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RESEARCH PAPER

Acid-Responsive Polymeric Nanocarriers for Topical Adapalene Delivery

Chenchen Guo • Rajeshree H. Khengar • Mingjing Sun • Zheng Wang • Aiping Fan • Yanjun Zhao

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ABSTRACT

Purpose The acne skin is characteristic of a relatively lower pH microenvironment compared to the healthy skin. The aim of this work was to utilize such pH discrepancy as a site-specific trigger for on-demand topical adapalene delivery.

Methods The anti-acne agent, adapalene, was encapsulated in acid-responsive polymer (Eudragit® EPO) nanocarriers *via* nanoprecipitation. The nanocarriers were characterized in terms of particle size, surface morphology, drug-carrier interaction, drug release and permeation.

Results Adapalene experienced a rapid release at pH 4.0 in contrast to that at pH 5.0 and 6.0. The permeation study using silicone membrane revealed a significant higher drug flux from the nanocarrier ($6.5 \pm 0.6\ \mu g.cm^{-2}.h^{-1}$) in comparison to that ($3.9 \pm 0.4\ \mu g.cm^{-2}.h^{-1}$) in the control vehicle (Transcutol®). The *in vitro* pig skin tape stripping study showed that at 24 h post dose-application the nanocarrier delivered the same amount of drug to the *stratum corneum* as the positive control vehicle did.

Conclusions The acid-responsive nanocarriers hold promise for efficient adapalene delivery and thus improved acne therapy.

KEY WORDS acid-responsive · acne · adapalene · nanocarrier · topical

C. Guo · Z. Wang · A. Fan · Y. Zhao (✉)
Tianjin Key Laboratory for Modern Drug Delivery & High Efficiency
School of Pharmaceutical Science & Technology, Tianjin University, 92 Weijin Road, Nankai District, Tianjin 300072, China
e-mail: zhaoyj@tju.edu.cn

R. H. Khengar
Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0HS, UK

M. Sun
College of Science, Tianjin University of Science & Technology, 29 TEDA 13th Avenue, Tianjin 300457, China

ABBREVIATIONS

ANOVA	Analysis of variance
DLS	Dynamic light scattering
FTIR	Fourier transform infrared spectroscopy
HPLC	High performance liquid chromatography
MWCO	Molecular weight cut-off
NMR	Nuclear magnetic resonance
PVA	Poly(vinyl alcohol)
SC	Stratum corneum
SDS	Sodium dodecyl sulphate
THF	Tetrahydrofuran
Transcutol®	Diethylene glycol monoethyl ether
XRD	X-ray diffraction

INTRODUCTION

Acne vulgaris, as a common skin disease, affects about 80% of teenagers (ca. 50 million) to a certain degree at some point (1). Its pathophysiology involves excess sebum secretion stimulated by dihydroxy testosterone and dehydroepiandrosterone, abnormal proliferation and differentiation of keratinocytes, obstructed follicle opening, proliferation of *Propionibacterium acnes* (*P. acnes*), and an inflammatory response initiated by bacterial antigens and cytokines. The typical symptom of acne includes comedones, papules, pustules, and scarring. In anaerobic conditions, *P acnes* can transform nutrients to propionic acid and acetic acid by fermentation (2). The presence of these acids reduces the comedones and skin surface pH down to 4.0 for acne patients in comparison to the average pH of 5.5 for healthy skin (3).

The choice of acne treatment depends on the type and severity of the disorder; retinoids are the first-line treatments if acne is mainly comedonal. Adapalene, a third generation retinoid, has been commercially available in the form of topical gel and cream (0.1%) for the management of mild to

moderate acne where comedones, papules, and pustules predominate. It acts *via* normalizing the differentiation of follicular epithelial cells resulting in decreased microcomedone formation (4,5). However, topical adapalene therapy encounters the most common adverse effect known as "retinoid reaction" that is dose-dependent and characterized by erythema, dryness, scaling, and a burning sensation at the sites of application. Such reaction has been revealed as a consequence of the presence of free carboxylic acid at the polar end of the agent (6). Furthermore, to address the poor aqueous solubility of adapalene, certain alcohols *e.g.* propylene glycol, phenoxyethanol, and some surfactants are often formulated in commercial adapalene products. These excipients can also induce skin irritation *via* interaction with the *stratum corneum* (SC), the uppermost layer of the skin and the major barrier of drug penetration (7). Since the acne treatment usually necessitates continuous use of adapalene medication for several weeks, irritation can seriously diminish patient compliance.

To circumvent the above irritation issues that are drug concentration-dependent and vehicle-dependent, previous investigations have attempted to employ a microparticulate system to load the active agent (8,9). This aim of this is to eliminate the rapid liberation of a high dose of the drug to the application site, enable controlled or sustained drug release, and thus reduce the side effects (10). A clinical study in 175 patients demonstrated that microparticulate adapalene therapy provided a better tolerability with reduced irritation compared to conventional adapalene formulations without compromising the efficacy (11). Loading adapalene in a carrier system dispersed in the aqueous medium can also avoid/minimize the use of alcohols and surfactants, and thus reduce vehicle-related skin irritation (12).

