Original Article

ตำรับคาเฟอีนเจลสำหรับทาบนผิวหนัง

Caffeine Topical Gel Formulation

ธนภร อำนวยกิจ*[1], สุทธิมาลย์ อิงคถาวรวงศ์[1], ดวงแข มณีนวล[1], กิตติโชติ วรโชติกำจร[1]

Thanaporn Amnuaikit*[1], Suthimaln Ingkatawornwong[1], Duangkhae Maneenuan[1], Kittichote Worachotekamjorn[1]

[1]ภาควิชาเทคโนโลยีเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยสงขลานครินทร์ หาดใหญ่ สงขลา 90112

Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla 90112, Thailand.

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Abstract

Caffeine was used topically as one of many ingredients in various cosmetic preparations for reducing under-eye puffiness and dark circles. Gels containing 3% w/w caffeine as an active ingredient were prepared in this study. Suitable co-solvent systems and gel-forming concentrations were studied. Their effects on caffeine release from formulation were also studied. Suitable gel formulations consisted of carbopol Ultrez-21 as a gel-forming agent and propylene glycol (PG) as a co-solvent. The result showed that the increased concentration of Carbopol Ultrez-21, affected the formulation and thereby giving higher viscosity. However, all concentrations of Carbopol Ultrez-21 studied (0.2%, 0.5%, 1%, 2% and 4%) did not affect caffeine release significantly. The percentage of PG in the formulation greatly affected caffeine release. Formulation containing 15% and 30% w/w PG gave release rate from Higuchi's equation of 2.47 $\pm$ 0.26 mg/cm^2/h$^{1/2}$ and 2.37 $\pm$ 0.17 mg/cm^2/h$^{1/2}$, respectively which were lower when compared to release rate of 2.67 $\pm$ 0.07 mg/cm^2/h$^{1/2}$ from formulation containing 7.5% w/w PG. The best formulation of caffeine gel with good physical appearance and good release rate comprised of 3% caffeine, 0.5% carbopol Ultrez-21 and 7.5% PG.

Keywords: Caffeine gel, Carbopol, Propylene glycol

บทคัดย่อ

คาเฟอีน เป็นสารหนึ่งที่มีการใช้ในผลิตภัณฑ์เครื่องสำอาง สำหรับลดอาการบวม และรอยคล้ำรอบดวงตา ในการศึกษาครั้งนี้มีการเตรียมคาเฟอีน 3% w/w ในรูปแบบเจลโดยศึกษาหาตัวทำละลายร่วมและปริมาณสารก่อเจลที่เหมาะสม รวมถึงผลที่มีต่อการปลดปล่อยสารสำคัญออกจากตำรับ สารก่อเจลที่นำมาใช้ประกอบด้วยคาร์โบพอล อัลเทร็ซ 21 (Carbopol Ultrez-21) ซึ่งมีโพรไพลีนไกลคอล (PG) เป็นตัวทำละลายร่วมในตำรับ ผลการศึกษาพบว่า การเพิ่มความเข้มข้นของ Carbopol Ultrez 21 ส่งผลให้ความหนืดของตำรับเพิ่มขึ้นแต่ไม่มีผลต่อการปลดปล่อยของ

* ผู้เขียนที่สามารถติดต่อได้ : ธนภร อำนวยกิจ ภาควิชาเทคโนโลยีเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยสงขลานครินทร์

โทรศัพท์ 0-7421-2906 email : chomchan1@yahoo.com, chomchan.a@psu.ac.th

คาเฟอีนออกจากตำรับเจลในความเข้มข้นของสารก่อเจลที่ศึกษา (0.2%, 0.5%, 1%, 2% และ 4%) ในขณะที่ปริมาณ PG ส่งผลต่อการปลดปล่อยได้มากกว่า โดยอัตราการปลดปล่อยคาเฟอีนออกจากตำรับเจลที่มี PG 15% และ 30% w/w ตามสมการของฮิกูชิพบว่าเป็น 2.47 $\pm$ 0.26 $mg/cm^2/h^{1/2}$ และ 2.37 $\pm$ 0.17 $mg/cm^2/h^{1/2}$ ตามลำดับ ซึ่งมีค่าต่ำกว่าอัตราการปลดปล่อยคาเฟอีนจากตำรับเจลที่มี PG 7.5% w/w คือ 2.67 $\pm$ 0.07 $mg/cm^2/h^{1/2}$ ดังนั้นตำรับคาเฟอีนเจลที่ดีที่สุดซึ่งมีคุณสมบัติทางกายภาพดีและอัตราการปลดปล่อยตัวยาได้ดีประกอบด้วย คาเฟอีน 3% Carbopol Ultrez 21 0.5% และ PG 7.5% w/w

