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Review article

The use of polymers for dermal and transdermal delivery

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Abstract

The use of polymers for skin preparations is manifold. Requirements of such polymers are dependent on the formulation types. The most applied polymers on skin belong to various classes, for example to cellulose derivatives, chitosan, carageenan, polyacrylates, polyvinylalcohol, polyvinylpyrrolidone and silicones. They are gelating agents, matrices in patches and wound dressings, anti-nucleants and penetration enhancers. Correlations between commercially available products and results of new scientific investigations are often difficult or not possible, because of the lack of comparative data especially for transdermal patches. Finally, two promising future trends of polymeric systems, gene delivery and tissue engineering, are discussed.
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Keywords: Skin; Gel; Emulsion; Wound dressing; Scar treatment; Supersaturation; Penetration enhancer

1. Introduction

The skin is a very heterogeneous membrane but the layer that controls absorption is the outermost layer, the stratum corneum. This layer is only between 20 and 25 μm thick, but nevertheless provides a very effective barrier towards penetration and the impermeability is a considerable problem in the delivery of medicines both to and through the skin. The exact nature of the barrier function has been investigated over many years and recent advances in biophysical techniques have provided interesting insights into the mechanisms of absorption at a molecular level [1–4].

For skin preparations the vehicle has a more pronounced influence than on any other membrane. The term vehicle is very common for a complex system and implies a differentiation between active and inactive principles, whereby the active principle is embedded into a matrix, the vehicle. With the aid of the vehicle the active principle is delivered to the application site or the target organ, respectively, where the desired effect is achieved.

There is a broad spectrum of polymers as vehicles and in vehicles on skin. Polymers can be gelating agents of gel systems but they are also found in emulsions and creams as consistency excipients. They can be the matrix in patches and wound dressings and they are used as skin adhesives in transdermal systems. Besides all these, a supersaturation can be maintained by using polymers and they may be used as penetration enhancers.

2. Emulsions and creams

The main components of emulsions and creams are lipids and water. These two immiscible phases are stabilised by an emulsifier. Modern formulations, which are called emulsifier free, are composed of polymers, water and oil. Several cosmetic and pharmaceutical preparations have been developed containing sodium polyacrylate dispersed in the oil phase as the main emulsifier or co-emulsifier for topical application. These formulations have very high skin compatibility as they are surfactant-free or with low emulsifier content. The O/W emulsions have a velvet-like and soft touch skin feeling without any tackiness compared to traditional thickeners and are suitable to realise light gel cream textures [5].

Hydrophobically modified acrylic acid copolymers (acrylates/C10-30 alkyl acrylate cross-polymer) are called Pemulen®. They form O/W emulsions, where the lipophilic portion of the polymer absorbs at the oil-water interface

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and the hydrophilic portion swells in water. A gel network around the oil droplets provides excellent emulsion stability to a broad range of oils. Pemulens® have been designed to act both as primary emulsifiers and viscosity increasing agents. Aside from a number of benefits, emulsions based on Pemulens® are characterised by a relatively large average droplet size of about 50–100 μm and larger. They should be combined with non-ionic emulsifiers with an HLB of 8–12. It was shown that temperature changes did not significantly influence the droplet size and emulsion polydispersity, nor were the profiles of sample flow curves altered. However, the use of Pemulen® polymeric emulsifiers in low concentration levels produced the physically most stable low viscosity O/W emulsions [6].

An interesting comparative study between different formulations containing polymers dealt with drug release and skin irritancy. As drug, kojic acid, an antimelanogenic agent was incorporated in different preparations like cream bases of mineral oil with caprylic capric triglyceride (MultiCream) and hydrophilic polymers such as chitosan (ChitoGel), Carbopol®, and poloxamer (Pluronics®). Pluronic®-based gels (PluGel) and Carbopol®-based gels (CarboGel) revealed controlled release of drug to some extent, followed by the square root-time kinetics. ChitoGel and MultiCream were equivalent because of the similar skin irritancy score in the rabbit skin irritation test [7].

3. Gels

In contrast to emulsions, gels generally do not comprise two immiscible phases of opposite lipophilicity. Therefore, the polarity and solubility characteristics of the incorporated substances are either hydrophilic in hydrogels or lipophilic in lipogels. The consistency of gels is caused by gelating agents, which belong mainly to polymers. These polymers build up a three dimensional network. Intermolecular forces bind the solvent molecules to this polymeric network and thus, due to the reduced mobility of these molecules in structured systems with increased viscosity, exhibit viscoelastic properties. Recently, an excellent overview not only of polymeric gels but also of other innovative gels was presented [8].

