Thermosensitive Hydrogels in Dermatology: A Multidisciplinary Overview

22

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22.1 Introduction

The hospital triad formed by the dermatologist, the pharmacist, and the nurse is involved in the prescription, the preparation, and the administration of adapted, efficient, and safe medicines. Each professional defines specific requirements concerning dermatological treatments which might be schematically conceptualized in Fig. 22.1. However, many medical and nursing requirements concerning topical treatments imply, for hospital pharmacist stuck "between the

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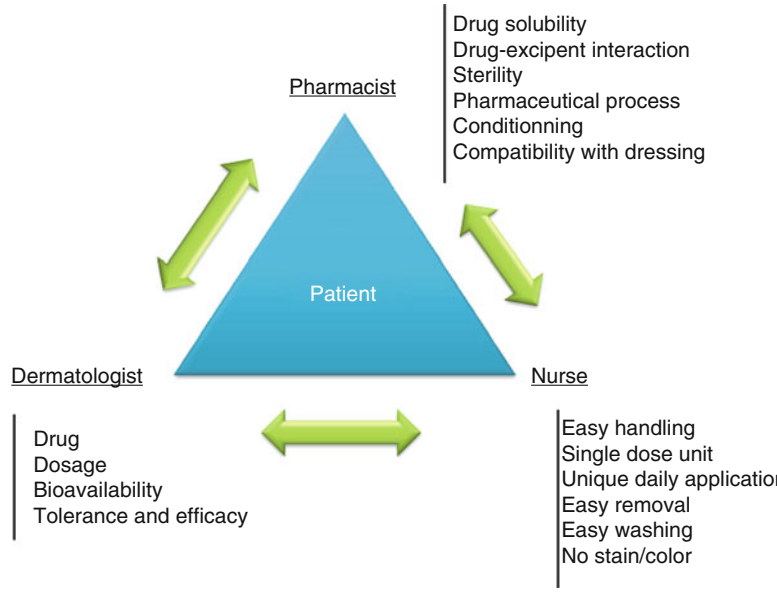


Fig. 22.1 The hospital triad involved in dermatological medicine management and major outcome that should be considered by each protagonist

mortar and the pestle", numerous practical considerations.

Firstly, active pharmaceutical ingredients (APIs), currently prescribed by dermatologist, exhibit low aqueous solubility (e.g., class II, diclofenac; class IV, sulfadiazine) and low permeability (e.g., class III, acyclovir, and class V, acetazolamide) which complicate the selection of excipients for compounding. Therefore, pre-formulation studies are usually necessary for screening appropriate excipients when compounded preparations prescribed are not detailed or indexed in the Pharmacopeia and the Formulary (i.e., national compendia for chemical and biological drug substances, dosage forms, and compounded preparations, excipients, medical devices, and dietary supplements). Both national compendia display substantial heterogeneity in their contents over the world.

Secondly, although medical and scientific literature detailed many original excipients, alone or in combination, enabling the formulation of APIs for topical treatment, few topical preparations are reported in the Pharmacopeia and the Formulary.

Thirdly, the suppliers of pharmaceutical grade excipients necessary for dosage forms and compounded preparations are (1) scarce, (2) sometimes located in foreign country limiting importation and/or exportation of pharmaceutical products, (3) not permanently approved by local health and safety regulatory authorities, and (4) not scaled for small production, packaging, and shipment of excipients and APIs to health-care hospital or clinical establishments.

Fourthly, the safety of excipients is recurrently questioned by authorities from the analysis of notable adverse effects imputable to excipients shifting their status from inactive to mystery ingredients, reducing again the width of the field of choice (Noiles and Vender 2010).

Fifthly, the conservation, the packaging, and storage of topical formulations is a major concern since the use and reuse of the preparation is an obvious source of human and exogenous contamination, a factor of physicochemical degradation (e.g., hydrolysis, oxidation) of APIs and excipients, and an issue for formulation instability (e.g., syneresis, creaming, sedimentation).

Again, the degree of purity of excipients, from different origins (i.e., from biological or mineral to chemical-based synthesis), is often weakened by concomitant components or processing aids, and the final use of excipients is not always known by the supplier. Therefore, the choice of appropriate excipients for topical compounding is also a com-

promise between pharmaceutical state of the art and the regulatory and availability status of excipients. Facing (i) the pharmaceutical compounding challenge, (ii) the inherent restrictions of available, authorized, and harmless excipients, (iii) the package features, surely, the simplest drug-excipient combination for ready-to-use and easy-handling product is highly needed for the formulation development of topicals.

