Lipid-Based Delivery System for Topical Phenytoin

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ABSTRACT

The wound healing effect of topical phenytoin has been reported but its effective delivery system is still under-researched. The present work aimed to formulate topical lipid-based gels for effective delivery of phenytoin. Three lipid-based emulsions with different droplet sizes were prepared using coconut kernel oil (CKO) and soybean oil (SBO) blends as an oil phase. Stable lipid-based emulsion with 100% emulsion stability index (ESI) over seven heating/cooling cycles could only be formed when the oil droplet satisfied the nano size criterion, as demonstrated by nano-emulsion. The stability of macro-emulsion and cream could be enhanced by the addition of Aristoflex ammonium acryloyldimethyl-taurate/VP (AVC) copolymer as the gelling agent. These gels, designated as nano-emulgel, macro-emulgel and cream-gel, were subsequently loaded with phenytoin. All gels exhibited non-Newtonian and shear-thinning flow behavior, with high yield stress ranged 18.8 – 51.5 Pa. The *in vitro* drug release profiles of all formulations followed the first-order kinetic model, with $R^2 > 0.95$. It was found that lipid nano-emulgel demonstrated the highest release rate of phenytoin, with 93.12% drug released in 12 hours, followed by cream-gel with 56.42% and macro-emulgel with 51.51%. CKO/SBO nano-emulgel was identified as the most suitable lipid topical gel formulation for effective delivery of phenytoin.

INTRODUCTION

Phenytoin was first introduced in 1938 as an antiepileptic agent as the first-line therapeutic approach for various generalized convulsive disorders. Many studies showed that 50% of the patients receiving long-term oral phenytoin treatment were presented with a side effect of gingival hyperplasia (Shaw *et al.*, 2007). This apparent stimulatory effect on the connective tissues suggested that phenytoin has wound healing effect (Simsek *et al.*, 2014; Spaia, 2004). The clinical effects of topical phenytoin on wound healing have been systematically reviewed by Shaw *et al.* (Shaw *et al.*, 2007). Various clinical trials have reported an improved healing rate of cutaneous wounds, decubitus ulcers, diabetic foot ulcers, burn wounds, traumatic wounds and abscesses with reduced inflammation and edema (Bahmani *et al.*, 2011; Fonseka *et al.*, 2010; Hokkam *et al.*, 2011; Rashidi *et al.*, 2012; Rhodes *et al.*, 2001). To-date, despite the extensive studies was done on the

wound healing effect of topical phenytoin, it is still used as off-label medications. Its widespread use in clinical settings was restricted by the fact that the delivery method of topical phenytoin has not been adequately studied and thus the best formulation to deliver the drug is not known (Smith, 2010). Rhodes *et al.* reported that majority of studies merely stated that a uniform, thin layer of phenytoin powder was applied to the wound surface (Rhodes *et al.*, 2001). However, powders are difficult to be held on the skin in addition to the difficulty in putting the recommended amount of the powder on the affected area. Topical phenytoin sodium suspensions (2 and 4% w/w) had been using to apply directly to the wounds. Nevertheless, the efficiencies of these formulations remained controversial due to the low contact period of phenytoin over the wounds and difficulty for even application (Rhodes *et al.*, 2006; Almousilly *et al.*, 2012; Fonseka *et al.*, 2010). Thus, a novel drug carrier is needed to be developed for effective control and improved drug delivery of topical phenytoin. For decades, lipids have gained much interest as the promising pharmaceutical carriers for delivery of drugs and enhancing the bioavailability of poorly water-solubility drugs, (Almousilly *et al.*, 2012; Pouton, 2006; Shrestha *et al.*, 2014).

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These lipid-based drug delivery system (LBDDS) have been widely investigated to encapsulate or solubilize the anticancer, antibacterial and antiviral drugs (Jones *et al.*, 2004; Mehanna *et al.*, 2012; Yadav *et al.*, 2013). The key advantages of lipid-based formulations are (1) enhanced drug bioavailability, (2) increased drug solubility and (3) negligible toxicity. Lipid-based formulations may include oil solutions or suspensions, emulsions, self-micro or self-nano emulsifying drug delivery systems (SMEDDS/ SNEDDS) (Čerpnjak *et al.*, 2013). An appropriate selection of lipid phase, formulation strategies, and rational delivery system design can lead to the success of LBDDS formulations (Dahan and Hoffman, 2008).