It depends mainly on the physical–chemical properties of the drug whether it can pass the skin and exhibit a systemic effect. The vast majority of drugs incorporated in gels do not pass the skin, but act locally mainly on the skin surface or in the whole epidermis.

The most important and already well-known polymers for forming hydrogels are polyacrylic acid derivatives like Carbomers®, different cellulose derivatives like hydroxyethyl cellulose, hydroxypropyl cellulose and croscarmellose-sodium. During the last years new polymers have been tested. In a number of studies big efforts were undertaken to improve the technical properties by derivatisation. For example, employing chitosan, a natural polycationic copolymer consisting of glucosamine and *N*-acetylglucosamine units, a novel anionic polymer (Chitosan–EDTA) was generated by the covalent attachment of EDTA to chitosan [9]. Results demonstrated that Chitosan–EDTA was able to form stable, colourless, completely transparent hydrogels at a polymer concentration of 0.5%. The novel polymer displayed the lowest incompatibility with multivalent cations as well as with ethanol, and exhibited significantly the best swelling properties among several tested polymers like HPMC, NaCMC, Carbopol® and polycarbophil. Chitosan–EDTA exhibited additionally high antimicrobial activity compared to other hydrogels. This could be explained by the highest binding affinity of Chitosan–EDTA towards magnesium, stabilising the outer membrane of Gram-negative bacteria.

An increasing number of reports is available about the use of carrageenan as a gelling agent, which showed excellent transparency and gel breaking strength [10]. It is further suggested for retexturisation of skin, producing significantly improved smoothness as well as significantly increased firmness and moisture content of skin. It regulates wrinkles of human skin together with improving the overall tone and decreasing the level of free radicals in skin [11,12].

Novel implant hydrogel systems loaded with anti-inflammatory drugs based on gelatine of varying cross-linking are currently tested. Either gelatine was chemically cross-linked with glutaraldehyde or polyethyleneglycol diacrylate was photopolymerised around gelatine to form interpenetrating networks. In general, dexamethasone intensified the anti-inflammatory response. The loss of material mass did not correlate directly with the degree of cellular inflammatory response, but increased with longer implantation time and decreased with more extensive fixation [13]. The bioavailabilities of ibuprofen and ketoprofen in rats were significantly higher when released from xyloglucan gels compared to poloxamer (Pluronic® F127) gels [14].

Gels are considered to be the most suitable delivery vehicles for iontophoresis, as they can be easily amalgamated with the iontophoretic delivery system and can also match the contours of skin. A gel formulation of insulin was formulated using poloxamer (Pluronics®) and was evaluated by ex vivo and in vivo skin permeation studies in rat in combination with enhancers. In ex vivo studies, both linoleic acid and menthone in combination with iontophoresis showed a synergistic enhancement of insulin permeation. The plasma insulin concentration was highest with linoleic acid pre-treatment. However, iontophoresis alone or in combination with linoleic acid produced a reduction in glucose level of 36–40%. A combination of chemical enhancers and iontophoresis caused greater skin irritation than the gel alone [15].

Hydrogel-based iontotherapeutic devices as drug reservoir matrices for peptide-based pharmaceuticals were investigated for transdermal delivery of three model peptides, insulin, calcitonin, and vasopressin. The swelling

behaviour of this polyacrylamide-type hydrogel as a function of its monomer and cross-linker concentration was studied and a hydrogel with minimal swelling properties was synthesised. The permeability coefficients for these peptides across the hairless rat skin were evaluated using the hydrogel formulations prepared from polyacrylamide, *p*-hydroxyethyl methylacrylate and Carbopol®. The permeability coefficient is a coefficient associated with simple diffusion through a membrane that is proportional to the partition coefficient and the diffusion coefficient and inversely proportional to membrane thickness.

A rank order of vasopressin > calcitonin > insulin was obtained in accordance with the order of molecular size [16].

Physically cross-linked chitosan hydrogels with lauric, myristic, palmitic or stearic acid were prepared by freeze-drying and have been studied for topical use. A study selected propranolol hydrochloride as a hydrophilic model drug. The effect of the nature of the cross-linker on drug permeation through porcine skin and the main permeation parameters were investigated. All the chitosan hydrogels analysed provided more transcutaneous permeation of propranolol hydrochloride than the corresponding solution of the drug. Among the different chitosan vehicles, chitosan–laurate and chitosan–myristate hydrogels enhanced lyophilised drug diffusion through skin with respect to chitosan–palmitate and chitosan–stearate hydrogels. This could be explained by the interaction of the hydrogels with the stratum corneum, increasing the solubility of the drug in the skin [17].

