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Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs

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Abstract

In this work, a hydrogel-thickened nanoemulsion system (HTN) with powerful permeation ability, good stability and suitable viscosity was investigated for topical delivery of active molecules. HTN was prepared to deliver an oily mixture of 5% camphor, 5% menthol and 5% methyl salicylate for topical therapy of arthritis, minor joint and muscle pain using soybean oil as the oil phase, soybean lecithin, Tween 80 and poloxamer 407 as the surfactants, propylene glycol as the cosurfactant, carbomer 940 as a thickening agent. The HTN system was found to combine the o/w microstructure of nanoemulsion with the gel network of hydrogel and had a suitable viscosity of 133.2 Pa S. The system had small average diameters and good long-term stability. The abilities of HTN to deliver the high amounts of camphor, menthol and methyl salicylate were evaluated using the in vitro permeation studies. The permeation rates of camphor, menthol and methyl salicylate from the optimal HTN formulation were 138.0 ± 6.5, 63.6 ± 3.3, $53.8 \pm 3.2\ \mu g\ cm^{-2}\ h^{-1}$ and showed the significant advantages over the control gel. The HTN with good stability and powerful permeation enhancing ability and suitable viscosity might be a promising prospective carrier for topical delivery of lipophilic drugs.

Keywords: Nanoemulsion; Topical delivery; Camphor; Menthol; Methyl salicylate

1. Introduction

Recently, much attention has been focused on the colloidal drug delivery systems such as microemulsions, solid lipid nanoparticles and liposomes for topical delivery of drugs because of low side effects, high bioavailability, good patient compliance, etc. (Rosen and Abribat, 2005; Moshfeghi and Peyman, 2005; Service, 2005). Emulsions with nanometric droplet size (typically in the range of 20–200 nm) is often referred to submicron emulsion, which is only a non-equilibrium system unlike thermodynamically spontaneous microemulsion (Solans et al., 2005, 2002; Buszello and Müller, 2000). Nanoemulsion has been widely used in pharmaceutics, cosmetics and it also plays important role as reaction template for synthesis of polymer dispersions and nanoparticles, because of the controllable droplet size, relatively long-term stability, powerful solubilization ability and so on (Sonneville-Aubrun et al., 2004; Zhang et al., 2005; Tadros et al., 2004). Especially, during the recent several decades, nanoemulsions have been designed to deliver drugs by various routes of administration (e.g., intravenous, oral, ocular or gene delivery) for therapeutic needs (Youenang Piemi et al., 1999; Santos-Magalhães et al., 2000; Wu et al., 2001; Nicolaos et al., 2003; Tamilvanan, 2004; Rabinovich-Guilatt et al., 2004; Bivas-Benita et al., 2004; Tamilvanan et al., 2005; Yilmaz and Borchert, 2006). Though, nanoemulsions as the topical carrier are rarely studied, it might offer several significant advantages including low skin irritation, powerful permeation ability and high drug-loading capacity for topical delivery when compared with the other carriers such as microemulsions, liposomes or solid lipid nanoparticles (Solans et al., 2005; Sonneville-Aubrun et al., 2004; Tadros et al., 2004).

Many lipophilic drugs, e.g., menthol, ibuprofen and ketoprofen are required to be delivered through skins at high concentrations for enhancing the topical uptake with low skin irritation (Chen et al., 2006a; Maestrelli et al., 2006; Valdez et al., 1999). It is a challenge to enhance the permeation ability of

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drugs using drug delivery system with high drug-loading capacity, powerful permeation ability and low skin irritation via topical administration. The active molecules including camphor, menthol and methyl salicylate have been used topically as analgesics and rubifacients. The formulation consisting of 5% camphor, 5% menthol and 5% methyl salicylate with good safety has clinically used in the treatment of arthritis, minor joint and muscle pain (Valdez et al., 1999). However, the poor penetration and drug-loading capacity of common products such as cream, gel or patch limited their topical therapeutic effects. So, it is necessary for exploring nanoemulsion to enhance the topical uptake of these drugs.

