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SMGA gels for the skin permeation of haloperidol

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Abstract

Small molecule gelling agent (SMGA) gels were developed using the gelator GP-1 in the solvents, namely, isostearyl alcohol (ISA) and propylene glycol (PG), to deliver haloperidol through the skin. The concentrations of the drug, haloperidol, the enhancer, farnesol and the gelator, GP-1 are 3 mg/ml, 5% (w/v) and 5% (w/v), respectively. The study employed a three-factor full factorial statistical design to investigate the influence of factor level changes on the permeability coefficient and permeation lag-time of haloperidol. Gels were prepared by raising temperature to 120 °C, followed by natural cooling under room temperature of 22 ± 1 °C. The rheological properties of the gels were examined with a strain-controlled dynamic mechanical method. The in vitro permeation study was conducted with automated flow-through type cells. The gels successfully incorporated the drug and enhancer without losing their aesthetic properties. The in vitro human skin permeation study showed the permeation of the drug in ISA-based gels reached the pseudo steady state faster than PG-based gels and were less affected by gelator. PG-based gels delivered the drug at a faster rate with the incorporation of the enhancer. GP-1 did not influence the drug permeation rate but it increased permeation lag-time. The co-existence of gelator or enhancer increased the lag-time to a larger extent than when used separately. The novel SMGA gels are suitable for topical or transdermal delivery.

Keywords: Organogel; Gelator; GP-1; SMGA; Skin; Transdermal drug delivery; Factorial design; Gels; Permeation enhancer

1. Introduction

Small molecule gelling agents (SMGA) or low-mass gelling agents (LMGA), of molecular weights less than 3000, can form supramolecular networks and immobilize water or organic solvents to yield SMGA gels [1–3]. The gelators for organic solvent are classified into five categories: fatty acids, steroids and their derivatives, anthracene derivatives, *cyclo*-(dipeptides), and sorbitols [2,4]. Hydrogelators consist mainly of four classes: conventional amphiphiles, bola amphiphiles, Gemini surfactants and sugar-based systems. SMGA can be used as gelling agents for almost all kinds of polar and non-polar liquids. The inherent

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physicochemical properties of gels, such as hardness, elasticity, clarity, and liquid-carrying capacity, depend on the microstructure of the fiber network structure of SMGA, which in turn is determined by the mutual interactions between SMGA molecules and solvent, the degree of supersaturation, and branching agents [5–7]. The thermomechanical processing conditions such as the stress, strain, and temperature, also have influence on the microstructure formation and macroscopic properties of the gels [8]. The gelation process is controlled by a crystallographic mismatch branching that leads to the formation of the Caley fractal-like interconnecting fiber network structures in the liquid [9]. These networks form highly porous superstructures and immobilize a large volume of liquid efficiently via capillary and other related forces. It is known that a SMGA can form a gel in one solvent, but may fail to form a gel in other isomeric solvents, or if formed, the network structure and properties may differ.

The gels are prepared by dissolving or dispersing the gelator in the organic solvent to prepare the sol phase which, on cooling, sets to the gel state. Cooling the sol phase results in a self-assembly of the gelator molecules into 3-D permanent interconnecting nanocrystal fibrous networks, which immobilize the organic solvent. In contrast, systems consisting of nonpermanent or transient interconnecting fibers or needles can only form weak and viscous paste at low concentrations. The resultant organic gels are opaque or transparent in some cases, and thermoreversible in nature. On heating, the gel normally melts to the sol phase with an increase in the solubility of the gelator, but in some cases, complexes between gelator and solvent form at low temperature and the resulting solution will gelate with rising temperature [10]. The transition is thermoreversible in both cases.

