking
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***Conflict of Interest**

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

none