Even though nanoemulsions show several advantages for topical delivery and some attempts to enhance the topical uptake have also been made, for example, positive submicron emulsions with permeation enhancement effect were used, there is lack of the relative research about nanoemulsions with powerful penetration ability and good long-term stability for topical delivery of lipophilic drugs (Youenang Piemi et al., 1999; Sznitowska et al., 2002). So far it is still difficult to stabilize nanoemulsions containing high concentrations of drugs via electrostatically or sterically stabilized mechanisms during a long-term storage (Solans et al., 2002; Sznitowska et al., 2001).

Additionally, the low viscosity of nanoemulsion restrains its clinical application due to inconvenient use. Our previous studies showed that hydorgels such as carbomer 940 and xanthan gum can thicken microemulsions without the loss of stability and permeation rates (Chen et al., 2006a). There is lack of information (e.g., stability, permeation rate) about the influence of the addition of hydrogels on nanoemulsions, even though some hydrogels as thickeners have recently been reported to change the rheology properties of nanoemulsions for topical delivery (Sonneville-Aubrun et al., 2004; Yilmaz and Borchert, 2006).

In this work, we reported a hydrogel-thickened nanoemulsion (HTN) system with good stability, powerful permeation ability and suitable viscosity for the topical delivery of 5% camphor, 5% menthol and 5% methyl salicylate as the model drugs. The long-term aim is to develop a topical formulation using HTN system for clinical use. The present study focused on the preparation, characterization, stability and permeation ability of HTN.

2. Materials and methods

2.1. Materials

Soybean oil (SO) was purchased from Tieling Beiya Pharmaceutical Corp., China. Soybean lecithin (SL) was provided by Shanghai Jinban Food Corp. (Shanghai, China). Poloxamer 407 was obtained from BASF, Germany). Tween 80, propylene glycol (PG) and triethanolamine (TEA) was obtained from Shanghai Chemical Reagent Corporation, China. Carbomer 940 was purchased from Beijing Huiyou Chemical Factory, China. Menthol was provided by Taidao Menthol Pharmaceutical Corp., China. Other chemicals are of HPLC or analytical grade.

2.2. Preparation of HTN

2.2.1. Preparation of nanoemulsions

The nanoemulsion formulations were selected as described in Table 1. In order to prepare the drug-loaded nanoemulsions, the clear oily phase was obtained by mixing Camphor, menthol and methyl salicylate with the SO. The aqueous phase was prepared by dissolving SL, Tween 80, poloxamer 407 and PG into water (50.0 g) under magnetic stirring. Then aqueous phase was mixed with the oily phase using high-shear mixer (Model 1001, Shanghai Weiyu Corp., China) at 6000 rpm for 15 min and then the coarse emulsion was obtained. The coarse emulsion was further homogenized with a high pressure homogenizer (APV 2000, Denmark) and the nanoemulsion containing 5% camphor, 5% menthol and 5% methyl salicylate were prepared at various cycles and homogenization pressures at ambient temperature.

2.2.2. Preparation of HTN

Carbomer 940 was added to the residual water for swelling and then TEA was added to the swollen carbomer 940 for adjusting pH value of gel matrix (Yilmaz and Borchert, 2006). The gel matrix was mixed with nanoemulsions and HTN was prepared after stirring for 10 min at 500 rpm.

The gel matrix was also mixed with the coarse emulsion with the composition of HTN A to obtain the control gel.

2.3. Characterization of nanoemulsions

2.3.1. Photon correlation spectroscopy

HTN were diluted by 40 times for the measurement of droplet size. The average diameters and polydispersity index of samples were measured by photon correlation spectroscopy (Nano ZS90, Malvern Instruments, UK) at 633 nm. The measurements were performed at 25 °C using a He–Ne laser (Chen et al., 2006a,b).

