Liposomal Gels in Enhancing Skin Delivery of Drugs

23

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Contents

Abbreviations

Chol	Cholesterol
DSPC-Chol	Distearoyl-glycero-PC and cholesterol
EPC	Egg phosphatidylcholine
EPC-Na	Egg phosphatidylglycerol sodium
HEC	Hydroxyethyl cellulose
HPC	Hydrogenated PC
HPMC	Hydroxypropyl methylcellulose
PC	Phosphatidylcholine

23.1 Introduction

Transdermal drug delivery (TDD) is an administration route used for potent, low-molecular-weight therapeutic agents which cannot withstand the hostile environment of the gastrointestinal tract and/or are subject to considerable first-pass metabolism by the liver (Prausnitz and Langer 2008). TDD provides controlled and constant administration of the drug, allows continuous input of therapeutics with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Skin has been considered as a promising route for the administration of drugs because of its accessibility and large surface area. It is a very heterogeneous membrane that provides a very effective barrier towards the penetration of drugs both to and through it, thanks to

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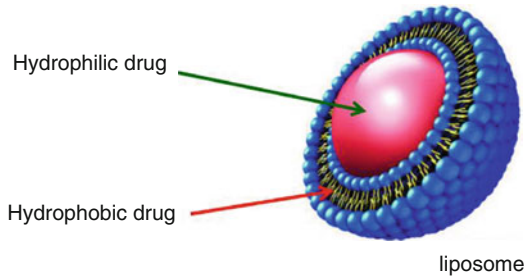

Fig. 23.1 Schematic representation of a liposome

its outermost layer, the stratum corneum (SC), a multilayered wall-like structure in which corneocytes are embed in a matrix of lipids (Bronaugh and Maibach 1985). Since this barrier represents a significant obstacle for transdermal permeation of most drugs, enhancement strategies are necessary to overcome it, thus improving drug release: among these, penetration enhancers, supersaturated solutions, physical methods and specific delivery systems such as vesicular systems (liposomes and niosomes) or vesicular hydrogels represent powerful approaches receiving considerable attention (Barry 1983).

23.1.1 Liposomes

Liposomes are microscopic vesicles that contain amphipathic phospholipids arranged in one or more concentric bilayers enclosing an equal in number of aqueous compartments (Fig. 23.1): In this form, as a spherical shell, they resemble biological membranes (Gregoriadis and Florence 1993). The ability of phospholipids to form bilayers is due to their amphipathic nature: the presence of a hydrophilic or polar region in the head (attracts water) and a nonpolar region or lipophilic tail (repels water). In this light, drug molecules can be encapsulated in the aqueous space (hydrophilic compounds) or intercalated into the lipid bilayer (lipophilic compounds) depending upon their physico-chemical characteristics. Due to their entrapping ability, biodegradable and non-toxic nature, liposomes have been reported to have several potential applications (Allen and Curtis 2013).

Particularly, liposomes have been shown to be a promising skin drug delivery system: their use may produce severalfold higher drug concentrations in the epidermis and dermis and lower systemic concentrations when compared to conventional dosage forms (El Maghraby 2008). Clearly, their topical use depends on their characteristics as size, surface, charge and chemical composition. Mezei and Gulasekharam in 1980 were the first to employ liposomes as skin drug delivery systems: they demonstrated that vesicles of dipalmitoylphosphatidylcholine (DPPC) and cholesterol (CH) (1.1:0.5, molar ratio) increased the concentration of triamcinolone acetonide in the epidermis and dermis by four- to fivefold and reduced percutaneous absorption compared with a standard ointment (Mezei and Gulasekharam 1980). Several mechanisms have been suggested for liposomes acting as skin drug delivery systems. According to the free drug mechanism, the drug may permeate the skin independently after exiting from the vesicles, since the liposomes themselves enhance the transdermal drug delivery by lowering the permeability barrier of the skin, changing the ultrastructures of the intercellular lipids and the enthalpy of the lipid-related transitions of the stratum corneum (Bernadete et al. 2011). In some cases, the vesicles may adsorb to the stratum corneum surface with subsequent transfer of drug directly from vesicles to the skin (El Maghraby et al. 2008). Moreover, vesicles have been reported to fuse and mix with the stratum corneum lipid matrix, increasing drug partitioning into the skin (El Maghraby et al. 2008). The possibility that intact vesicles penetrate human skin acting as carriers and go deep enough to be absorbed by the systemic circulation has been also suggested (El Maghraby et al. 2008).

Different novel vesicular systems derived from liposomes have been proposed as a valid alternative and among these, niosomes, nonionic surfactant-based vesicles, represent one of the most suitable options: niosomes appear to be similar in terms of their physical properties to liposomes, but they are preferred in topical delivery because of chemical stability and low cost of production (Schreier and Bouwstra 1994).