One product which is already on the market is Testogel®, which contains testosterone and is based on carbomer, a polyacrylate. Its indication is hypogonadism due to androgen deficiency in men (over 18 years). Daily a thin layer of gel has to be applied on clean, dry, healthy skin such as shoulders, arms or abdomen, immediately after the sachet is opened. The disadvantage is the high activity of the drug, therefore it is recommended to wash the hands with soap and water after application and shower or bath should be avoided for at least 6 h.

Therefore the use of drug-loaded patches with a defined amount of drug seems to be more convenient.

4. Transdermal patches

The transdermal route cannot be employed for a large number of drugs because the skin is a very efficient barrier allowing only small quantities of drug penetrating the skin. To date, only about eight different drugs are available in form of transdermal systems, which belong to potent steroid hormones, nicotine, nitroglycerine and analgesics like fentanyl or buprenorphine [18]. Transdermal patches have the aim to transport drugs through the skin into the blood circle. One of the proposed advantages of transdermal delivery is the possibility to attain sustained and constant drug levels [2].

From the historical point of view the patches are divided into membrane controlling and matrix type plasters [19]. The first matrix type systems contained an additional adhesive layer, whereas modern systems consist of self-adhesive matrices [20]. In contrast, membrane systems are constructed of a rate controlling membrane mainly of poly(ethylenvinylacetate) or polyethylene.

In case of matrix controlled systems the drug is dissolved or suspended in a hydrophilic or lipophilic matrix.

An example for an advanced transdermal system which is already on the market is Transtec®, a buprenorphine containing slow-release matrix patch for the treatment of intermediate to severe pain [21]. It contains the active drug incorporated into a polymer matrix, which is the adhesive layer at the same time. The patch is able to control the drug delivery rate and produce stable plasma concentrations. This transdermal system provides excellent analgesia and a low incidence of adverse events. Its ease of use results in good compliance [22].

There are many studies on transdermal systems with other drug candidates being in different stages of development.

One approach is the improvement of the adhesiveness on skin by combining different polymers or by polymer derivatisation. The effect of a combination of the adhesive polymethyl methacrylate (PMMA) with cellulose ethers or polyvinylpyrrolidone (PVP) was evaluated by a peel adhesion test. The addition of PVP resulted in a 40-fold improved creep compliance. The significant increase of the matrix cohesion was due to interactions between the amide group of PVP and the carboxylic acid group of PMMA. The new system could be removed from the skin easily, was suitable for repeated applications on the same site and had adhesive properties that could be modified by changing the component ratios [23].

Transdermal patches are also promising candidates for veterinary use. A formulation with controlled release based on silicone as carrier for ivermectin, a veterinary product, was designed. With this formulation a linear release of ivermectin was obtained. Additional polyethylene glycol 4000 accelerated the ivermectin release. By subcutaneous administration of this patch to mice the ivermectin blood concentration was maintained over a period of 3 months [24].

Percutaneous absorption studies with of patches containing verapamil hydrochloride with Eudragit® RL, Eudragit® RS100, hydroxypropyl methylcellulose and ethyl cellulose of varying degrees of hydrophilicity and hydrophobicity were carried out. The pharmacokinetic parameters calculated from blood levels of the drug revealed a profile typical of a sustained release formulation with the ability to maintain adequate plasma levels for the patch containing Eudragit® RL and hydroxypropyl methylcellulose in the ratio 8:2 [25].

Another matrix-dispersion-type transdermal drug delivery system containing propranolol was prepared by

using different ratios of mixed polymeric grades of Eudragit®. After in vitro dissolution experiments, in vivo evaluation was carried out on nine healthy human volunteers by analysing the blood and urine samples. Unfortunately these systems were not compared to other commercially available forms [26]. The most promising in vitro results with propranolol–hydrochloride were obtained from HPMC matrices coated with an aqueous dispersion of an acrylic copolymer (Ucecryl MC808) and propylene glycol [27].

Oral administration of the antihistaminic triprolidine causes many adverse effects such as dry mouth, sedation or dizziness, therefore transdermal drug delivery was considered. A poly(4-methyl-1-pentene) membrane with good mechanical strength served as rate controlling membrane for triprolidine. In a first in vitro study different formulations were tested and optimised [28]. Further investigations on the permeation of triprolidine through excised mouse skin were performed in combination with penetration enhancers. Polyoxyethylene-2-oleyl ether showed the best enhancement ratio [29].