2.3.2. Size distribution analysis by disc centrifuge

A disc centrifuge system (Chemical Process Specialists, Gorham, USA) and its Disc Centrifuge Control software were used to characterize droplet size of nanoemulsion (Elizalde et al., 2000). The instrument provides a high centrifugal force in a disk, which was filled with the spin fluid and driven by a motor. The sample was injected near the axe of the disk and allowed to

Table 1
The composition of the different HTN formulations (g)

HTN	Menthol	Camphor	Methyl salicylate	SO	Tween 80	Poloxamer 407	SL	PG	Carbomer 940	TEA	H_2O
A	5	5	5	3	4	1.0	0.5	10	0.25	0.25	66.0
B	5	5	5	3	4	1.5	0.5	10	0.25	0.25	65.5
C	5	5	5	3	4	1.0	1.0	10	0.25	0.25	65.5

sediment by centrifugation at 12,000 rpm in a sucrose density gradient. The separation of particles is based on the Stokes law for spherical particles (Sznitowska et al., 2001). The concentration of particles at each size was determined by continuously measuring the turbidity of the fluid near the outer edge of the rotating disc and the turbidity measurements were converted to a weight distribution using Mie Theory light scattering calculations (Bondoc and Fitzpatrick, 1998). The analysis continued for 39 min at 25 °C.

2.3.3. Transmission electron microscopy

Transmission electron microscopy (TEM) was performed to characterize the microstructure of HTN. Samples were placed on a carbon-coated copper grid and then a drop of 1% phosphotungstic acid covered on HTN. The superfluous phosphotungstic acid on sample was wiped off by filter paper. The TEM images were obtained using a Tecnai G2 20 TEM (FEI Corp., Germany).

2.3.4. Viscosity of nanoemulsion

The viscosities of samples were measured at 25 °C using a NDJ-8S digital viscometer (Shanghai Precision & Scientific Instrument, Shanghai, China) with a No. 4 rotor at 3 rpm.

2.4. Gas chromatography

Camphor, menthol and methyl salicylate were analyzed using GC-9790 gas chromatography system (Fuli Analysis Instrument Corp., Zhejiang, China). The column was a SE-54 column (30 m × 0.32 mm, 0.2 μm). Cyclohexanone was used as the internal standard. The detector is Flame Ionization Detector. The injector port is 230 °C and the detector temperature is 250 °C. Initial column temperature was maintain at 110 °C for 6 min, ramped at 10 °C min^{-1} to 150 °C and then held for 3 min. The flow rate of carrier gas is 3 ml min^{-1}. The assay was linear ($r^2 = 0.9999$) in the concentration range of 0.178–1.602 mg ml^{-1} for camphor ($r^2 = 0.9999$), 0.172–1.548 mg ml^{-1} for menthol ($r^2 = 0.9998$) and 0.399–3.591 mg ml^{-1} for methyl salicylate ($r^2 = 0.9999$), respectively. The average recovery is 98.9%, 99.0%, 98.3%, respectively. All relative standard deviations (R.S.D.) are less than 2% ($n = 9$). The method is simple, accurate and reproducible (Valdez et al., 1999).

2.5. Stability of nanoemulsions

The chemical and physical stabilities of HTN were evaluated at 25 °C for 6 months via clarity, droplet size and GC analysis of drugs. The centrifuge test was also carried out to assess the physical stability of the HTN. The HTN were centrifuged for 15 min at 4000 rpm in the centrifuge tests (Chen et al., 2004).

2.6. In vitro skin permeation studies

The abdominal skins were obtained from male rats weighing 250 ± 10 g. The permeation experiments were performed using a diffusion instrument (TK-12A, Shanghai, China) with a recirculating water bath and 12 diffusion cells. The skins were placed between the donor and the receiver chambers of vertical diffusion cells with an effective diffusion area of 2.8 cm^2 and a 7 ml cell volume. The receiver chambers were filled with freshly water containing 20% ethanol. The receiver chambers were set at 37 °C and the solution in the receiver chambers was stirred continuously at 300 rpm. The formulations (1.5 g) were gently placed in the donor chamber. At 2, 4, 6, 8 h, 0.5 ml of the solution in the receiver chamber was removed for GC analysis and replaced immediately with an equal volume of fresh solution. Each sample was performed three times. The cumulative corrections were made to obtain the total amounts of drugs permeated at each time interval (Chen et al., 2006b).