However, the pharmacist experiences that, at some points, the development of topical preparation leads to consider top-ten recommendations:

1. Avoiding the use of many excipients, to prefer straightforward process of preparation where APIs are quickly dissolved, miscible, or suspended in aqueous solvent supplemented by not more than three excipients
2. To choose excipients insuring both physical and chemical stability of APIs, excipients, and formulation
3. To reduce pH variation of formulation over time during skin exposure (skin surface – pH ~5.5)
4. To check the probability to reuse and to avoid contamination of formulation
5. To guarantee easy spreading and removal, sustainability, and aesthetical acceptability (i.e., feel, color, fragrance, absorbability) of formulation
6. To permit optimal API penetration into skin structures (dermal delivery)
7. To permit optimal API permeation through skin structures (transdermal delivery)
8. To favor or to limit the buildup of APIs and excipients into the skin
9. To improve the cutaneous tolerance to APIs and excipients
10. To improve the efficacy of APIs into the skin or after percutaneous delivery

Therefore, few excipients might fulfill prerequisites detailed above. Among likely candidates, excipients forming thermosensitive (also called thermoresponsive or thermoreversible) hydrogels offer many advantages which have been extensively detailed in reviews published in the last decade (Jeong et al. 2012; Klouda and Mikos 2008; Ruel-Gariépy and Leroux 2004). The main intrinsic advantages of thermosensitive hydrogel are as follows: (1) high water content, (2) solubilizing properties for hydrophobic APIs, (3) control of swelling properties and gelling temperature, (4) adaptation for tailor-made formulations in specific dermatologic diseases, and (5) versatile skin drug delivery from either surface application, intradermal or subcutaneous injection.

In the followings sections, physicochemical properties of current and innovative thermosensitive polymers are presented, and then the actual and prospective dermatological applications of thermosensitive polymer-based formulations are emphasized.

22.2 Thermosensitive Polymers

22.2.1 General Considerations About Hydrogels

The gelation in the aqueous solvent is a complex phenomenon where a polymer initially soluble in water becomes more hydrophobic by (1) interaction with mineral ions (e.g., gellan gum, natural anionic heteropolysaccharide, sodium alginate, natural polysaccharide), (2) variation of pH (e.g., polymers carrying carboxylic acid, phosphoric acid, and amine groups) leading to a change of conformation and swelling behavior (Schmaljohann 2006), or (3) modification of temperature. As a result, a transparent or translucent semisolid polymeric matrix is obtained where the fluid flow is limited by entrapment and immobilization of the solvent molecules and possesses remarkable mechanical properties (deformation, viscoelastic properties) which facilitate further cutaneous spreading.

The regional ionic strength upon the outermost layer of the skin, the *stratum corneum*, is likely insufficient to elicit gelation with ionic-responsive polymers (i.e., making necessary pregelation of formulation containing appropriate ionic strength) (Aust et al. 2012), while acidic pH (~5.5) at the skin surface do not allow a gelation of common acidic polymer (e.g., carbomer).

Besides, the regulation of body temperature, one of the major skin functions in homeostasis, might be exploited for the successful development of thermosensitive hydrogels.

Moreover, interactions between skin and thermosensitive polymers have been of growing interest in the past decades as (1) intimate properties and mechanics of such polymers were gradually documented and (2) skin is regarded as a promising alternative to traditional oral or parenteral routes for the administration of active pharmaceutical ingredients. Furthermore, interesting parallels between skin or subcutaneous tissues and hydrogels in terms of chemical and physical characteristics draw exciting perspectives for future developments in experimental and clinical fields (Lee et al. 2009).

22.2.2 General Considerations About Thermosensitive Hydrogels

The ability for a solution of polymer to modify its bulk viscosity in response to temperature variation is called thermosensitivity. Generally natural polymer solutions form gels at low temperature and liquefy when temperature rises, but chemically modified polymers or synthetic polymers may exhibit opposite behavior defined as reverse thermosensitivity. As the physical state (i.e., free flowing or non-flowing during usage time) can be controlled by thermal modulation, formulas containing those polymers may have innovating pharmaceutical applications due to control of solute transport abilities and biocompatibility. Various polymeric molecules exhibit thermosensitive properties such as natural polymers (e.g., gelatin, agarose, carrageenans), modified natural polymers (e.g., cellulose derivatives, chitosan, dextran, xyloglucan), synthetic polymers (e.g., N-isopropylacrylamide and its copolymers), or poloxamers (i.e., poly(ethylene oxide)/poly(propylene oxide), polyethylene glycol/polyester copolymers) (Table 22.1) (Jeong et al. 2012; Klouda and Mikos 2008; Ruel-Gariépy and Leroux 2004).

Figure 22.2 shows the literature content and patent applications over the last decade underlying the importance of natural and modified natural polymers in the dermatological research and subsequent clinical outcomes. Although well known and considerably used, cellulose derivatives and chitosan still motivate some intellectual property issues.