In an in vitro study polyurethane matrices containing terpenes were tested. Release of the terpenes directly to the acceptor fluid as well as through isolated human epidermis and dermis, was studied. There were no differences to other studies with different polymers on epidermis. In the opinion of the authors the permeation enhancement of terpenes was only limited by the stratum corneum [30].

Polycarbophil-cysteine (PCP-Cys) conjugate, a partly thiolated polymer, was tested as a matrix for transdermal delivery with the advantage of good cohesiveness within the polymer film. Because of the excellent adhesiveness on skin no additional adhesive was required. In studies with porcine skin higher progesterone permeation could be demonstrated from PCP-Cys compared to PVP/HPMC and PVP/PVA formulations. The hydrophilic thiolated polymers might be promising candidates as carriers for transdermal delivery systems [31].

In contrast to hydrophilic-based, lipophilic-based polymers, for example silicones, can also be used in transdermal patches. They were investigated since the 1980s. One interesting study employed such a silicone polymer loaded with coumarin. To these preparations different amounts of excipients were added and evaluated in vivo. From all tested formulations the area under the blood level-time curve of the propylene glycol containing system was twice that of the device without propylene glycol [32]. Glycerol, ethylene glycol or polyethylene glycol 400 are also able to influence the properties of silicone matrices significantly [33].

By screening the literature concerning new studies with transdermal systems it is often very difficult to distinguish between practicable patches and early stage studies. Bioavailability is generally measured in a comparative sense. The absorption from a test product is compared to that from a reference system containing the same drug. With systemic administration the blood concentration is usually the most appropriate measure for absorption. In spite of published in vivo data it is very difficult to assess the bioavailability because of the lack of in vivo data of current peroral preparations on the market.

5. Wound dressings

The administration of topical medication to wound sites is one of the most documented areas in medical history [34]. Beside the drugs, the used polymers are of great interest. A review of the current literature suggests that mainly sponge-type wound dressings and hydrogels as wound dressings are in use. Such wound dressings are still developed to prevent bulk loss of tissue or non-healing wounds such as burns, trauma, diabetic, decubitus and venous stasis ulcers. They cover the wound area, protect the damaged tissue and, if possible, activate the cell proliferation and stimulate the healing process.

5.1. Sponge systems

A picture of a typical sponge type wound dressing is presented in Fig. 1. As seen, it consists of a polymeric bilayer with one sponge like layer and one layer like a dense skin but permeable to oxygen and to some extent to water. General requirements for such wound dressings are on the one hand the avoidance of wound dehydration and bacterial penetration by occlusive characteristics and on the other hand the permeability for wound exudates to prevent bullae formation.

Different types of underlying sponge-layer are in use, for example collagen [35]. In this case cellular ingrowth within the sponge depended on the porosity and the presence of fibrous structure. Now-a-days, collagen has been

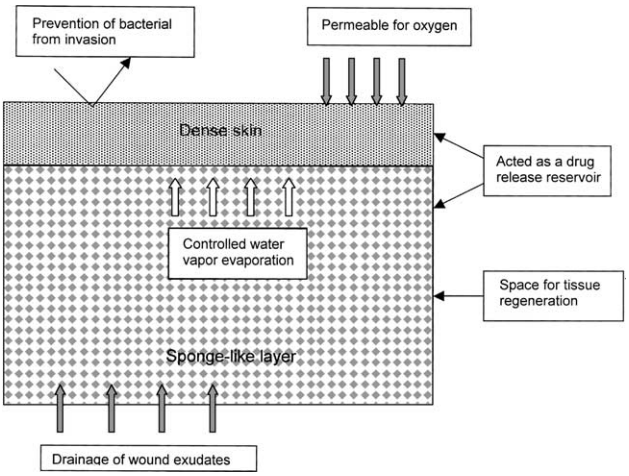

Fig. 1. Sponge type wound dressing: a polymeric bilayer with a sponge like layer and a layer like a dense skin; from Ref. [44]. (Fig. 1 is reprinted from Journal of Membrane Science, Vol. 212, F.L. Mi et al., Asymmetric chitosan membranes prepared by dry/wet phase separation: a new type of wound dressing for controlled antibacterial release, pp. 242, © (2003) with permission from Elsevier.)

re-discovered again. Collagen is a natural substrate for cellular attachment, growth and differentiation and promotes cellular proliferation. Recently, in an excellent review the effects of collagen matrices on dermal wound healing including a cellular and cell-containing products were discussed in detail [36].

Another sponge-type was an absorbable sponge, composed of gelatine and alginate. These sponges were loaded with silver sulfadiazine or gentamicin sulfate and they slowly released drugs for up to 4 days [37].

