Chapter 7

Cellulose-Derivatives-Based Hydrogels as Vehicles for Dermal and Transdermal Drug Delivery

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Additional information is available at the end of the chapter

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Abstract

The use of water-soluble polymers of natural, semisynthetic, and synthetic origin for dermal and transdermal drug delivery systems is manifold. Among the most used biopolymers in the formulation of skin preparations, the cellulose ether derivatives as representatives of semisynthetic polymers distinguish through their specific physicochemical properties, by which the pharmacist can select the appropriate cellulose derivative for a particular purpose. The hydrogels containing cellulose derivatives as gelling agents are widely used as water-soluble ointment bases, because they usually associate the characteristics of both conventional and innovative hydrogels, including especially safety, biocompatibility, biodegradability, and a relatively easy way of preparation and low price. The present chapter describes the following issues: the physicochemical properties of water-soluble cellulose derivatives in relationship with their type and grade; physical and chemical properties of cellulose-derivatives-based hydrogels and their compatibility with other auxiliary substances commonly used in the formulation of pharmaceutical hydrogels; the development and manufacturing of these hydrogels on both small and large scales; the characterization of cellulose derivatives hydrogels as pharmaceutical dosage forms through different compendial and noncompendial methods; and well-recognized and novel applications of cellulose-derivatives-based hydrogels for dermal and transdermal drug delivery.

Keywords: cellulose derivative, hydrogel, dermal, drug delivery, gelation, viscosity

1. Introduction

Over the past decades, the delivery of drugs to and through the skin has gained an increased interest in research and in the pharmaceutical industry, mainly due to the fact that the skin is

an easily accessible and painless route for drug administration, which in turn leads to increased patient compliance. Furthermore, dermal and transdermal drug delivery represents an attractive alternative to the conventional oral and parenteral route of administration, as it offers several advantages.

In present-day pharmaceutical and dermatological practice, most of the drug products applied to the skin for either localized or systemic effects are semisolid preparations, such as ointments, creams, and gels. Hydrogels, as conventional semisolid vehicles with hydrophilic properties, are highly valued in dermatology because they are transparent, completely water washable, greaseless, thixotropic, easily spreadable, suitable for the incorporation of lipophilic compounds or insoluble solids, and present good bioadhesive properties. In addition, innovative hydrogel formulations recently developed show other advantageous characteristics, namely biocompatibility, biodegradability, and sensitivity to various external stimuli. Biodegradability is nowadays a preferred and even a required property considering the need for environmentally friendly materials and technologies in different domains.

Hydrogels generally consist of two main components, the gelling agent responsible for the network formation and an aqueous liquid vehicle. Among the gelling agents extensively used in the pharmaceutical compounded and industrialized topical hydrogel formulations are cellulose derivatives (also referred to as cellulosics) such as methylcellulose, carboxymethylcellulose, and hydroxypropylmethylcellulose (HPMC). The cellulose-derivatives-based hydrogels are particularly attractive as ointment bases because they usually associate the characteristics of both conventional and innovative hydrogels. Moreover, the large availability in nature, nontoxicity, and the low cost of cellulose derivatives represent other important features, which recommend these polymers as first choice raw materials for the preparation of pharmaceutical hydrogels.

This chapter focuses on the current design, development, and applications of cellulose-derivatives-based hydrogels as semisolid pharmaceutical dosage forms intended for dermal and transdermal drug delivery.

2. Classification of cellulose derivatives

Cellulose is the most abundant naturally occurring biopolymer, found as the major component of annual plants and natural fibers (e.g., cotton, hardwoods and softwoods, linen, jute, and hemp) and also produced by some bacteria, fungi, and animals [1–5]. This glucose polymer is extensively used in pharmaceutical applications as it fulfills the two essential requirements: biocompatibility and biodegradability [6].

Plant-derived cellulose occurs as fibers, formed of macromolecules that contain hundreds of glucose molecules, determining the variability in chain length and molecular weight. The cellulose molecular weight can reach 1500 Da, each 40–50 glucose units being associated with longitudinal formations, named crystallites, which are oriented parallel to the longitudinal axis of the fiber and have 600–650 nm in length. In cellulose, as a linear polysaccharide polymer,

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the glucose monomers in pyranose form are linked to unbranched chains by β-1,4-glucosidic bonds, every glucose monomer being flipped related to the next one. Due to this structure, cellulose shows high crystallinity and rigidity and is practically insoluble in water and most organic solvents [7, 8].

In order to alter these disadvantageous properties, which limit its biomedical applications, chemical modification of cellulose, involving reactions of hydroxyl groups such as esterification or etherification, was performed. The extension of these reactions is expressed through the degree of substitution (DS), representing the average number of hydroxyl groups replaced by the substituents; the maximum value of DS is 3. For the cellulose derivatives used in pharmaceutical domain, the DS values correspond to pharmaceutical grades [8, 9].

Cellulose derivatives, named cellulosics, fall within the general class of hydrophilic colloids and have in common that they are hydrophilic, semisynthetic linear macromolecules obtained through chemical modification of cellulose. A more specific classification of cellulose derivatives can be made on the basis of other criteria, namely type of chemical modification of cellulose (etherification or esterification), electrolytic dissociation, and water solubility. Such classifications are useful because they facilitate the discussion of cellulose derivatives properties. Thus, based on the type of chemical modification of cellulose, cellulosics can be divided into two major groups:

- *polymers formed by hydroxyl etherification* with the appropriate alkyl halide of previously alkalinized cellulose. Principal examples of cellulose ethers derivatives used in pharmaceutical applications include methylcellulose (MC), ethylcellulose (EC), benzylcellulose (BC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyethylmethylcellulose (HEMC), and sodium carboxymethylcellulose (CMCNa);

- *polymers formed by hydroxyl esterification* with various organic acids, in the presence of a strong acid as catalyst. Some of the most important cellulose esters derivatives used in pharmaceutical domain are: cellulose acetate, cellulose nitrate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and hydroxypropylmethylcellulose acetate succinate.

Table 1 presents the general chemical structures of cellulose ether derivatives and the formulas of the R groups in these biopolymers, which are further discussed in this chapter.

Cellulose derivatives may also be classified according to their electrolytic dissociation or charge as *nonionic (uncharged) polymers* that do not have an electric charge (i.e., MC, EC, HEC, HPC, HEMC, and HPMC) and *ionic (anionic and cationic) polymers* with electric charge. Among the above-mentioned cellulose derivatives, only NaCMC is an anionic or negatively charged polyelectrolyte at pH values above its isoelectric point, being sensitive to pH and ionic strength variations [9–11].

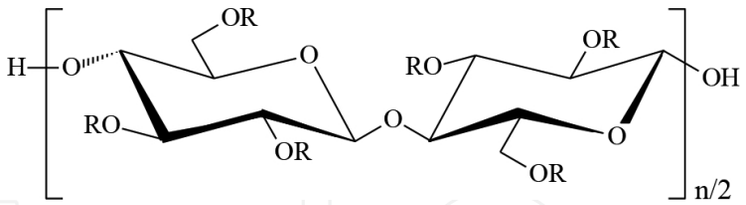
Cellulose ether derivatives	R groups
	
Methylcellulose	H, CH_3
Ethylcellulose	H, CH_2CH_3
Hydroxyethylcellulose	H, $[CH_2CH_2O]_nH$
Hydroxypropylcellulose	H, $[CH_2CH(CH_3)O]_nH$
Hydroxyethylmethylcellulose	H, CH_3, $[CH_2CH_2O]_nH$
Hydroxypropylmethylcellulose	H, CH_3, $[CH_2CH(CH_3)O]_nH$
Carboxymethylcellulose	H,CH_2COONa

Table 1. Chemical structures of some important cellulose ether and ester derivatives.

In addition, the cellulose derivatives can also be categorized based on their water solubility into two groups: *water-soluble polymers*, including most of the cellulose ethers, and *water-insoluble polymers*, including the cellulose esters and both EC and BC from the group of cellulose ethers. It is to be mentioned that the water-insoluble cellulose derivatives are soluble in various organic solvents.

3. Water-soluble cellulose derivatives

In this section, it will be discussed in detail the physical and chemical properties of several water-soluble cellulose ether derivatives including methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), and sodium carboxymethylcellulose (CMCNa), which are widely used as polymeric gelling agents in pharmaceutical hydrogels.

The commercial types of cellulose ethers for pharmaceutical applications are available in various grades, with different molecular weight, structural formula, and distribution of substituent groups and with different degree of substitution. These specific characteristics determine the physicochemical properties of cellulose ethers, such as solubility, viscosity in solution, surface activity and stability to biodegradation, heat, and hydrolytic and oxidative degradation. The solubility and the thermal gelation temperature of aqueous solutions of cellulose ethers are affected by their degree of substitution. But the viscosity of their solutions is directly related to their molecular weight and degree of polymerization. Therefore, the pharmacist has the possibility to select the appropriate cellulose derivative for a particular purpose [12].

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3.1. Methylcellulose (MC)

Methylcellulose is included in various pharmacopoeias as *methylcellulose* (i.e., British Pharmacopoeia, BP; Japanese Pharmacopoeia, JP; European Pharmacopoeia, PhEur; United States Pharmacopoeia, USP; and International Pharmacopoeia) and is commercially available as different trade names *Benecel*, *Methocel*, *Metolose*, *Tylose* etc [13].

It is a nonionic, linear, and filiform macromolecule of cellulose, in which approximately 27–32% of the hydroxyl groups are in the form of methyl ether. At present, there are various grades of MC commercially available, having degrees of polymerization in the range of 50–1000, molecular weights (number average) in the range 10,000–220,000 Da, and a degree of substitution in the range 1.64–1.92 [13].

Methylcellulose occurs as a white, fibrous powder or granules, practically odorless and tasteless, and slightly hygroscopic. It swells and disperses slowly in cold water (1–5°C), forming a clear to opalescent, viscous colloidal dispersion, with pH 5.0–8.0. MC is practically insoluble in hot water (70°C), ethanol (95%), and glycerol. This methyl derivative of cellulose has the specific property of forming thermally reversible hydrogels on heating, being classified as a lower critical solution temperature polymer. In addition, other typical physicochemical properties of methylcellulose, which are to be considered for its selection as gelling agent in a pharmaceutical formulation, are presented in **Table 2**.