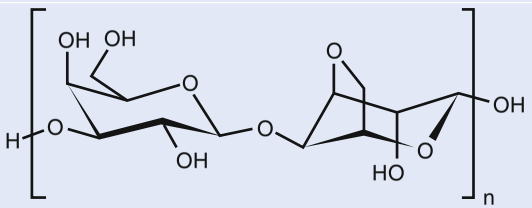
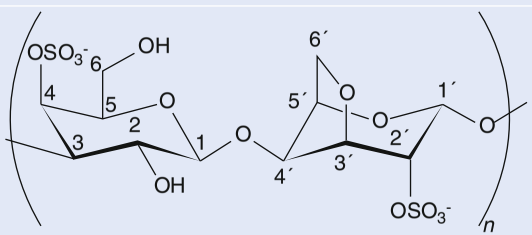
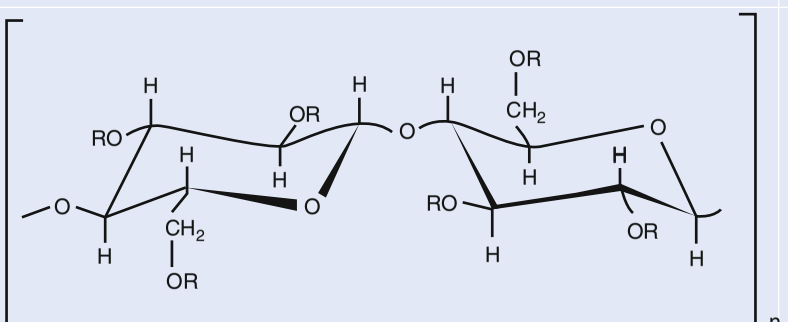
22.2.3 Physicochemical Characteristics of Thermosensitive Hydrogels

Many thermosensitive polymers are amphiphilic block copolymers with A-B or A-B-A type structures (A: hydrophilic block; B: hydrophobic block) that will form micelles in aqueous solvents. Polyethylene glycol (PEG) is commonly used as hydrophilic block due to biocompatibility and high water solubility. Hydrophobic block usually forms the drug-binding core of the system in hydrogels showing a large variety of structures such as polypropylene glycol and polyesters such as poly(lactide-co-glycolide) and poly(lactide-co-caprolactone) (Rijcken et al. 2007). Usually, polymer concentration in solvent will determine gelation temperature (Lenaerts et al. 1987). Nature and ionic content of thermosensitive polymer gel solvents is of great importance as it can significantly modify drug release properties (Pandit and Wang 1998; Ur-Rehman et al. 2010) and gelation ability (Pandit and Kisaka 1996). Also, ionic content has an influence on pH and drug ionization state which is an important issue to consider regarding skin-formulation interactions.

22.2.4 Rheological Properties of Thermosensitive Hydrogels

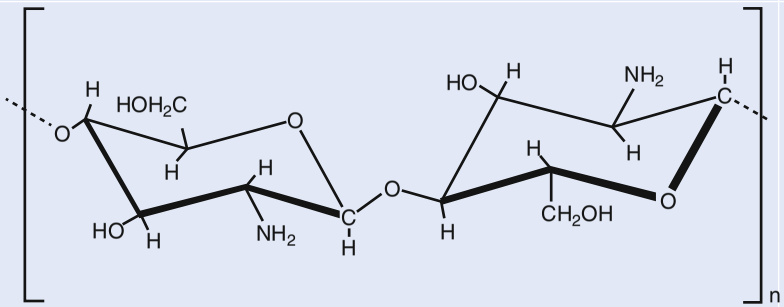
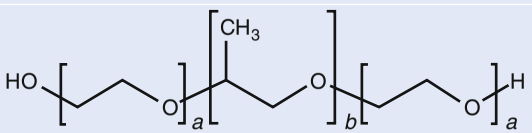
The mechanism of this viscosity change, called sol→gel transition when viscosity increases or gel→sol transition when it decreases, is dependent on molecular interactions within the polymer solution. Natural polymer solutions mostly form a gel phase when temperature is low and liquefy on heating. In these hydrogels, polymer molecules arrange in a partial helicoidal architecture that destructures in a random coil conformation when temperature rises (Ruel-Gariépy and Leroux 2004).

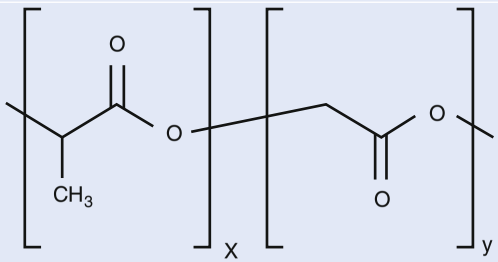
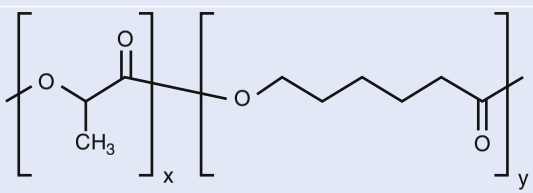
Table 22.1 Structures and formulas of polymers currently used for thermosensitive hydrogel formulations in commercial products or pharmaceutical compounding