Other porous scaffolds are composed of gelatine and β-glucan. To mimic the normal human skin fibroblasts and keratinocyte cells, they were co-cultured in gelatine/β-glucan. In an in vivo study treatment with the cell-containing scaffold showed an advanced re-epithelialisation of skin compared to the scaffold without additional cell-layer [38].

Several studies on different combinations of gelatine and polyurethane as external layer with incorporated drugs like antibiotics and epidermal growth factor offering preliminary in vitro data, are available. [39–41].

In a number of studies silver sulfadiazine was incorporated into chitosan and found to be of advantage for further investigations [42–44].

Scientific interest is also focused on derivatives of hyaluronic acid and chondroitin sulfate as basic polymers for wound dressings [45,46]. In such dressings microspheres of antibiotic loaded poly-L-lactic acid were incorporated [47]. Unfortunately these wound dressings were found to be unsuitable for clinical use because of preservation problems [48].

In contrast to the two layered wound dressings there are interesting tri-layered copolymer systems described. Such systems are composed of A-B-A-block copolymers. For example the A-component is composed of poly (L-leucin) and the B-component is composed of poly (ethylene glycol). Also in this case the polymers were impregnated with silver sulfadiazine. In cytotoxicity tests, cell damage did not occur by the release of silver sulfadiazine from the sponge matrix. Granulous tissue formation and wound contraction for the impregnated wound dressing was faster than for the control group without impregnation in vivo [49].

Like the two layer system [45,46] trilayer wound dressings can also be composed of chondroitin-6-sulfate. With these wound dressings the wound site had totally recovered after 4 weeks, which was significantly faster than with other tested materials [50].

5.2. Hydrogel systems

In contrast to the sponge like systems the hydrogel wound dressings consist of a very dense highly concentrated gel with more than 3 mm in diameter.

One of the most important polymers for such hydrogels is hyaluronan. In order to achieve a suitable thickness of the hydrogel-layer different cross-linking materials are used [51–53].

Another polymer for hydrogels is poly(vinyl alcohol). In an in vivo study a rather big piece of such a hydrogel was tested on burns at the back of marmots. Advantages of the hydrogel over a gauze dressing were homogeneous adhesion to the affected parts, easy removal without damage to renewed skin and slightly faster rate of reconstruction of the injured skin [54].

Another synthetic polymer poly(*n*-vinylpyrrolidone) was used in a tropical environment. To achieve the thickness, additional additives like agar or polyethylene glycol were used. The resulting hydrogels were elastic, transparent, flexible, impermeable to bacteria and easy to remove. Because of their low water vapour transmission rate they were suitable for applying in tropical environments [55].

Another possible base for hydrogels can be calcium alginate. Additional incorporation of antibiotics like vancomycin improved the wound healing procedure [56].

The advantage of wound dressing hydrogels is the achievement of high density and high thickness. Therefore, a lot of products are on the market. We chose three examples: Acticoat®, DuoDerm E® and SureSkin®.

The silver antimicrobial barrier dressing Acticoat® consists of a rayon/polyester non-woven core laminated between an upper and lower layer of silver coated high-density polyethylene mesh. The silver coated polyethylene mesh layers are designed to be barriers against microbial infection of the wound. Acticoat® burn dressing was evaluated in different assays. To achieve antimicrobial activity a rather long time was required [57]. DuoDerm E® and SureSkin® are both hydrocolloid dressings. In a clinical trial they were compared in terms of healing time. As control Jelonet®/Gauze dressing was used. Under DuoDerm E® and SureSkin® the donor sites healed in a significantly shorter time than under the control. Histological biopsies confirmed these clinical results [58].

Instead of hydrogels or sponges also films can be used e.g. chitin films as occlusive, semi permeable film wound dressings [59].

5.3. Scar treatment

Topical agents that fall under the category of wound care are also used in the treatment of many skin-healing defects, which fall outside the common classification. Most common among these are hypertrophic and keloid scars. The formation of hypertrophic and keloid scars both represent a defect in the normal wound repair process, which results in excessive fibroblast activity and collagen deposition. Locally applied collagen facilitates scar free healing [36].

Hypertrophic scars are characterised by reddened and raised scar tissue, which grows within the confines of the original wound area [34]. Many techniques for management of hypertrophic scars and keloids have been proven through extensive use, but few have been supported by prospective

studies with adequate control groups. Several new treatments showed good results in small-scale trials, but they have not been confirmed in larger trials with long-term follow-up. Silicone gel sheeting is one treatment, which is recommended by several experts [60]. It has been widely used as treatment of hypertrophic scars and keloids since the early 1980s. Despite initial scepticism there is now good evidence of its efficacy [61]. Results from at least five randomised controlled trials demonstrate silicone gel sheeting as a safe and effective management option for hypertrophic scars and keloids [62–67]. Silicone gel sheeting may be especially useful in children and others who cannot tolerate the pain of other management procedures [65].