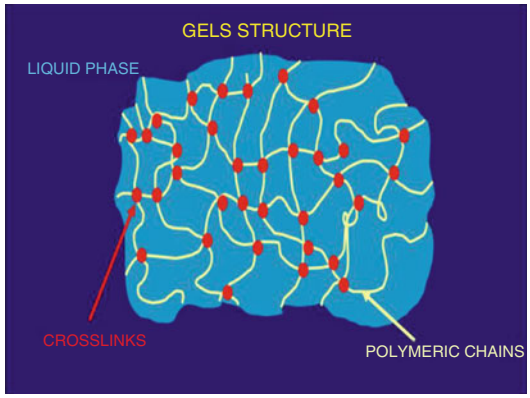

Fig. 23.2 Schematic representation of a gel system

23.1.2 Gel Systems

The term gel was introduced in the late 1800s to name semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix of natural or synthetic gums with a high degree of physical or chemical cross links, as shown in Fig. 23.2 (Narin 1997). Gel forming polymers include natural polymer (proteins and polysaccharides), semisynthetic polymers (cellulose derivatives), synthetic polymers (carbomers and poloxamers) and surfactants (cetostearyl alcohol and polyoxyethylene glycol alkyl ethers (Brij™, Croda International PLC)). Gel also possess a degree of flexibility very similar to natural tissue, and due to their high water content, they resemble natural living tissue more than any other type of synthetic biomaterial. Moreover, they have significant roles in pharmaceutical and cosmetical fields because of their biocompatibility, non-toxicity and good skin adhesion (Peppas 1986). Additionally, their insoluble cross-linked structure allows medium for dissolution of hydrophilic drugs, and since only the dissolved drug presented to the skin is able to enter the stratum corneum, gels could represent a strategy to enhance the percutaneous drug absorption and release across the skin in well-defined specific manner (Wichterle and Lim 1960).

Clearly, the type of vehicle used to formulate a topical dermatological product greatly influences its effectiveness. Gels prepared with organic polymers, such as carbomers, impart an aesthetically pleasing, clear, sparkling appearance to the products and are easily washed off from the skin with water; vehicles containing large amounts of oleaginous substances provide an emollient effect to dry irritated skin; bases made up of non-volatile oleaginous substances can form an occlusive barrier on the skin that prevents the escape of moisture from the site of application, causing hydration of the stratum corneum and increase of opening up of intra- and intercellular channels for easier passage of drug molecules (Hoare and Kohane 2008).

23.2 Liposomal Gel Systems

23.2.1 Introduction

Taking into account all the previously mentioned reasons, the incorporation of vesicular systems into a gel dosage form has been designed as a new strategy to improve drug percutaneous permeation: the resulting multicomponent systems, named *liposomal gel* (Fig. 23.3), may possess the advantages of the individual formulations (vesicular suspensions and gel systems) and some other important benefits (Foldvari 1996).

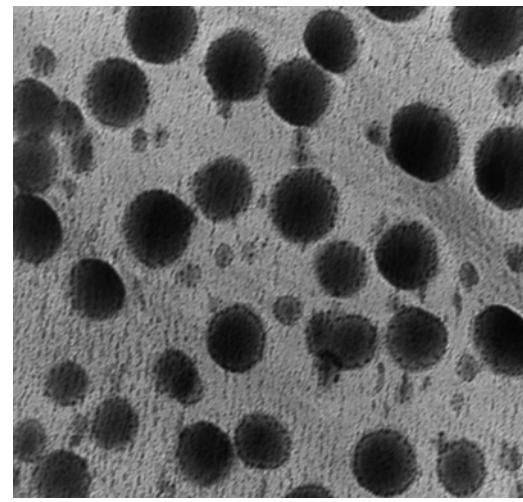

Fig. 23.3 Photomicrographs of a vesicles-gel system as seen by transmission electron microscopy (TEM) (Adapted from reference Antunes et al. 2011)

Since topically applied liposomal suspensions may leak from the application site, they could be mixed with gels in order to obtain semi-solid formulations. In addition, liposomal gels were found to enhance the skin retention of drugs and to provide higher and sustained skin concentrations of therapeutics compared to conventional gels and creams, without enhancing their systemic absorption (Pavelic et al. 2005). In addition, the stability of the liposomes (membrane integrity and mechanical stability) has been reported to increase when incorporated into a gel matrix (Mourtas et al. 2007). Additionally, liposomal gels have been demonstrated to have better rheological characteristics with respect to the liposomal dispersion (easiness of application and removal from the skin), to ensure an appropriate release of the active principle (compatibility with most active substances) and increased skin tolerance and compliance for patients. Clearly the type and concentration of the polymer forming the gel matrix has been reported to influence the stability and release rate of the active substance, whereby an assessment of the physico-chemical properties of the drugs, liposomes and polymeric gel must be made to avoid adverse effect and chemical, physical and biological incompatibility (Mourtas et al. 2008).