Polymers	Formula	Molecular weight ($g.mol^{-1}$)	USP/Eur. Ph	CAS number
Gelatin[2]	e.g., -Ala-Gly-Pro-Arg-Gly-Glu-4Hyp-Gly-Pro-	15,000–250,000	Referenced/ referenced	9000-70-8
Agarose[2] (Agar)		306 • n	Referenced/ referenced	9063-31-4
Carrageenans[2]		451 • n	Referenced/*not referenced*	9000-07-1
Cellulose derivatives	 R = -H, $-CH_3$, $-CH_2CH_2OH$,$-CH_2CH(OH)CH_3$ $-CH_2OCH_2COONa$			

(continued)

Table 22.1 (continued)

Polymers	Formula	Molecular weight ($g.mol^{-1}$)	USP/Eur. Ph	CAS number
Methylcellulose[④]		10,000–220,000	Referenced/ referenced	9004-67-5
Hydroxyethylcellulose[②]		–	Referenced/ referenced	9004-62-0
Hydroxypropyl-cellulose[①]		50,000–1,250,000	Referenced/ referenced	9004-64-2
Hydroxyethyl methylcellulose[①]		–	*Not referenced/not referenced*	9032-42-2
Hydroxypropyl-methylcellulose[①]		10,000–1.500,000	*Not referenced/* referenced	9004-65-3
Carboxymethyl cellulose sodium[②]		90,000–700,000	Referenced/ referenced	9004-32-4
Chitosan[②]		320 • n	*Not referenced/* referenced	9012-76-4
Poloxamers				
124[⑤]	*a:* 10–15; *b*: 18–23	2,090–2,360	Referenced/ referenced	9003-11-6
188[⑤]	*a*: 75–85; *b*: 25–30	7,680–9.510	Referenced/ referenced	9003-11-6
237[⑤]	*a*: 60–68; *b*: 35–40	6,840–8,830	Referenced/ referenced	9003-11-6

338®	*a*: 137–146; *b*: 42–47	12,700–17,400	Referenced/ referenced	9003-11-6
407®	*a*: 95–105; *b*: 54–60	9,840–14,600	Referenced/ referenced	9003-11-6
Polyesters copolymers[a]		2,000–100,000 or higher	*Not referenced/not referenced*	
Poly(lactide-co-glycolide)				30846-39-0 26780-50-7
Poly(lactide-co-caprolactone)				70524-20-8 65408-67-5

Reference of polymers in the United States (29) and European Pharmacopoeia (7.6) as monographs is reported as well as chemical abstract service (CAS) numbers. Dynamic viscosity behavior as a function of heating is reported as follows: ① sol→gel transition, ② gel→sol transition, ③ sol→gel→sol transitions, and ④ gel→sol→gel transitions

[a]Hydrophobic moieties of polyester copolymers are presented as poly(lactide-co-glycolide) and poly(lactide-co-caprolactone). Hydrophilic moieties linked to hydrophobic polyesters determining thermosensitive properties are, e.g., polyethylene glycol blocs

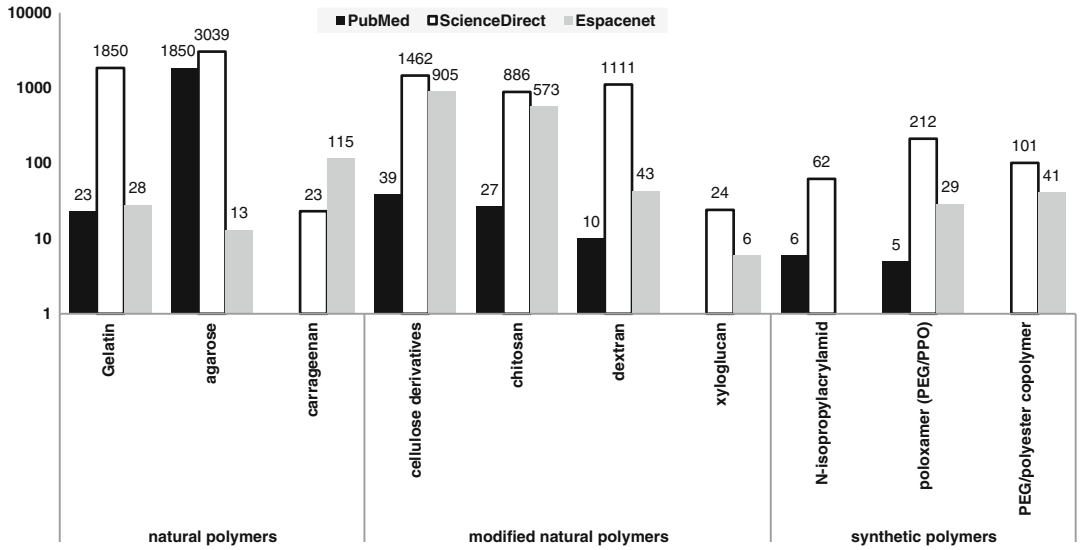


Fig. 22.2 Review of the literature was built by using bibliographic (*PubMed* and *ScienceDirect*) and patent research (*Espacenet*) databases running "*polymer* (e.g., gelatin) and skin" keywords for the last decade. In spite of the growing interest for synthetic polymers, research studies, medical applications, and intellectual property still focus on natural and modified natural thermosensitive polymers