Specific property	Methylcellulose
Surface tension	MC has an important surface activity, decreasing the surface tension of water from 72.8 dyn/cm to 45–55 dyn/cm for a 0.1% (w/v) solution at 20°C
Stability	Solutions of methylcellulose are stable to alkalis and dilute acids at pH 3–11, at room temperature. At pH less than 3, acid-catalyzed hydrolysis of the glucose-glucose linkages occurs and the viscosity of methylcellulose solutions is reduced
Incompatibilities	MC is incompatible with various drugs (i.e., chlorocresol, mercuric chloride, phenol, resorcinol, tannic acid, silver nitrate, tetracaine), antimicrobial preservatives (i.e., cetylpyridinium chloride, methylparaben, propylparaben and butylparaben), salts of mineral acids, and strong oxidizing agents

Table 2. Several specific properties of methylcellulose important as selection criteria in the formulation stage of a pharmaceutical gel.

3.2. Hydroxyethylcellulose (HEC)

The grades of HEC used in pharmaceutical applications comply with the specifications defined in the *hydroxyethylcellulose* monograph included in different pharmacopoeia (i.e., BP, PhEur, USP, and International Pharmacopoeia). Commercially, HEC is available in different trade names such as *Cellosize HEC*, *Natrosol*, *Tylose H* etc.

Hydroxyethylcellulose, a partially substituted poly(hydroxyethyl) ether of cellulose, is a nonionic, hydrophilic polymer, with a linear and filiform chain, having a degree of substitution of minimum 1.5 (three hydroxyls substituted/two units). With a further increase in DS over this minimum, the water solubility of HEC is increased.

There are available several grades of HEC, which differ in viscosity (determined by molecular weight) and in degree of substitution; further, some grades are modified to improve their water dispersibility. Also, HEC may contain a suitable anticaking agent. HEC appears as a white, yellowish-white or grayish-white, odorless and tasteless, and hygroscopic powder. It dissolves readily in either hot or cold water, forming clear, smooth, uniform solutions, with pH 5.0–8.5. HEC is practically insoluble in acetone, ethanol (95% m/v), ether, and most other organic solvents, but it swells or is partially soluble in polar solvents, usually those that are miscible with water such as glycols, dimethyl formamide, dimethyl sulfoxide, and ethanol:water mixtures (70:30, 60:40, 30:70 by weight) [13, 14].

Since the aqueous formulations of HEC are sensitive to biological contamination, a water-soluble antimicrobial preservative should be added for a prolonged storage (i.e., sodium benzoate, sorbic acid, and methyl-propylparaben combinations).

In **Table 3**, other HEC typical properties of interest for its incorporation into a pharmaceutical formulation are presented.

Specific property	Hydroxyethylcellulose
Surface tension	HEC has an insignificant surface activity that lead to a negligible lowering of water surface tension, from 72.8 dyn/cm to 66.8 dyn/cm for a 0.1% (w/v) solution at 20°C
Stability	Although the aqueous solutions of hydroxyethylcellulose are stable over the pH range of 2–12, at room temperature, their greatest stability is achieved in the pH range of 6.5–8.0. The solutions are less stable below pH 3 and under highly alkaline conditions, due to acid hydrolysis and oxidative degradation respectively
Compatibilities	Due to its water solubility and nonionic character, HEC is soluble in many salt solutions that will not dissolve other water-soluble polymers
	For example, HEC dissolves in most 10% salt solutions and many 50% salt solutions, with several exceptions which are mentioned below. Further, HEC is compatible with a wide range of water-soluble materials, including other cellulosic hydrosoluble polymers, natural gums, and surfactants
Incompatibilities	HEC will precipitate in sodium carbonate and sodium sulfate 10% solutions, and in 50% (saturated) solutions of sulfates of bi- and trivalent metals (i.e., magnesium, zinc, and aluminum), di- and trisodium phosphate, ferric chloride, sodium nitrate, sodium sulfite. HEC is also incompatible with some quaternary disinfectants and partially compatible with the following water-soluble compounds: casein, gelatin, methylcellulose, polyvinylalcohol, and starch
Safety	Generally, HEC is considered as an essentially nontoxic and nonirritant material, being mainly used in ophthalmic and cutaneous pharmaceutical formulations

Table 3. Some specific properties of hydroxyethylcellulose as gelling agent.

3.3. Hydroxypropylcellulose (HPC)

According to Ph. Eur. and USP-NF, hydroxypropylcellulose intended for pharmaceutical use, is a partially substituted poly(hydroxypropyl) ether of cellulose, which may contain no more than 0.6% of silica or another suitable anticaking agent. HPC, also known as hyprolose and

oxypropylated cellulose, is made by the Aqualon Division of Hercules Inc. and Nippon Soda Co., Ltd. (NISSO) under the brand names Klucel and NISSO HPC, respectively. The pharmaceutical grades of HPC are commercially available in several different viscosity types with molecular weight in the range of 50,000–1,250,000, depending on the degree of polymerization.

This ether of cellulose is a hydrophilic, nonionic, linear thread-like polymer where some of the hydroxyl groups of the cellulose have been hydroxypropylated, forming $–OCH_2CH(OH)CH_3$ groups. Moreover, the added hydroxypropyl groups can also be etherified during HPC preparation, leading to a value of moles of substitution (the number of moles of hydroxypropyl group per glucose ring) higher than 3. Hence, HPC with good water solubility must have a DS value of 2.5 and an MS value of approximately 4.

Hydroxypropylcellulose occurs as a white to slightly yellow-colored, odorless and tasteless powder. It feature a remarkable combination of properties: solubility in cold or hot polar organic solvents such as methanol (1:2), ethanol 95% (1:2.5), isopropyl alcohol (1:5), propyleneglycol (1:5); water solubility (1:2) below 38°C, forming a smooth, clear, colloidal solution; surface activity; aqueous thickening and stabilizing properties. HPC is insoluble in hot water, precipitates as a highly swollen floc in the temperature range 40–45°C, but this precipitation is completely reversible; thus, the gelation of HPC occurs on heating and yields to thermally reversible gels, similar to MC. It is also practically insoluble in aliphatic and aromatic hydrocarbons, glycerin, and oils [13, 15, 16].

In addition, other physical and chemical properties of pharmaceutical grades hydroxypropylcellulose are indicated in **Table 4**.

Specific property	Hydroxypropylcellulose
Surface tension	HPC is a surface active cellulose polymer, lowering the surface tension of water, from 72.8 dyn/cm to 46.3 dyn/cm for a 1% (w/v) solution, at 20°C
Stability	Aqueous solutions of hydroxypropylcellulose are stable in the pH range of 6–8, at room temperature. However, under highly acid or alkaline conditions, the degradation of polymer can occur, due to acid hydrolysis or alkaline oxidation
Compatibilities	The compatibility of hydroxypropylcellulose with inorganic salts varies according to the salt and its concentration For example, HPC dissolves in most 2–3% salt solutions and few 10% salt solutions. Further, HEC is compatible with a wide range of organic materials, including water-soluble as well as solvent-soluble resins, polymers (i.e., natural gums, semisynthetic, and synthetic polymers), surfactants, and organic liquids
Incompatibilities	In aqueous solutions, HPC will precipitate in the presence of 10% aluminum, ammonium or sodium sulfates, disodium phosphate, sodium acetate, carbonate, chloride, and thiosulfate. This polymer tends to be salted out in the presence of high concentrations of other dissolved compounds
Safety	Generally, HPC is considered as an essentially nontoxic and nonirritant material, being widely used as excipient in oral and topical pharmaceutical formulations. It does not exhibit skin irritation or skin sensitization. It is GRAS listed and is included in the FDA Inactive Ingredients Database (for oral solid dosage forms such as capsules and tablets, and also for topical and transdermal preparations)

Table 4. Some typical properties of hydroxypropylcellulose used in pharmaceutical applications.

3.4. Hydroxypropylmethylcellulose (HPMC)

It is also known as hypromellose, a nonproprietary name under which this cellulose derivative is found in different pharmacopoeias (BP, JP, PhEur, and USP) or their current editions. In addition, hydroxypropylmethylcellulose intended for use in pharmaceutical applications is produced by different manufacturers and commercialized under several trade names such as *Benecel MHPC*, *Methocel*, *Metolose*, *Pharmacoat*, *Tylopur*, *Tylose MO* [17–21].

Hypromellose is the propyleneglycol ether of methylcellulose, described by the PhEur as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. This nonionic, water-soluble polymer is available in several grades that differ in viscosity and extent of substitution. Different viscosity grades of HPMC are identified by an attached number indicating the apparent viscosity, in mPa s, of a 2% (w/w) aqueous solution at 20°C. The substitution type of hypromellose is specified in the pharmacopoeias as a four-digit number following the nonproprietary name, e.g., hypromellose 2208. The first two digits indicate the approximate percentage content of the methoxy group (OCH_3) and the second two digits indicate the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis.

***Methocel* and *Metolose* grades**	**Compendial (JP, PhEur, USP) substitution type**	**Nominal viscosity (mPa s)**
Methocel K3 Premium LV	2208	3
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15,000
Methocel K100M Premium	2208	100,000
Methocel E3 Premium LV	2910	3
Methocel E5 Premium LV	2910	5
Methocel E6 Premium LV	2910	6
Methocel E15 Premium LV	2910	15
Methocel E50 Premium LV	2910	50
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel F4M Premium	2906	4000
Metolose 60S	2910	50, 4000, 10,000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15,000

Table 5. The substitution type and typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Wolff Cellulosics) and Metolose (Shin-Etsu Chemical Co. Ltd.). Viscosities measured at 20°C [13, 17, 20, 21].

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In the case of *Methocel* products of Dow Wolff Cellulosics, the substitution type is incorporated into the product name as an initial letter "*E*", "*F*," and "*K*," the number that follows stands for the viscosity (in mPa s) of that product measured at 2% concentration in water at 20°C; further, in referring the viscosity, the letter "*C*" is frequently used to represent 100 and the letter "*M*" is used to represent 1000 (**Table 5**). Also, several suffixes are used to identify special products: "*P*" denotes Methocel Premium grade products which means they are compliant with the USP, PhEur, and JP; "*LV*" stands for Low Viscosity products; "*CR*" refers to a Premium, Controlled Release grade (**Table 5**). On the other hand, the *Metolose SH* types of Shin-Etsu Chemical Co. Ltd. may be distinguished based on the degree of substitution by a number preceding the initial letters "*SH*" which identify the hypromellose products (**Table 5**) [13, 17, 20, 21].