Moreover, liposomes in a gel can be more stable to environmental stimuli compared with bare liposomes in a dispersion, and when a drug is placed inside the liposomal core and the liposomes are included in a gel network, the drug will experience a combination of transport resistances due to the liposomal bilayer and the network itself: this results in a release of the drug over a longer period of time. Additionally, this can also avoid the problem of "burst release" seen with some polymer gels where a large bolus of drug is released initially from the gel, which can cause toxicity (Lee et al. 2012).

The first study on the incorporation of liposomes in a gel dosage form was reported by Mezei and Gulasekharam in 1982 (Mezei and Gulasekharam 1982). They compared the permeation of triamcinolone from plain and liposomal gel and they found that the application of the liposomal gel resulted in a concentration of triamcinolone acetonide approximately five times higher in the epidermis and three times higher in the dermis, than application of the conventional drug gel. The results of this study and those reported earlier by the same researchers (Mezei and Gulasekharam 1980) suggested the inherent potential of liposomes (when applied in a gel) as a drug delivery system for cutaneous application and the role of liposomes in the formation of a large drug reservoir in the skin, which is useful in local treatments. Since then, a lot of researchers explored the potential of liposomal gel systems in transdermal drug delivery (Gabrijelcic and Sentjurc 1995).

The most used polymers to obtain liposomal gels are carbomers, cellulose derivatives and poloxamers. Carbomers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They swell in water up to 1,000 times their original volume to form a gel when exposed to a pH environment above 4.0–6.0. Because the pKa of these polymers is 6.0–0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer (Florence and Pu 1994). Carbomer polymers are very well suited for aqueous formulations of the topical dosage forms: many commercial products available today have been formulated with these polymers, as they provide numerous benefits to topical formulations. Carbomer polymer possesses low toxicity and low irritancy potential and they are non-sensitizing even upon repeated usage. In addition, due to their extremely high molecular weight, they cannot penetrate the skin or affect the activity of the drug. Because of their excellent thickening, suspending, emulsification and suitable rheological properties, good tissue compatibility and convenience in handing and ease of application, carbomer gels represent a good alternative to oil-based formulations (Jian Hwa 2003).

Cellulose polymers (hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose) are examples of polymers that have been reported to possess adhesive properties (Jones et al. 1997). Chemically, these linear polymers are cellulose derivatives possessing various degrees of substitution and may be ionic or non-ionic; following addition to an aqueous phase,

these cellulose derivatives undergo swelling prior to dissolution. Pharmaceutically, water-soluble cellulose polymers have found widespread applications, e.g. in the formulation of solid dosage forms, aqueous disperse systems as viscosity enhancing agents and in products for topical application (Peppas et al. 2000).

Poloxamers are polymers consisting of a relatively long hydrophobic poly(propylene oxide) (PPO) middle block and two hydrophilic poly(ethylene oxide) (PEO) end blocks and are commercially available as Pluronics® (BASF, Hanover, Germany). In the presence of a either solvent selective for the hydrophilic PEO blocks, such as water, PEO–PPO–PEO block copolymers self-organize into a variety mesophases with lamellar, hexagonal or cubic structure (Batrakova and Kabanov 2008). Pluronics® have attracted particular interest in the design of dermal and transdermal delivery systems, with a view to promoting, improving or retarding drug permeation through the skin. Moreover, they possess specific pharmacological actions, in particular the dynamic PEO chains prevent particle opsonization and render them 'unrecognizable' to reticuloendothelial system (RES) and macrophages (Tavano et al. 2010). Several studies reported the advantageous interactions between Pluronics® and liposomes: in particular, these polymers have been used to sterically stabilize the vesicles and, hence, to prolong their half-life after parenteral administration (Kostarelos et al. 1999).

23.2.2 Overview on Liposomal Gel Systems Used for Dermal Drug Delivery

A summary of recent works in the area of novel liposomal gel formulations for dermal drug delivery is provided below.

Pavelic et al. in 2001 developed a liposomal gel system able to provide sustained and controlled release of calcein, as model drug, for local vaginal therapy (Pavelic et al. 2001). Traditional liposomes were prepared from egg phosphatidylcholine (EPC) and egg phosphatidylglycerol sodium (EPG-Na); they were incorporated in gels of polyacrylate, i.e. carbomer gels (Carbopol 974P NF or Carbopol 980 NF, BF Goodrich, Belgium). In vitro release of encapsulated calcein from both liposomal gels was tested and compared with that of liposomes dispersed in buffer (control). A slower release of calcein from liposomal gel was achieved: in fact, after 24 h, more than 80 % of the originally encapsulated calcein was retained in liposomes embedded in gel with respect to the control (60 %, respectively). The authors ascribed these results to the increased viscosity of the gel system which reduced migration of drug molecules, acting as drug reservoir system, while preserving the structure and integrity of liposomes.