Oppositely, reverse thermosensitive polymer solutions are liquid when temperature is low and gelify on heating. Temperature variations modify the affinity (i.e., hydrophilicity, hydrophobicity) between polymer solution components (i.e., polymer molecules and solvent molecules) resulting in changes in the intimate architecture of the solution. Globally, an increase in polymer's solvent solubility results in low viscosity (sol), whereas a decrease in polymer's solvent solubility results in polymer molecule network formation and therefore gelation (Klouda and Mikos 2008).

Experimental determination of the boundary between sol and gel states is compulsory to thermosensitive formulation characterization. The simplest method is the tube inversion method where a test tube containing polymer solution is tilted to evidence formulation flow under different temperature conditions with standardized test parameters (i.e., time, tilting rate, tube diameter, and amount of solution). Another simple method is the falling ball method where a small dense ball is deposited on the top of the gelified polymer solution. The temperature point at which the ball penetrates the solution under standardized conditions is the gel→sol transition temperature. Differential scanning calorimetry (DSC) may be used to determine transition temperature by detection of gelation endothermic peak and also gives information about enthalpy of gelation. Eventually, dynamic mechanical analysis by a rheometer in a thermally controlled environment enables to obtain precise data about sol→gel and gel→sol transition (Jeong et al. 2012).

22.3 Formulation of Thermosensitive Polymers

22.3.1 Gel Preparations

Semisolid formulations, commonly called gels, are convenient for dermatological applications as they may incorporate various APIs within their internal network structure and provide physical stability towards (1) sedimentation, (2) creaming, and (3) flocculation due to high viscosity. Nature is rich in semisolid elements (e.g., connective tissues, extracellular matrix), and many natural polymers can be used in pharmaceutical formulations. Relatively recent concerns about the environment have led to the discard of petroleum-based synthetic polymers despite their low-cost and biochemical inertness. Modern

analytical methods enable to understand the microstructure/function relation in polymers and open the way to optimized biocompatible modified natural polymers (Yu et al. 2006).

Chen et al. described a PEG/poly(lactide-co-glycolide) hydrogel matrix meant for prolonged subcutaneous delivery of porcine growth hormone (pGH). The preparation was very simple, consisting in a single homogenization of polymer and pGH in aqueous solution. Subcutaneous injection in rabbits of low dose (0.12 %) and high dose (0.42 %) pGH-loaded hydrogel matrix enabled constant prolonged delivery of pGH for about 4 weeks, i.e., 5–15-fold that of aqueous solution for subcutaneous injection. Cell viability study in growth media containing polymer extract was the same as control (Chen and Singh 2008).

Furthermore, poloxamers can be used to enhance aqueous solubility of poorly soluble drugs such as anti-inflammatory drugs. In an earlier study, poloxamer 407 aqueous formulation containing various cosolvents and surfactants allowed a 2,000-fold increase in tolfenamic acid solubility. The release profile of API was independent of bulk viscosity suggesting dependence on gel microstructure. Solvent composition is known to influence gel microstructure and therefore can be adapted to obtain desired drug release profile from poloxamer 407 hydrogel formulations (Cafaggi et al. 2008; Ivanova et al. 2001).

22.3.2 Carrier Systems

Polymer incorporation into structures of vesicular systems enables to produce nano- or microscaled delivery systems that respond to environmental signal (e.g., light, temperature, chemicals, and biomolecules). Thermosensitive polymers are especially interesting in this perspective, and their properties can be combined to other responsive polymers (e.g., photosensitive, pH sensitive) to produce complex vesicular systems responding to multiple external signals. Desired properties of such polymers are (1) high selectivity in stimuli recognition, (2) amplification of the signal, and (3) transduction of the signal into changes in the system's properties (Motornov et al. 2010).

Recently, Choi et al. described a thermosensitive polymer-based nanocarrier for transcutaneous protein delivery. A chitosan-poloxamer 407-conjugated nanocarrier was able to efficiently encapsulate insulin due to thermosensitive swelling and surfactant properties of poloxamer 407. Enhanced cutaneous permeation was allowed by chitosan's properties (i.e., loosening of keratin structure in the *stratum corneum* and transient opening of tight junctions) (Choi et al. 2012).