The chosen lipid phase in this study was a blend of coconut kernel oil (CKO) and soya bean oil (SBO). CKO is saturated lipid with medium-chain triglycerides (MCTs) extracted from the kernel of coconuts harvested from the coconut palm (*Cocos nucifera*); whereas SBO is long-chain triglycerides (LCTs) obtained from soybeans (*Glycina maxima*). According to reported literature data, MCTs exhibit better self-dispersing ability, greater self-emulsification ability and higher chemical stability compared to LCT. However, LCT has higher solubilizing capacity than MCT for highly lipophilic drugs (Prajapati *et al.*, 2012; Bolko *et al.*, 2013). Hence, mixed lipid phase composed of both MCT and LCT was expected to have better physicochemical properties in preparing the LBDDS formulations for this study.

Herein, the present work describes the formulation and characterization of the LBDDS for topical application of phenytoin. Lipids were formulated into nano-emulgel and the efficacy of the *in vitro* release of phenytoin from this formulation was compared with those of macro-emulgel and cream-gel. The storage stability, rheological properties and release kinetics of each formulation system were evaluated to assess their suitability as drug delivery formulations for topical phenytoin.

MATERIALS AND METHODS

Chemicals

Tween 80 and sodium benzoate were purchased from Fisher Scientific Sdn. Bhd. (Selangor, Malaysia). Aristoflex ammonium acryloyldimethyl-taurate/VP (Aristoflex® AVC) copolymer was purchased from Cosmatrixx Sdn. Bhd. (Selangor, Malaysia). Phenytoin was purchased from Sigma-Aldrich Sdn. Bhd. (Kuala Lumpur, Malaysia). Coconut kernel oil (CKO) and soybean oil (SBO) were gifted from MOI Foods Sdn. Bhd. (Selangor, Malaysia). All chemicals were of reagent grade and used as received.

Formulation of lipid-based delivery system

Three types of topical gels (designated as nano-emulgel, macro-emulgel and cream-gel) were formulated from CKO/SBO blend as an oil phase, Tween 80 as the non-ionic surfactant, distilled water containing 0.1% w/w sodium benzoate and 1% w/w Aristoflex® AVC as a gelling agent. To prepare a nano-emulgel, nano-emulsion was first prepared from the mixture of oil, surfactant and water using phase inversion temperature (PIT) method described by Shinoda (Shinoda *et al.*, 1969). The mixture was stirred in a vessel continuously using a magnetic stirrer at 250 rpm and warmed up gradually using a water bath. The change of conductivity was measured as a function of temperature using a conductivity meter. The PIT of each formulation was determined using Oakton Con II conductivity meter. After the phase inversion point had reached, the emulsion was rapidly cooled by immersion in an ice bath with continuous stirring. The resultant emulsion was blended with a gelling agent and homogenized at room temperature at 10,000 rpm for 10 minutes. The macro-emulgel was prepared by first mixing the oil and surfactant into a vessel agitated with a magnetic stirrer at 250 rpm. The mixture was slowly titrated with water at room temperature until a concentration of 90% w/w was reached. The gelling agent was then added to the resultant emulsion and homogenized at room temperature at 10,000 rpm for 10 minutes. The cream gel was prepared by first mixing the oil and surfactant into a vessel with constant stirring at room temperature. The gelling agent was then sprinkled into the mixture. Subsequently, water in approximately equal proportions with oil was added to the mixture and homogenized at 10,000 rpm for 10 minutes.

Phenytoin-loaded topical gels were formulated by first mixing 0.20% w/w of phenytoin into the mixture of oil and surfactant at room temperature. The mixture was vortexed thoroughly at 1400 rpm until a clear dispersion was formed, indicating the completion of drug solubilization. The mixture followed the steps as described above to obtain drug-loaded nano-emulgel, macro-emulgel and cream gel formulations.