The percentage content of methoxy and hydroxypropoxy groups affects both the molecular weight that is approximately 10,000–1,500,000, and the physicochemical properties of HPMC, such as solubility, surface activity, and thermal gelation [13]. HPMC appears as a white or creamy-white fibrous or granular powder, which is odorless and tasteless. It is soluble in cold water, forming a transparent, viscous, and surface active colloidal solution (the surface tension range from 42 dyn/cm to 64 dyn/cm). Certain types and grades of hypromellose are also soluble in various binary cosolvent systems such as ethanol/water, isopropanol/water, ethanol/dichloromethane, isopropanol/dichloromethane, providing a unique combination of solubility in organic solvents and water. However, hypromellose is practically insoluble in hot water, chloroform, ethanol (95%), and ether.

Another interesting characteristic of HPMC is the thermoreversible gelation behavior in aqueous media, which can be explained as follows: the aqueous solutions of hypromellose, obtained at room temperature, turn into gels when heated to their specific gel temperature (50–90°C); the resulting gels are completely reversible and liquefy upon cooling to room temperature, returning to their solution form. The thermoreversible gelation of hypromellose is particularly affected by several factors, such as its concentration in solvent media and the nature of additives. Thus, the additives that impart a solubilizing effect (i.e., ethanol, propyleneglycol, PEG 400) raise the gel point of HPMC, whereas the additives that exhibit a coagulant effect (i.e., glycerol, sorbitol, and most electrolytes) lower the gel temperature. In the past decade, numerous studies on thermoreversible gelation behavior of HPMC solutions have been carried out [22–26].

In addition, hypromellose possesses several other physicochemical characteristics, which are generally, similar to those of the above described cellulose ether derivatives of pharmaceutical grade. Some of these properties are presented below: HPMC in powder form is a stable material, although it is hygroscopic; aqueous solutions of HPMC are predisposed to microbial spoilage and require the addition of an antimicrobial preservative; in solution, hypromellose is stable in a wide pH range (3–11); HPMC is incompatible with some oxidizing agents, but exhibits a higher tolerance for salts in solution than MC; it is generally regarded as nontoxic an nonirritating excipient, being extensively used in topical pharmaceutical formulations and cosmetics; also, it is GRAS listed [13].

3.5. Carboxymethylcellulosesodium (CMCNa)

Among the two salt forms of carboxymethylcellulose (calcium and sodium) available for industrial use, sodium carboxymethylcellulose is commonly used for pharmaceutical preparations, including hydrogels. This cellulose ether derivative, also known as carmellose sodium, must comply with the compendial requirements of *carmellose sodium* or *carboxymethylcellulose sodium* monographs listed in BP, PhEur, JP, and respectively USP, which describe it as the sodium salt of polycarboxymethyl ether of cellulose, with a 6.6–10.8% sodium content. It is commercially available as various trade names such as *Akucell*, *Aqualon CMC*, *Aquasorb*, *Blanose*, *Tylose CB*, and *Walocel C*.

CMCNa is a hydrophilic, anionic polymer, with a linear, filiform chain, prepared by partial substitution of the two, three, and six hydroxyl groups of cellulose by carboxymethyl groups. The carmellose sodium pharmaceutical grades are available in a wide variety of types with regard to the degree of substitution, viscosity, and particle size. The value of DS varies in the range 0.6–1, affecting some of the polymer physicochemical properties. Hence, as the DS value is higher, the solubility in water and sodium content of CMCNa increase and a better polymer tolerance for other components in solution is achieved. The viscosity of different types of carmellose sodium depends on their polymerization degrees and molecular weights which are of 100–2000 and 90,000–700,000, respectively. Particle size has a pronounced effect on the ease of dispersing and dissolving CMCNa.

Sodium carmellose occurs as granular or fibrous, white to slightly off white, odorless, tasteless, and hygroscopic powder. It is slightly soluble in water at all temperatures, forming clear, viscous colloidal solutions, but is practically insoluble in most organic solvents such as ethanol (95%), methanol, acetone, ether, and toluene. However, it can be dissolved in aqueous mixtures if the content in water-miscible solvent is less than 40% (by weight). The powder of CMCNa presents a high chemical and microbiological purity and stability, and is not surface active. The aqueous solutions of carboxymethylcellulose sodium exhibit maximum viscosity and stability at pH 7–9, although they are stable over a broad pH range (2–10); at pH < 2, precipitation of CMC acid can occur, and at pH > 10 the viscosity of solutions decreases rapidly. Similar to HPMC, sodium carmellose exhibits thermoreversible gelation behavior in aqueous media. Also, its aqueous solutions are sensitive to microbiological attack and should contain a preservative for prolonged storage [13, 27, 28, 29].

Being a polyelectrolyte, CMCNa is sensible to pH and ionic strength variations. Therefore, its compatibility in solution with other components (**Table 6**) is another critical characteristic for the formulation of a pharmaceutical hydrogel.

In the past decade, cross-linked networks of CMC have been obtained and reported by applying chemically and physically cross-linking technologies. The chemically cross-linking method involves the use of bifunctional cross linkers such as epichlorhydrin [30], multifunctional carboxylic acids [31–34], ethyleneglycol diglycidyl ether [32], and polyethyleneglycol diglycidyl ether [35]. However, some of these reagents such as epichlorhydrin and ethyleneglycol diglycidyl ether produce large amounts of toxic byproducts under the cross-linking conditions, requiring their elimination through extensive washing, thus affecting the biocom-

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patibility of the resulted hydrogel and the environmental safety of the production process. Considering these environmental and health safety risks, a physical cross-linking method, namely the radiation technology based on γ or electron-beam irradiation under relatively mild conditions, has attracted increased interest [36, 37]. This method presents some advantages: the addition of chemical reagents is not required, the side products are not present, and the simultaneously sterilization of the final hydrogel is possible.

Common excipients compatible with CMCNa in solution	Common excipients incompatible with CMCNa in solution
Most hydrophilic nonionic and anionic polymers and gums	Xanthan gum
	Gelatin, pectin and collagen forming complexes
Most 10% and 50% inorganic salts of monovalent cations, which form soluble salts of carboxymethylcellulose, with a prerequisite condition: the polymer should be dissolved in water before adding the salt	Most inorganic salts of bivalent (Ca^{2+}, Ba^{2+}, Mg^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, and Zn^{2+}) and trivalent cations (Al^{3+}, Fe^{3+}), and also trace amounts of heavy metals cations (Ag^{+}, Cu^{2+}, Pb^{2+}, Zr^{2+}), which form precipitates

Table 6. Compatibility of carboxymethylcellulose sodium with other components in solution.

Although cross-linked CMC is a water-insoluble biopolymer, it is capable to absorb large amounts of water and swells to form superabsorbent hydrogels that exhibit superior mechanical properties and viscoelasticity compared with conventional sodium CMC-based hydrogels [38]. Due to this characteristic, the cross-linked CMC-based hydrogels were recently studied as potential wound dressing materials, as well as dermal and transdermal drug delivery systems [35, 38, 39].

Similar to the others cellulose ether derivatives, sodium carmellose is a safe excipient, being regarded as nontoxic and nonirritant. It is GRAS listed and included in different databases of inactive ingredients. Consequently, this polymer is extensively used in oral, topical, and some parenteral formulations, in cosmetics, toiletries, and food products [13].

4. Colloidal dissolution and gelation as processes involved in the formation of cellulose-derivatives-based hydrogels

To obtain a topical semisolid drug product, such as a medicated hydrogel, which meets the specific requirements, one of the major objectives of its formulation is the excipients selection and preparation of the base (hydrogel base) with semisolid consistency, jelly-like structure, and bioadhesive properties. Further, the hydrogel base must be stable, formed of compatible components, and therapeutically acceptable. Due to the specific jelly-like structure, hydrogels preserve their shape during the stockage, spread evenly, and adhere to the skin surface. In order to achieve this goal of hydrogel formulation, the knowledge of processes involved in the formation of hydrogels, such as colloidal dissolution and gelation of

hydrophilic polymers, are of great importance as they are closely related with the physical and chemical properties of the gelling agent.

Based on the jelly-like structure, cellulose derivatives hydrogels are categorized as single-phase, reversible (or physical) gels composed of a network of organic macromolecules dissolved in water, without the existence of definite boundaries between the two components. However, due to the large size of the dissolved molecules, cellulose derivatives hydrogels are considered, on the microlevel, as biphasic colloidal systems, consisting of colloidal polymer and a liquid phase (water) [16, 40].

According to the formation mechanism of hydrogel, all cellulose derivatives described in the previous section are biopolymers that form hydrogels independently of pH, but in the case of MC, HPC, and HPMC the hydrogel formation is temperature dependent. Usually, the water-soluble cellulose derivatives form hydrogels in the concentrations of 1–10% (by weight), depending on the polymerization degree. The gelation of cellulose ether derivatives has been extensively studied for decades and numerous of these studies have been reviewed in several scientific journals and books [24, 39–47].

It is generally accepted that the gelation of water soluble cellulose ether derivatives is due to some physical processes such as molecular entanglements, hydrophobic associations between macromolecules and hydrogen bonding. The filiform macromolecules chains connect at both ends by forming some intermolecular bonds as a result of interaction between the existing functional groups. Also, entanglements develop from the interpenetration of random-coil flexible chains of polymers. Thus, they form a continuous three-dimensional network that occupies the entire system and entraps the entire amount of water. The formation of cellulose-derivatives-based hydrogels occurs in three stages. The first stage, identified as the diffusion of water molecules into the polymer network, is attributed to hydrogen bonding between the water molecules and the hydrophilic functional groups of macromolecules including carboxyl and hydroxyl groups. So, the solvent molecules will be oriented along the polymer chain, increasing the rigidity of the dispersed system. The second stage, correspond to relaxation of the polymer chains by hydration, when large amounts of water permeated into the polymer network are spontaneously absorbed by the macromolecules that swell and therefore greatly enhance the gel volume. In this stage of hydrogel formation, the interactions between polymer and water molecules through coordinate bonds lead to the formation of very stable complexes of hydration. Also, wetting determines the enhancement of macromolecule chains permeability and their stretching, accompanied by a more or less linear arrangement. The third stage, namely the polymer network expansion displayed through the increase of the gel volume, is due to water absorption and swelling of macromolecules. The stronger macromolecules hydration is the lower mobility of water molecules and the higher stability of the cross-linked gel network [9, 11, 16, 48].