The cumulative amounts of drug permeated through rat skins were plotted as a function of time. The permeation rates of drug at a steady-state (J, μg cm^{-2} h^{-1}) through rat skins were calculated from the slope of linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot.

2.7. Data analysis

All the skin permeation experiments of each preparation were repeated three times and data were expressed as the mean value ± S.D. The statistical data were analyzed using nonparametric test with a Wilcoxon test. $P < 0.05$ was considered to be statistically significant.

3. Results and discussion

3.1. Preparation of HTN

In our previous studies, we used a great amount of soybean oil as the oily phase for dissolving these drugs. But methyl salicylate with lipophilic property and soybean oil require high amounts of surfactants for the emulsification of oily droplets and the nanoemulsions have high droplet size. We found that the lipophilic methyl salicylate can also act as the oily phase, which is easy to dissolve menthol and camphor. So the amount of SO was reduced and 3% SO was suitable in this work. Additionally, HTN was obtained by mixing nanoemulsions with gel matrix, so water was used to prepare not only nanoemulsions but also gel matrix. In preparation, the pressure and cycle times of homogenization showed significant influence on droplet size of nanoemulsions. The droplet size of nanoemulsions with the same composition of HTN C at 400, 600, 800 bar with eight cycles of homogenization are shown in Fig. 1(a). The increased pressure resulted in the decrease of droplet size of nanoemulsions. The droplet size of nanoemulsion obtained at 600 bar is 50.2 nm, which showed significant size decrease of 20 nm when compared with that obtained at 400 bar. The increase of the homogenization pressure from 600 to 800 bar only resulted in a decrease of 0.35 nm. The influence of cycle times on droplet size of nanoemulsions at the pressure of 600 bar was presented in Fig. 1(b). According to Fig. 1(b), droplet size of nanoemulsion decreased from 88.6 to 50.16 nm and PDI was also found to decrease from 0.312 to 0.269 with the increase of cycle times. So, the nanoemulsions prepared at 600 bar with eight cycles showed small diameters and a narrow distribution and then was

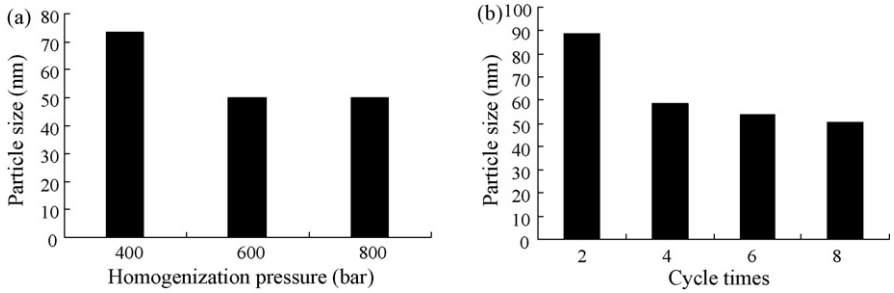

Fig. 1. The influence of homogenization pressure (a) and cycles (b) on droplet size of nanoemulsions.

selected as the optimum process for constructing the nanoemulsions. Sonneville-Aubrun et al. reported the nanoemulsions with diameters range of 50–100 nm for skincare products and the high pressure of 1200 bar was used to prepare the nanoemulsions. Youenang Piemi et al. also used a high pressure to prepare the charged nanoemulsions with diameters of about 125–140 nm (Youenang Piemi et al., 1999). Yilmaz et al. prepared positive nanoemulsion at the pressure of 500 bar, however the diameter of nanoemulsions was about 200 nm, which might was disadvantageous for the long-term storage of nanoemulsion. In this work, a relatively low pressure of 600 bar resulted in the formation of nanoemulsions with the average diameters of about 60 nm. It might be attributed to the formation of sterically stabilized effect and low surface tension at the interface of droplets in presence of various surfactants (Solans et al., 2005).