Physico-chemical evaluation of lipid emulsions

Emulsions were subjected to droplet size determinations. The measurements of droplet size were performed using a Zetasizer ZEN 3600 (Malvern, Worcestershire, UK) at room temperature. Droplet size measurements were determined using dynamic light scattering (DLS) and calibrated using polystyrene latex standard. The pH of gel formulations was assessed using Mettler Toledo S220 Seven Compact pH meter. All measurements were performed in triplicate.

Emulsion stability index

All emulsions were subjected to heating/cooling test for seven cycles, where storage temperature was changed between 4°C and 40°C in an incubator (Heraeus, Hanau, Germany) for the duration of 14 days. Emulsion stability index (ESI) of each emulsion was measured to evaluate the degree of phase separation using the equation as shown below.

$$ESI = \frac{HE - HC}{HE} \; X100 \; \rightarrow Eq. 1$$

where HC is the height of cream layer and HE is the initial emulsion height.

Rheology study

The rheological properties of gels were evaluated using a Rheolab MC1 rheometer (Anton Paar, Österreich, Austria) at room temperature. The mode of measurement was viscometry sweep, employing cylinder-cone method with a gap of 0.1 mm. Two rheograms were obtained by plotting apparent viscosity against shear rate and shear stress against shear rate. The rheological data obtained were fitted to the power law model as shown in the following equation.

$$\tau = K\dot{\gamma}^{n} \rightarrow Eq.\,2$$

In which τ is the shear stress, $\dot{\gamma}$ is the shear rate, K is the consistency index (Pa.s^{n}) and n is the flow behavior index.

Drug loading and entrapment efficiency

The drug loading and entrapment efficiency of phenytoin in lipid emulsions were determined using a high-performance liquid chromatography (HPLC) method (Teo *et al.*, 2015). Aliquots of samples were dispersed in the mobile phase of acetonitrile and ultrapure water (50:50). A sample volume of 20 µL was injected at a flow rate of 1.0 mL/min. The test system used was a reverse phase HPLC system (1200 series, Agilent Technologies) equipped with a pump, injector valve with 20 µL sample loop, ZORBAX Eclipse Plus C-18 analytical column (250 mm × 4.6 mm, 5 µm particles), and UV detector with the data processor (Chem Station Software). A standard curve of peak area against the concentration of phenytoin was plotted and the drug content of each sample was determined by comparison with the standard curve. The following equations were used to calculate the percentage of drug loading and encapsulation efficiency of the emulsions.

$$\text{Drug loading (\%)} = \frac{\text{Total weight of drug}}{\text{Total weight of sample}} \times 100\% \rightarrow Eq.\,3$$

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100\% \rightarrow Eq.\,4$$

In vitro drug release study

The drug release of phenytoin from gel formulations was investigated using Franz diffusion cells (PermeGear, USA). About 1 g of gel formulation was placed on a 0.45 µm pore size, cellulose acetate membrane in the donor compartment. The receptor compartment was filled with 14 mL of ethanol 96% which was maintained at 32 ± 0.5°C. Aliquots of the receptor medium were withdrawn and replaced with the same amount of fresh receptor medium at time intervals of 1, 2, 4, 6, 8, and 12 hours. The withdrawn aliquots were analyzed by ultraviolet–visible spectrophotometer (Perkin-Elmer, Malaysia) at 240 nm wavelength. The cumulative percentage of drug release was calculated and plotted against time. Franz diffusion cell study for each formulation was conducted in triplicates and the averages were reported. The release characteristics of gel formulations were further determined by fitting the release data to the following equations of zero-order, first-order and Higuchi models which are given by the following equations.

$$Q = k_0 t \rightarrow Eq.\,5$$

$$In\,(Q_0 - Q) = In\,Q_0 - k_1 t \rightarrow Eq.\,6$$

$$Q = k_2\sqrt{t} \rightarrow Eq.\,7$$

where Q_0 is the initial amount of drug, Q is the amount of drug released at time t, k_0, k_1 and k_2 are the rate constants for zero-order, first-order and Higuchi models respectively.