SMGA gels are intrinsically different from microemulsions or polymeric gels. The essential components of microemulsion are oil, water and surfactant, which form circular units, stabilized by surfactant, dispersed in the leftover water or oil, i.e., the continuous phases [11]. The formation process is achieved by strong mechanical forces. Polymers immobilize bulk solvents by forming networks with their covalently connected long chains, such as the organogels formed by PG and Carbopol [12]. Some copolymers with relatively low molecular weights and narrow molecular-weight distributions possess self-assembly property, but their molecular weights are generally two magnitude higher than the range of SMGA, below 3000 [13–15]. For SMGA gels, the self-assembled three-dimensional fibrous network structures are formed by interconnecting nanosized fibers. The strands of SMGA gels are organized through noncovalent interaction, one of the reasons that make them thermoreversible. Apart from this, in the area of colloidal and nanoscale physics, the networks of aggregations are often found to have fractal geometry.

These supramolecular materials find many applications in various fields, such as nanomaterials, lithography, biomaterial processing, tissue engineering, water purification and so on [2,16–18]. In the fields of drug delivery, however, SMGA gels remain largely unexplored. The few cases that have been reported so far were briefly reviewed as follows. It is reported that a non-ionic surfactant, sorbitan monostearate, can gelate biodegradable oils and the SMGA gels formed may be suitable for a depot preparation for intramuscular administration [19]. Another study shows that L-alanine derivatives, as the gelling agent, immobilized soybean oil and medium-chain triglycerides, which can lead to in situ formation of an implant [20]. The most remarkable study is that the antibiotic, vancomycin, is derivatized into a hydrogelator by adding a pyrene group to its molecule. The modified vancomycin, 11-fold more powerful than vancomycin, can dissolve in water to form a gel without additional heating. The novel mechanism of targeted delivery based on this argued that these gelator-antibiotic molecules formed a lethal layer of SMGA gel encapsulating the bacteria through self-assembly. The results could have opened a new area of drug design and delivery [21,22].

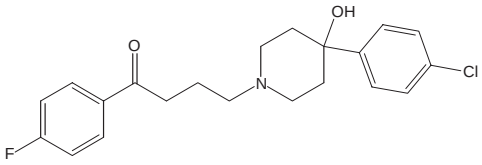
For topical or transdermal applications, only microemulsion-based organic gels have been previously reported [23–25]. The application of SMGA gels in transdermal drug delivery is thus investigated for the first time, to our best knowledge. Two SMGA gels are prepared by dissolving a small molecule gelling agent, *N*-lauroyl-L-glutamic acid *di*-*n*-butylamide (GP-1), into propylene glycol (PG) or isostearyl alcohol (ISA). While the ISA gels have

already been extensively studied, PG is found to be gelated by GP-1 for the first time. Its rheological properties were studied by a rheological expansion system. The organogels are employed as the matrix to deliver a lipophilic drug, haloperidol, which is a suitable transdermal candidate, through human skin [26]. It is a hydrophobic molecule with low molecular weight (Fig. 1). The only long-lasting formulation is its ester, the haloperidol decanoate, for intramuscular injection, which, however, has such disadvantages as injection pain, marked inter-individual variation and complex administration regime [27,28]. Therefore, it is important to develop an alternative for its maintenance therapy to prevent the relapse of psychosis. A skin penetration enhancer, farnesol, is also incorporated. The effects of enhancer, gelator and solvent on skin permeability process are evaluated by means of in vitro skin permeation study, via a factorial design.

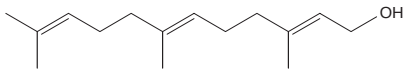
2. Materials and methods

2.1. Materials

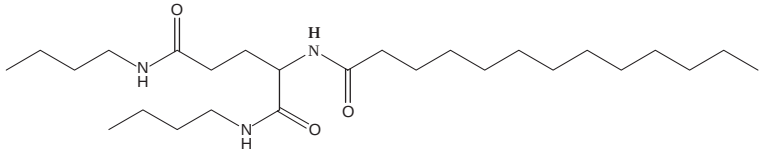
Haloperidol, DL-lactic acid, antibiotic antimycotic solution (100X), PG and sodium *di*-hydrogen phosphate monohydrate were purchased from Sigma Chemical Company. ISA was purchased from Kishimoto Sangyo Asia Ltd (Singapore) and GP-1 (95%) from Ajinomoto Co (Japan). Farnesol (96.6%) was obtained from TCI (Japan). All other chemical reagents were of at least reagent grade and all materials were used as supplied. The molecular structures of