คำสำคัญ: คาเฟอีนเจล, คาร์โบพอล, โพรไพลีนไกลคอล

Introduction

Caffeine is a mild stimulant to the central nervous system when taken orally (Reynolds, 1993) and used topically as one of many ingredients in various cosmetic preparations for reducing under-eye puffiness and dark circles. In one study, it was used topically as cream preparations for reducing erythema and itching in dermatitis (Knight et al., 2003).

This study was aimed to formulate topical gels containing caffeine as an active ingredient using suitable co-solvent systems and gel forming agents. It will be used as topical vasoconstrictor gels for various applications. Most topical caffeine preparations were used in cosmetic purpose, gel formulation is more suitable due to its aesthetic appearance and cooling effect. Regarding to the study of Dias et al., 1999, commercially available topical creams containing 3% caffeine were prepared whereas solubility of caffeine in water is 21.74 g/l or topical caffeine gels could be prepared to give maximum concentration of only 2.17%. Therefore, co-solvent systems were required to obtain topical gels containing 3% caffeine.

Co-solvents such as ethanol, propylene glycol, polyethylene glycol and glycerin are usually used as aids to the solubilization of drugs in aqueous vehicles and all of them were used in this study. In the case of gel forming agent, poloxamer F127 and carbopol Ultrez-21 were used in various concentrations in order to find out the good topical gel formulation of caffeine. Poloxamer and carbopol are synthetic gel forming agent that is popular when used in cosmetics because of stability of products (Schmolka, 1967; Chu et al., 1992). To determine good formulation, physicochemical properties, stability and release characteristic were considered. Freeze-thaw process was applied to examine stability of formulation.

Materials and Methods

1. Materials

Caffeine anhydrous (Zhejiang Medicines, China), Carbopol Ultrez-21(Merck, Germany), Poloxamer or Lutrol® F127 (INCI, USA), Glycerin, Polyethylene Glycol (PEG) 400 and Propylene Glycol (PG) (P.C. Drug Center, Thailand), Triethanolamine, Uniphen P-23 (INCI, USA), Cellulose acetate membrane dialysis molecular weight cut off 3500 dalton (Chemoscience, Thailand), Ethanol (Sigma, USA) were commercially purchased. Other chemicals obtained commercially were of reagent grade.

2. Methods

2.1 Co-solvent system investigation

Caffeine anhydrous was solubilized 3% w/w in co-solvent system which composed of PEG 400, PG, ethanol, glycerin and purified water in various ratios, by sonicating for 10 minutes. Clear solution was evaluated at room temperature (25°C).

2.2 Preparation of caffeine gel

Caffeine gel composed of different concentrations of poloxamer F127 and carbopol Ultrez-21 were prepared. In the case of poloxamer F127, cold water process was used; poloxamer was solubilized in cold water (5°C) then the clear solution of caffeine was added and warmed to room temperature to get gel formulation. For carbopol Ultrez-21, it was dispersed and solubilized in caffeine solution with magnetic stirrer and sonication. Triethanolamine was added to adjust pH 5.5 for increasing viscosity of gel formulation.

2.3 Determination of caffeine content in gel

Caffeine content in gel was evaluated by a spectrophotometric method. A known weight of gel was dissolved and diluted subsequently with pH 7.4 phosphate buffer solution (PBS), and the concentration of caffeine was spectrophotometrically measured at 273 nm (Spectronic Genesys™5, Miltol Roy Company, USA) against the blank gel base containing the same amount of gel forming agent and other ingredients without caffeine.

2.4 Physicochemical properties

The physical appearance of formulation, pH, and viscosity were evaluated. pH was measured by a pH meter (ORION model 410A,USA). Viscosity was measured by a Brookfield viscometer with RV-7 spindle at 5 rpm, room temperature (RV model, USA).