Niosome systems formed by poloxamers allowed to improve skin permeation of class IV APIs (sulfadiazine) (Muzzalupo et al. 2001), while chlorhexidine-loaded poly-ε-caprolactone nanocapsule suspension in thermosensitive hydrogel (i.e., carboxymethylcellulose or poloxamers) was proven efficient in sustaining antimicrobial activity after an unique application onto the skin surface (Nhung et al. 2007; Pirot and Falson 2009). Interestingly, poly-ε-caprolactone nanocapsules might be freeze-dried and rehydrated *in situ* in the presence of moisture on the skin surface or wounds and reform locally thermosensitive hydrogel (unpublished data, Fig. 22.3).

22.4 Dermatological Applications

Hydrogels are easy to formulate and handle, enabling interesting drug therapy applications in dermatology (Fig. 22.4). Consequently, thermosensitive polymers are currently used in (1) cutaneous, (2) intradermal, or (3) subcutaneous commercial formulation (Fig. 22.5). At the opposite, in developing countries, compounding dermatologic preparations for treating the most common dermatologic disorders revealed a minimal use of thermosensitive polymers as compared to, e.g., white petrolatum (Lamarre et al. 2009).

22.4.1 Topical Delivery

Heilmann et al. investigated thermosensitive hydrogels (i.e., poloxamer and hydroxyethylcellulose) for opioid local delivery in patients with severe skin wounds. Such formulation