The use of nanoparticles presents an additional another alternative approach to address the irritation of topical adapalene, while preserving the therapeutic efficacy. Compared to microparticles, nanoparticles are highly versatile topical carriers since the formulation aesthetics are enhanced and the drug release rate can be manipulated efficiently in a controlled way due to the large surface area of nanoparticles (13). Moreover, nanoparticles have been shown able to target the hair follicles, which is beneficial for the management of follicular diseases such as acne (14–16). Hence a number of previous reports describe the employment of polymeric and lipid nanoparticles to encapsulate various anti-acne agents such as triclosan, tretinoin, and cyproterone acetate (17–20).

Balancing the affinity of the nanoparticles and the active agent is crucial to achieve an efficient delivery (13). Low affinity can lead to limited drug loading, premature drug release and crystallization prior to dose application. In contrast, high affinity can address the above issues, but can induce the problem of poor drug release before skin penetration. Triggering the release of active agents upon response to the microenvironment pH of normal or diseased skin has been an attractive means to speed up the drug release from the particles (21,22). A variety of strategies have been available for generating pH-responsive polymeric nanoparticulate drug delivery systems (23,24). Among these approaches, the use of pH-liable polymethacrylate polymer (Eudragit® EPO) is promising for skin delivery as it is not only a safe excipient listed by major pharmacopeia, but also its aqueous solubility is highly pH-dependent (soluble in water up to pH 5.0). Taking the advantage of the pH discrepancy between healthy skin and skin affected by acne, the aim of this study was to investigate the *in vitro* delivery efficiency of acid-responsive nanocarriers for site-specific adapalene delivery. Disintegration of nanoparticles formed from pH liable polymers is hypothesized under the acid microenvironment of acne skin, and thus the facilitation of enhanced drug delivery and efficacy.

MATERIALS AND METHODS

Materials

Adapalene was purchased from Beijing Huafeng United Technology Co. Ltd. (Beijing, China). Citric acid, disodium phosphate, sodium hydroxide, sodium dodecyl sulphate (SDS), and poly(vinyl alcohol) (PVA) with a molecular weight of 13,000–23,000 Da and a hydrolysis degree of 87–89% were purchased from Tianjin Guangfu Fine Chemical Research Institute (Tianjin, China). Regenerated cellulose membranes with a molecular weight cut-off (MWCO) of 7,000 Da were obtained from Baisaisi Bio-technology Ltd. (Tianjin, China). Poly(dimethylsiloxane)/silicone membrane (127 μm thick) was obtained from Bioplexus (Ventura, USA). High performance liquid chromatography (HPLC) grade acetonitrile and tetrahydrofuran (THF) were sourced from Sigma-Aldrich (Beijing, China). Acetone was obtained from Concord technology Ltd. (Tianjin, China). Diethylene glycol monoethyl ether (Transcutol®) was from ACROS Organics (Beijing, China). Eudragit® EPO (a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate) was from Evonik Industries AG (Shanghai, China). Deionized water from the laboratory supply was used in the whole study.

Drug Assay

Quantitative analysis of drug content in this study employs previously published HPLC methods with minor modification (25,26). The assay was carried out using an Agilent HP 1100 system with a UV detector (230 nm) and a Gemini C18 column (5 μm, 250×4.6 mm) (Phenomenex, Beijing, China) at ambient temperature. The injection volume was 20 μl and

the mobile phase was a mixture of acetonitrile, tetrahydrofuran, water, and hydrochloric acid (60:30:10:0.1, v/v).

Drug Loading

Adapalene (10 mg) and Eudragit® EPO (50 mg) were dissolved in the mixture of acetone (2.5 mL) and THF (2.5 mL). This organic solution was added to 12.5 mL aqueous PVA solution (1%, w/v) with continuous stirring. The organic solvent was removed by evaporation for 24 h at ambient temperature. The nanocarriers were then obtained *via* centrifugation and washed with water in triplicate followed by lyophilization. The drug content was determined by dissolving the freeze-dried samples in a mixture of phosphate buffer (pH 4.0) and THF (1:1, v/v) followed by HPLC assay.