We chose 0.25% carbomer 940 as the gelling agent for constructing HTN. The gel matrix was prepared by adjusting the swollen carbomer 940 using TEA. The HTN could be easily prepared by mixing nanoemulsions with gel matrix. An immediate whitening of nanoemulsions was observed when gel matrix was added. This phenomenon accorded with the results obtained by Sonneville-Aubrun (Sonneville-Aubrun et al., 2004). The thickened nanoemulsions are expected to offer good biophysical and sensorial benefits for topical delivery (Sonneville-Aubrun et al., 2004). Additionally, carbomer 940 could also be directly added to nanoemulsion by stirring for 30–60 min to prepare HTN without being swollen gel matrix (Yilmaz and Borchert, 2006). However, this system showed a reduced viscosity, poorer stability and more significant ununiformity when compared with the former.

3.2. Characterization HTN

The average diameters of HTN from photon correlation spectroscopy are presented in Table 2. According to Table 1, HTN A and B had similar average diameters. HTN C showed obvious decrease of droplet size when compared with HTN A and B, which might attribute to the increase of SL. However, the increase of poloxamer 407 in HTN showed no influence on average size. Poloxamer 407 might act as more important role in stability as a steric stabilizer than in emulsification. Tween 80 as the surfactant had significant influence on the droplet size and 4% Tween 80 could result in the smallest diameter of nanoemulsion. The addition of carbomer 940 to nanoemulsions showed no significant influence on droplet size of nanoemulsions.

The sedimentation analysis by disc centrifuge (Fig. 2) showed that weight mean size of the nanoemulsion with the same composition of HTN C is 56.4 nm, which is accorded with the result (60.9 nm) of HTN C obtained from photon correlation spectroscopy. The results showed that the addition of carbomer 940 did not result significant influence on droplet shape of nanoemulsions.

Fig. 3 showed the TEM images of the HTN C, which had spherical droplets. The viscosity of HTN C is 133.2 Pa S. According to Figs. 2 and 3, the addition of carbomer 940 into nanoemulsion also had no significant influence on droplet size. It is possible that the gel network have no influence on the o/w structure of nanoemulsion, even though the gel network increased the viscosity of nanoemulsions. Carbomer 940 as an aqueous gel matrix could lead to the formation of the gel network in continuous phase and the droplets might locate in the gel network (Lapasin et al., 2001).

3.3. Stability of HTN

All HTN formulations were physically stable at 25 °C during 6 months. No change of droplet size, phase separation and degradation of drugs were observed during 6 months. The centrifuge tests also showed that all HTN systems had good physical stability. Even though nanoemulsions might become very unsta-

Table 2
The physicochemical properties of the different formulations

Formulations	Size (nm)	PDI	J of camphor ($\mu g\,cm^{-2}\,h^{-1}$)	Lag time of camphor (h)	J of menthol ($\mu g\,cm^{-2}\,h^{-1}$)	Lag time of menthol (h)	J of methyl salicylate ($\mu g\,cm^{-2}\,h^{-1}$)	Lag time of methyl salicylate (h)
HTN A	67.2	0.148	138.0 ± 6.5	0.20	63.6 ± 3.3	0.65	53.8 ± 3.2	1.16
HTN B	66.4	0.217	142.0 ± 6.8	0.60	58.2 ± 2.8	0.87	49.1 ± 2.8	1.07
HTN C	60.9	0.136	147.8 ± 7.3	0.88	53.4 ± 2.7	1.10	56.9 ± 3.1	0.53
Control gel	–	–	118.8 ± 6.2	0.44	46.1 ± 3.0	0.84	41.1 ± 2.4	0.35