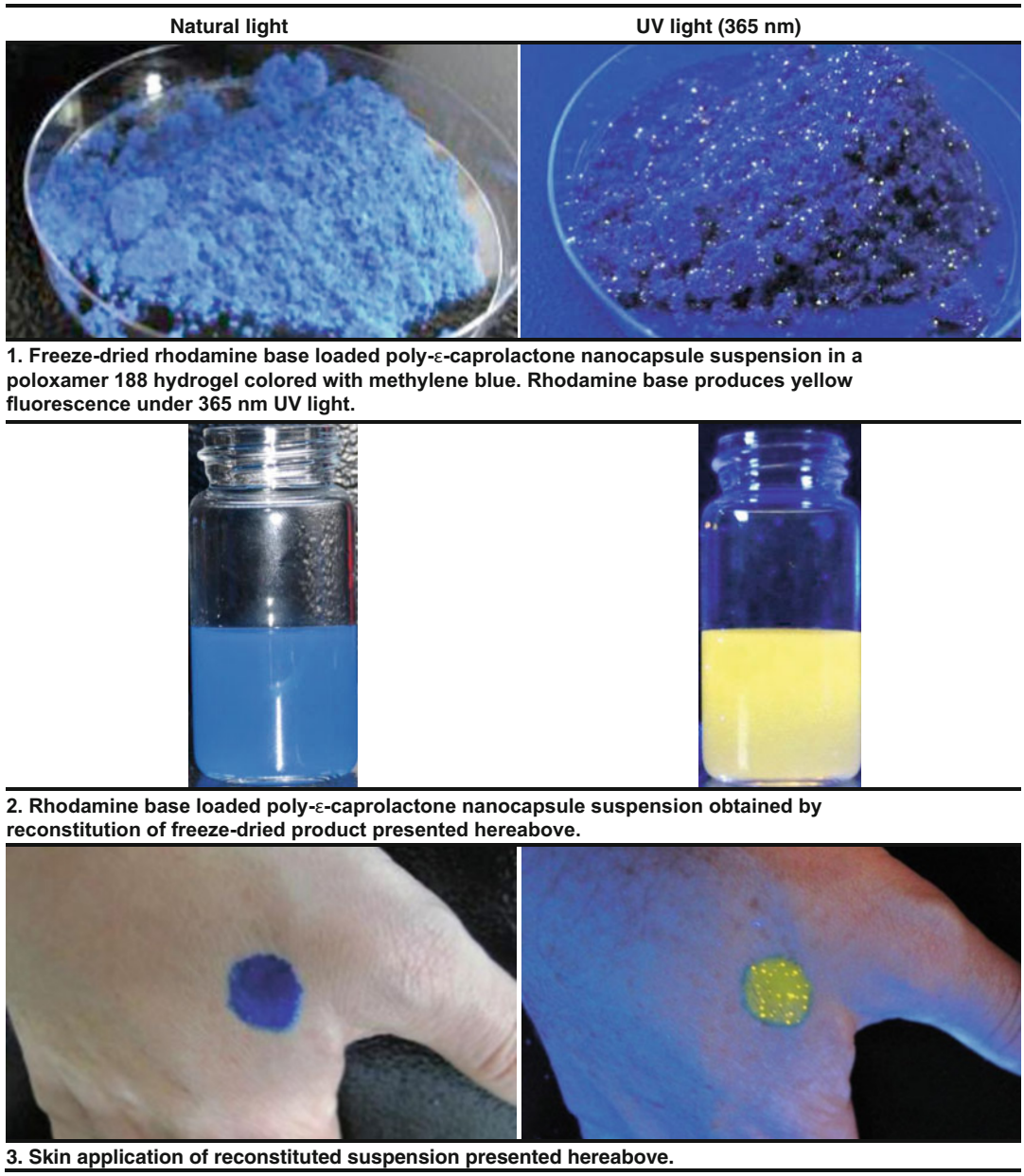


Fig. 22.3 Photographic pictures under (1) natural light and (2) UV light (365 nm) of rhodamine-base-loaded poly-ε-caprolactone nanocapsule suspension in poloxamer 188 hydrogel after (step 1) freeze-drying, (step 2) resuspension in water, and (step 3) application onto the skin

should (1) be able to deliver pain relieving amounts of morphine for a long period of time, avoiding multiple dressing changes and should (2) not impair wound healing. Hydrogels are known to provide a moist environment that favors skin reparation, and poloxamer gels have previously been described as potent "artificial skin" in the treatment of severe burns. A 25 % poloxamer 407 hydrogel was found to be an efficient topical formulation vehicle enabeling 24 hours sustained release of morphine in addition to be conveniently applicable and no impairing natural skin healing (Heilmann et al. 2013).

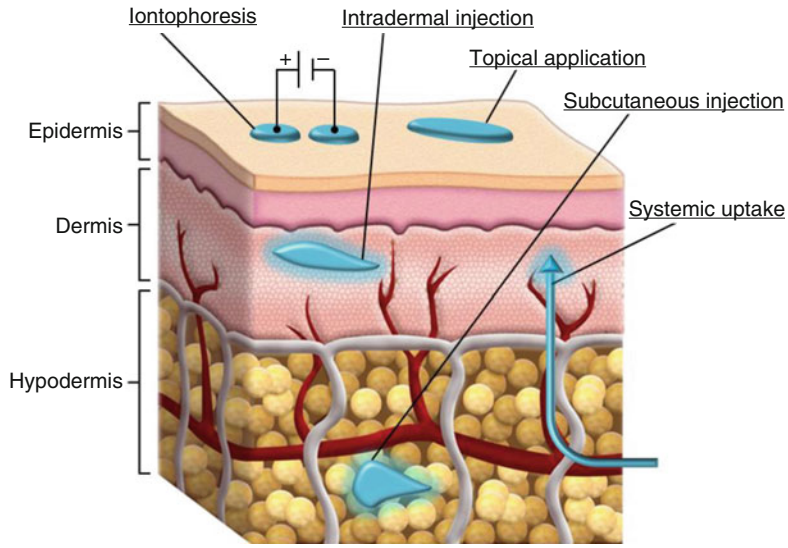


Fig. 22.4 Schematic view of possible skin-related administrations of API-loaded thermosensitive gel (*blue* spot) showing dermatological interest (Presented view is adapted from http://whgormanmd.com/plastic-surgery-educational-images/)

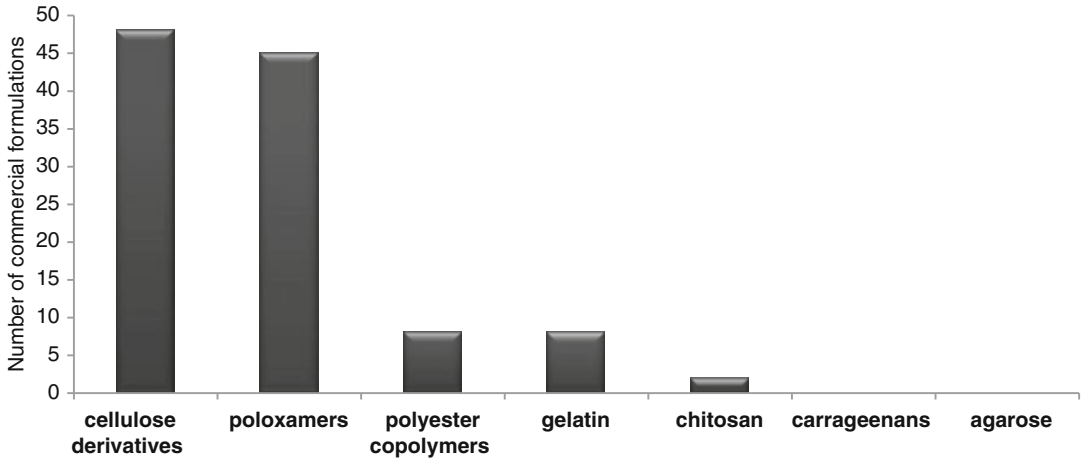


Fig. 22.5 Histogram showing the number of approved (1) cutaneous, (2) intradermal, or (3) subcutaneous commercial formulations containing thermosensitive polymers (Source www.theriaque.org)