Similar results were obtained by Glavas-Dodov and collaborators in 2002 (Glavas-Dodov et al. 2002). The authors compared the in vitro drug release properties of free and liposomally entrapped lidocaine hydrochloride hydrogels. As expected, hydrogel formulations showed higher release rate of lidocaine hydrochloride compared to liposomal gel. Moreover, the release kinetic in the case of liposomal gels can be described as diffusion controlled, while a steady-state release, achieved after the third hour, suggested that liposomes act as a reservoir system for continuous delivery of the drug and for these reasons they could have a potential as dermal delivery systems with prolonged and sustained drug release.

Another delivery system based on liposomal gels containing vitamin E acetate was designed in 2006 by Padamwar and collaborators to improve topical drug delivery (Padamwar and Pokharkar 2006). The prepared liposomal dispersion showed sevenfold increase in drug deposition in rat skin compared to the control (plain drug dispersion), and the liposomal gel formulation demonstrated sixfold and fourfold increase in drug deposition in rat skin compared to the control gel and marketed cream, respectively. Moreover, the liposomal gel formulation was found to be more stable than the corresponding liposomal in terms of drug entrapment efficiency and uniformity up to 3 months.

Mura et al. in 2007 designed and evaluated the potential of a liposomal gel formulation for the topical delivery of benzocaine as a model drug (Mura et al. 2007). Drug permeation from

liposomal dispersions (based on mixtures of phosphatidylcholine, cholesterol, ethanol and water) as such or formulated in a carbomer gel was evaluated both through artificial lipophilic membranes and excised abdominal rat skin, whereas in vivo anaesthetic effect was tested in rabbits. Liposomes were prepared with drug encapsulated in the hydrophilic core or incorporated in the hydrophobic bilayer. The results of the benzocaine release study across artificial membranes showed that the presence of the polymeric network in the case of liposomal gels gave rise to a general reduction of the drug permeation rate and allowed obtainment of a more regular release profile as a function of time, with respect to simple liposomal dispersions. Interestingly, drug-loaded gels showed a faster drug release in respect to the gel-containing liposomes with the drug in the lipophilic phase, but slower than that obtained from liposomal gels with the drug encapsulated in the aqueous phase. In permeation studies using rat skin, a higher reduction of drug permeation rate was noted, due to the more complex permeation process through rat skin than across artificial membranes. In percutaneous permeation studies across rat skin, the difference between the use of the liposomal dispersion as such or formulated in the carbomer gel was less evident, probably due to the major controlling effect exerted by the skin on the drug permeation rate. Moreover, an initial lag phase was present in respect to the permeation studies thought artificial membranes, which was attributed to the longer time necessary to saturate the skin membrane and to reach a pseudo steady-state flux condition between donor and receiver compartments. Finally, the lowest drug permeation was observed from the conventional gel in comparison to all liposomal gel formulations (containing drug concentrations ranged from 0.05 to 0.5 % w/w), confirming the hypothesized permeation enhancing effect of liposomal vesicles on drug delivery, which cannot be efficiently estimated by using the artificial membrane.

Mourtas et al. in 2007 evaluated the effect of liposomes, drugs and gel properties on drug release kinetics (Mourtas et al. 2007). They studied the release of two model compounds, one hydrophilic (calcein) and one lipophilic (griseofulvin, GRF), when dissolved directly in hydrogels (control gels) or dispersed in hydrogels in the form of liposomes (liposomal gels). Drug-loaded liposomes based on PC or DSPC/Chol were dispersed in carbomer, i.e. Carbopol® 974 (Chemix S.A, Athens, Greece), HEC (Natrosol 250 HX, Hercules Inc, Athens, Greece) or a mixture of these two hydrogels. Results demonstrated that depending on the intended use of a liposomal gel formulation, the first parameter that should be considered is whether the drug is hydrophilic or lipophilic. In fact, the release of calcein from liposomal gels was slower compared to that obtained from conventional gels and strongly dependent on the liposome-membrane rigidity. If the drug was encapsulated in DSPC/Chol liposomes and dispersed in gels, it was released significantly slower compared to the corresponding formulation based on PC liposomes. In the case of GRF, the release from liposomal gels was determined by drug loading. At high drug loading levels, GRF is released steadily from liposomal gels irrespective of liposome type (PC or DSPC/Chol). Moreover, in the case of the lipophilic drug, liposomes provided means for substantially increased drug loading in gels acting as reservoirs which released the drug in a sustained manner. Finally, the authors demonstrated that in the case of liposomal carbomer (Carbopol®) gels that behave predominantly as elastic solids and have substantially different flow properties (compared with HEC-based gels), increased release rates for free calcein and GRF, indicating easier diffusion of the compounds through this system, were obtained.