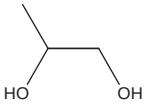
Haloperidol (MW=375.86, Log P=3.49)



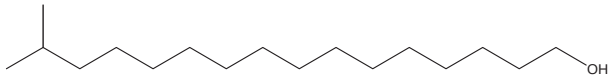
Farnesol (MW=222.37, Log P=2.47)



N-lauroyl-L-glutamic acid di-n-butylamide (GP-1) (MW=453.70, Log P=5.02)



Propylene glycol (MW=76.09, Log P=-0.81)



Isostearyl Alcohol (ISA) (MW=270.49, Log P=7.19)

Fig. 1. The molecular structures of haloperidol, farnesol, GP-1, PG and ISA. The log *P* values were given by ChemDraw Ultra®.

the chemicals are shown in Fig. 1. Water purified by the Milli-Q system was used.

2.2. Experimental design

A 2^3 full factorial design is used to study the effect of three factors, i.e., the permeation enhancer, the gelator and the solvent, each at two levels, on the in vitro permeation profiles of the drug in solutions/gels, with specific focus on the permeability coefficient K_p and lag-time Lt. For enhancer and gelator, the high level indicates their presence in the formulation and low level indicates their absence from the formula. The high and low levels of solvent are ISA and PG, respectively. Eight formulations were generated following the Yate's order (Table 1) [29,30]. Concentrations of haloperidol are 3 mg/ml in all the 8 formulations, respectively. The concentrations of farnesol or GP-1 are 5% (w/v), respectively, when applicable in the formulations. Data were analyzed by the statistical software Minitab®.

2.3. Preparation of the solutions and gels

Farnesol is easily miscible with PG or ISA. Clear solutions were obtained at 37 °C for all the formulae without GP-1 (Table 1). For the 4 gel formulae, GP-1 was weighed into a test tube and the organic solvent PG or ISA was added. The mixture was heated to 120 °C in an oven to dissolve GP-1 [7]. Upon dissolution haloperidol or farnesol was added and the solution was vortexed until haloperidol was completely dissolved, normally within 30 min at about 60–120 °C. On cooling at room temperature of 22 ± 1 °C, the solution became a white, opaque or translucent organogel. For the 4 solution formulae, PG or ISA was heated to 60 °C to accelerate the dissolution of haloperidol and the solution was vortexed till haloperidol dissolved completely. Haloperidol is photosensitive but very stable in solution [31,32]. The preparation of the 8 formulae was done in darkness. The first-order rate constant of its degradation is 0.0248 day^{-1} at 110 °C [32]. So only 0.0517% of the drug decomposed within the 30 min preparation period.

2.4. Strain-controlled dynamic mechanical spectroscopy

A strain-controlled dynamic mechanical spectrometer with a temperature range from −150 to 600 ± 0.1 °C (ARES, Rheometric Inc., US) was used for the linear viscoelastic measurements [7,33]. A mixture of air and liquid nitrogen was used to control the cooling rate and the temperature. The sample was placed between two circular plates of diameter 25 mm having a gap of 1.5 mm between, and then subjected to sinusoidal oscillations by moving both the upper and lower plates. The frequency was set to 0.1 Hz. The amplitude of the oscillations was controlled to obtain a 0.1% maximum strain in the sample. Under this strain limit, the structure of supramolecular materials would not be destroyed by the measurements. The instant measurement of the applied stress and the resultant strain allowed the calculation of the storage modulus G' and the loss modulus G'', and consequently the complex modulus $G^*(G^* = \sqrt{(G')^2 + (G'')^2})$.