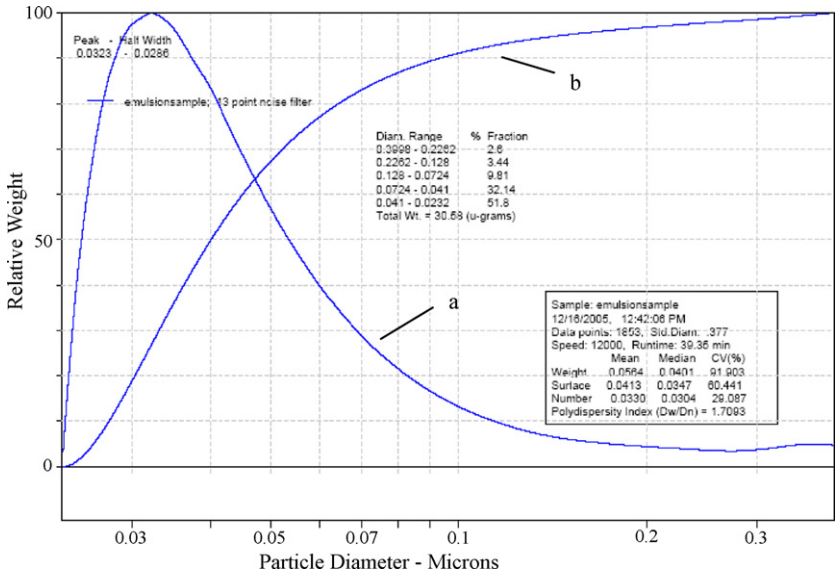

Fig. 2. The weight size distribution (a) and cumulative distribution (b) of HTN C in absence of gel matrix obtained from sedimentation analysis by disc centrifuge.

ble upon addition of drugs due to absence of the emulsifier, the lipophilic camphor, menthol and methyl salicylate in oily phase showed no significant influence on the physical stability of nanoemulsion (Sznitowska et al., 2001). In fact, the drugs in oily phase acted as the oily molecules, which were solubilized by surfactants. The influence of the addition of these drugs on stability had close affinity with the stability of oily droplets in HTN.

Carbomer 940 in HTN resulted in a high viscosity and oily droplets might be distributed in gel network, which might contribute to the enhancement of the stability of droplets in nanoemulsion. However, the essential stability of HTN actually depended on nanoemulsions. The instability of droplets in nanoemulsion originates from drop coalescence and Ostwald ripening (Capek, 2004; Sajjadi, 2006.). Coalescence is often considered as the most important destabilization mechanism nanoemulsions. It can be prevented by emulsification of surfactants, which are located at the droplet surface and form barriers against the transfer of the oil phase from one droplet to another droplet (Capek, 2004). Additionally, the very small droplet size of about 60 nm could reduce the creaming movements of droplets and the high viscosity of HTN could also restrain the Brownian motion. Second, the steric stabilization of polymeric emulsifiers (poloxamer 407) also prevented the flocculation or coalescence of the droplets. It should attribute to the combination of the steric stabilization of Tween 80 and poloxamer 407 and the charge repulsion effect of SL (Vleeschauwer and der Meeren, 1999). Especially, poloxamer 407 may contribute to the droplet stabilization through the formation of a thick steric barrier at the droplet interface, which reduces the rate of ripening by several orders of magnitude (Capek, 2004).

We also compare the influence of poloxamer 407 and poloxamer 188 on the physical stability of HTN system. Poloxamer 407 exhibited more significant advantage of the physical stability in HTN system when compared with poloxamer 188. Additionally, PG as a cosurfactant acted as an important role at the formation of interfacial membrane of nanoemulsions. In conclusion, the good stability of HTN systems should be attributed to the overall stabilizing effects of small diameters, carbomer 940 and surfactants (SL, Tween 80, poloxamer 407 and PG) (Yilmaz and Borchert, 2006).

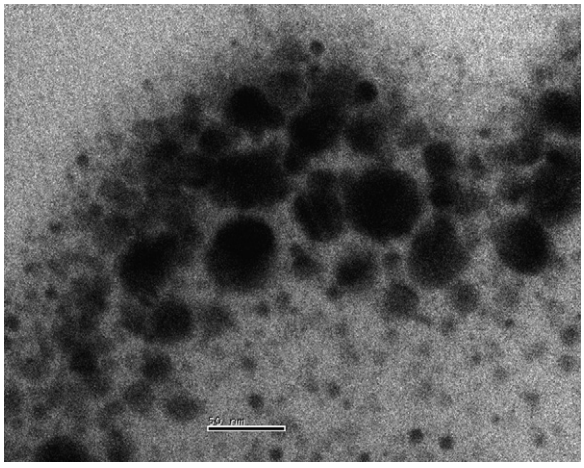

Fig. 3. The TEM imaging of HTN C.