In the following year, Mourtas et al. investigated the effect of added liposomes on the rheological properties of a hydrogel containing 0.40 % w/v of carbomer, i.e. Carbopol® 974 NF (Chemix S.A., Athens, Greece) and 1.5 % w/v of HEC (Mourtas et al. 2008). PC or HPC liposomes, plain or mixed with Chol, were used to prepare liposomes. As reported by other authors, the lipid composition of liposomal bilayers was found to strongly influence the rheological properties of liposomal gels. Zero-rate shear viscosity and power law index values revealed that addi-

tion of PC liposomes to the hydrogel had the smallest effect on its rheological properties, even when the highest lipid concentration was used (20 mg/ml). Oppositely, incorporation of HPC (or HPC/chol) liposomes into gels resulted in a significant increase of the elastic character of the gel, which increased with increasing lipid concentration. Since drug rate permeation was found to be dependent on gel viscosity, authors demonstrated that liposomal gel based on HPC could be used to act as drug reservoir and to ensure a slow drug release over a prolonged time period, while liposomal gel based on PC could be used to obtain faster drug permeation.

Manosroi et al. in 2008 developed a new formulation in which elastic (containing ethanol) and conventional niosomal vesicles containing diclofenac diethylammonium (DCFD) were incorporated into a gel base containing 0.2 % w/w carbomer (Carbopol® 980, Noveon, India) (Manosroi et al. 2008). Authors reported that the cumulative amounts of drug in stratum corneum, viable epidermis and dermis and the receiving solution, obtained upon the application of niosomal gel, were higher compared to the commercial emulgel (containing 1.16 % (w/w) of DCFD) and conventional gel without vesicles. They suggested a synergistic mechanism between ethanol, vesicles and skin lipids to improve drug permeation. Moreover the developed niosomal gels showed an 18.92 % of inhibition of rat ear oedema (after 1 h of application) higher than the commercial emulgel (2.70 %) and conventional gel (5.41 %), indicating an in vivo anti-inflammatory activity enhancement of DCFD when entrapped in vesicles. This study demonstrated that the gel containing the novel vesicular system entrapped with DCFD may be a promising formulation to be used in the topical non-invasive treatment of inflammation.

The effect of incorporation of surfactants into hydrogels to increase drug loading concentration and attenuate the topical release rates was also investigated by Kapoor et al. in 2008 (Kapoor and Chauhan 2008). They demonstrated that the presence of 0.25, 0.6 and 1.5 % w/w polyoxyethylene (20) oleyl ether (Brij™ 98, Sigma–Aldrich Chemicals, St. Louis, MO) as surfactant into a polyhydroxy ethyl methacrylate (p-HEMA) hydrogel affected the loading of cyclosporine A in the matrix and controlled the drug release rate, depending on Brij™ concentration. At concentrations of Brij™ above the critical micellar concentration (CMC), the surfactant forms micellar than from the liposomal gel, but the lower value obtained by the multicomponent system was suggestive for prolonged and sustained drug release, because of the presence of several lipid bilayers that released the drug more aggregates, into which the hydrophobic drugs can partition preferentially.

The objective of the work performed by Patel in 2009 was to formulate a 1 % carbomer gel-containing ketoconazole-loaded liposomes and to study the in vitro drug release, skin retention and in vitro antifungal activity (Patel et al. 2009). The in vitro permeation of ketoconazole from liposomal gel through wistar albino rat skin was compared with that of the corresponding conventional cream and gel. From the results it can be concluded that the cumulative drug permeation was significantly higher from the conventional gel slowly. The higher skin retention of the drug achieved in the case of the liposomal gel was found to depend on the creation of the reservoir effect due to the presence of liposomes. In addition, the gel-containing liposomal ketoconazole showed the highest antifungal activity after 30 h compared to the conventional ketoconazole gel and cream formulations, by using the cup plate (or cylinder plate) method.

The main aim of the study published by Nina Dragicevic-Curic et al. in 2009 was to develop a temoporfin-loaded liposomal hydrogel which would be able to deliver the photosensitizer in an efficient dose into the stratum corneum and deeper skin layers (Dragicevic-Curic et al. 2009). Results showed that the presence of the polymeric network in the liposomal gels systems led to a slower drug release and lower permeation rate compared to liposomal dispersions and that the increase in polymer concentration from 0.5 to 1 % w/w, resulting in an increase of the viscosity of the systems, led to lower skin penetration of temoporfin. Despite this, authors demonstrated that liposomal gel formulations were able to deliver a sufficiently high amount

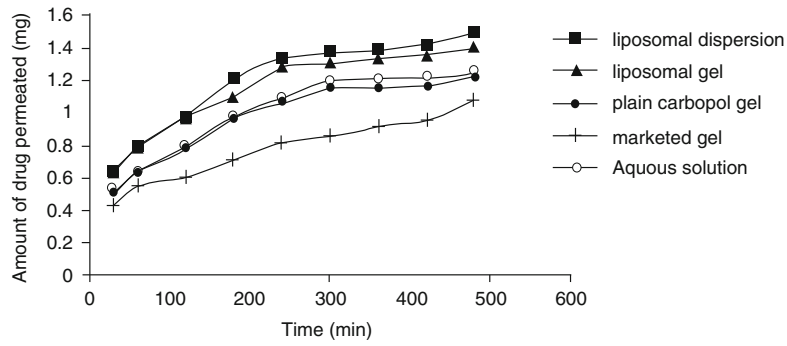

Fig. 23.4 Permeation profile of different fluconazole containing systems (Adapted from reference Mitkari et al. 2010)

of temoporfin into and also into the deeper skin layers, because they ensure long contact time of the formulation with the skin. For these reasons, these new formulations have been suggested as advantageous against cutaneous malignant (basal cell carcinoma) or non-malignant diseases (psoriasis, acne, etc.).

