DEVELOPMENT OF PLAI EMULGEL FOR THERAPEUTIC ULTRASOUND APPLICATION

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ABSTRACT: Plai oil extracted from *Zingiber cassumunar* Roxb. rhizome which contained (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD) as active ingredient has been proved to show the anti-inflammatory effect. This research aims to find out the suitable plai emulgel formulation which could be used as an alternative medicine combining with ultrasound physical therapy for either acute or chronic muscle inflammatory treatment. 18 formulas of plai emulgel were formulated by various type and concentrations of gel forming agents (1-2% w/w), such as carbopol 121, carbopol 934, carbopol 940, hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), and methyl cellulose (MC), combined with similar amount of plai oil (5% w/w), propylene glycol (20% w/w), EDTA (0.2% w/w) and paraben concentrate (0.2% w/w) in individual formula. These formulas were physical property, chemical property stability, and allergic skin test analyzed, in order to find out the suitable formula which is appropriated for applying with ultrasound transmission through gel. By this experiment, the formula numbered 4 which contained 1% carbopol 934 was found to be the suitable formula, which resulting in good appearances with good texture and spreadability. The chemical properties stability of this formula was also analyzed, by measuring content of the marker compound, (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD). After keeping at 15°C, the remaining content of this marker was still more than 95%.

Keywords: Plai, emulgel, *Zingiber cassumunar*, ultrasound treatment

INTRODUCTION

Ultrasound has been used by physical therapists since the 1940s. Ultrasound is applied using a round-headed wand or probe that is put in direct contact with the patient's skin. Ultrasound gel is used on all surfaces of the head in order to reduce friction and assist in the transmission of the ultrasonic waves [1]. Analgesic or anti-inflammatory drugs could be added into ultrasound gel for improving treatment efficacy [2, 3]. According to ultrasound wave caused temporary skin changing, so drug molecules could be absorbed through the skin, point to inflammatory area and muscle pain will relieve. Drugs added in ultrasound gel must not block the intensity or power density of ultrasound wave [4]. Diclofenac emulgel had been studied for combination using with ultrasound therapy. In order to reduce treatment cost for patients, some herbal medicines such as plai emulgel might be substituted for diclofenac emulgel in ultrasound therapy [5]. Plai emulgel was formulated from oil of *Zingiber cassumunar* Roxb. rhizome. This essential oil has been used for a long time for treatment muscle inflammation according to its oil contains (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD) as active ingredient which proven to be anti-inflammatory agent [6]. Plai oil has been developed in various dosage forms such as cream or gels, which have been sold in market; however, any emulgel form plai oil has not been produced. Hence, the objective of this experiment was to developed topical plai emulgel for applying to ultrasound treatment. This emulgel was also physical property, and chemical property stability, in order to find out the suitable formula which is appropriated for applying with ultrasound therapy.

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MATERIAL AND METHODS

Carbopol 121, carbopol 934, carbopol 940, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and methyl cellulose (MC) were used as gel forming agents, while propylene glycol (PG), triethanolamine (TEA), EDTA and paraben concentration were used as solvent, pH adjusting agent, chelating agent, and preservative, respectively. All these chemicals specified were pharmaceutical grade, and Plai oil was purchased from Kovic Kate International (Thailand) Co., Ltd. (Lot no. RC 1104001)

Table 1 Type and content of ingredient used in plai emulgel formula number 1-18

Ingredients (g)	Formula number																	
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Plai oil	5																	
Carbopol 121	1	1.5	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 934	-	-	-	1	1.5	2	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 940	-	-	-	-	-	-	1	1.5	2	-	-	-	-	-	-	-	-	-
HPC	-	-	-	-	-	-	-	-	-	1	1.5	2	-	-	-	-	-	-
HPMC	-	-	-	-	-	-	-	-	-	-	-	-	1	1.5	2	-	-	-
MC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1.5	2
PG	20																	
TEA	qs.																	
EDTA	0.2																	
Paraben conc.	0.2																	
Water qs.	100																	

Table 2 The viscosity and pH value of formulas number 4-8 measured at day 0 and 30