Table 1
The formulae of the 8 solutions/gels, the permeability coefficient K_p and the lag-time Lt of the drug haloperidol

Foumula Name	Enhancer (factor A)	Gelator (factor B)	Solvent (factor C)	Permeability coefficient $K_p^* 10^4$ (cm/h)	Lag-time Lt (h)
1	−	−	PG	1.35 ± 0.21	17.98 ± 1.37
a	+	−	PG	16.13 ± 7.15	32.27 ± 6.77
b	−	+	PG	0.52 ± 0.09	38.52 ± 7.50
ab	+	+	PG	40.69 ± 27.32	98.27 ± 11.24
c	−	−	ISA	5.52 ± 0.09	11.52 ± 0.49
ac	+	−	ISA	4.19 ± 0.46	10.69 ± 0.63
bc	−	+	ISA	5.28 ± 1.73	9.14 ± 2.70
abc	+	+	ISA	4.71 ± 0.66	9.41 ± 0.63

Factor A refers to farnesol and factor B refers to GP-1. The plus sign stands for presence (high level) and minus sign for absence (low level). The low and high levels of factor C are propylene glycol (PG) and isostearyl alcohol (ISA), respectively. ($n = 3$ or 4).

2.5. Analytical method

Drug concentrations were determined by a reversed phase HPLC method (C_{18} column, Waters Corporation) at 254 nm [26]. Mobile phase consisted of 0.05 M phosphate buffer pH adjusted to 3 and acetonitrile with a ratio of 50:50. Droperidol was used as an internal standard. Flow rate was 1.3 ml/min and injection volume was 100 μl. Retention times of the internal standard and drug were approximately 4 and 6.5 min, respectively. Mean peak area ratios of the drug and internal standard in 0.03% (v/v) lactic acid were linearly related to the drug concentrations for the samples containing 20 ng/ml to 1000 ng/ml ($r^2=0.9990$).

2.6. Preparation of human epidermis

Chinese female skin was obtained from a plastic surgery patient with informed consent at the Singapore General Hospital, Singapore. Epidermis was prepared by immersing the whole skin in 60 °C water for 2 min, followed by careful removal of the epidermis from the connective tissues. Samples were stored in plastic bags at −80 °C until use [34]. Prior to permeation experiments, membranes with stratum corneum side up were floated over 0.9% (w/v) sodium chloride solution containing antibacterial antimycotic solution (1 in 100 dilution) at 22 ± 1 °C for 2 h for equilibration.

2.7. In vitro permeation study with human epidermis

Flow-through type diffusion cells were used for permeation studies [35]. Human epidermis was mounted between donor and receptor compartments and excessive skin at the sides was trimmed off to minimize lateral diffusion. Stratum corneum faced towards the donor compartment and the circular skin area for permeation was 0.785 cm^2. Since the solubility of HP in 0.03% (v/v) lactic acid solution is approximately 1 mg/ml, 500 ml of 0.03% (v/v) lactic acid solution containing 1% (v/v) antibacterial antimycotic solution was placed in the reservoir bottle as the receptor solution, which flows through the receptor compartment at 0.75 ml/h [36]. The pH of the receptor solution was approximately 3 but that did not affect the integrity of the epidermis [26,37]. Receptor solution was thoroughly degassed to prevent the formation of bubbles beneath the membrane. Antibacterial and antimycotic solution was added to receptor solutions to maintain the integrity of the skin throughout the experiment and to minimize the microbial contamination in samples during the analysis. One milliliter of the solutions/gels was added to the donor compartment and covered with parafilm to minimize the contamination of the solution. Ambient temperature of the cells (PermeGear, US) was controlled at 37 °C by a heater/circulator (Haake, Germany). The receptor solution is pumped by a 16-channel peristaltic cassette pump (Ismatec, Switzerland) continuously through the receptor compartment and received by the tubes sitting in a fraction collector (ISCO Retriever IV, US). Cumulated receptor liquid samples were taken at 6-h intervals for HPLC assay.