Statistical analysis

In vitro drug release data of different lipid gel formulations were subjected to multiple t-test using Microsoft Excel 2013. The t-test was performed to find out if there was any significant difference in the release pattern of groups of nano-emulgel and cream-gel; nano-emulgel and macro-emulgel; cream-gel and macro-emulgel, over the release intervals of 12 hours. Analysis outcomes showing P <0.05 were considered statistically significant.

RESULTS AND DISCUSSIONS

Physicochemical properties of lipid emulsions

Three oil-in-water (O/W) CKO/SBO emulsions, namely nano-emulsion, macro-emulsion and cream were formulated with the same ingredients as listed in Table 1 but differed in droplet size. From Table 1, the oil-to-surfactant ratio of 1:9 was apparently needed to maintain the stability of the emulsions especially with the presence of the long hydrocarbon chain length of SBO in the lipid blends. This is because oil with longer hydrocarbon chain length would exert higher interfacial tension against the aqueous phase, thus leading to high physicochemical stress. Though oils with long hydrocarbon chains like SBO is difficult to be emulsified compared to medium-chain triglycerides like CKO, the solubilizing capacity of oil for lipophilic moiety increases with the chain length of oil. Hence, the formulation of CKO/SBO blends is a compromise between the solubilizing potential and ability to facilitate the formation of emulsion for entrapping drugs. Previous studies have shown that inclusion of highly saturated medium-chain triglycerides (MCT) into long-chain triglycerides (LCT) yields more stable emulsions than pure LCT by avoiding droplet coalescence (Tamilvanan and Benita, 2004). Table 2 shows the physico-chemical properties of the emulsions. Particle size measurement indicated that PIT method can produce clear and transparent nano-emulsion with a droplet size of 11.4 nm. The formation of finely dispersed oil droplets took place when the system crosses a point of zero spontaneous curvature followed by minimal surface tension during the rapid cooling stage in PIT (Ng *et al.*, 2014).

Table 1: Formulations of lipid emulsions.

Emulsion	Percentage weight per weight (% w/w)				Oil-to-surfactant ratio	Oil-to-oil ratio
	CKO	SBO	Tween 80	Water		
CKO/SBO	1.4	0.6	18	80	1:9	70:30

Table 2: Physico-chemical properties of lipid emulsions.

Emulsion	Droplet size (nm)	Zeta potential (mV)	pH	Visual observation
Nano-emulsion	11.4 ± 0.01	-2.90 ± 0.01	6.6 ± 0.01	Clear and transparent
Macro-emulsion	595.6 ± 0.02	-0.02 ± 0.03	6.5 ± 0.01	Translucent white
Cream	167.9 ± 0.03	-1.45 ± 0.01	6.6 ± 0.02	Translucent

Table 3: Emulsion stability indices of lipid emulsions.

Emulsion	ESI (%) per cycle							
	0	1	2	3	4	5	6	7
Nano-emulsion	100	100	100	100	100	100	100	100
Macro-emulsion	100	100	100	94.8	84.5	72.7	61.0	50.2
Cream	100	100	100	100	100	100	98.6	98.7

All emulsions exhibited zeta potentials within -2.90 to -0.02 mV which was due to the presence of a non-ionic surfactant, Tween 80, in which the negatively charged oil droplets were resulted from the absorption of hydroxyl ions on the droplet surface. It was noticed that the pH values were in the range of 6.5 - 6.6, which implies that these emulsions would not induce irritations or alterations of the cutaneous tegmentum if applied topically on the skin (Lucero *et al.*, 1994). Table 3 summaries the emulsion stability indices of lipid emulsions. From Table 3, nano-emulsion indicated excellent thermodynamically stable with 100% ESI and no sign of phase separation throughout the heating/cooling test for seven cycles. Cream presented relatively good stability with no significant phase separation up to 5th heating/cooling cycles but macro-emulsion exhibited the poorest emulsion stability with 100% ESI up to 2nd heating/cooling cycles. This suggests that stable lipid emulsions could be formulated with oil droplets in nano-size range. The utilization of high amount of non-ionic surfactant Tween 80 (18% w/w) was necessary for all formulations to reduce the interfacial tension between the two phases and form sufficient surfactant films around the oil phase droplets to prevent coalescence. Furthermore, surfactants of high HLB like Tween 80 was reported to increase the permeability of the drug by loosening the tight junctions around the structural organization of membrane components (Gurram *et al.*, 2015).