Several groups developed liposomal gels to be used for the dermal delivery of fluconazole. In 2007, Zhao et al. designed a new liposomal gel based on lecithin/cholesterol liposomes and carbomer (Carbopol® 941, Beijing Haidian Huiyou Fine Chemical Plant, China). They evaluated fluconazole skin permeation from the liposomal gel across rat skin and compared it to the corresponding conventional gel (Zhao et al. 2007). Results indicated that the cumulative amount of drug permeated through rat skin in the case of the liposomal gel was lower than that found upon the application of the conventional gel. Moreover, as reported in analogue studies, the addition of the drug into multicomponent systems significantly increased the deposited amounts of drug in the rat skin and resulted beneficial for topical use.

Differently, Mitkari et al. in 2010 designed a liposomal gel based on hydrogenated PC (Phospholipon 90H, Phospholipids GmbH, Germany) and carbomer (Carbopol® 934 NF, Noveon, India) and demonstrated that fluconazol skin permeation increased in the case of the liposomal gel compared to the drug solution, plain carbomer gel and marketed gel (Flucos® gel, Cosme Health Care, Goa, India) as represented in Fig. 23.4 (Mitkari et al. 2010).

In 2010, Jithan et al. formulated a diclofenac sodium-loaded liposomal gel to improve its anti-inflammatory activity and compared it to the traditional gel formulation (Jithan and Swathi 2010). In vitro drug release and ex vivo permeation studies showed that the liposomal gel provided a more sustained drug release and prolonged anti-inflammatory effect compared to the control gel formulation.

In a recent study, Lingan et al. formulated topical gel-containing clobetasol propionate vesicles to prolong the duration of the drug effect and to prevent its side effects (Lingan et al. 2011). The vesicles were prepared by varying the ratios between nonionic surfactants such as sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate (Span® 40, 60, 80, S.D. Fine chemicals, Mumbai, India) and cholesterol. Afterwards, the vesicles were incorporated into a 2 % w/w carbomer gel. The conventional carbomer gel and marketed gel (Clobevate, Stiefel Laboratories Pakistan (PVT) Pakistan) showed cumulative percentage of drug release (in respect to the initial applied dose) of about 98 % in 300 min, respectively, while the multicomponent formulation showed 51 % of drug release within 24 h. In addition, results demonstrated that the percentage of reduction in paw oedema was gradually increased in the case of niosomal gels up to 8 h, whereas in marketed gel it gradually increased up to 4 h and later it declined at 6 h and 8 h, revealing that the multicomponent systems had a sustained as well as prolonged action.

Recently, Megha et al. examined the ability of a new developed liposomal carbomer (Carbopol® 934, Noveon, India) gel loading selegiline, to deliver the active substance across the skin, and demonstrated that this novel sys-

tem provided a prolonged and sustained selegiline release rate. This gel could represent an attractive device for transdermal applications (Megha et al. 2012).

The objective of the study performed by Mansoori et al. in 2012 was to develop a ketoprofen liposomal gel to enhance the drug's anti-inflammatory activity and reduce its adverse effects (Mansoori et al. 2012). Carbomer (Carbopol® 934) gel was used as a vehicle (1 % w/w) and liposomes at different lipid concentration were incorporated. Drug release profiles of the different formulations were determined by using Franz diffusion cell up to 24 h and compared with that of a marketed gel (control) The results showed that the marketed gel released approximately 92 % of the drug within 24 h, while liposomal gel formulations showed percentage of drug release ranging from 81 to 87 %, indicating that the multicomponent formulations provided a more retarded and controlled drug release compared to the commercial gel. Finally, the ketoprofen liposomal gel showed a significantly enhanced retention of drug molecules in the skin.

The aim of a recent study performed in 2012 by Patel et al. was to develop a niosomal gel as a new transdermal device to improve the systemic availability of lopinavir (Patel et al. 2012). Skin permeation profiles of lopinavir was studied from a conventional gel, optimized niosomal and ethosomal dispersions, niosomal gel and ethosomal gel, after their non-occlusive application onto rat abdominal skin ex vivo. Interesting results were obtained: in terms of overall skin permeation of lopinavir (including percentage deposited within the skin and percentage permeated into the acceptor medium), the ethosomal gel appeared to be more efficient than the niosomal gel. However, the major fraction of lopinavir delivered via the ethosomal gel remained deposited within the skin, while the niosomal gel efficiently delivered the drug deeper into the skin and released 21.24 ± 0.23 % of the drug in 24 h, representing an amount significantly greater than that released via the ethosomal gel (11.15 ± 0.15 %). Moreover the percentage of drug permeated and deposited in the skin when using the niosomal gel was higher than that obtained from the niosomal dispersion (18.32 ± 0.18 %).