Nanocarrier Characterization

The hydrodynamic particle size was analysed by dynamic light scattering (DLS). The samples were suspended/diluted with HPLC grade water in differing ratio prior to analysis. Transmission electron microscope (FEI TeCnai G2 F20) was also used to analyse the nanoparticle size. Zeta potential of the nanoparticles was assessed by the Malvern Zetasizer Nano ZS; prior to analysis the purified nanoparticles were suspended in an aqueous medium containing 1 mM sodium chloride. Freeze-dried drug-loaded nanoparticles together with Eudragit® EPO polymer and adapalene were analyzed by a Tensor 27 Fourier transform infrared spectrometer; the typical KBr method was employed. The X-ray diffraction (XRD) analysis was carried out using a Rigaku D/max 2500 diffractometer with a Cu Kα radiation (40 kV/100 mA). The scanning range was from 5 to 50° (2θ) and the scanning speed was 4°/min with a step size of 0.02°. The differential thermal analyser (Netzsch DSC 404C) was further employed to assess the polymer-drug interaction in the nanoparticle samples. The samples were heated from ambient temperature to 350° C at a speed of 20°C/min.

Skin Preparation

Unboiled fresh pig back skin was obtained from a local butcher. Following the standard protocol, the skin was reduced to ca. 1 mm thick containing stratum corneum, viable epidermis and some dermis (27). In brief, the skin surface was first washed with 70% ethanol and blotted with soft household paper prior to storing at 4°C for ca. 24 h. Then the skin was cut to strips (10×20 cm) before removing the subcutaneous fat and then being reduced to a constant thickness (1 mm). Afterwards, the skin was covered with aluminum foil and stored below 20°C until required (<1 month). Prior to use the skin was thawed at ambient temperature and cut to appropriate size (ca. 2.5 cm in diameter) using a cork borer to fit the Franz diffusion cells (ca. 2 cm^2 diffusion area, 17 ml receiver volume). The normal skin surface pH was expected within 5.0–6.0 based on a previous report (22).

Drug Release Study

The *in vitro* drug release experiments were carried out using the static Franz type diffusion cells with a diffusion area of ca. 2 cm^2 and receiver compartment volume of ca. 17 mL. The regenerated cellulose membranes with a molecular weight cut-off of 7,000 Da were cut to appropriate size with scissors, mounted and sealed between the two chambers of the cell with a magnetic stirrer in the receptor chamber. The receiver fluid was citric acid-disodium phosphate buffer (pH 4.0, 5.0, and 6.0) containing 5% (w/v) SDS. The cells were checked for leaking by inversion and placed on a submersible stir plate in a pre-heated water bath set at 32°C to maintain the membrane surface at 32°C. The cells were left to equilibrate for 1 h prior to the application of the donor formulation, which consisted of an infinite dose of nanoparticulate formulations to assess the drug permeation profiles. Drug diffusion through the membrane and into the receiver fluid was monitored by removal of a small amount of samples (*e.g.* 0.5 mL) out of the Franz cell sampling arm, which was followed by the drug content analysis *via* HPLC; the sample volume of fresh receiver fluid was added to maintain the fixed total volume. The cumulative amount of drug penetrating the unit surface area of the membrane was corrected for sample removal and plotted against time. Steady-state release rate was calculated using the line of best fit over at least five time points with a linearity of $R^2 \geq 0.98$. Over the time course of release experiment, the size of nanoparticles in the donor compartment was recorded *via* DLS to test the integrity of the nanoparticles (28).

Drug Permeation Study

The same type of Franz cells was employed to carry out the *in vitro* permeation study. Silicone membrane or pig skin (full thickness) was selected as the membrane. The cells were maintained in a pre-heated water bath set at 37°C to maintain the membrane surface at 32°C. The donor formulations (1 mL) were adapalene aqueous nano-suspension or the adapalene solution in Transcutol® with the identical drug concentration (0.05%, w/v). The receiver fluid was a mixture of citrate buffer (pH 4.0) and THF (8:2, v/v) containing 2% (w/v) SDS. All other experimental details, sampling and drug quantification were the same as the release experiment settings described above. However, for the pig skin permeation study, the samples were centrifuged prior to drug quantification by HPLC. The method was validated in advance to ensure that the HPLC peaks of the proteins and lipids from skin did not interfere with the drug analysis.

Fluorescent Analysis

For the silicone membrane permeation study, the donor formulations (nano-suspension or Transcutol® solution) were carefully removed at different time points (3, 6, and 12 h). The Franz cells were then dismantled and the membrane was cleaned prior to fluorescence assessment. The emission spectra of adapalene-containing silicone membranes were recorded using a Fluorolog-3-21 fluorometer (Jobin Yvon) within the range of 350–700 nm. The excitation wavelength was set at 320 nm with a bandwidth of 1 nm.

Tape Stripping

At the end of the pig skin permeation experiments, the formulation residues on the skin surface were carefully cleaned. An adhesive Scotch® tape (previously tested to show no interfering peak in the HPLC spectrum with adapalene) was placed onto the skin surface, followed by gentle pressure to ensure good contact, and subsequently removed by a sharp upward movement. This procedure was repeated 20 times to remove all layers of SC based on a standard protocol (13). The drug content in each layer was then quantified by HPLC.