The two main processes, namely colloidal dissolution and gelation, involved in the formation of cellulose-derivatives-based hydrogels, depend on several physicochemical factors (i.e., properties of cellulose-based polymers determined by chemical structure, macromolecular chain configuration, molecular weight, degree of substitution and also by the composition of the aqueous media, the pH, and the temperature) and thus influence to a great extent the

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formulation of a suitable pharmaceutical hydrogel. In general, lower temperature, higher concentration, and higher molecular weight of polymer promote gelation of cellulose ether derivatives, leading to firmer hydrogels. In most cases, the gelation of polymer is affected in the presence of relatively high concentrations of electrolytes, surfactants, sugar, or some natural gums, which reduce the polymer hydration and consequently the gelation temperature by the "salting out" phenomenon; the magnitude of this effect depends not only on the nature and concentration of the other dissolved components, but also on the substitution degree of the polymer. Generally, the cellulose ether derivatives with lower substitution degrees tend to exhibit a higher tolerance for the other dissolved components in the system. Due to the stability of aqueous solutions of water-soluble cellulose derivatives in a wide range of pH values (3–11), the gel formation is affected only under highly acid or alkaline conditions [9, 11, 16, 48].

Among the water soluble cellulose derivatives, MC, HPC, and HPMC are lower critical solution temperature polymers (**Table 7**) that form thermoreversible hydrogels [49, 50].

In order to understand and clarify the thermal gelation of these biopolymers, in the past two decades a large number of studies have been performed using different techniques. However, it was not reached a consensus in all cases, due the complexity of this process involving several different phenomena which can occur during the sol-gel transition.

Cellulose derivative	Trade name and type	Methoxy, DS	Methoxy, wt%	Hydroxypropoxy, MS	Hydroxypropoxy, wt%	Gelation temperature (°C)
MC	Benecel™ A	1.8	27.1–31.5	–	–	56
	Methocel A	1.8	30	–	–	50
	Metolose SM	1.8	Not specified	–	–	50–55
HPC	Klucel™ HPC	–	–	3.4–4.4	Not specified	40–45
	Nisso HPC	–	–	Not specified	53.4–77.5	40–45
HPMC	Benecel™K	Not specified	20.0–24.0	Not specified	7.0–12.0	80
	Benecel™E	Not specified	28.0–30.0	Not specified	7.0–12.0	63
	Methocel E	1.9	29.0	0.23	8.5	63
	Methocel F	1.8	28.0	0.13	5.0	63
	Methocel J	1.3	18.0	0.82	27	62
	Methocel K	1.4	22.0	0.21	8.1	85
	Metolose 60SH	1.9	28.0–30.0	0.25	7.0–12.0	65–66
	Metolose 65SH	1.8	27.0–30.0	0.15	4.0–7.5	61–65
	Metolose 90SH	1.4	19.0–24.0	0.20	4.0–12.0	75

Table 7. Thermal gelation temperatures of various grades and types of methyl- and/or hydroxypropyl-derivatives of cellulose.

In the case of the above-mentioned three cellulose derivatives (MC, HPC, and HPMC) is generally accepted that the formation of thermoreversible hydrogels occurs in two stages: (1) the formation of water clusters around the methyl or hydroxypropyl substituents of the polymer chains (the hydrophobic portions), which will be isolated one from another at low temperatures (below 50°C); (2) the phase separation accompanied by gelation at high temperatures (above 50°C).

For methylcellulose, the sol-gel transition is currently defined as the transformation from a clear solution to a turbid strong gel. Although the gelation of MC has been extensively studied by various analytical techniques (NMR, differential scanning calorimetry, IR attenuated total reflectance spectroscopy, small-angle neutron scattering, static and dynamic light scattering, and rheology) and the researchers have proposed different gelation mechanisms, the specific molecular interactions that govern this process is still unclear. However, the results of various studies, which were in good agreement one with another, indicated several factors and/or phenomena which play an important role in the gelation of MC [24, 51–64]:

- the first stage (pregel state) is mainly governed by hydrophobic interactions between highly methylated glucose regions, but also by bundles of residual native cellulose crystals, liquid crystal phases, and intermolecular bonding between unsubstituted hydroxyl groups along the polymer chains;
- the second stage (gel state), when the phase separation and gelation occur almost simultaneously, results from micellar interactions, formation of crystallites of trimethylated glucose rings, hydrophobic polymer-polymer interactions, and entangled physical cross links between chains leading to a three-dimensional network.

Recently, it was confirmed experimentally by rheological measurements that a nucleation and growth mechanism is also involved in the gelation of MC, as the gelation temperature depends on the heating rate [65].

The same group of researchers has also demonstrated by cryogenic transmission electron microscopy and small-angle neutron scattering that MC hydrogels have a heterogeneous fibrillar structure that is responsible for their turbidity [66, 67].

For HPMC, the formation of thermoreversible hydrogels is, similar to MC, a two-stage process. Conventionally, it is considered that the mechanism of HPMC gelation involves polymer reptation and dissociation of cellulosic bundles followed by exclusion of water (syneresis) from heavily methoxylated regions of the macromolecule. This syneresis allows hydrophobic interactions between the respective macromolecules accompanied with the formation of polymer clusters, which further associate in a three-dimensional network. This specific mechanism of gelation is supported by the results obtained from several experimental techniques including: differential scanning calorimetry, IR attenuated total reflectance spectroscopy, UV/VIS and fluorescence spectroscopy, polarized light microscopy, and oscillatory rheometry [22, 26, 68–71].

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However, several studies have indicated some differences between MC and HPMC regarding thermal gelation properties and gel network structure. Generally, these differences are generated by the presence of hydroxypropyl substituents along the HPMC polymeric chains that hinder the gelation process by inhibiting intermolecular association. This observation is supported by the fact that HPMC has a higher gelation temperature and forms weaker thermosensitive gels compared to MC. Also, as the temperature rise to ca. 55°C, hydroxypropyl derivative of MC precipitates and causes only clouding of the solution, but no gelation, unlike MC [53, 72–74].

On the other hand, hydroxypropylcellulose being soluble in water at room temperature undergoes the gelation in these conditions. Increasing the temperature above the cloud point (40–45°C), the resulted hydrogel suddenly becomes opaque, loses its gel-like characteristics (evidenced by a marked reduction in/rapid decrease in viscosity) and exhibits a sudden shrinking in volume. These effects are due to separation of the polymer as a highly swollen precipitate at the above-mentioned temperature that corresponds to its phase transition temperature (or lower critical solution temperature). However, the polymer precipitation is reversible, because upon cooling the system below 40°C, redissolution of polymer and restoring of original viscosity take place [13, 15].

In contrast to MC and HPMC, only a few studies have investigated the gelation mechanism of HPC by NMR spectroscopy and thermal analysis [75, 76].

As the results from all these studies fitted well one with another, it was proposed the following plausible explanation of the HPC gelation mechanism. At room temperature, due to its high DS and uniform distribution of substituents along the polymeric chains, the HPC backbone has a little hydrophilic character that promotes a hydrophobic effect with water in solution, being extended, and mobilized. At elevated temperature, this hydrophobic structure breakdown and the cellulose backbones of the polymer chains coil into supramolecular helical structure. Although the cellulose backbones of the polymer chains are immobilized in this way, the hydroxypropyl substituents remain solvated projecting outward from the coiled backbone into the solvent and exhibiting a cilia-type motion. These cilia keep adjacent coils apart, leading to a highly dispersed solid phase (precipitate), with no gel-like properties.

Finally, the only one "smart" cellulose derivative, namely sodium carboxymethylcellulose, does not form thermoreversible hydrogels and is soluble in either hot or cold water, because it is an anionic polyelectrolyte. Consequently, the three-stage process of hydrogel formation, described above, is mainly determined in the presence of electrostatic charges attached to the polymer network, which enhance the polymer swelling capability in water by two mechanisms: (1) due to the electrostatic repulsion between the electric charges of the same sign, the macromolecule chains are forced to get more elongated than in a neutral network; (2) enhanced water penetration in the polymer network, due to the presence in the hydrogel of counterions to ensure the electrical neutrality [39]. Nevertheless, the gelation of sodium carboxymethylcellulose is influenced by pH and ionic strength variations (due to the presence of different inorganic salts). In addition, it is generally accepted that the firmness of NaCMC hydrogels

increases with the increase in carboxymethyl substitution, molecular weight and polymer concentration [13, 28, 29].

5. Physical and chemical properties of cellulose derivatives hydrogels

Cellulose derivatives hydrogels are interesting as water-soluble ointment bases and topical drug delivery systems, because they present several advantageous characteristics: transparency (especially HPMC- and NaCMC-based hydrogels); high water content (80–95%), which is responsible for their favorable cooling effect and washability; nongreasy, being practically free from fats or fatty substances; porosity; nonocclusive; safety, as they are nontoxic and nonallergenic; are well tolerated by skin and different mucosa (oral, buccal, ophthalmic, nasal, auricular, vaginal, and rectal); are mucoadhesive and bioadhesive materials, adhering well to skin, mucosa and suppurative wounds, and providing intimate contact between the drug and the site of action; can be safely sterilized. They also may be formulated to ensure excellent spreading properties or to optimize drug delivery. Other important advantages of cellulose derivatives hydrogels include biocompatibility, biodegradability, smart stimuli-responsive behavior (in the case of NaCMC), compatibility with most active substances and auxiliary pharmaceutical components (excepting NaCMC which is an anionic polyelectrolyte). Also, the availability in nature and the low cost of cellulose derivatives make them more attractive as gelling agents [16, 45, 39, 77–81]. It is noteworthy that the cellulose derivatives hydrogels are considered biocompatible because they are similar to living tissues, with regard to physical properties, based on their water content, soft consistency, and low interfacial tension with water or biological fluids [39, 82].

The physical properties of cellulose derivatives hydrogels can be divided into two groups: transitional properties (including swelling behavior, sol-gel transition or gel point, and physical aging) and rheological properties (including rigidity, yield point, and rupture strength). These properties of cellulose derivatives hydrogels are directly related to their structure through their polymeric composition, because the selected cellulose derivative decisively influences the network structure as well as the final hydrogel properties [80].

5.1. Transitional properties

5.1.1. Swelling behavior

The capacity to absorb water or aqueous solutions and the permeability (the rate at which the liquid is absorbed into the hydrogel structure) are the most important features characterizing hydrogels, including those based on cellulose derivatives. Generally, the amount of the aqueous medium incorporated in a hydrogel is determined gravimetrically and is expressed as fractional hydration (W) or as swelling ratio (r):

$$W = (w_1 - w_0) / w_1 \text{ or } r = (w_1 - w_0) / w_0$$

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where w_1 and w_0 are the weights of the swollen and dry gels, respectively. Also, the amount of water absorbed by a polymer can be described by the equilibrium swelling as the maximum degree of the polymer swelling.