In 2011, Vyas et al. developed a new topical niosomal gel loaded with benzoyl peroxide (commonly used for the treatment of acne) to avoid drug side effects like skin redness, irritation, itching and oedema (Vyas et al. 2011). Several vesicular formulations were prepared to achieve the best performance in terms of size and entrapment efficiency and the optimized niosomal formulation was incorporated into 2 % w/w HPMC K15 (Colorcon Asia, Mumbai). Drug leakage studies revealed that vesicles incorporated in the multicomponent system were significantly more stable, because of the prevention of niosomes' fusion. In vitro drug release profiles revealed higher amount of released drug from plain gel and marketed gel in respect to niosomal gel, thus demonstrating a prolongation of drug release in the case of the multicomponent system. Drug retention in the skin has been shown to be higher (41.53 %) with the niosomal gel in respect to the plain gel (21.45 %) and marketed gel (24.88 %) after 24 h. Further, prolonged drug permeation was observed from the niosomal gel in respect to the plain gel and marketed gel, which may be due to slower diffusion of the drug across the skin and to the creation of a drug reservoir.

Recently, El-Nabarawi and collaborators developed a liposomal gel formulation to be used for transdermal paroxetine (PAX) delivery (El-Nabarawi et al. 2013). Selected drug-loaded liposomes were incorporated into HPMC E-4M gel (Tama, Tokyo, Japan) and then fabricated into transdermal patches. In vitro release profiles were evaluated and the transdermal patches were applied to rabbits for in vivo bioavailability study. Authors demonstrated that the diffusion of paroxetine from different liposomal gels in vitro through the artificial membrane was apparently dependent on the concentration of HPMC E-4M, where the increase in polymer concentration was associated with a decrease of the permeation rate due to the increase of gel viscosity. The percentages of paroxetine released from liposomal gels through artificial membrane were compared to that permeated from liposomal dispersions, and results indicated that the incorporation of liposomes into the gel resulted in a more delayed

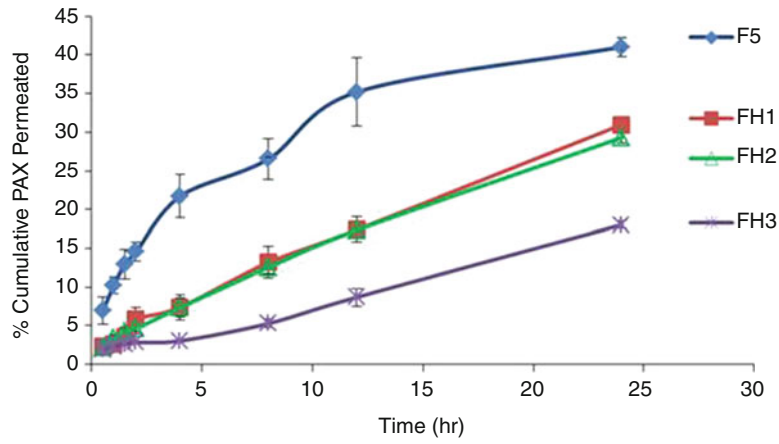

Fig. 23.5 Cumulative percentage of paroxetine (PAX) permeated from different formulations: F5 liposomal dispersion, FH1 liposomal gel (2 % of polymer), FH2 liposomal gel (4 % of polymer), FH3 liposomal gel (6 % of polymer) (Adapted from reference El-Nabarawi et al. 2013)

release due to the presence of the polymer network that act as an additional diffusion barrier to the drug release (Fig. 23.5).

In 2003, liposome gels bearing 5-fluorouracil (5-FU) as an antineoplastic agent, intended for transdermal application, have been prepared and in vitro drug release properties have been evaluated by Glavas-Dodov et al. (2003). Different liposomal formulations, prepared by varying the lipid phase composition, hydration conditions of the dry lipid film and drug concentration, were incorporated into a chitosan gel base (1 %, w/w, Katakura Chikkarin, Japan). Afterwards, 5-FU release profiles from conventional liposomes, conventional hydrogel as well as drug aqueous solutions were estimated. Results demonstrated that 5-FU was fully released from aqueous solutions within a period of 4 h, while the entrapment of 5-FU into conventional chitosan gel resulted in a prolonged release rate, due to the polymeric network of the hydrogel. Moreover, the release of 5-FU from the liposomal gel was significantly slower (40 % released within 8 h) than from all other formulations, confirming that its encapsulation into liposomes resulted in a prolonged and sustained drug release. In addition, drug release profiles of 5-FU obeyed the Higuchi diffusion model, thus liposomes have been demonstrated to act as reservoir systems for continuous delivery of the antineoplastic drug.