Formula number	Mean of viscosity (cps.)		pH	
	Day 0	**Day 30**	**Day 0**	**Day 30**
4	78,567.98	77,577.20	5.56	5.51
5	98,239.03	98,041.58	5.54	5.50
6	130,066.00	103,513.76	5.60	5.60
7	102,290.67	102,056.05	5.53	5.52
8	132,471.73	133,030.92	5.62	5.61

Plai emulgel preparation [7-10]
Plai solution was prepared by dissolving plai oil (5% w/w) in propylene glycol (PG) and then adding in various types and concentrations of gel forming agents (1-2% w/w), such as carbopol 121, carbopol 934, carbopol 940, hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), for plai emulgel development. Several formulas of the emulgel were pH adjusted to 5.5 by triethanolamine (TEA) and then appearances were observed.

Study on physical property stability [11-17]
The suitable plai emulgel formulas resulting in good appearances with good texture and spreadability were chosen for further studying on physical property stability, which were viscosity and pH value, at day 0 and 30. The viscosity was measured by Brookfield Model DV-II viscometer (spindle no. S 96, 6 rpm, 30°C). This stability studied was also tested by temperature cycling (6 cycles) method at 4 and 40°C.

Study on the ultrasound transmission through gel [18]
The suitable plai emulgel formulas were tested for ultrasound transmission through gel at day 0 and 30. Ultrasound wave intensity (I) was varied from 0.1-3 watt/cm^2 along with ultrasound waved induction (mV) was measured. Both values were curve plotted and linear regression value (R^2) of each line was then calculated. The good resulted formula of ultrasound transmission through gel showed R^2 value related to 1.

Study on chemical property stability [11-17]
The suitable plai emulgel formulas which were kept at 15°C, and 30°C and sampled at day 15, 30, 90 and 180, were chemical property stability analyzed by using Gas Chromatography (GC) whilst (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD) content was chosen to be the marker. The GC column was DB-5 (30m x 0.32 mm); oven temperature programming was 70-240°C (4°C/min); injector and detector temperatures were 175°C and 225°C, respectively; sample injection volume was 1 μl; split ratio was 100:1; and carrier gas was Helium.

RESULTS AND DISCUSION

Plai emulgel preparation
Eighteen formulas of plai emulgel were developed by varying types and concentrations of gelling agents, combined with similar amount of propylene glycol (20% w/w), EDTA (0.2% w/w) and paraben concentrate (0.2% w/w) in individual formula as shown in Table 1 and 2. The appearances of formulas numbered 1-3 and 10-12 were quite watery meanwhile formula number 13-18 were thick and sticky, hence spreadability quite badly. Formulas numbered 4-8, which carbopol 934 (1-2% w/w) and carbopol 940 (1-1.5% w/w) were used as gelling agent, showed good appearances in texture, moderately turbidity, and well-spreadability.

Table 3 Turbidity, pH value and viscosity of formulas number 4-8 observed before and after temperature cycling (6 cycles) method at 4 and 40 °C.

Formula number	Before			After		
	Turbidity*	pH	Viscosity**	Turbidity*	pH	Viscosity**
4	-	5.56	+	-	5.52	+
5	+	5.54	++	+	5.50	++
6	++	5.60	+++	++	5.61	+++
7	++	5.53	+++	++	5.53	+++
8	+++	5.62	++++	+++	5.61	++++

* Turbidity = +++, ++, +, and – (high to low)