Hydrogels of cellulose derivatives are considered highly swollen gels (containing large percentages of water), because of the high solubility of these polymers in water, high flexibility of the polymeric chains and a large free volume available between polymeric chains [40, 83–85].

However, the water content at the swelling equilibrium of cellulose derivatives hydrogels is influenced basically by the nature of the monomer that makes them up, by the type and density of the cross link (entanglements) and also, by other factors including temperature, pH, and the composition of the hydration medium (the presence of salts and nonsolvents). So, dynamic and equilibrium studies carried out by the Peppas group on hydrogel discs of HEC, HPC, HPMC K4M, and HPMC K100M [44] showed that the volume-swelling ratio and the swelling time (the time when hydrogel discs reached the equilibrium state, namely the gel thickness became essentially constant) of the polymer were dependent on their hydrophilicity and number of junctions or entanglements per original chain. Thus, the equilibrium state for HEC was reached after 240 h, for HPC and HPMC K100M after 260 h, and for HPMC K4M after 170 h, whereas the obtained volume-swelling ratios up to 190 h of swelling ranked the polymers as follows: HPC < HPMC K4M < HPMC K100M < HEC. The swelling kinetics of the studied HPMC polymers in the dynamic state was accurately described by the equation used to calculate the volume-swelling ratio, Q:

$$Q = V_s / V_d$$

where V_s is the volume of the swollen gel and V_d is the initial volume of the dry disc. At equilibrium, the swelling kinetics of HPMC polymers correlated well with the Flory-Rehner equation, describing the average molecular weight between two consecutive entanglements, $\overline{M_e}$:

$$\frac{1}{\overline{M_e}} = \frac{2}{\overline{M_n}} - \frac{\left(\frac{v}{V_1}\right)\left[ln\left(1-v_{2,s}\right)+v_{2,s}+x_1 v_{2,s}^2\right]}{\left(v_{2,s}^{1/3}-\frac{v_{2,s}}{2}\right)}$$

where $\overline{M_n}$ is the number average molecular weight of the cellulose ether tested, v is its specific volume, V_1 is the molar volume of water, $v_{2,s}$ is the polymer fraction in the swollen gel at equilibrium ($v_{2,s} = 1/Q$), and x_1 is the Flory or polymer-water interaction parameter [44]. From detailed explanation given in this paper, further references are made only for HEC and HPC. In the swollen state, HEC formed the thicker hydrogel layer, signifying that the largest amount of water is physically and chemically trapped in the HEC hydrogel structure. This entrap-

ment was attributed to the relatively high number of entanglements which holds the network structure together at equilibrium. In contrast, HPC formed the thinnest hydrogel layer, meaning that the interactions between the HPC chains are very strong and that water molecules occupy a smaller volume than in the case of HEC. This behavior is supported by the higher number of entanglements and the relatively high molar substitution for HPC, and also by the large volume occupied by hydroxypropyl substituents in the network structure of the HPC hydrogel [44].

As in the case of other hydrogels, the equilibrium degree of swelling influences different properties of cellulose derivatives hydrogels, including permeability, surface properties and surface mobility, optical properties, mechanical properties, and solute diffusion coefficient through these hydrogels. Consequently, the knowledge of the swelling characteristics of cellulose derivatives is of great importance in their pharmaceutical applications [80, 83].

5.1.2. Sol-gel transition (gel point)

Sol-gel transition is an essential property of most cellulose derivatives hydrogels as they are thermoreversible and is dependent on several factors, including polymer concentration and temperature.

The critical gelling concentration is the concentration below which the polymer and the solvent form a sol rather than a macroscopic gel, under the current experimental conditions [86]. For thermoreversible hydrogels of cellulose derivatives (MC, HPC, and HPMC), the critical gelling concentration obviously depends on temperature because, above the melting temperature, this concentration is nominally infinite, requiring a maximum gelation temperature and a critical gelation time [87]. The critical gelling concentration of cellulose derivatives depends on the polymer-polymer and polymer-solvent interactions, their hydrophilic-lipophilic character and molecular weight, and the flexibility of the chain [16, 88, 89]. Moreover, certain additives such as electrolytes, sorbitol, sucrose, and solvents (glycerin, ethanol, propyleneglycol, and polyethyleneglycol 400) can have different effects on the gel point and critical gelling concentration of cellulose derivatives [23]. Thus, it was demonstrated that most electrolytes, as well as sorbitol, sucrose and glycerin depress the gel point, whereas other cosolvents (ethanol, propyleneglycol, and polyethyleneglycol 400) raise the gel point of various grades of methylcellulose [90]. In **Table 8**, the minimal concentration domains for the most used cellulose derivatives as gelling agents in pharmaceutical hydrogels are listed.

Cellulose derivative	Gelling concentrations (wt %)	Required additives
Carboxymethylcellulose	4–6	Na^+
	10–25	Na^+
Methylcellulose	2–4	
Hydroxypropylcellulose	8–10	
Hydroxypropylmethylcellulose	2–10	

Table 8. Gelling concentrations of cellulose derivatives commonly used in topical hydrogels [18].

5.1.3. Physical aging

As the structure of cellulose derivatives hydrogels have not reached the equilibrium, these gels physically age as they move toward respective equilibrium. It is important to consider this physical aging of cellulose derivatives hydrogels, because it is accompanied by changes in gels microstructure where noncovalent cross links are breaking and reforming [16].

5.2. Rheological properties

The mechanical properties of cellulose derivatives hydrogels as water-soluble ointment bases must be considered during the development of a topical medicated hydrogel, as they are very important not only for the establishment of the topical drug formulation and the manufacturing method, but also for packaging, storage, and application.

Due to their semisolid consistency, cellulose derivatives hydrogels are viscoelastic, semistiff gels that exhibit a pseudoplastic flow [91]. These rheological properties are strongly related to the concentration and average molecular weight of the polymer, the gel structure and interchain interactions, and entanglements. So, the hydrogels of methylcellulose and hydroxypropylcellulose of 3–6% concentration exhibit a pseudoplastic character, while those of sodium carboxymethylcellulose types of high molecular weight and low substitution, with a concentration of 5–6% exhibit thixotropy, in addition to pseudoplastic flow. The apparent viscosity or gel strength of cellulose derivative hydrogels increases with an increase in their effective cross-link density or in the concentration and molecular weight of the polymer. Also, a rise in temperature decrease the apparent viscosity of these hydrogels, but under normal conditions, this effect is reversible. In addition, as it was discussed in the previous section, changes in apparent viscosity and consequently in other rheological properties of cellulose derivatives hydrogels can occur when different components such as salts, surfactants, solvents or nonsolvents, and other compatible polymers are added in the formulation. The effects of these additives have been extensively studied in the past decades and are presented in each cellulose derivative technical book [15, 17, 28, 29, 92–94].

6. Preparation of cellulose-derivatives-based hydrogels as pharmaceutical dosage forms

Cellulose-derivative-based hydrogels are relatively easy to prepare. In pharmaceutical applications, these hydrogels can be formulated with or without a drug substance. Medicated dermal gels can contain, in addition to the cellulose derivative as gelling agent and active substances, antimicrobial preservatives (i.e., methylparaben and propylparaben, or chlorhexidinegluconate), stabilizers (i.e., edetate disodium), dispersing agents (i.e., alcohol and/or glycerol, propyleneglycol, sorbitol), and permeation enhancers [95–98]. Minimum gel-forming concentrations of cellulose derivatives are different, based on the type and the molecular weights of these derivatives, but the medium range is about 4–6% (w/v), as mentioned

before (**Table 8**). The most widely used hydrophilic external phase, in the preparation of these gels, is purified water. If the addition of cosolvents as dispersing agents is necessary, care should be taken to avoid their evaporation or degradation during gel preparation.

In manufacturing of dermal pharmaceutical cellulose derivatives hydrogels on a small scale (as in extemporaneous compounding), but also on a large scale (industry), the obtaining of an uniform preparation depends in a great extent on several factors including order of mixing, processing conditions, duration of swelling, and removal of entrapped air.

Mixing the above-mentioned components with the gelling agent should be made considering their influence on the gelling process. If the rate and extent of swelling of the gelling agent is affected by these ingredients, they are mixed after the gel formation. If such interference does not occur, the drug and the other additives are mixed prior to the swelling process; in this case, the effects of swelling duration, mixing temperature, and other processing conditions on the physicochemical stability of the drug and additives are also to consider. In general, the following order of mixing is recommended: (1) the drug substances are dissolved or suspended in the hydrophilic phase necessary for the gel preparation; (2) the other additives are dissolved in the obtained solution or in a small amount of the hydrophilic phase respectively; (3) if necessary, the drug dispersion is mixed with the additives solution; (4) the powder of the gelling agent is added under light stirring in the obtained solution/dispersion and allowed to swell.

In the preparation of cellulose derivatives hydrogels, the temperature and pH of the dispersion are critical parameters, as the gelation mechanism of these polymers is temperature dependent and their optimum stability depends on pH. Thus, the macromolecules dispersion is recommended to be heated either before, or after the polymer swelling. In case of MC and HPMC, the heating is indicated before the swelling occurs, but in case of HPC, HEC, and NaCMC, which dissolve better in hot water, the heating of their molecular dispersions is performed after de particle swelling. Practically, the general preparation method of most cellulose derivatives hydrogels involve the dispersion of polymer powder in cold water by using mechanical mixing to form uniform lump-free dispersion, followed by heating to about 60–80°C of the obtained dispersion, which is then gradually cooled to room temperature to form a gel. Also, there are differences regarding the pH values of dispersion medium favorable for gel formation: NaCMC, MC, and HPMC form gels over a wide pH range (4–10), whereas HPC and HEC form gels at a pH of 6–8 and respectively at alkaline pH condition. Another critical parameter in the preparation of cellulose derivatives hydrogels is the duration of polymer swelling. Generally, a swelling duration of about 24–48 h helps in obtaining homogeneous gels, as the cellulose polymers require about 48 h for complete hydration.