A prospective controlled clinical trial comparing two commercially available products namely Silastic Gel Sheeting® and Cica-Care® in the treatment of hypertrophic scars was performed. The efficacy of the two gels was not significantly different, but Cica-Care®, being more adhesive was more comfortable to use for the patients [68].

Some groups started to combine silicone sheets with active ingredients, for example vitamin E. This resulted in a significantly faster scar improvement than with the silicone sheet solely [69].

The positive effect of silicone cream containing 20% silicone oil on hypertrophic scars and keloids in humans was the highest when occlusively attached [70]. This technique was further evaluated in an open clinical study. Keloids were randomly selected and treated with silicone cream occlusive dressings. The effectiveness was assessed using a scoring system involving elevation, redness, hardness, itching and tenderness of pain of the lesions. Nearly 80% showed significant improvements after using this silicone cream occlusive dressing for 6 months. None of the keloids progressed [71].

A relatively new plaster for prevention of keloid formation in wounds comprises a silicone gel layer laminated between a flexible backing layer and a release liner. The backing layer is supposed to be permeable to water vapour. An absorptive excipient could be incorporated or it might be coated with some adhesive [72].

One innovative new product is Dermatix®, a transparent scar treatment in form of a gel. After applying on the scar the gel dries and an elastic film should be built up. This formulation offers the possibility of treating scars, which are difficult to cover with silicon sheet, for example on face or neck. Moreover, it is possible to cover the dried silicon film with make up.

Despite the numerous studies demonstrating successful scar treatment with silicone sheeting there are also reports about no significant positive effects or even a failure of such products [73–75].

6. Polymers as penetration enhancers

An overview of the common absorption enhancers and their mode of action is given in Table 1. As seen, chitosan salts as well as trimethylchitosan are able to enhance the paracellular permeability of mucosal epithelia like intestine, nasal and buccal by transiently opening the tight junctions, thereby increasing the paracellular absorption of hydrophilic and macromolecular drugs. Schematic tight junctions are depicted in Fig. 2 [76]. In the last years it has been proven that tight junctions occur also on skin. They have

Table 1
Classes of absorption enhancers and their mechanisms of action; from Ref. [76]

Class	Examples	Mechanism	Transport ways
Surfactant	Na-laurylsulfate	Phospholipid acyl chain perturbation	
	Polyoxyethylene-9-laurylether		Transcellular ↑
	Bile salts:		
	Na-deoxycholate	Reduction mucus viscosity	
	Na-glycocholate	Peptidase inhibition	Paracellular ↑
	Na-taurocholate		
Fatty acids	Oleic acid	Phospholipid acyl chain perturbation	Transcellular ↑
	Short fatty acids		Paracellular ↑
Cyclodextrins	α-, β- and γ-cyclodextrins	Inclusion of membrane compounds	Transcellular ↑
	Methylated β-cyclodextrins		Paracellular ↑
Chelators	EDTA	Complexation of Ca^{2+}	Transcellular ↑
			Paracellular ↑
	Polyacrylates	Opening of tight junctions	Paracellular ↑
Positively charged polymers	Chitosan salts	Ionic interactions with negatively charged groups of glycocalix	
	Trimethyl chitosan		Paracellular ↑

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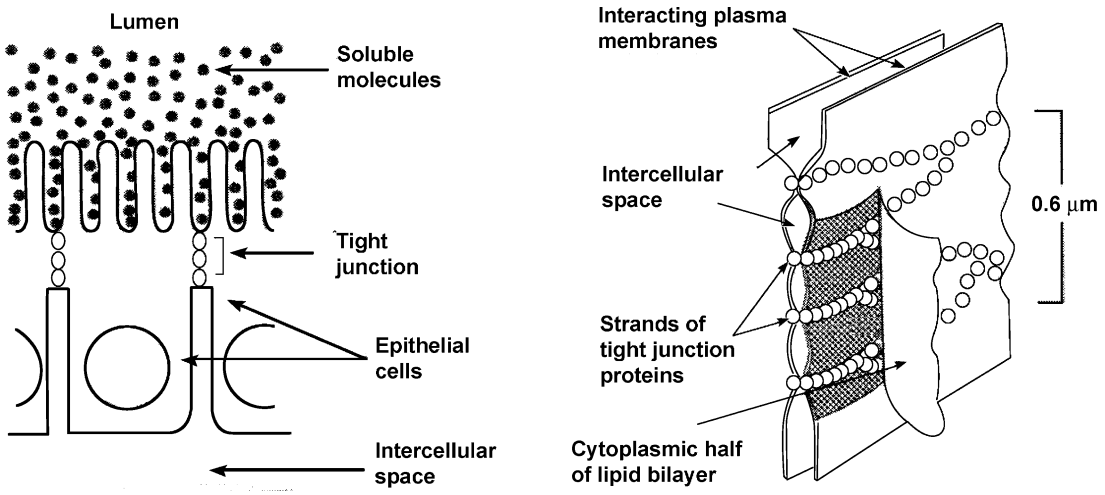