Statistical Analysis

Statistical analysis of data was performed using SPSS software with a minimal level of significance of 0.05. Non-parametric Mann–Whitney tests were used to analyse the permeation data; other data were analyzed using the t-test or ANOVA (analysis of variance).

RESULTS & DISCUSSION

Adapalene was loaded within Eudragit® EPO polymer *via* the typical nanoprecipitation method (29). The obtained nanocarriers had a drug loading of 3.5±0.3% (w/w). The data was consistent with previous investigations as polymeric nanocarriers often show limited loading capability (<5%, w/w) (30,31). The nanocarriers exhibited a positive surface, which was proved by the zeta potential analysis (18.4± 2.9 mV), which was believed due to the dimethyl amino groups in the polymer. The drug-loaded nanocarriers showed a spherical morphology and a hydrodynamic size of 125.8± 3.5 nm (Fig. 1).

The interaction between the polymer and adapalene was first assessed by XRD (Fig. 2). The XRD pattern of adapalene demonstrated its crystalline nature, which was evidenced by a number of sharp and intense peaks from 10 to 30° (2θ). The presence of diffused peak proved the amorphous nature of the polymer. Similarly, the diffraction pattern of drug-loaded nanocarrier showed the disappearance of the characteristic crystalline peaks of adapalene, suggesting a new solid phase with a lower degree of crystallinity. The shift of band at ca. 17.5° (2θ, polymer) to 18.2° (2θ, nanocarrier) also indicated the existence of certain type of polymer-drug interaction(s). Such phenomenon was also observed in a previous investigation that employed the same type of polymer, but a different model drug, indomethacin (32). The thermal analysis revealed that the polymer did not present any phase transition peak within the experimental temperature range (Fig. 3). This was a consequence of the low glass transition temperature of the Eudragit® EPO polymer (ca. 46°C) (33). It was found that melting peak of adapalene shifted from 322 to 223°C upon being loaded in the polymeric nanocarrier, which suggested the decrease of drug crystallinity. In contrast to the thermograms of a typical solid dispersion system, the drug-loaded nanocarrier in the current study was not totally amorphous. In spite of this, the decreased crystallinity of adapalene would still favour its dissolution upon contact with the release medium and hence a rapid onset of therapeutic action.

Further Fourier transform infrared spectroscopy (FTIR) analysis provided more spectral information on the polymer-drug interaction (Fig. 4). Due to the conjugation of carboxylic acid to the aromatic ring, the C=O stretch of adapalene was at 1,686 cm^{-1}. Both the polymer and drug-loaded nanocarrier presented a C=O ester stretch peak at 1,730 cm^{-1}. The strong peak at 2,899 cm^{-1} was due to the adapalene carboxylic OH stretch. The peak at 2,956 cm^{-1} was assigned to the polymer CH stretch. For the nanocarrier, the peaks at 2,908 and 2,943 cm^{-1} might originate from the drug OH and polymer CH vibration, respectively. Nevertheless, these peak shifts signified the potential hydrophobic and hydrogen bonding interactions between adapalene and Eudragit® EPO. The hydrophobic interaction was presumed to exist between the polymer backbone and the aromatic ring of adapalene; the aminoalkyl group of Eudragit® EPO and the carboxyl group from the drug could form a hydrogen bond (Scheme 1). The analysis was consistent with previous work, where the high resolution magic-angle spinning nuclear magnetic resonance spectroscopy was employed to prove the presence of both hydrogen bonding and hydrophobic interactions between Eudragit® EPO and mefenamic acid that also contains the aromatic rings and carboxyl group (34). Interestingly, the appearance of a new broad peak at 3,369 cm^{-1} was mainly due to the hydroxyl group of PVA stabilizer (35,36). Although FTIR has been proven to be a useful technique to determine the polymer-drug interaction, the presence of PVA stabilizer complicated the elucidation of hydrogen bonding formation, which still needs further investigation.

The effect of environmental pH on the *in vitro* release of adapalene from polymeric nanocarriers was investigated using the diffusion cells coupled with porous cellulose membrane. Since the drug showed very limited solubility in water, the aqueous receiver fluid contained 5% (w/v) SDS surfactant to

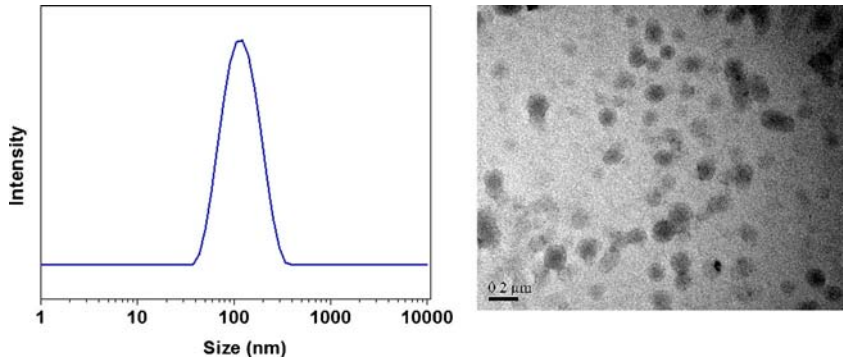


Fig. 1 The typical hydrodynamic size profile (*left*) of adapalene-loaded nanocarriers and their morphology picture by transmission electron microscopy (*right*) with the scale bar of 200 nm.