Finally, removal of the entrapped air is also an important issue to consider in the manufacturing of cellulose derivatives hydrogels, because the presence of air bubbles in the gel, which is inevitable, affects their transparency. The incorporation of air bubbles into the gel can be minimized by positioning the propeller at the bottom of the mixing container. Further removal of air bubbles by different methods including long - term standing, low -temperature storage, sonication, or inclusion of silicon antifoaming agents is commonly used. In addition, in

large scale production vacuum vessel deaerators are used to remove the entrapped air [95, 97–99].

Figure 1 shows the flow chart of the fabrication process of a cellulose derivative hydrogel.

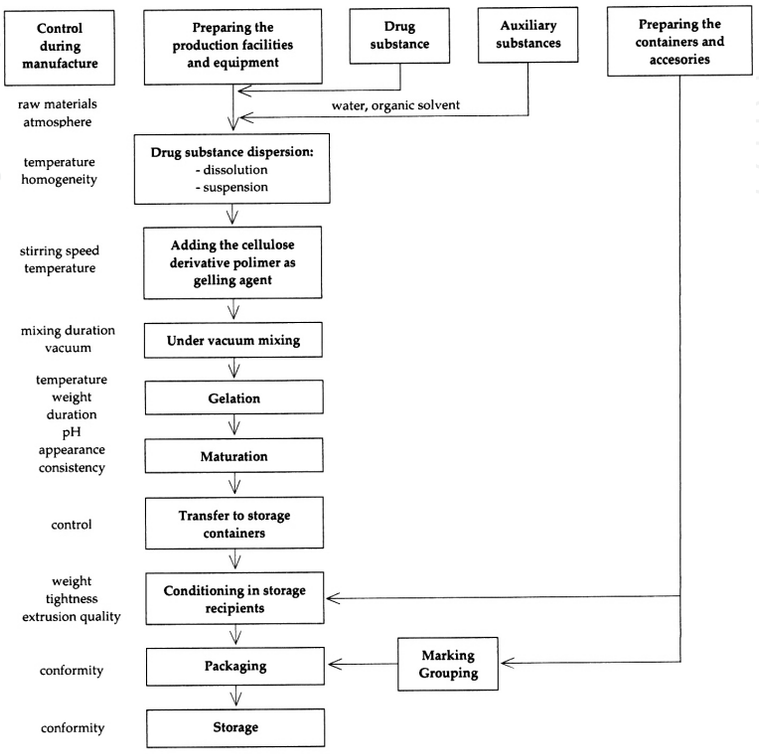

Figure 1. Flow chart of the manufacturing processes of a cellulose derivative hydrogel.

In small scale, the preparation of hydrogels by dispersing of polymer by hand or mechanically, in hot/cold water or in a nonsolvent, is carried out using simple equipment and utensils existing in the pharmacy laboratory, such as: mortars and pestles of porcelain or glass, beakers, magnetic stirrers, and different propeller mixers. In large scale production of pharmaceutical cellulose derivatives hydrogels, different mills, separators, mixers, deaerators, and shifters are used. **Figure 2** present two different processing machines for the hydrogels preparation: a single mixing kettle equipment with slow agitation to avoid air entrapment (a) and "one bowl" vacuum processing machine (b) which is designed to control the processing temperature, and to mix (using a counterrotating mixing system), homogenize (using a high-shear rotor/stator system) and remove the entrapped air (during the product recirculation) [95, 98].

7. Characterization of cellulose derivatives hydrogels as dermal pharmaceutical dosage forms

The physicochemical, microbial and biological characteristics of cellulose-derivatives-based hydrogels are evaluated by a variety of pharmacopoeial and nonpharmacopoeial tests that are

carried out to assess the quality and performance of hydrogel formulations and to minimize the batch-to-batch variations. Generally, the US, European, Japanese, and many other pharmacopoeias recommend the following tests: appearance (transparency or clarity), homogeneity, particle size analysis, pH, minimum fill, rheological measurements (viscosity, consistency), stability, microbial screening, *in vitro* drug release testing and assay. Consequently, a range of experimental techniques are used, more often in tandem, to characterize these hydrogels, providing appropriate evidences for their quality and performance.

The transparency or "clarity" of hydrogels is determined by visual methods or is measured as light transmittance by spectroscopy. Their homogeneity is usually assessed by visual examination and the surface morphology by scanning electron microscopy, which analyze under an electron microscope the lyophilized hydrogel gold sputter coated [99, 100]. Optical microscopy, dynamic light scattering and laser diffraction are currently used to determine the size, shape and granulometric distribution of particles of the suspended active substances, as these particles characteristics can influence several properties of a medicated hydrogel such as the rheological properties, stability, and therapeutic activity. Since these properties of cellulose derivatives hydrogel may be also affected by their pH, this parameter must be considered in their quality control. The pH is measured by potentiometry, using either special pH electrodes designed for viscous gels, or conventional pH electrodes for water diluted gels [101]. The content uniformity assessment of hydrogel product can be supported by the minimum-fill test that is performed to compare the weight of product filled into each container labeled with their weight.

Rheological analysis of cellulose derivatives hydrogels is very important for their characterization and quality control, providing valuable information for their formulation, manufacturing, use, and therapeutic activity. Rheological properties of cellulose derivatives hydrogels are determined by mechanical techniques using more often small-deformation and penetrometric measurements. Small-deformation measurements can be performed under both continuous shear and dynamic oscillatory conditions, being used to determine the viscoelastic properties of these gels. Continuous shear instruments (i.e., rotational viscosimeter, cone-

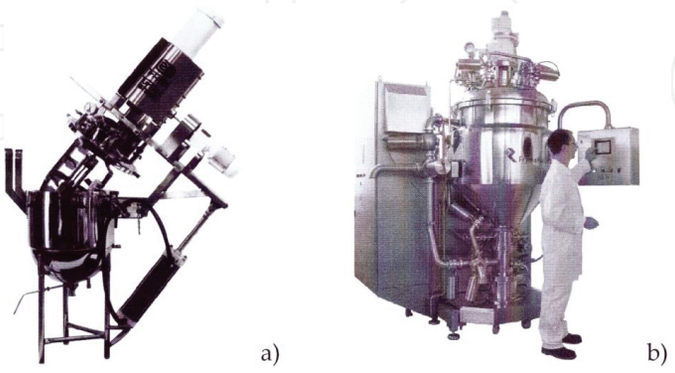

Figure 2. Processing machines for the hydrogels preparation: (a) Stainless steel jacketed kettle with agitator (courtesy of Lee Industries, Inc., Philipsburg, Pennsylvania); (b) vacuum processing machine used for the preparation of gels (courtesy of Fryma Koruma, Rheinfelden, Switzerland).

and-plate viscosimeter) measures the apparent viscosity, yield stress, and shear modulus *G*(or modulus of rigidity), and generates a complete rheogram for a particular hydrogel, allowing to identify its flow behavior. Unlike continuous shear measurements, dynamic oscillatory testing, using rheometers, does not modify the hydrogel microstructure and measures another two important parameters, namely the storage modulus *G*′ and the loss modulus *G*″, reflecting the hydrogel viscoelasticity [23, 102–105]. The consistency determination is a specific test for semisolids, including the hydrogels and is performed by penetrometry, according to pharmacopoeial specifications [101]. This compendial method measures the hardness of hydrogels, but the other rheological characters of these systems reflected by consistency (i.e., rigidity, spreadability, elasticity, and adhesiveness) can be also measured by different noncompedial techniques, using modern instruments such as texture analyzers [106]. Further, as it was mentioned in Section 5, rheological measurements are powerful experimental techniques for probing both the sol-gel transition and swelling behavior of cellulose derivatives hydrogels.

Due to their high water content, cellulose derivatives hydrogels are susceptible to physical, chemical, and microbial stability alterations. Syneresis, a commonly observed phenomenon of physical instability of these hydrogels, can be determined by water loss from the gel network after a heating-cooling cycle. In the case of medicated cellulose derivatives hydrogels, the chemical stability of active substances into the gel is evaluated by accelerated aging studies, which use different analytical methods to evidence the possible drug degradation in the hydrogel, under extreme conditions of temperature, moisture and light [95].

Although is a noncompendial test, *in vitro* drug release testing is of high interest as it can reflect the combined effects of several formulation parameters (i.e., the type of cellulose derivative as gelling agent, the drug concentration, the pH, and viscosity of hydrogel) on the *in vitro* drug release and permeation parameters. In the last decade, continuous efforts in international harmonization have been made to standardize the methodology and the study protocols of *in vitro* drug release from dermal products [107, 108].

8. Applications of cellulose-derivatives-based hydrogels for dermal and transdermal drug delivery

Cellulose-derivatives-based hydrogels, as pharmaceutical dosage forms, have been developed with their end use mainly in topical drug delivery [109]. These hydrogels are widely used as water-soluble ointment bases usually for dermal and, in a lesser extent, for transdermal delivery of various categories of drugs including nonsteroidal anti-inflammatory agents, antifungals, antibiotics, anesthetics, analgesics, antiallergics, antiseptics, keratolytics, revulsive agents, β-blockers etc. From the formulations intended for dermal delivery, the drug has to pass through the *stratum corneum*, the outermost layer of the skin to reach the subjacent skin layers. Therefore, medicated dermal formulations ensure the drug localization in the skin layers. Instead, from transdermal formulations the drug is transported in the skin dermis and then enters into the systemic circulation [110]. However, the excellent barrier properties of the

stratum corneum limit the drugs penetration through the skin in both dermal and transdermal drug delivery. Therefore, several strategies have been used to enhance and control the drug transport across the skin, and to increase the number of the delivered drugs. These strategies involve both chemical methods, based on the use of penetration enhancers that temporarily increase the skin permeability, and physical methods, in which a driving force is provided to act on the drug [110].

8.1. Dermal drug delivery

Dermal medicated hydrogels based on cellulose derivatives are intended to treat different acute or chronic, mild or moderate skin conditions (i.e., eczema, dermatitis, psoriasis, acne, warts, inflammations, and allergies).

Medicated gel formulations based on cellulose derivatives were obtained by dispersing the drug directly into the hydrogel vehicle or by entrapping the drug in colloidal carriers (micro- and nanoemulsions, liposomes, niosomes etc.) acting as percutaneous enhancers. In the past decades, the favorable effect of cellulose derivatives hydrogels on dermal drug delivery has been demonstrated by a large number of published original scientific papers, academic reviews, monographs and books focused on preparation, characterization and applications of cellulose derivative hydrogels [85, 89, 111–117].