Nie and co-workers in 2011 designed an in situ gel system based on liposome-containing paclitaxel, by using 18 % w/w poloxamer (Pluronic® F127, BASF, Hanover, Germany) as thermoreversible gel, with the aim to control drug release and improve its antitumor efficiency (Nie et al. 2011). In vitro release experiment showed that liposomal gel exhibited the longest drug release period compared to liposomes, conventional gel and corresponding commercial gel formulation (Taxol, Bristol-Myers Squibb, China). This effect was presumably due to the increased viscosity of the liposomal gel, which has the effect of creating a drug reservoir. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and drug uptake studies showed that the treatment with the paclitaxel-loaded liposomal Pluronic® F127 gel yielded cytotoxicity, intercellular fluorescence intensity and drug concentration in keratinocyte cancer cells lines (KB cells) much higher than that of conventional liposomes.

In 2011, the influence of nonionic niosomes on the rheological behaviour of poloxamer (Pluronic® F127, BASF, Hanover, Germany) gel was investigated by Antunes and co-workers, with the aim to develop new devices for the controlled topical delivery of diclofenac sodium salt (Antunes et al. 2011). Results showed that the presence of surfactant aggregates in the polymer network clearly enhances the network strength, because of polymer-vesicle hydrophobic associ-

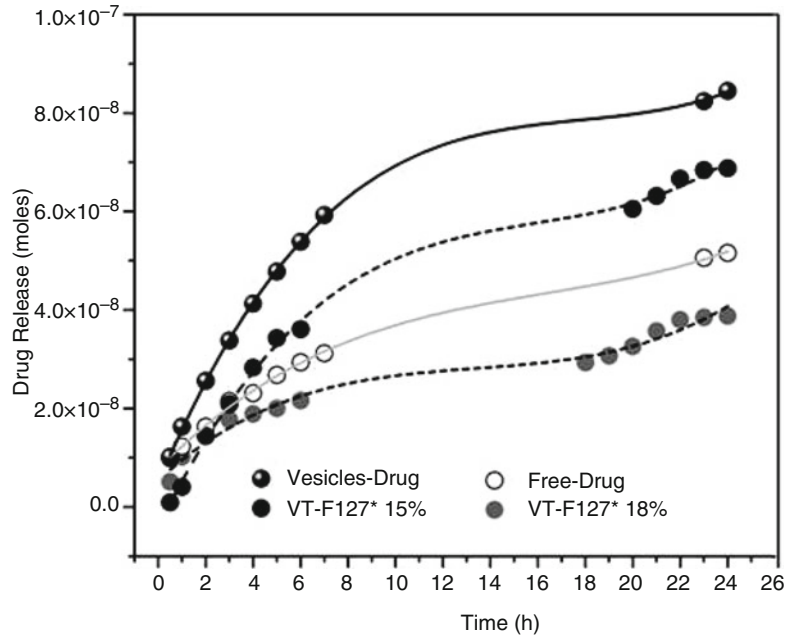

Fig. 23.6 Cumulative drug amount versus time of permeated diclofenac sodium salt at 37 °C from different formulations (*niosomal gels with 15 and 18 % w/w Pluronic® F127) (Adapted from Antunes et al. (2011))

ation and the increase of density of active links present in the polymer network. This resulted in a thickening effect, being optimal to enhance the suitability of vesicular suspensions as transdermal delivery devices, since traditional niosomal formulations are in liquid state. Interestingly, the niosomal size increased upon polymer addition, probably due to the formation of a polymer layer along the vesicle surface. As reported in (Fig. 23.6) higher percutaneous permeation of diclofenac sodium salt from niosomal formulation in comparison to drug solution has been found. Interestingly, in the study of Antunes, the drug cumulative amounts permeated from the niosomal gel decreased with increasing the polymer concentration. In fact, vesicle gel system at 15 % w/w of Pluronic® F127 provided higher amount of permeated drug compared to the mixture of 18 % w/w Pluronic® F127 gel and drug solution. The higher values of cumulative diclofenac sodium salt permeated were obtained by the niosomal dispersion. Unexpected, the cumulative permeated drug amount from niosomal gel at 18 % w/w Pluronic® F127 was found to be lower than that achieved by using drug solution due to the higher viscosity of the network gel.

Conclusions

Over the last two decades, several researchers have attempted to combine the properties of liposomes and polymer gels within the same material, embedding the vesicular systems in the polymer matrix.

These novel materials have demonstrated some attractive features, including the fact that liposomes in a gel resulted more stable to environmental stimuli compared with liposomes in solution. Moreover, some workers demonstrated that when a drug was placed inside the liposomal core and the liposomes have been included in a gel network, the drug experienced a combination of transport resistances due to the liposomal bilayer and the network itself, ensuring a release over a longer period of time and in a sustained manner.

Finally, liposomal gel formulations have been reported to provide therapeutically better effects than the conventional formulations, as topical dosage forms with prolonged and controlled drug release, which may lead to improved therapeutical effectiveness and better patient compliance.

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