increase drug solubility and thus maintain the sink conditions. No organic solvents were incorporated in the receiver fluid, which excluded their possible influence on nanocarrier collapse and subsequent burst release of the active agent. The aqueous solubility of Eudragit® EPO is highly pH-dependent; the low pH (<5.0) favours its solubilisation in water, which is a consequence of the ionization of amino groups. The adapalene release profile agreed well with the expectation (Fig. 5). At the lowest pH condition (4.0), adapalene experienced a fast release, which was a result of acid-responsive particle breakdown and thus rapid drug liberation. At the elevated pH conditions (5.0 and 6.0), owing to the poor aqueous affinity of Eudragit® EPO, the particle kept its integrity and the drug release was a very slow process, which was because the particle wetting, and the drug diffusion from particle interior to the outside posed additional barriers (37). This was verified by the intermittent monitoring the size of nanoparticles during the experiment by DLS. For the release experiment at pH 4.0, the nanoparticles experienced a fast breakdown, which was evidenced by the fact that the particle size dramatically increased to ca. 2,000 nm within 1 h. Nevertheless, for the release experiment at pH 5.0 and 6.0, such phenomena were not observed, which concurred well with the release profiles.

The process of drug delivery to the skin from nanoparticulate carriers is a multiple-step process. The drug must be liberated from particles to the vehicle, after which it can permeate into the skin. Cellulose membrane is porous, while silicone membrane is non-porous in nature. For *in vitro* topical formulation assessment, the former is often employed for drug release studies and the latter for permeation study, respectively.

The *in vitro* permeation study was carried out using synthetic silicone membranes to mimic the SC barrier of human skin. In contrast to the porous cellulose membrane, silicone membrane presents a non-porous hydrophobic matrix, which makes it ideal to study the behaviour of drug partitioning between the vehicle and the membrane, as well as drug diffusion in the membrane (38,39). Apart from 2% (w/v) SDS, the receiver fluid in this experiment also contains 20% (v/v) THF to keep the sink conditions. The permeation result showed that the steady state drug flux for the aqueous nanocarrier suspension donor was 6.5 ± 0.6 ($\mu g.cm^{-2}.h^{-1}$), whilst the flux for the Transcutol® solution donor was 3.9 ± 0.4 ($\mu g.cm^{-2}.h^{-1}$) (Fig. 6). There was a significant difference

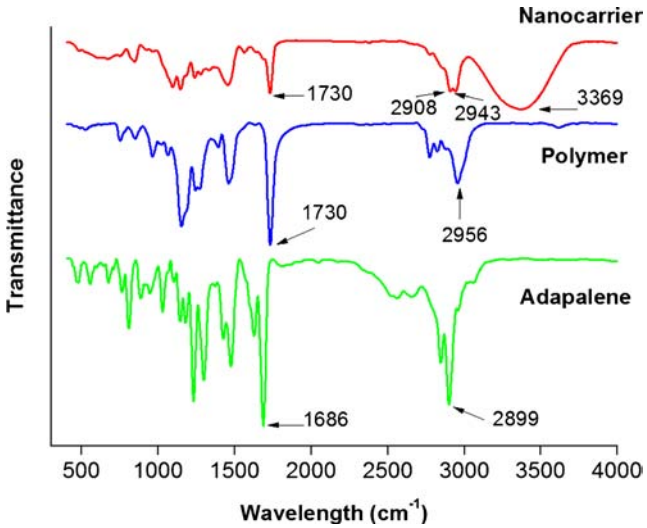


Fig. 2 The FTIR spectra of adapalene, Eudragit® EPO polymer, and adapalene-loaded nanocarrier.

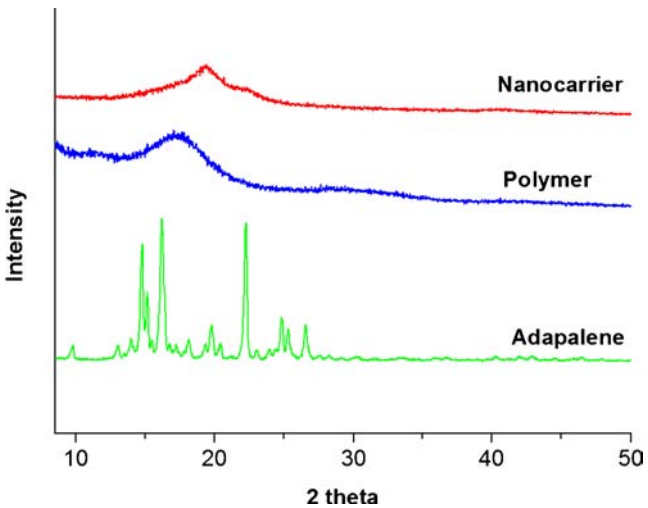


Fig. 3 The XRD patterns of adapalene, Eudragit® EPO polymer and adapalene-loaded nanocarrier.