Fig. 2. Tight junctions are intercellular connections that hold epithelial cells together at their apical end (left). An enlargement of a tight junction is also presented (right); from Ref. [76]. (Fig. 2 is reprinted from Pharmaceutical Science and Technology Today, Vol. 1, H.E. Junginger and J.C. Verhoef, Macromolecules as safe penetration enhancers for hydrophilic drugs—a fiction?, pp. 372, © (1998) with permission from Elsevier.)

recently been characterised in the granular cell layer of human epidermis, and the role of these junctions in the epidermal barrier is now being re-evaluated [77]. Therefore, it could be possible that some of these polymers also exhibit percutaneous penetration enhancement by this mechanism.

Two other polymers, one synthesised by the reaction of poly(4-vinylpyridine) and hexadecyl bromide and another synthesised by radical polymerisation of the cationic surfactant monomer, *p*-vinyl benzyldimethyl alkyl ammonium chloride with a long alkyl group, were established. Differential scanning calorimetry studies of full thickness skin and stratum corneum, treated with these polymers, showed an interaction with proteins as well as lipids [78,79].

7. Supersaturation

Numerous studies tried to show the role of supersaturation for improvement in drug delivery. Supersaturation can be achieved by the use of co-solvent mixtures like microemulsions [80], by certain co-excipients like phospholipids [81] or by temperature changes [82].

Supersaturated formulations are inherently thermodynamically unstable and the drug recrystallises over time. Nevertheless, it was shown that the addition of stabilising polymers can be used to retard the kinetics of recrystallisation. In numerous studies hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene glycol or Eudragit® are reported as anti-nucleant polymers [83–87]. Whether or not supersaturation occurs is dependent on the nature of the drug and the complex physical–chemical interactions between polymer and drug molecules.

As seen in Fig. 3 the hydrocortisone acetate flux increased with increasing polymer concentration, reached a maximum and decreased at higher polymer percentages. Hydrocortisone acetate could be prevented from nucleating if small amounts of hydroxypropyl methylcellulose were present. There was infrared evidence for hydrogen bonding between the –OH groups on the drug and the polymer [85,88].

In contrast to these data the results of another study demonstrated only to a very limited extent the stabilisation of supersaturated lavendustin-solutions by addition of sodium carboxymethyl cellulose. The effects may have limited duration once the formulation is agitated [89].

8. Skin irritancy

The majority of the polymers, which are considered in dermal formulations, are probably non-irritant to skin, however, the used penetration enhancers may cause some risks. The polyacrylates and chitosan derivatives showed no acute toxicity and were not absorbed. These characteristics favour the conclusion that both types of polymers are safe

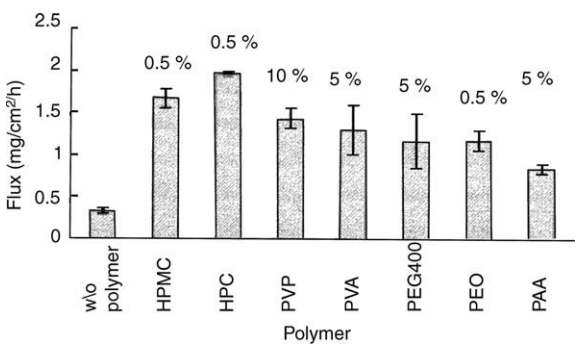

Fig. 3. Percentage of polymer needed to achieve maximum enhancement for the different polymers; from Ref. [85]. (Fig. 3 is reprinted from International Journal of Pharmaceutics, Vol. 221, S.L. Raghavan et al., Membrane transport of hydrocortisone acetate from supersaturated solutions; the role of polymers, pp. 99, © (2001) with permission from Elsevier.)

penetration enhancers for transmucosal delivery of hydrophilic drugs and offer promising prospects for novel pharmaceutical applications [76]. Also the other polymers developed as transdermal penetration enhancing systems could be evaluated as safe. Despite the interactions of the polymers with lipids and proteins of the membranes of the stratum corneum, they may not penetrate into deeper layers of the skin. The absence of irritation of the tested polymers to skin was confirmed by the Draize test [79].