2.8. Permeation parameters and nonlinear regression

The following nonlinear model was used to estimate the permeability coefficient K_p and the lag-time Lt, from which $K_p=K'D'$ and $Lt=1/(6\ D')$ [38,39].

$$Q = AK'C_0\left[D't - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}e^{\left(-D'\pi^2n^2t\right)}\right]$$

The parameters are Q, cumulative amount of permeated drug; A, the area of permeation; K' or D', the intermediate parameters defined by K, the partition coefficient between skin and donor solution, D, the diffusion coefficient and l, path length of diffusion, ($K'=Kl$ and $D'=D/l^2$, respectively); C_0, the concentration of the drug; and time t. Nonlinear regression analysis was carried out with the statistical software, S-plus®.

3. Results

3.1. SMGA gels

The PG gels start to gelate almost immediately after the ambient temperature changed from 120 °C to room temperature (22 ± 1 °C) whereas the ISA formulation began to gel an hour later and the process was much slower than for the PG gels. For both ISA and PG gels, the formulae without farnesol gelated

faster than those with farnesol. Flake-like white spots appear ubiquitously in the clear solution and intensify slowly until a uniform gel was formed. The PG gels (formula 'b' and 'ab') are opaque and white in color while the ISA gels are translucent, indicating that PG gels possess thicker fibers and a lower degree of network branching than the ISA gels. The improved clarity of ISA gels is due to the formation of thinner fibers and more densely branched three dimensional network structures [8].

The structure of interconnecting fiber networks is directly associated with the rheological properties. As shown in Fig. 2, where the moduli were recorded as a function of time, the elastic and viscous moduli gels formed at 0.01% of strain, 20 °C and 1 Hz frequency and are almost parallel to each other; therefore the gels possess the mesh-like interconnecting networks of micro/nano structures. Fig. 3 shows the change of the moduli of the gels as functions of various oscillating strain amplitudes, γ. The strain corresponds to the deformation of the networks caused by the applied shear stress. The storage modulus, G', remains stable under small strains and decreases abruptly when γ exceeds a certain value γ_0, which corresponds to the breakage of the junctions in the networks. The gels can withstand up to 0.25% of the strain. Below this strain the mesh-like micro/nanostructure is intact and above this, it crumbled.

3.2. In vitro permeation study

The original permeation data are shown in Fig. 4. The estimated values of K_p and Lt are given in Table 1, and as the response variables for the three factors, their changes in response from low levels to high levels of the factors were analyzed with a statistical model and results are shown in Table 2.

For the permeability coefficient K_p, factor A and C are significant, which indicates the enhancer and solvent exerted their influences upon K_p when changing from low level to high level, but the gelator did not. The effect of enhancer farnesol is positive, showing it can increase K_p when present in the formula. The factor C, solvent, shows a negative effect, which indicates that when the solvent changed from low level (PG) to high level (ISA), the permeability coefficient K_p decreased. Therefore PG delivered haloperidol at a faster rate than ISA on average. One of the two-way interactions, A*C, also showed significant negative effect. This can be explained that the enhancer is less effective in ISA than in PG. The three-way interaction term is not significant.