Rheological behavior of lipid gels

Gels are three-dimensional colloidal semisolid formulations having better percutaneous drug absorption and solubilization. Topical gel formulations have a high patient acceptability due to their favorable properties like easily spreadable, long shelf life, greaseless and easily removable. In this study, Aristoflex® AVC was added in all topical gel formulations to increase the viscosity of the medium, which helps create and maintain the suspension of oil droplets within the medium. The addition of Aristoflex® AVC in both nano-emulsion and macro-emulsion has successfully modified the fluidity of the emulsions to produce emulgels of higher viscosity. Aristoflex® AVC was also added to the cream to produce cream-gel which has pleasant skin

feel like creamy without tackiness. This cream-gel is also expected to have lower irritation potential compared to the conventional cream formulation. From Fig. 1, the gel systems of all topical formulations were found to exhibit non-Newtonian fluid behavior, showing no linear proportionality between shear rate and shear stress. A plot of viscosity as a function of shear rate (Fig. 2) demonstrates that the apparent viscosities of the gel formulations decreased gradually with increasing shear rate. This might due to the deformation of oil droplets flocculations that had previously aggregated by weak forces took place as the shear rate increased (Rao, 2014). From Fig. 2, the flow behavior also indicated that these gels were shear-thinning or pseudoplastic in nature. These findings were further supported by their flow indices with the magnitude of n < 1, as shown in Table 4, which implied the degree of their pseudoplasticity.

Table 4 shows that all gel formulations exhibited relatively high yield stress, indicating that these gel formulations were relatively stable towards creaming. This was attributed to the highly cross-linked structure of the Aristoflex AVC polymer which has successfully trapped the oil droplets in the water/polymer matrix. This resulted in changes in the structural features and the rheological properties of the continuous phase, thus opposing the motion and mutual contact of droplets, leading to prolong stability of the formulations. The facts that macro-emulgel possessed the highest yield stress implied that oil droplets with bigger size are caged more firmly in the network meshes and thus high shearing force was required to trigger its fluid nature. On the other hand, the nano-emulgel showed the highest flow indices (n) pertaining to its lowest pseudoplasticity and superior mobility which could be contributed by its nano-sized oil droplets. Viscosity is dependent on the concentration, size and shape of the suspended particles and how they interact with the continuous phase (Barnes, 2002). However, there was no clear correlation between particle size and viscosity can be concluded when comparing cream-gel and macro-emulgel with nano-emulgel in terms of their droplet size. Agreement with this can be seen for the trend shown in flow indices (Table 4), viscosity (Fig. 2) and droplet size (Table 2).
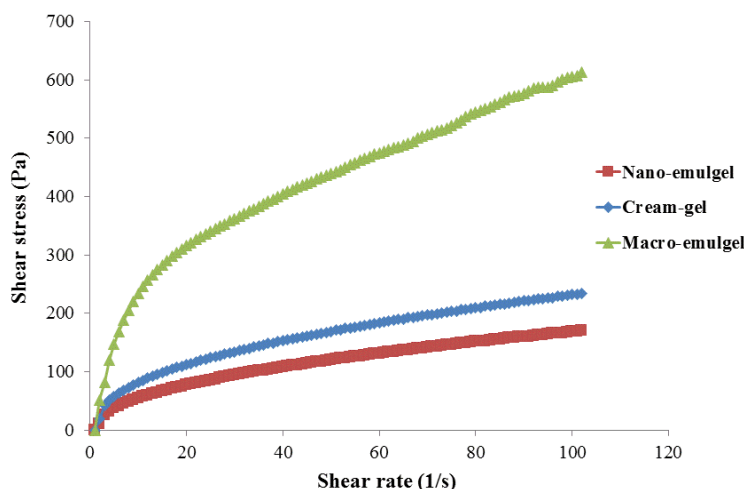
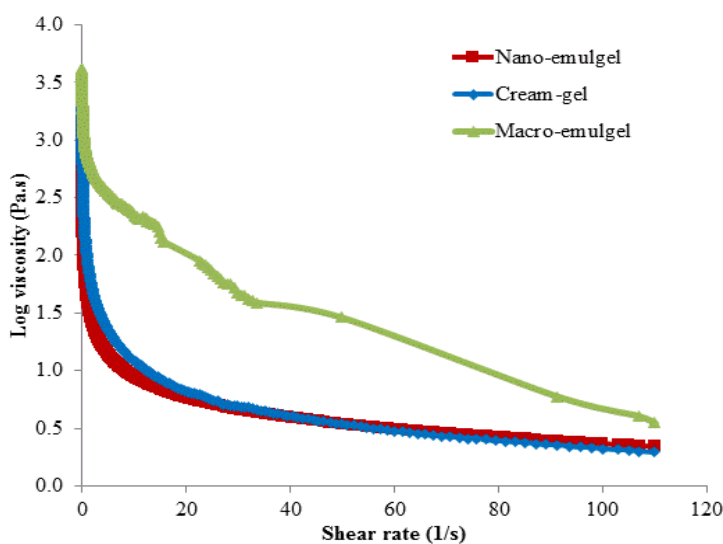**Fig. 1:** The flow curves of lipid gels