2.5 Stability study

Stability studies were carried out under freeze-thaw conditions, -10°C and 45°C 48 h., for 6 cycles. Product performance such as physical appearance, pH, viscosity and content were determined.

2.6 *In vitro* drug release study

The release of caffeine from gel formulation was examined using Dissolution Apparatus II, USP XXIV with the aid of the Enhancer Cell™ 4 cm^2 section (Vankel VK 7000, USA). The 1 g. gel put in a cell was covered with cellulose acetate. The Enhancer Cell™ was placed in dissolution vessel containing 900 ml PBS, thermoregulated with water bath at 37°C and paddle stirred at 50 rpm (Bonacucina et al., 2006). Samples (10 ml) were withdrawn at 0.5, 1, 2, 4, 6, 8 and 12 h. An equal volume of fresh PBS was immediately added to the vessel after each sampling. The concentration of caffeine was spectrophotometrically determined at 273 nm.

2.7 Statistical analysis

Results are expressed as the mean ± S.D. of at least three replicates. Analysis of variance (ANOVA) was used to test the statistical significance of difference among groups. Statistical significance in the difference of the mean was determined by Dunnet's method or Student's *t*-test.

Results

Caffeine anhydrous was dissolved in various ratios of co-solvent systems were evaluated appearance of clear or turbid of solution (Table 1). Co-solvent system consisted of 4%, 7.5%, 15% and 30% of PG in water were selected to formulate gel. Poloxamer F127 was not suitable to be use as gel forming agent for caffeine because of its insoluble white color gel formulation (Figure 1A). Carbopol Ultrez-21 was selected to be used as gel forming agent in various concentrations along with other ingredients as shown in Table 2. All formulations were determined for their physicochemical properties such as pH, viscosity and appearance (Table 3). Needle form of caffeine crystals were observed from

gel formulation with 4% PG, after keeping at room temperature for 3 days (Figure 1B), while the increase of carbopol Ultrez-21 significantly enhanced the viscosity of gel. Gel formulation with suitable appearance, pH and viscosity were further studied for their stability under freeze-thaw condition as shown in Table 4. Caffeine was uniformly distributed through out the gel and no significant effect of freeze-thaw condition on its contents.