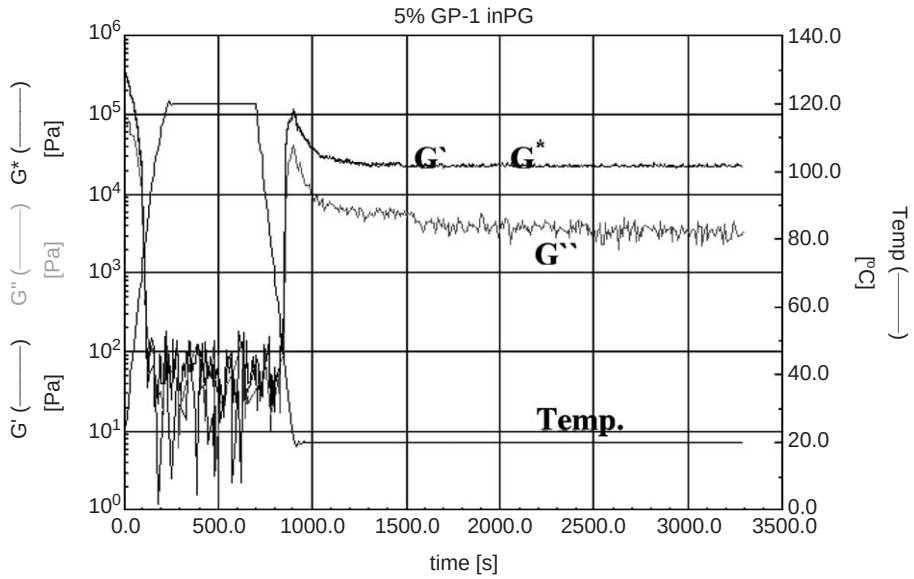


Fig. 2. Dependence of the storage modulus G', the loss modulus G'', and the complex modulus G^* on time. Time sweep method for formula 'ab' gel at 20 °C.

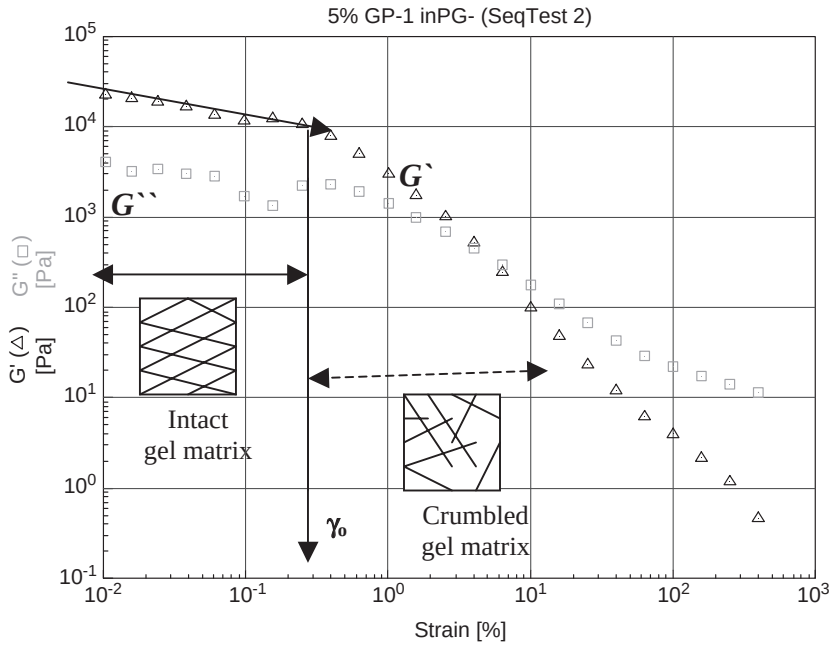


Fig. 3. Dependence of the storage modulus G', the loss modulus G'', and the complex modulus G^* on strain. Dynamic strain method for formula 'ab' gel at 20 °C.