Fig. 2: The apparent viscosities of lipid gels

Table 4: The rheological properties of lipid gel formulations.

Lipid gel	Yield stress, γ (Pa)	Consistency index, K (Pa·s)	Flow index, n
Nano-emulgel	18.8	35.79	0.40
Macro-emulgel	51.5	97.39	0.39
Cream-gel	34.1	42.39	0.26

Drug loading and entrapment efficiency of lipid emulsions

       In the present study, drug loading and entrapment efficiency of phenytoin were measured in nano-emulsion and macro-emulsion since the preparation of macro-emulsion and cream-gel were rather similar except in the sequence of gelling agent addition. The measured drug loading of phenytoin was recorded as 2 mg/mL in all formulations, with the encapsulation efficiency was calculated as 98.5±0.9% and 95.7±0.2% in nano-emulsion and macro-emulsion, respectively. This indicates that phenytoin was successfully encapsulated in the emulsions.

***In vitro* drug release study of lipid gel formulations**

       As shown in Fig. 3, the cumulative percentage of phenytoin released, in a decreasing order was 93.12% from

nano-emulgel, 56.42% from cream-gel and 51.51% from macro-emulgel. It was apparent that smaller droplet size provides a larger surface area for drug permeation through the membrane at the donor compartment, which resulted in a higher concentration gradient that acts as the driving force for drug permeation. The superior drug release of nano-emulgel compared to macro-emulgel and cream-gel might be also due to the higher lipophilic drug solubilizing capacity of nano-emulgel that leads to an improved topical phenytoin availability. Nano-emulgel with fine droplet size offers advantages over the other two as it improves hydration of stratum corneum, which will increase the drug dermal permeation and skin flux. From Fig. 3, the *in vitro* release of phenytoin in descending manner (nano-emulgel > cream-gel > macro-emulgel) appeared to be obvious after 2 hours where the cumulative % of

drug released of nano-emulgel was significantly dominated over the other two but the drug release pattern of cream-gel and macro-emulgel were quite close after 6 hours. Statistical t-test analysis of the data was done to find out whether there was any significant difference in the release profile between the formulations. Nano-emulgel exhibited significant higher cumulative % of drug release than macro-emulgel except at time intervals of 0 and 1 hour. Drug release profile of nano-emulgel was also found to be significantly greater than those of cream-gel except at the release intervals of 0, 1 and 2 hour. It was found that the drug release of cream-gel was only significantly higher than macro-emulgel at the first 2 and 4 hours but there was no statistically significance detected between them following the remaining release time intervals as the calculated P value was greater than 0.05. This indicated that the release profiles of both cream-gel and macro-emulgel were similar after 6 hours of release intervals. This indicated that there were two phase of phenytoin release profiles for both cream-gel and macro-emulgel. Initially, macro-emulgel with higher viscosity exhibited slower phenytoin released than cream-gel from 0 to 6 hours. When the viscosity is higher, the density of the gels' microstructure increased which limits the area of movement for phenytoin, thus leading to a slower release of phenytoin as observed in macro-emulgel formulation. Nie *et al.* has demonstrated that faster drug release rate could be achieved from the formulation with low viscosity formulation than that from the high viscous formulation (Nie *et al.*, 2011). However, from Fig. 3, it was also found that the phenytoin release practically stop after 6 hours from both cream-gel and macro-emulgel.