** Viscosity = ++++, +++, ++, and + (high to low)

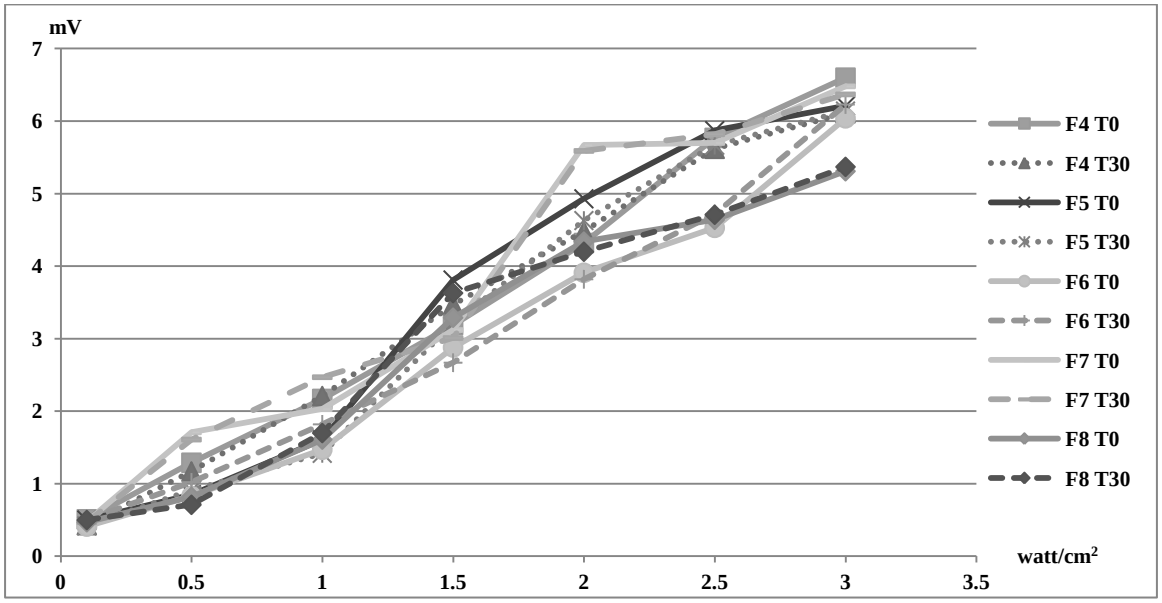

Figure 1 Ultrasound wave intensity (watt/cm^2) and ultrasound waved induction (mV) value formulas number 4-8 at day 0 and 30

Table 4 Linear regression of transmission through gel of formulas number 4-8 at day 0 and 30

Formula number	Linear regression (R^2)	
	Day 0	Day 30
4	0.9951	0.9930
5	0.9625	0.9738
6	0.9845	0.9864
7	0.947	0.9550
8	0.9888	0.9585

Therefore formula number 4-8 were chosen for further studied.

Study on physical property stability

Good appearance formulas numbered 4-8 were further studied on physical property stability by viscosity and pH measuring at day 0 and 30, along with temperature cycling (6 cycles) method at 4 and 40°C. Results were displayed in Table 2 and 3.

Study on the ultrasound transmission through gel

At day 0 and 30, formulas numbered 4-8 were also selected for further tested with ultrasound transmission. Ultrasound wave intensity (I) and ultrasound waved induction (mV) value plotted on X and Y axis, respectively, were exhibited in Figure 1. The linear regression value (R^2) of each line was then calculated and displayed in Table 4. Formula numbered 4, which contained 1% carbopol 934, were selected to be the best formula which is used for ultrasound transmission through gel according to its linear regression line (R^2 value) both in day 0 and 30 related to 1.

Table 5 The remaining content (% w/w) of (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD) in formula numbered 4

Day	Temperature (°C)	
	15	**30**
0	100.00	100.00
15	99.70	93.1
30	99.55	91.7
90	98.19	86.42
180	97.29	78.52

Study on chemical property stability

The appropriated formula (number 4) was further chemical property studied by using Gas Chromatography (GC). It was kept at 15°C and 30°C, before being analyzed. Area under curve of the marker, (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD) was calculated for its remaining content (%) as shown in Table 5.

CONCLUSION

Plai emulgel were developed in this experiment by using various types and concentrations of gel forming agents. The formulas represented good result in appearance were numbered 4-8 which containing carbopol 934 (1-2% w/w) and carbopol 940 (1-1.5% w/w) as gel forming agent. These 5 formulas were physical properties and ultrasound therapy combination analyzed. The best formula shown outstanding result was numbered 4 which containing 1% carbopol 934 as gel forming agent along with 5% plai oil, 20% propylene glycol, 0.2% EDTA and 0.2% paraben concentrate. This formula was also chemical property stability analyzed by measuring (*E*)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD) remaining content. After day 180, the remaining content of the marker (DMPBD) in this formula, which kept at 15°C was still more than 95%, meanwhile in formula which kept at 30°C was lower than 80%. Therefore this plai emulgel formula should be kept at 15°C for preserving the active ingredient, DMPBD.

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