Due to their specific properties, some of gel-forming cellulose derivatives, such as NaCMC and MC are used for the development of wound dressings, usually in combination with other hydrophilic polymers and propyleneglycol, which act as humectant and preservative. These hydrogels proved to be effective as treatment for burned tissues and nonhealing diabetic ulcers [16, 39, 118, 119].

In **Table 9** are included the main studies that have been conducted in the past decade on cellulose-derivatives-based hydrogels as vehicles for dermal delivery of different drugs.

This section provides a survey of the relevant results of the recent reports published in the last decade.

Kouchak and Handali [121] studied the effect of some skin penetration enhancers, including sodium tauroglycocholate, lauric acid, and ethanol on the *in vitro* permeation of aminophylline from 3% HPMC-based hydrogels through snake skin. Sodium tauroglycholate and ethanol at concentration of 100 μg/ml and 60%, respectively, produced a 6-fold increase of the permeation parameters (flux and permeation coefficient), being the optimum enhancers for aminophylline, intended to be used as anticellulitic agent.

From the class of antifungal agents, clotrimazole, bifonazole, and fluconazole were selected as model drugs that were solubilized in emulsion or microemulsion systems, which were then loaded in a cellulose derivative-based hydrogel in order to improve the viscosity of the emulsion/microemulsion and make it suitable for cutaneous application. Shahin et al. [125] studied several jojoba oil-based emulgel formulations as potential clotrimazole delivery vehicles. Jojoba oil was used as lipophilic phase, Span 60 and Brij 35 were used as surfactants, propyleneglycol was selected as humectant and for its aesthetic benefits, and hydroxy-

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propylmethylcellulose and/or Carbopol 934P were chosen as gelling agents; triethanolamine was used to neutralize the formula containing carbomer to the pH range 5.5–6.5. It was found that the concentration and type of the gelling agent significantly influenced the viscosity and the consistency of the examined systems. Also, the *in vitro* clotrimazole release data showed an inverse correlation between the concentration of the gelling agent and the extent of the released drug. The formulation containing the combination of two gelling agents, HPMC and Carbopol 934P, in concentrations of 1% and 0.2%, respectively, showed stable rheological properties (shear thinning behavior with little thixotropy), high extent of drug release and superior antifungal activity in comparison to a commercially available preparation [125].

Drug	Cellulose derivative as gelling agent	Pharmaceutical dosage form	References
Alaptide	HEC, HPC, MC	Hydrogel	[120]
Aminophylline	HPMC	Hydrogel	[121]
Bifonazole	HPMC	Microemulsion-loaded hydrogel	[122]
Clarithromycin	HPMC	Emulgel	[123]
Chlorphenesin	HPMC	Emulgel	[124]
Clotrimazole	HPMC	Emulgel	[125]
Diclofenac sodium	CMCNa	Hydrogel	[126]
Etoricoxib	HPMC	Hydrogel	[127]
Fluconazole	CMC	Emulgel, microemulsion-loaded hydrogel	[128]
	HPMC	Hydrogel	[129]
Ketorolac tromethamine	HPMC	Hydrogel	[130]
Lidocaine	HPC	Hydrogel	[131]
Lidocaine hydrochloride			
Meloxicam	HPC	Hydrogel	[132, 133]
Mepivacaine		Hydrogel	[134]
Piroxicam	HPMC	Emulgel	[135]
	MC, HPMC, CMC	Microemulsion-loaded hydrogel	[136]
Propranolol hydrochloride	HPMC	Hydrogel	[137]

Table 9. Overview of cellulose-derivatives-based hydrogels as vehicles for cutaneous delivery of drugs.

In order to improve the solubility and skin permeability of bifonazole, Sabale et al. [122] investigated several oil-in-water microemulsion-loaded hydrogels composed of bifonazole (1%) water, oleic acid as oil, Tween 80/isopropyl alcohol as surfactant/cosurfactant mixture, and two grades of HPMC (K15M and K100M) in concentrations of 1, 1.5, and 2%. After optimization of the microemulsion formulation by 3^2 factorial design and of the polymer concentration for preparation of microemulsion-loaded hydrogel based on viscosity, the composition of the optimized microemulsion-loaded hydrogel was bifonazole (1%), oleic acid (6.25%), Tween 80/isopropyl alcohol (55%, 3:1), water (38.75%), and HPMC K100M (2%).

The results of the *ex vivo* permeation study through excised rat skin indicated that bifonazole presented a permeability of 84% within 10 h and a sustained release from the optimized formulation, due to the presence of the gelling agent; the drug release was accurately described by the zero order model. Also, the developed preparation exhibited a good stability over a period of 3 months, no skin irritancy and an antifungal activity comparable with a marketed bifonazole cream [122].

Salerno et al. [128] studied the *in vitro* fluconazole release from different topical dosage forms, aiming to determine a formulation with the capacity to deliver the whole active compound and maintain it within the skin, in order to be considered as a useful formulation, either for topical mycosis treatment or as adjuvant in a combined therapy for Cutaneous Leishmaniasis. Sodium carboxymethylcellulose was used for emulgels and microemulsion-loaded hydrogels as gelling agent, and propyleneglycol and diethyleneglycol monoethyl ether (Transcutol P®) were used for each dosage form as solvent for the drug and also as penetration enhancers. The microemulsion-loaded hydrogel containing Transcutol P® delivered the whole applied dose of fluconazole, and showed the highest ability to penetrate pig skin (a four times greater of total amount drug released than that from lipogels) and an important ability to keep the drug within the skin layers; also this formulation proved to be the most effective in regard of the *in vitro* antifungal activity. Further, the authors concluded that in the case of CMCNa-based dosage forms (emulgels and microemulsion-loaded hydrogels), the viscosity was not the main parameter governing the fluconazole release, as these systems showed similar viscosity, but different rates of the released drug [128]. Other study investigated the *in vitro* release of fluconazole from different hydrophilic gels, containing HPMC, chitosan or poloxamer 407 as gelling agents, propyleneglycol as cosolvent and various penetration enhancers (glycerol, PEG 400, Tween 80, and cetrimide). Among the studied hydrogels, those based on HPMC produced the higher percentages of fluconazole released after 6 h, either in the presence or absence of glycerol (66.66 and 71.65%, respectively), glycerol was found to be the most effective release enhancer [129].

Nonsteroidal anti-inflammatory agents, such as diclofenac sodium, oxicams (piroxicam, meloxicam), and ethoricoxib, were used as model drugs in several studies investigating the effects of the structure and the components of the vehicle on drug release and penetration from cellulose-derivative-based hydrogels [126, 127, 130, 132, 133, 135, 136]. A base-gel formulation consisting of 2.5% hydroxypropylcellulose (Klucel), propyleneglycol, ethanol, and water (1:1:1) was selected to investigate the effect of four penetration enhancers (dimethylsulfoxide, Tween 20, oleic acid, and menthol) on *in vitro* permeability of meloxicam through IPM-saturated cellulose membranes and human cadaver skin [132]. Permeation studies through human cadaver skin showed that the highest flux value (2.43 ± 0.47 μg/cm^2/h), with a corresponding enhancement ratio of 27.5, was obtained from HPC-based hydrogel containing 5% menthol as penetration enhancer. According to the authors, the developed meloxicam gel formulation consisting of 2.5% Klucel® gel, 0.3% meloxicam, 5% menthol, and the mixture of propyleneglycol, ethanol, and water (1:1:1) offers the possibility to deliver through the skin therapeutically effective amounts of meloxicam [132]. The potential of 2.5% hydroxypropylcellulose hydrogel, containing a combination of enhancers, to produce a required flux

of meloxicam to maintain therapeutic concentration, was confirmed by another study performed by Chang et al. [133]. The effects of a combination of four penetration enhancers (ethanol, propyleneglycol, menthol, and azone) acting by different mechanisms, on the penetration of meloxicam sodium from HPC-based hydrogels through rat skin, was investigated by the response surface methodology. Also, the uniform design technique was applied to prepare systematical model formulations, which were composed of four formulation factors (the content of ethanol, propyleneglycol, menthol and azone); the penetration rate (flux) was chosen as the response. The obtained results demonstrated, on one hand, that the optimal meloxicam sodium hydrogel formulation can be designed using this response surface methodology, and on the other hand, that menthol influenced, in the greatest extent, the skin permeation of meloxicam sodium, followed by azone, ethanol, and propyleneglycol respectively. The optimal transdermal formulation, containing 1% meloxicam, 2.5% HPC, 37.1% ethanol, 15.4% propyleneglycol, 2.9% menthol, 4.3% azone, and water, had appropriate flux value (467.6 ± 89.3 μg/cm^2/h) which met the required flux value of meloxicam (400 μg/h) for maintaining a therapeutic concentration. Further, the *in vivo* absorption study showed that meloxicam could be determined at 1 h after 2.3 cm^2 topical administration and reached steady-state concentration in about 12 h; the bioavailability of the optimal meloxicam sodium gel was about 50.1% [133]. In another study, aiming to determine the optimal base that promote the *in vitro* release of piroxicam, several gel bases consisting of different polymers in various concentrations (3% MC, 2% CMC, 3% HPMC, 0.5% Carbopols 934 and 940, and 20% Pluronic F-127) were evaluated [136]. In each of these gel bases, piroxicam (0.5%) was incorporated as such and in the form of a microemulsion, consisting of oleic acid as oil, Tween 80 as surfactant and propyleneglycol as cosurfactant. The developed gel formulations were evaluated for their rheological properties, stability and *in vitro* piroxicam release through an artificial membrane. Comparison of the *in vitro* release results showed that the 3% MC and 3% HPMC gel bases loaded with piroxicam-microemulsion released the higher amounts of drug after 180 min (97% and 94%, respectively). However, considering also the rheological properties and shelf life, the above mentioned HPMC gel-base loaded with microemulsion was proposed as the most suitable vehicle for topical delivery of piroxicam [136].

Prakash et al. studied the *in vitro* release of ethoricoxib through rat epidermis and human cadaver skin from several hydroethanolic gels based on different polymers as gelling agents (Carbopol, HPMC K4M, MC, and HPC) in the presence of various permeation enhancers such as DMSO, lemongrass oil, menthe oil, and oleic acid [127]. The results of *ex vivo* permeation study revealed that hydroethanolic gel containing 2% HPMC with 2% lemongrass oil produced the highest cumulative amounts of ethoricoxib permeated at 6 h (99.28%), similarly as the studied marketed product (99.89%). Also, this formulation showed comparable anti-inflammatory activity with the marketed product.