3.4. Permeation studies

The permeation abilities of the various HTN systems were evaluated using the in vitro permeation experiments. The permeation parameters of camphor, menthol and methyl salicylate from the tested HTN and control formulations are presented in Table 2. The permeation profiles of camphor, menthol and methyl salicylate through rat skins from various HTN are shown in Fig. 4. The steady increase of these drugs in the receptor chambers with time was observed. The permeation profiles of drugs followed zero order release kinetics.

The permeation rate of camphor from HTN C had the highest rate of $147.8 \pm 7.3\ \mu g\ cm^{-2}\ h^{-1}$, which showed statistically significant when compared with that of control gel. However, the

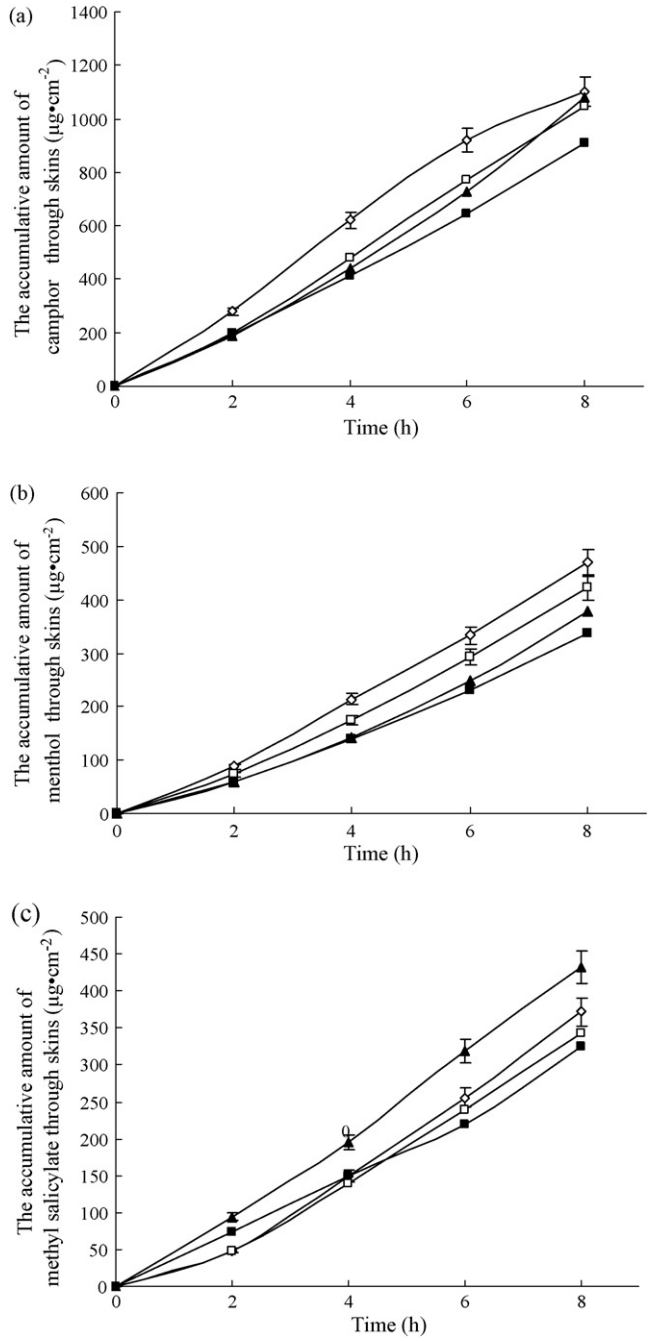

Fig. 4. The permeation profiles of camphor (a), menthol (b) and methyl salicylate (c) through excised rat skins from HTN. (□) HTN A, (◊) HTN B, (▲) HTN C, (■) control gel.

accumulative amount of camphor from HTN C through skin is only about $1078 \pm 37\ \mu g\ cm^{-2}$, which was lower than the accumulative amount of about $1100.3 \pm 40.0\ \mu g\ cm^{-2}$ from HTN A. HTN A had the shortest lag time of and HTN C had the longest lag time. The long lag time resulted in the decrease of accumulative amount of camphor through skins.