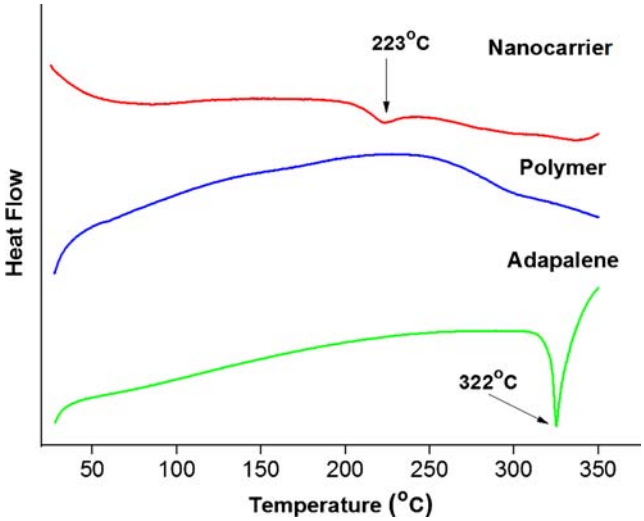


Fig. 4 DTA thermograms of adapalene, Eudragit® EPO polymer, and drug-loaded nanocarrier.

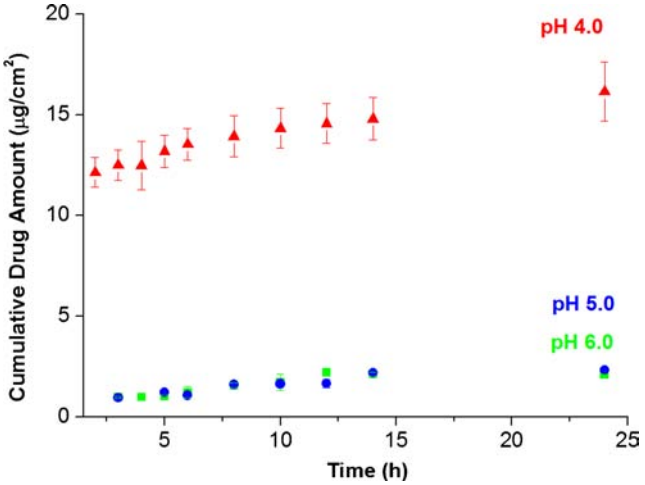
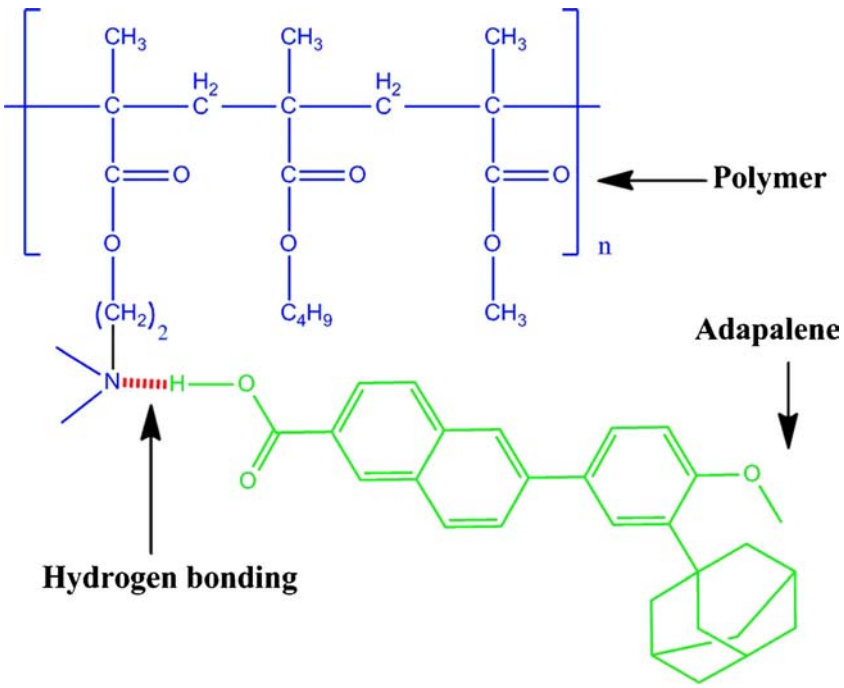