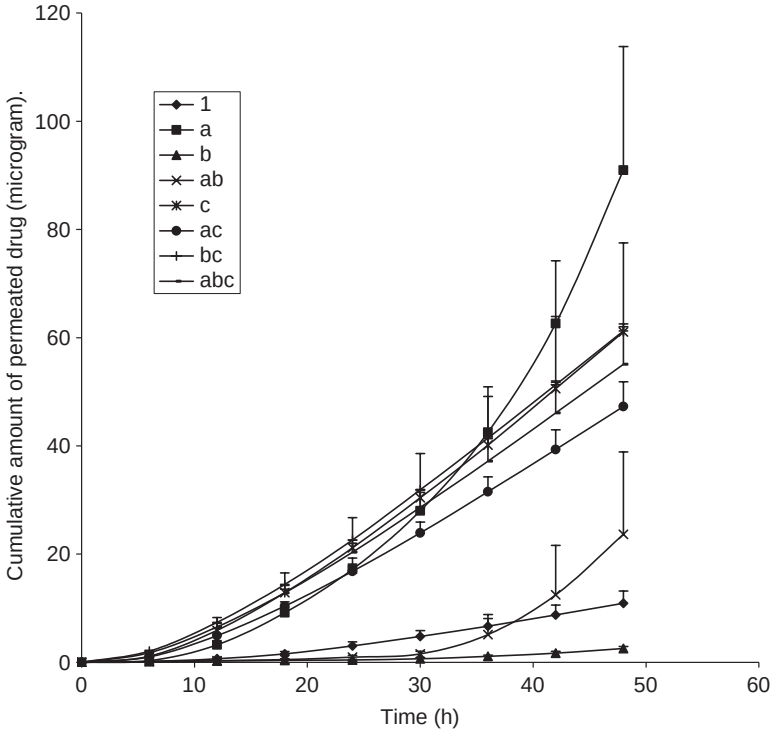


Fig. 4. Time course of mean cumulative amounts of haloperidol permeated through 1 cm^2 of human epidermal membrane in the solutions/gels formulated according to Table 1. Each point represents mean ± SD (n = 3 or 4).

Table 2
The effects and significance levels of the factors and their interaction terms

Factors and interactions	Effect on K_p	P-value of the coefficient of the effect on K_p	Effect on Lt	P-value of the coefficient of the effect on Lt
A	13.388	0.006*	18.36	0.000*
B	6.016	0.180	20.74	0.000*
C	−9.738	0.036*	−36.55	0.000*
A*B	6.583	0.144	11.63	0.000*
A*C	−14.167	0.004*	−18.65	0.000*
B*C	−5.931	0.186	−22.53	0.000*
A*B*C	−6.029	0.179	−11.10	0.000*

The results were confirmed by ANOVA tests ($p<0.05$*).

Unlike K_p, the lag-time Lt, is sensitive to all the three factors, as well as their combinations. The enhancer and gelator can increase lag-time, while ISA decreased the lag-time compared to PG. The positive two-way interaction term shows that when the gelator is present, the enhancer will increase lag-time to a larger extent than when there is no gelator in the formula and vice versa. The other two negative two-way interactions show ISA can counteract the elongation effect of the enhancer or the gelator on drug permeation. The three-way interaction is negative, for which the most intuitive explanation is that when the solvent is ISA, the A*B interaction is not as strong as when the solvent is PG, therefore the enhancer/gelator will not increase the lag-time much more than when the gelator/enhancer is absent, respectively.

4. Discussion

The gels can accommodate both the drug and the permeation enhancer while still retaining their rheological and aesthetic properties, which showed that SMGA gels have potential for delivery of drugs through the skin. In vitro permeation study was, therefore, conducted to evaluate the performance of the gels for the transdermal delivery of the drug, haloperidol.

The permeability coefficient, K_p, and the lag-time, Lt, defined a permeation curve of the cumulative permeated drug against time with all the other parameters kept constant. Pseudo-steady permeation with a flux of K_pC_0 is expected after a transitional period of 3 times Lt [38,40]. Both parameters can be influenced by the three factors and their interaction terms, all of which are estimated in the factorial design as shown in Table 2.

The factor A, a skin penetration enhancer, may increase K_p by modifying the lipid compositions and structures. The factor C is the solvent. PG is an established solvent for transdermal delivery, miscible with water. It can dissolve many essential oils, but is immiscible with fixed oils. ISA is a saturated fatty alcohol, clear and viscous. It is a biocompatible solvent widely used in cosmetic industry. Factor B is the gelator, the SMGA, also being used for cosmetics, such as lipstick, eyeliner, deodorant and makeup lotions [41–46]. It may retard the permeation process by its steric supramolecular structure, reducing the permeation area on the skin and by Fick's law this is linearly related to K_p.