Thus, it is proposed that phenytoin with highly hydrophobicity has a high affinity for the lipid gel formulations, particularly those with larger droplet size or smaller surface area for drug permeation. This is because for mass transfer to take place, the drug must have preferably lesser affinity for the vehicle in order to maximizing the thermodynamic leaving potential. Therefore, this further substantiate the importance of the nano-emulgel formulation in the delivery of topical phenytoin. The release characteristics of lipid gel formulations were further identified by fitting the release data into the equations of zero-order, first-order and Higuchi models. From Table 5, the best-fit release of these three formulations followed the first-order model with $R^2 > 0.95$. Therefore, the drugs released from the three formulations were concluded as drug concentration dependence.

CONCLUSION

Three lipid-based gels, namely nano-emulgel, macro-emulgel and cream-gel were successfully developed from CKO/SBO blended at a ratio of 70:30. These gels demonstrated non-Newtonian, shear-thinning behavior with acceptable viscosity range for the topical application. The *in vitro* drug release study showed that all lipid-based gels were able to sustain the release of phenytoin within 12 hours which followed the first-order kinetic model. Nano-emulgel showed the highest phenytoin release rate of 93.1%. Hence, nano-emulgel with the nano-emulsion droplet size was identified as the most significant lipid-based delivery system for topical delivery of phenytoin.
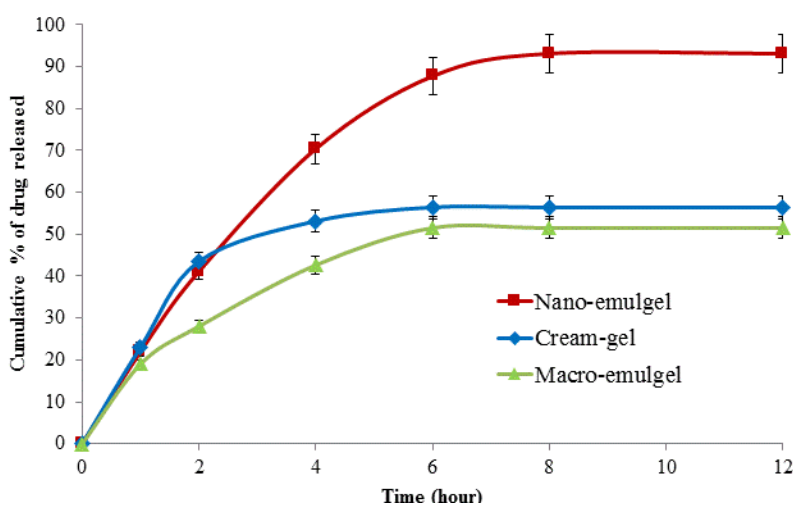

Fig. 3: Cumulative percentage of phenytoin released from lipid gel formulations

Table 5: The release kinetics of different topical phenytoin-lipid gel formulations.

Formulation	Zero-order kinetics		First-order kinetics		Higuchi model	
	R_0^2	K_0	R_1^2	K_1	R_H^2	K_H
Nano-emulgel	0.78	13.70	0.99	-0.16	0.94	40.57
Macro-emulgel	0.65	9.73	0.99	-0.05	0.94	32.75
Cream-gel	0.57	15.99	0.96	-0.08	0.93	32.58

CONFLICT OF INTEREST STATEMENT

Authors declare that they have no conflict of interest in the research.

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