Fig. 5 The release profile of adapalene across regenerated cellulose membrane at 32°C from aqueous nanocarrier suspension. The drug concentration was fixed at 0.05 (w/v) and the pH of receiver fluid was maintained at 4.0, 5.0 or 6.0 ($n = 3$).

between both fluxes ($p < 0.05$). Since the adapalene concentration was the same for the above two donor systems (0.05%, w/v), the higher flux for the nano-suspension system dictated a higher drug thermodynamic activity according to the Higuchi equation (40). This can be explained by the much higher drug solubility in Transcutol® (ca. 2.4 mg/ml) at ambient temperature that was nearly three orders of magnitude larger than the aqueous solubility of adapalene. Taking advantage of the inherent fluorescence property of adapalene, the drug content in the silicone membrane at different time points of permeation study was qualitatively assayed *via* the fluorescence analysis. At a fixed time point, the fluorescence intensity for the nano-suspension donor system was much higher than that from the Transcutol® system (Fig. 7). This demonstrated a larger amount of adapalene in the membrane, which could be explained by the higher partition coefficient between the silicone membrane and aqueous nano-suspension in contrast to that between the membrane and Transcutol®. This also is consistent with the flux data in Fig. 6.

The isotropic silicone membrane offers the advantage of reproducibility and good control in tissue variability. However, biological skin is a heterogeneous complex tissue and the profile of drug permeation across skin might be very different

Scheme I The proposed mode of hydrogen bonding between adapalene and Eudragit® EPO polymer.



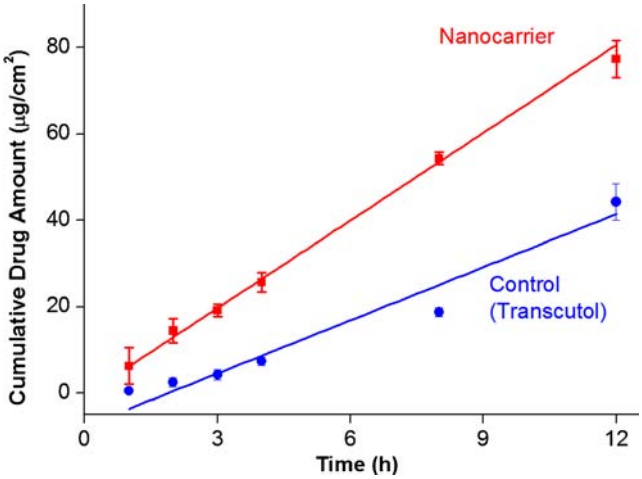


Fig. 6 The permeation profile of adapalene across silicone membrane at 32° C from aqueous nanocarrier suspension and Transcutol® solution as the control; the drug concentration was fixed at 0.05 (w/v) for both donor systems ($n = 3$).

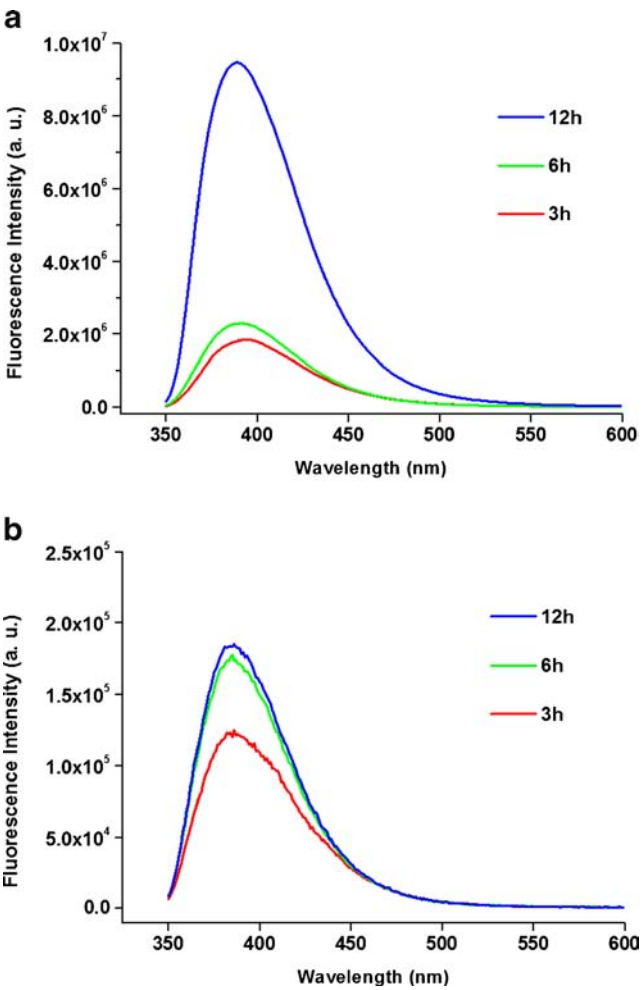


Fig. 7 Qualitative analysis of adapalene content in the silicone membrane at different time points of permeation study *via* the fluorescence spectroscopy (excitation wavelength at 320 nm). The donor systems for permeation study was aqueous nanocarrier suspension (**a**) and Transcutol® solution (**b**); the drug concentration was fixed at 0.05 (w/v) for both systems.