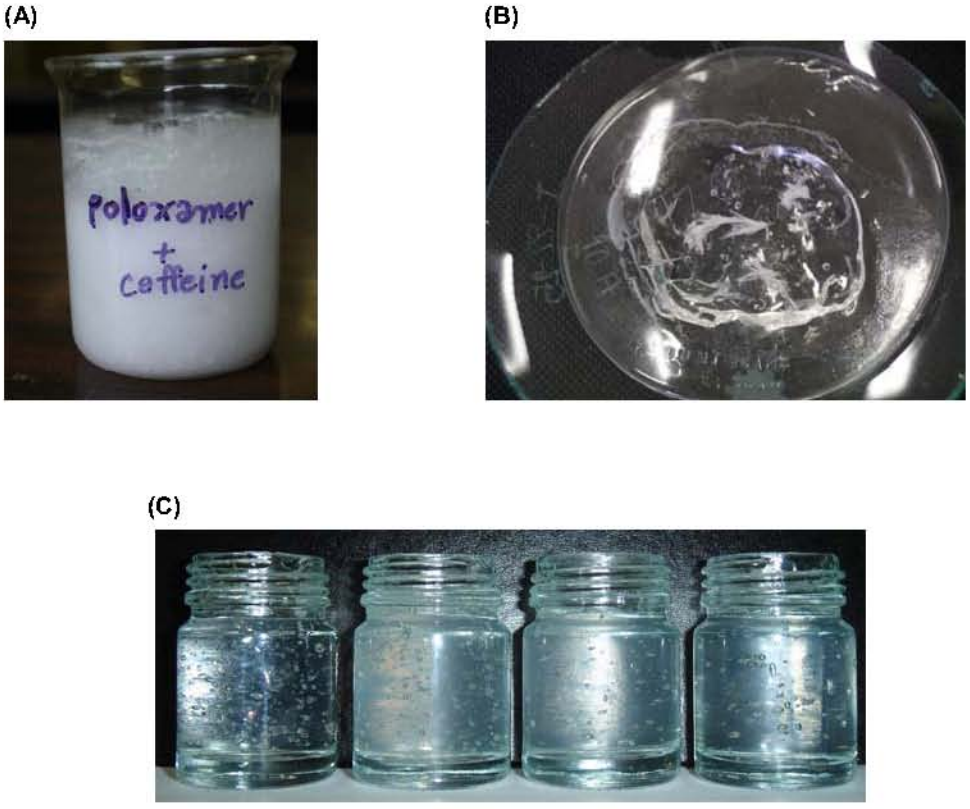

Figure 1 **(A)** Insoluble Caffeine in poloxamer gel, **(B)** Needle form of caffeine crystals in carbopol gel containing 4% w/w of PG, **(C)** Gel formulations, 1) gel base containing 0.5% w/w of carbopol and 7.5% w/w of PG without caffeine, 2) caffeine gel containing 0.5% w/w of carbopol and 7.5% w/w of PG, 3) caffeine gel containing 0.5% w/w of carbopol and 15% w/w of PG and 4) caffeine gel containing 0.5% w/w of carbopol and 30% w/w of PG.

Table 1 Co-solvent system for solubilizing of 3% w/w of caffeine.

Caffeine %w/w	Co-solvent system % w/w					Solution Appearance
	PEG400	Ethanol	Glycerin	PG	Water	
3	97	-	-	-	-	Turbid
3	90	-	-	-	7	Turbid
3	80	-	-	-	17	Turbid
3	-	97	-	-	-	Turbid
3	-	90	-	-	7	Turbid
3	-	80	-	-	17	Turbid
3	-	-	97	-	-	Turbid
3	-	-	90	-	7	Turbid
3	-	-	80	-	17	Turbid
3	-	-	-	97	-	Clear
3	-	-	-	90	7	Clear
3	-	-	-	80	17	Clear
3	-	-	-	30	67	Clear
3	-	-	-	15	82	Clear
3	-	-	-	7.5	89.5	Clear
3	-	-	-	4	93	Clear

Table 2 Ingredients of caffeine gel formulations in various concentrations.

Ingredients %w/w	Rx1	Rx2	Rx3	Rx4	Rx5	Rx6	Rx7	Rx8	Rx9	Rx10	Rx11	Rx12
Caffeine	3	3	3	3	3	3	3	3	3	3	3	3
Carbopol	0.2	0.5	1	2	4	0.2	0.5	1	2	4	0.5	0.5
PG	4	4	4	4	4	7.5	7.5	7.5	7.5	7.5	15	30
Ethanol	2	2	2	2	2	2	2	2	2	2	2	2
Uniphen P-23	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Triethanolamine	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Purified water to	100	100	100	100	100	100	100	100	100	100	100	100

Table 3 Physicochemical properties of caffeine gel formulations.

Rx	pH	Viscosity (centipoises, cPs)	Appearance of formulation
1	5.63±0.04	-	Clear gel, needle form of caffeine occurred when left it out for 3 days
2	5.54±0.12	-	Clear gel, needle form of caffeine occurred when left it out for 3 days
3	5.66±0.08	-	Clear gel, needle form of caffeine occurred when left it out for 3 days
4	5.70±0.01	-	Clear gel, needle form of caffeine occurred when left it out for 3 days
5	5.67±0.15	-	Clear gel, needle form of caffeine occurred when left it out for 3 days
6	5.77±0.00	41,000±500	Clear gel
7	5.60±0.10	78,000±866	Clear gel
8	5.51±0.17	174,000±500	Clear gel
9	5.53±0.05	428,000±854	Course clear gel, rigid
10	5.54±0.01	712,000±200	Course clear gel, rigid
11	5.54±0.02	98,000±150	Clear gel
12	5.51±0.03	86,000±264	Clear gel

Remark symbol "–" means no experiment in viscosity measured of that formulations.

Table 4 Physicochemical properties of caffeine gel formulations under room temperature and freeze-thaw condition.

Rx	Room temperature				Freeze-thaw			
	Drug content (% of Labeled amount)	pH	Viscosity (cPs)	Appearance	Drug content (% of Labeled amount)	pH	Viscosity (cPs)	Appearance
7 (7.5%PG)	110.92 ± 1.92	5.60±0.10	78,000±866	Clear gel	110.87 ± 1.31	5.64±0.00	80,000±0	Clear gel
11(15%PG)	105.91 ± 2.27	5.54±0.02	98,000±150	Clear gel	105.20 ± 1.64	5.56±0.03	97,000±500	Clear gel
12(30%PG)	106.61 ± 0.36	5.51±0.03	86,000±264	Clear gel	108.29 ± 1.82	5.57±0.05	86,500±200	Clear gel

Drug contents are expressed as the mean ± SD of three replicates.