The rates of menthol from HTN A and B through skins were 63.6 ± 5.5 and $58.2 \pm 5.1\ \mu g\ cm^{-2}\ h^{-1}$, respectively. Their lag time was 0.66 and 0.87 h, respectively. The accumulative amount of menthol from HTN C is $471.3 \pm 35.0\ \mu g\ cm^{-2}$. Both showed significant increase of permeation rates when compared with HTN C. HTN C had a relatively long lag time compared with the other HTN formulations.

According to Table 2, HTN A, B and C had higher permeation rates of methyl salicylate than that from control gel and showed only a slight increase of the permeation rate of methyl salicylate when compared with control gel. HTN C had the highest rate of $56.9 \pm 3.1\ \mu g\ cm^{-2}\ h^{-1}$, which showed statistically significant when compared with that of control formulation, but it is no significant difference between the permeation rate of HTN A and that of HTN C. The accumulative amount of methyl salicylate from HTN C through skin is $371.1 \pm 25.0\ \mu g\ cm^{-2}$, which was higher than that of the other formulations.

Table 2 and Fig. 4 showed HTN A and C had powerful permeation abilities for topical delivery of camphor, menthol and methyl salicylate. HTN A had higher accumulative amounts of camphor and menthol than HTN C, but had a slight decrease of the permeation rate of methyl salicylate when compared with HTN C.

There were a few mechanisms for elucidating the permeation enhancing ability of nanoemulsions for topical delivery. Youenang Piemi et al. reported that the surface charge-modified droplets had significant influence on the binding affinity of droplets to the skins, which could promote the bioavailability of drugs (Youenang Piemi et al., 1999). Wu et al. found that the w/o nanoemulsions facilitated follicular transport of drugs (Wu et al., 2001). The high permeation rates of HTN formulations should attribute to several factors. Firstly, the high concentration (5%) of drugs in HTN resulted in high concentration gradient, which might be the main permeation mechanism of drugs into the skin from HTN. HTN could act as drug reservoirs where drug is released from the inner phase to the outer phase and then further onto the skin (Peltola et al., 2003).

In addition, due to the small droplet diameters of HTN, the oily droplets might embed into the stratum corneum and the drug molecules could directly be delivered from oily droplets into the stratum corneum without a transfer via hydrophilic phase of nanoemulsions. Then drug molecules were easier to permeate into stratum corneum.

4. Conclusions

The nanoemulsions containing camphor, menthol and methyl salicylate were prepared using high pressure homogenization with 600 bar and eight cycles, followed by being dispersed into carbomer 940-based gel matrix to form HTN. The addition of carbomer 940 into nanoemulsion also had no significant influence on droplet size. The HTN formulations had spherical shape and small diameters. The HTN remained the o/w microstructure of nanoemulsion and the spherical droplets were found to distribute in the three-dimensional gel network of continuous phase. The overall stabilizing effects of small diameters, carbomer 940 and surfactants resulted in the good long-term stability of HTN systems. The HTN A containing 0.5% soybean lecithin, 4.0% Tween 80 and 1.0% poloxamer 407, 10.0% propylene glycol carbomer 940 was found to have high permeation rates with $138.0 \pm 6.5\ \mu g\ cm^{-2}\ h^{-1}$ of camphor, $63.6 \pm 3.3\ \mu g\ cm^{-2}\ h^{-1}$

of menthol and $53.8 \pm 3.2\,\mu g\,cm^{-2}\,h^{-1}$ of methyl salicylate. The powerful permeation ability might attribute to high concentration gradients, thermodynamic activity and small diameters.

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