to that across simple synthetic membrane since it involves the issues of metabolism, shunt route, and large variability *etc*. As the most relevant model for human skin, pig skin was also selected to investigate and compare the skin penetration of adapalene from different vehicles. For all three types of donors, the drug content in the receiver fluid was below the limit of detection after a period of 24 h. The drug amount in the SC was obtained by the tape stripping method, which has been proved useful in topical drug delivery research for selectively removing SC, the main barrier of the skin. Moreover, *in vitro* tape stripping can be a good model for mimicking *in vivo* conditions (41). Although the skin species, body sites, physiological and pathological factors all may affect drug permeation, the viability of the skin is not a pre-requisite for penetration testing, since the process depends on passive diffusion and not on active transport. Upon vigorous validation, the tape stripping technique is a valuable tool for assessing and discriminating different formulations. Due to the multi-step process of drug permeation, i.e. release from the particles, partition and diffusion into the SC, and then the viable epidermis, the tape stripping experiment can quantify the drug amount in the SC to evaluate the delivery efficiency of nanoparticles. For acid-responsive particles, rapid release will increase the drug thermodynamic activity in the vehicle, and thus enhance its permeation into SC, resulting in more drugs in this layer. The donor of saturated adapalene solution in Transcutol® as the positive control generated the highest drug content in the SC ($p < 0.05$), simply because of the maximum thermodynamic activity of the drug among the three systems investigated (Fig. 8). The reason to select Transcutol® as a vehicle is that adapalene shows excellent solubility therein. Although it is not acid-sensitive, Transcutol® has been proven to enhance drug permeation and thus can act as an excellent positive control vehicle. At the lower drug concentration (0.05%,

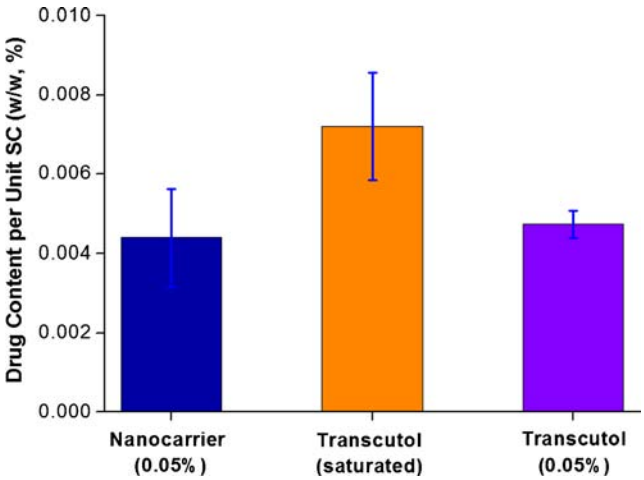


Fig. 8 Quantitative analysis of adapalene content in the stratum corneum (SC) of pig skin *via* tape stripping ($n = 6$). Three donor systems were employed: aqueous nanocarrier suspension (0.05%, w/v), drug solution in Transcutol® (0.05%, w/v), and saturated drug solution in Transcutol®.

w/v), the drug amount in the SC from aqueous nanocarrier suspension and unsaturated Transcutol® was not significantly different ($p > 0.05$). This did not occur with the trend observed in the *in vitro* fluorescence assay using silicone membranes (Fig. 7). Compared to the isotropic silicone membrane, skin is a more complicated heterogeneous membrane. In addition, Transcutol® has been shown as an effective skin penetration enhancer for a diverse range of topical therapeutics primarily *via* the mechanism of enhancing drug solubility in the skin (42,43). Therefore, due to the action of Transcutol® on the pig skin in the current study, the SC barrier property was compromised and thus drug partitioning from the vehicle into the SC was enhanced. However, due to the water vehicle being less irritating to the skin compared to Transcutol®, the adapalene-loaded aqueous nanocarrier system presents a superiority option in terms of long-term clinical application and patience compliance.

CONCLUSIONS

Adapalene-loaded polymeric nanocarriers were produced for on-demand drug delivery and skin-irritation reduction *via* utilizing the acidic microenvironment of acne skin. The polymer-drug interaction(s) enabled a lesser degree of drug crystalline post loading. The *in vitro* release study demonstrated rapid liberation of drug payloads by the nanoparticles under the acidic conditions which mimicked the conditions of acne skin. Both the silicone membrane and pig skin models demonstrated that the nanocarrier system may be as efficient as the Transcutol® vehicle as a positive control regarding drug delivery with minimum skin irritation potential. The results reported here suggest that the pH abnormality of diseased skin could be a useful trigger for tailor-making various acid-responsive nanoparticulate systems to enhance topical delivery.

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