In vitro release of caffeine from gel formulations was calculated, in term of caffeine release rate, according to Higuchi's model. As the regression analysis of obtained results for three kinetic models such as zero order (r^2 = 0.9722±0.016), first order (r^2 = 0.9838±0.006) and Higuchi's model (r^2 = 0.9983±0.001) showed that Higuchi's model gave the highest value of r^2 where the cumulative amount of released drug per unit area is proportional to the square root of time, is the most suitable model to describe the release kinetics of caffeine from the gel formulations examined in this study. Higuchi's rate constants calculated are summarized in Table 5. Figure 2 shows the release profile of caffeine from gel formulations containing various concentrations of carbopol Ultrez-21 and various concentrations of PG. The release rate of caffeine form gel formulation tended to decrease as PG concentration in the gel increased (Figure 2 and Table 5). On the other hand, the release rate of caffeine was not affected by the increase of carbopol Ultrez-21. All of the formulations were clear gels especially the one with higher PG concentration, the higher the concentration of PG the clearer the gel. However, high concentration of PG made gel seem greasy.

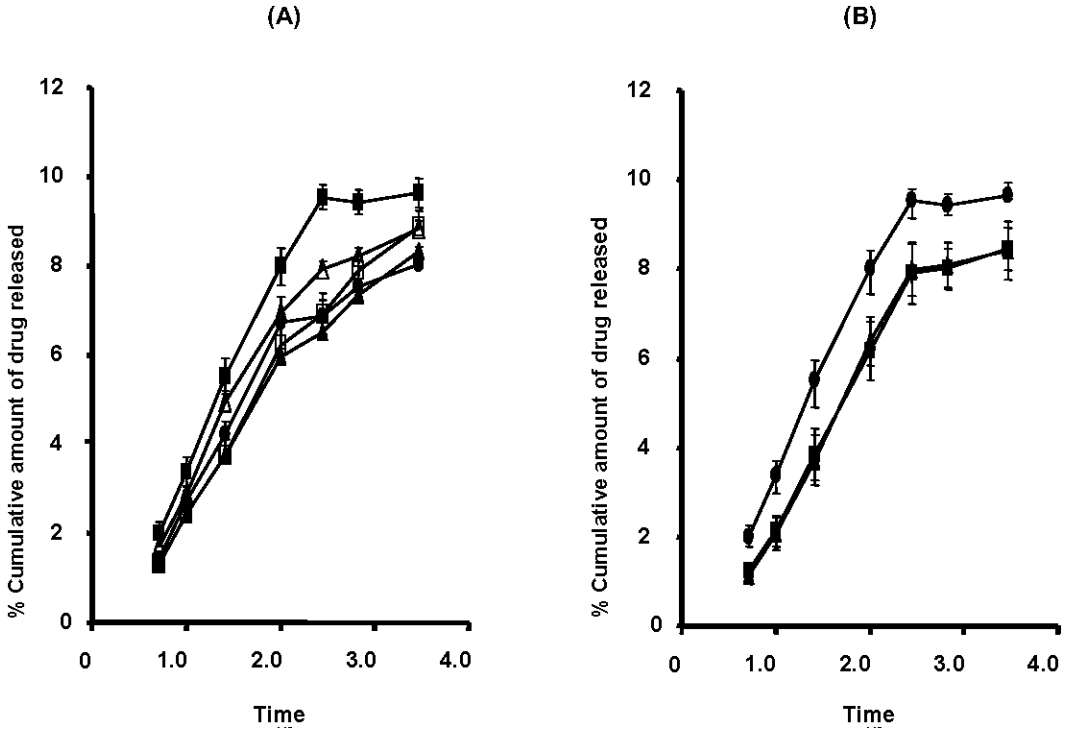

Figure 2 Effect of carbopol concentration **(A)** or PG concentration **(B)** on release profile of caffeine from gel formulations. (A) Carbopol was contained at 0.2% w/w (●) or 0.5% w/w (■) or 1% w/w (▲) or 2% w/w (□) or 4% w/w (△) in the gel containing 3% w/w of caffeine and 7.5% w/w of PG. (B) PG was contained at 7.5% w/w (●) or 15% w/w (■) or 30% w/w (▲) in the gel containing 3 % w/w of caffeine and 0.5% w/w of carbopol. Cumulative caffeine amount released was plotted against the square root of time, because Higuchi's model was found to be the suitable model for describing the release profile of caffeine. Results are expressed as the mean with the bars showing SD values of three different replicates.