In our research work, a hydroethanolic gel based on 2% HPMC and 60% ethanol was used as vehicle for a hydrophilic model drug (propranolol hydrochloride) in the presence of some terpenes as penetration enhancers (menthol, camphor, eucalyptol, thymol, and α-bisabolol) at 5% concentration [137]. The results of our *in vitro* permeation study through pig ear skin, indicated that eucalyptol and α-bisabolol were the most effective terpenes in enhancing the

skin transport of propranolol hydrochloride from HPMC-based hydroethanolic gels. Thus, we considered that the gel formulations consisting of 3% propranolol hydrochloride, 2% HPMC, 60% ethanol, and 5% terpene (eucalyptol or α-bisabolol) should be an alternative to oral dosage forms of this drug, recently reported as an effective treatment for infantile haemangioma [137].

These studies, but also many other, showed that the release properties of topical formulations and consequently of the base, are mainly controlled by the drug thermodynamic activity, particle size and diffusion through the preparation. Generally, the diffusion coefficient of a solute in a base is inversely related to the viscosity of the continuous phase. Consequently, the drug release decreases with the increase of viscosity, which is due to the increase in gelling agent concentration. Also, it was suggested that high polymer concentrations increase the resistance to diffusion in a greater extent than expected, because the drug particles are trapped by the polymer macromolecules and they are much closed to the respective entities. Moreover, at high polymer concentrations the density of chain structures increases, thus limiting the drug movement area. Therefore, in the case of gels, including those based on cellulose derivatives, it is considered more appropriate to relate the diffusion coefficient of drug particles in solution to the gel microviscosity, which controls the movement of the particles [138, 139].

8.2. Transdermal drug delivery

Nowadays, transdermal drug delivery is considered an attractive alternative to the conventional drug delivery methods (oral administration and injection) used for the systemic delivery of drugs. Hydrogels, including cellulose-derivatives-based hydrogels, were proposed and studied as transdermal drug delivery systems due to their several benefits including ease of application and delivery, sustained and controlled drug release, reduced systemic side effects, bypass of hepatic first pass effects and potential to provide a better feeling for the skin compared with conventional ointments and patches [140]. A recent research paper evidenced that a 1% HPMC-based hydrogel formulation produced higher permeation rates of diltiazem hydrochloride through rabbit skin (1569.5 $\mu g/cm^2$) than other studied gel formulations (organogels and bigels). Moreover, *in vivo* study of diltiazem hydrochloride as transdermally applied antihypertensive agent revealed that the HPMC-based hydrogel formulation produced a faster and sustained antihypertensive effect compared with other studied gels. The superiority of diltiazem hydrochloride hydrogel based on 1% HPMC in terms of drug permeation through the skin was attributed to high water content that facilitates the release of the hydrophilic drug from the gel-base and increases epidermal cell hydration, thus enhancing the drug diffusion across *stratum corneum* [141].

However, numerous drugs such as hydrophilic, high molecular weight, and charged active substances are not able to penetrate the skin, because of their structure and physicochemical properties. Therefore, in the recent past, physical penetration enhancement techniques including ionophoresis, sonophoresis, electroporation, and laser irradiation gained attention in transdermal drug delivery research. The therapeutic effects of above-mentioned electrically assisted techniques, used alone as well in combination or further, in conjunction with chemical enhancers, for transdermal drug delivery were intensively investigated [110, 142–147]. Furthermore, hydrogels proved to be suitable formulations for assisted transdermal

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delivery by ionophoresis, sonophoresis, and electroporation due to their advantageous characteristics such as ease of loading into the device, suitability with the electrode design, good flexibility and fitting with the skin contour, strength, transparency, stability, and high electrical conductivity, which is attributed to their high water content [116, 148, 149].

A number of studies reported the successfully transdermal delivery of different drugs from cellulose-derivatives-based hydrogels using ionophoresis alone and combined with other enhancement physical or chemical techniques. Tavakoli et al. [150] investigated the transdermal iontophoretic delivery of celecoxib from several gel formulations, containing different gelling agents (sodium alginate, sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, and Carbopol 934P). Among the studied gel-bases, the hydrogel containing 4% HPMC K4M was considered the optimal formulation for the iontophoretic studies, as it showed higher spreadability and ability to retain on the skin, and released the highest percent of celecoxib after 5 h (41.5%). The findings of the *ex vivo* studies showed that iontophoretic transport of celecoxib from HPMC K4M-based hydrogels through rat skin was 2-fold higher than the passive flux [150].

Recently, the feasibility of using a 2% HEC-based hydrogel as gel-base for successful iontophoretic transdermal delivery of the E-selectin antagonist CGP69669A, a sialyl Lewisx-glycomimetic with potential activity against inflammatory skin diseases was reported. Although the *in vitro* drug permeation through porcine and human skin from the hydrogel formulation was lower than from aqueous solution, the skin deposition (more relevant for the local treatment of dermatological conditions) was 3-fold higher, which was attributed to the occlusive effect of the gel layer on the skin surface, increasing the degree of dermal hydration and consequently promoting the permeation of the hydrophilic CGP69669A [151].

Nandy et al. studied the efficacy of iontophoresis used alone and in combination with chemical enhancers (L-menthol and Tween 20) on transdermal delivery of atenolol from an aqueous solution and several hydrogel formulations based on 3% sodium carboxymethly cellulose or 3% methylcellulose, through excised abdominal rat skin. The obtained results demonstrated that cellulose-derivatives-based hydrogels were more suitable than a solution as transdermal iontophoretic delivery systems, ensuring a sustained release of atenolol. Also, compared with passive delivery, iontophoresis increased the atenolol transport from all studied gel formulations through rat skin. Moreover, the synergistic effects of iontophoresis and chemical enhancers were revealed. Considering this and the superiority of L-menthol as penetration enhancer compared to Tween 20, the NaCMC- and MC-based hydrogel formulations, containing 1.5% atenolol and 2% L-menthol combined with iontophoresis were considered as the best drug delivery systems to achieve the desired drug level [152]. The advantageous combination of iontophoresis and penetration enhancers for transdermal delivery was also recently evidenced in the case of diclofenac sodium formulated as hydroxyethylcellulose-based hydrogels containing different terpenes. The diclofenac sodium hydrogel containing geraniol produced an iontophoretic flux 5.16-fold higher than the passive control, being considered as optimal formulation [153]. Another research report revealed the feasibility of using carboxymethylcellulose-based hydrogels for transdermal delivery of

buprenorphine under the application of iontophoresis or electroporation, separately or together [154].

8.3. Commercial products

A list of examples of pharmaceutical gel products, based on cellulose derivatives with their corresponding therapeutic activity, is shown in **Table 10**. The pharmaceutical gel products containing HPC offer the advantage of the polymer compatibility with high percentages of alcohol.

Commercial gel and manufacturer	Cellulose derivative	Drug and therapeutic activity
Persa-Gel 10 (Otho Derm)	Hydroxypropyl methylcellulose	Benzoyl peroxide; antibacterial
Diclac gel (Hexal AG)	Hydroxypropyl methylcellulose	Diclofenac sodium; antiinflammatory, analgesic
Xylocaine jelly (Astra)	Hydroxypropyl methylcellulose	Lidocaine HCl; anesthetic
ArthriCare triple-medicated gel (Commerce)	Hydroxypropyl methylcellulose	Methyl salicylate, menthol; analgesic, revulsive
Erygel (Herbert)	Hydroxypropylcellulose	Erythromycin; antibiotic for acnee
Retin-A gel (Ortho)	Hydroxypropylcellulose	Retinoic acid; antiacne
Compound W gel (Whitehall)	Hydroxypropylcellulose	Salicylic acid; keratolytic
DuoPlant gel (Schering-Plough)	Hydroxypropylcellulose	Salicylic acid; keratolytic
Hydrisalic gel (Pedinol)	Hydroxypropylcellulose	Salicylic acid; keratolytic
Keralyt gel (Summers)	Hydroxypropylcellulose	Salicylic acid; keratolytic
Fungicure-Tolnaftate gel (Alva-Amco Pharmacal Companies, Inc.)	Hydroxypropylcellulose	Tolnaftate; antifungal
Naftin (Merz Pharmaceuticals, LLC)	Hydroxyethylcellulose	Naftifine; antifungal
Nurofen gel (Reckitt Benckiser Healthcare Int. Ltd.)	Hydroxyethylcellulose	Ibuprofen; antiinflammatory, analgesic
IntraSite™ Gel (Smith and Nephew)	Sodium carboxymethyl cellulose	Wound dressing
GranuGel™ (ConvaTec)	Sodium carboxymethyl cellulose	Wound dressing
Purilon Gel™ (ColoPlast)	Sodium carboxymethyl cellulose	Wound dressing
Aquacel Ag™ (ConvaTec)	Sodium carboxymethyl cellulose	Silver ions; wound dressing

Commercial gel and manufacturer	Cellulose derivative	Drug and therapeutic activity
Silvercel™ (Johnson & Johnson)	Sodium carboxymethyl cellulose	Silver ions; wound dressing

Table 10. Some commercially available gels containing cellulose derivatives.

9. Conclusion

Due to their typical properties, several water-soluble cellulose derivatives, namely methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and sodium carboxymethylcellulose, have gained increasing interest for pharmaceutical applications, being currently used as gelling agents in the development of topical drug delivery systems. Among the specific properties, which support the extensively use of water-soluble cellulose derivatives as thickening agents in dermal gel formulations, it can be mentioned the diversity of cellulose derivatives, with broad compatibility with many active substances and wide range of viscosities correlated with variable polymer concentrations. In the presence of water, these hydrophilic cellulose derivatives form reversible hydrogels composed of networks of dissolved macromolecules, which possess specific properties in terms of swelling behavior, gel point and sensitivity to external stimuli. The cellulose-derivatives-based hydrogels are widely used as water-soluble ointment bases for dermal and transdermal drug delivery, due to their unique characteristics such as transparency, high water content, spreadability, good skin tolerability, bioadhesiveness, availability, and also biocompatibility and biodegradability, which make them similar with living tissues. In addition, these hydrogels with or without drug substances are relatively easy to prepare either on a small scale (as in extemporaneous compounding) and on a large scale (industry). Although numerous medicated and nonmedicated hydrogels based on cellulose derivatives have been developed, studied and even patented, only few have reach the pharmaceutical market. Therefore, more studies on this topic are expected so as to fully explore the potential of cellulose derivatives hydrogels as dermal and transdermal drug delivery systems.

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