22.4.2 *In Situ* Gelling Systems

In situ gelling systems are liquid aqueous formulations that gelify under physiological conditions. They have a wide range of pharmaceutical and medical applications, notably for (1) drug delivery, (2) cell encapsulation, and (3) tissue repair. Thermosensitive *in situ* gelling systems are polymeric solutions undergoing rapid change in viscosity upon administration as a consequence of temperature dependent rise of polymer hydrophobicity (Ruel-Gariépy and Leroux 2004). Local or systemic controlled long-lasting delivery of APIs is therefore made possible with minimal administration invasivity and frequency. Applications in local anticancer therapy (Desai et al. 2008) or hormone systemic delivery for contraception or substitution (Yoshida et al. 1991) are described in literature.

22.4.3 Iontophoresis and Electroporation

Iontophoretic delivery is a promising alternative to parenteral administration of active compounds with poor skin permeation potential, especially of high-molecular-weight molecules like proteins. However, technical issues need to be resolved to make this administration method clinically usable. Poloxamer 407 hydrogel containing insulin and permeation enhancers has been developed by Pillai et al. answering many of these technical issues. The reverse thermosensitive nature of this formulation enabled facilitated preparation and storage between +2 °C and +8 °C as it would remain liquid at such temperature. Application onto the skin and compatibility with iontophoresis device as the cool solution flowed easily onto the skin, forming a non-occlusive gel when reaching body temperature with excellent contact with the skin and device. Furthermore, the adaptability of electrical conductivity and pH of hydrogels and their ability to absorb sweat gland secretions, avoiding irritation under long-term occlusion, enabled ideal iontophoretic conditions (Pillai and Panchagnula 2003).

Electroporation consists in applying an electric field to the skin in order to temporarily create pores in the stratum corneum enabling skin permeation of unabsorbable molecules. Following the administration process, resealing of the pores to restore skin barrier function is desired to prevent further unwanted absorption. Poloxamer 188 solution applied after electroporation procedure *in vitro* enabled (1) significantly more rapid and efficient epidermal electric resistance recovery and (2) rapid skin permeability impairment of witness hydrophilic compound (i.e., glucose). The amphiphilic nature of poloxamer is believed to be responsible for this effect because of its ability to interact with skin lipids and therefore facilitates their reassembly from electroporation-induced vesicular structures to physiological lamellar structures (Burgess et al. 2007).

22.4.4 Subcutaneous Surrogates

Hydrogels exhibit physical similarities with human soft tissues. The interstitial space of all tissues, including skin, is composed of collagen fibers supporting fully charged glycosaminoglycan hydrogel at physiological pH (Porter et al. 2001). Physicochemical characteristics (e.g., osmolarity, pH, density, rheology, water content) of such hydrogel is possible to approach *in vitro* using previously described polymers, such as agarose, and adjusting their characteristics with adjuvants. Recently, Ostergaard's group described piroxicam diffusion from an oil solution into a poloxamer 407 and an agarose gel meant as subcutaneous matrix surrogates. Piroxicam diffusion inside the hydrogels was monitored in real time by UV imaging (Ye et al. 2012a, b). Yet unpublished data from our group have reported the effect of poloxamer 407 and hyaluronic acid on porcine ear *stratum corneum* and dermis hydration and water evaporation. Significant dehydration of skin samples was evidenced with 30 % poloxamer 407 gel as compared to 0.5 % hyaluronic acid or 0.9 % sodium chloride solution. The implication on wound healing after gastric endoscopic mucosal resection using poloxamer gels (Fernandez-Esparrach et al. 2009) is discussed. Such experimental approaches could lead to better understanding and *in vitro* characterization (e.g., molecular transport, tissular effect) of pharmaceutical products meant for subcutaneous or submucosal injection.

Conclusion

Thermosensitive polymeric systems forming hydrogels offer numerous applications in the field of skin-related therapy. Their versatility enables to consider various delivery systems, from a simple gel to complex nanostructured carriers. Moreover, they are relatively low-cost ingredients and might conveniently be selected and adapted to match suitable properties.

Conventional natural (e.g., gelatin) or modified natural polymers (e.g., cellulose derivatives)

are the most widely used polymers in hospital pharmacy daily practice and still provide the majority of literature content related to hydrogels. However, the growing interest in biocompatible synthetic polymers such as poloxamers and the ability to control intimately their microstructure and microreactivity make them an exciting object of study and application. The amphiphilic nature of these block copolymers supports subsequent capacity to interact with a large range of API classes (including class IV compounds and proteins of therapeutical interest) and many human body tissues and components. In the future, hydrogels, oleogels, and composite systems with responsive capacities to physiological stimuli will multiply pharmaceutical applications and open a window to long time announced and plebicited nanomedicine.

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