Table 5 Release rate of caffeine (3%w/w) from gel formulations calculated by following Higuchi's model.

Rx	Release rate of caffeine ($mg/cm^2/h^{1/2}$)
6 (0.2% carbopol, 7.5% PG)	2.39 ± 0.13
7 (0.5% carbopol, 7.5% PG)	2.67 ± 0.07^a
8 (1% carbopol, 7.5% PG)	2.45 ± 0.25
9 (2% carbopol, 7.5% PG)	2.56 ± 0.08
10 (4% carbopol, 7.5% PG)	2.23 ± 0.07
11 (0.5% carbopol, 15% PG)	2.37 ± 0.17
12 (0.5% carbopol, 30% PG)	2.47 ± 0.26

Results are expressed as the mean ± SD of three replicates. [a]$p<0.05$ when compared to 4% w/w of carbopol and 7.5% w/w of PG formulation.

Discussion

Poloxamer is a block polymer of polyoxyethylene and polyoxypropylene which can dissolve in water, weak acid and alcohol but will not dissolve in propylene glycol, glycerin and mineral oil (Collett et al., 1979). It was not an appropriate gel forming agent for co-solvent system chosen in the present study. In addition, the preparation method of poloxamer gel in cold water process easily enhanced precipitation of caffeine crystal and formed an insoluble gel (Figure 1A).

Carbopol is a synthetic gelling agent composed of carboxyvinyl polymer cross-linked with allyl sucrose (Secard, 1962). It is a hydrophilic colloid when dispersed in water to give solution turbidity and acidity. The carbopol solution was neutralized by sodium hydroxide or triethanolamine to get viscous gel preparation and clear appearance. Gel structure of carbopol was built by the process of carboxyl group on polymer chain highly dissociate in basic condition, which make carbopol molecule extended, strong and continuous gel structure. However, if the basic condition is too high it might lower the viscosity, then a suitable pH of formulation is necessary. Carbopol Ultrez-21 composed of acrylat C10-30 alkyl acrylate crosspolymer which is used in cosmetic formulation because it is easily dispersion characteristics. It can swell and absorbed water very well to form clear gel. Then the various concentrations of carbopol Ultrez-21 in this study might not affect the release of caffeine from gel structure. Bonacucina et al., 2006 reported that the release kinetics depended on the dissolution medium which easily made the drug release from its gel structure. The needle form of caffeine in gel formulation after 3 days can be explained that 3% w/w of caffeine dissolved in 4% PG co-solvent system might be saturated. Then, using this co-solvent in gel formulation together with other ingredients, especially gel forming agent, 4% PG might be insufficient to solubilized caffeine.

The analysis of drug release profiles showed that Higuchi's model was the most suitable for describing the release kinetics of caffeine from the gel formulation prepared in this study, which means that the release of caffeine from the gel preparation is regulated by the diffusion of caffeine within a gel structure as matrix. The reducing effect

of PG on Higuchi' rate constant for gel formulation (Table 5) has not been clearly understood. However, PG is a polyol solvent that classified as humectant (Barry, 1983; Motoyoshi et al., 1984) and has several characteristics that can decrease the release rate of drug, higher affinity of drugs for PG may contribute to the reduced drug release from formulation, the solubilizing effect of PG might lead to the decrease in the chemical potential of drug in the formulation, as the viscosity of solution is one of the factors that affect the diffusion of drug (Amnuaikit et al., 2005).

Conclusion

Topical gel formulations containing 3% w/w of caffeine were prepared with suitable co-solvent system and gel forming agent. The best formulation of caffeine gel which give good physical characteristic and good release rate composed of 3% caffeine, 0.5% Carbopol Ulterz and 7.5% propylene glycol with a suitable pH range between 5-6.

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