Hydroxypropyl methylcellulose and Carbopol® matrices were evaluated for skin irritancy. The gels were free from skin irritation [90]. Skin irritancy tests were carried out on human volunteers with transdermal films from hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, cellulose acetate and ethyl cellulose. The human volunteers did not show any signs of erythema or oedema [91]. Chitosan based gels were found to be non-irritating [7]. Poloxamer® 407 gels showed low toxicity as a topical drug delivery system [92].

Since an aqueous gel containing microspheres of poly(D,L-lactic-*co*-glycolic acid) was not irritating in a rabbit skin irritancy test, this formulation was applied onto forearms of human volunteers and found to be safe. Site-specific drug delivery was further evidenced by follicular biopsy [93].

Polyester and acrylic fibres often have prolonged contact with human skin and were tested for acute toxicity and then for sensitising potential on guinea pig skin. Human volunteer trials for skin irritancy and sensitisation followed. No adverse reactions were seen [94].

The available data suggests that severe irritancy problems on skin with the discussed polymers are not to be expected. However, no precise prediction is possible in case of combination of drugs and excipients like classic penetration enhancers.

9. Future trends

9.1. Gene delivery

At the moment the most promising gene delivery systems to skin cells are based on liposomes or polymers, respectively, whereby the development with liposomes seems to be more advanced.

Such formulations may be alternatives to virus-mediated delivery systems and therefore have opened the field of dermal gene therapy. In a comparative study in rats, liposomal systems versus polymer systems in delivering β-galactosidase and luciferase reporter genes into skin cells were tested. Although the liposomal systems were more effective compared to the used PINC polymer (protective, interactive, non-condensing polymers) research with other polymer types is in progress [95].

Currently, most pDNA delivery systems based on synthetic polymers are either non-biodegradable or not sensitive to the release environment. The aim of one study was to develop and evaluate an aqueous based, thermosensitive, biodegradable and biocompatible triblock copolymer based on poly[ethylene glycol-*b*-(D,L-lactic acid-*co*-glycol acid)-*b*-ethylene glycol] (PEG-PLGA-PEG) to control pDNA delivery in vitro and in vivo. The release of ^{32}P-labelled pDNA entrapped in aqueous dispersion of PEG-PLGA-PEG in 0.1 mol/l sodium phosphate buffer solution (pH 7.4) was studied at 37 °C under agitation. Gene transfection efficiency was evaluated in a skin wound model in CD-1 mice. The aqueous dispersion of PEG-PLGA-PEG formed a gel at 37 °C body temperature. The in vitro degradation of PEG-PLGA-PEG lasted for more than 30 days. The cytotoxicity of PEG-PLGA-PEG evaluated in HEK 293 cells was significantly lower than that of poly-L-lysine hydrochloride. The release profile of supercoiled pDNA from the polymer followed the zero-order kinetics up to 12 days. Maximal gene expression of luciferase was at 24 h in the skin wound of CD-1 mice and by 72 h, the expression dropped by nearly 94%. A hydrogel formed by PEG-PLGA-PEG could be a promising platform for non-viral delivery of pDNA for gene therapy in wound healing [96].

9.2. Tissue engineering

Despite the recent improvements in cell culture and dermal regeneration methods, tissue engineering is going to be widely used in the near future. The use of an appropriate biologically active matrix to speed up the healing of missing tissue will become a standard in skin reconstruction. Different sources of new cell populations for wound-healing are currently under investigation [97,98]. Stem cells are important targets for the local application of growth factors and for gene therapy and participate in the natural healing processes occurring during the wound organisation and renewing [99,100].

A brand new material for skin tissue engineering is silk fibroin nanofiber. These complex nanofibers were fabricated by a new electrospinning method and used as scaffold for growing human keratinocytes and fibroblasts [101].

10. Conclusion

Polymers belong to numerous chemical classes and play an important role in all fields of pharmaceutical technology. They are part of many preparations for dermal use and cover a broad spectrum from a very simple excipient like a thickening agent to a very complex formulation like a modern gene delivery system. Many of the polymers belong to naturally occurring polysaccharides like chitosan and derivatives. Today high amounts of such naturally compounds are available in standardised quality due to the improvement in analytical and purification methods. Therefore, they are expected to be used more extensively in the future.

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