On average, however, as the results have shown, the gelator did not influence K_p significantly as it did with Lt. This is also shown in Fig. 4, where the curve 'a' is well above curve 'ab', but the slopes of their linear parts are quite similar to each other. The definitions of permeability coefficient and lag-time are $K_p = K\frac{D}{l}$ and $Lt = \frac{l^2}{6D}$, respectively [38,47]. The partition coefficient between the donor solution and the top layer of the stratum corneum, K, is hard to define since there is no distinct interface in terms of lipids as the solvent vehicles pass through the stratum corneum. If K is assumed to remain constant with the introduction of the gelator to the delivery system, an explanation is that both the diffusion path length, l, and diffusion coefficient, D, increased while their ratio remains constant. The lipophilic gelator GP-1 (MW=453.70, Log P=5.02) could have posed some extra spatial hindrance to propylene glycol (MW=76.09, Log P=−0.81), which literally increased the path length. The increased D could be due to the synergistic effect between the enhancer, farnesol (MW=222.37, Log P=2.47), and the gelator, both lipids in nature. As for the other solvent, ISA, the scenario is partially different as the gelator in it did not affect either K_p or Lt significantly. As shown in Fig. 4, compared with formula 'ac', the presence of the gelator in formula 'abc' did not cause any significant effect on the permeation profile (two-sample t-test, p=0.05). The solvent ISA (MW=270.49, Log P=7.19) is similar to GP-1 structurally as well as sizably, and they are both lipophilic. The aliphatic long-chain gelator, GP-1, thus

presented a lesser permeation barrier to ISA than to PG. This ISA-controlled permeation was in line with the statistical result that ISA could significantly counteract the delayed effect of the enhancer or gelator on drug permeation.

Some other interaction effects among the three factors were also revealed by the statistical analysis, of which the most prominent one is that the enhancer performed much better in PG than in ISA, judging by K_p. In fact, the enhancer in ISA did not exert any significant effect (two-sample t-test, $p=0.05$). Since the main barriers are caused by the stratum corneum intercellular lipids, the penetration of PG is retarded, to some extent, due to its hydrophilicity [48–53]. The situation was changed with the addition of farnesol, which bridged the lipids and PG so that the solutions moved faster as a whole through the lamella of intercellular lipids [54,55].

The main components of these intercellular lipids, i.e., cholesterol, free fatty acids and ceramides are more compatible with ISA than with the enhancer, according to their lipophilic properties [56]. Thus the combination of ISA and farnesol did not facilitate drug permeation over ISA alone. In PG formulation, the gelator or enhancer would increase lag-time to a larger extent by their coexistence than alone. The synergistic effect could be due to the gelator increasing the amount of skin intercellular lipids since GP-1 by itself, is a lipid.

In summary, ISA-based delivery systems are robust, less susceptible to effects of the enhancer or gelator, which is preferable for dosage form design, but not for permeation enhancement. The four formulae of ISA share an almost identical permeation profile (two-sample t-tests, $p=0.05$). Solvent PG-based systems are sensitive to the level change of the three factors. With the addition of farnesol, the permeation coefficient increased 12 times. Further addition of the gelator results in a 3-fold increase of lag-time, but the increase of permeation coefficient is not significant due to the large variances involved (two-sample t-tests, $p=0.05$).

5. Conclusion

The SMGA gels developed for application on and permeation through the skin maintained their characteristically aesthetic and rheological properties with the incorporation of the drug and enhancer. These in vitro human skin permeation studies showed the gels possessed desirable properties for topical or transdermal delivery. The translucent lipophilic gels based on solvent ISA were stable and the permeation of the drug reached the pseudo steady state in less time compared to the PG-based gel. The latter, opaque white in color, delivered the drug at a faster rate with the addition of the enhancer. The gelator, GP-1, did not influence the drug permeation rate but it increased permeation lag-time.

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