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OPTIMISATION AND EVALUATION OF CAFFEINE ORALLY DISSOLVING FILMS

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ABSTRACT: Caffeine anhydrous is used as a stimulant to improve individual alertness and mental focus due to its ability of inhibiting the function of phosphodiesterase enzyme in the cells. Recent studies also discovered where caffeine reduced the risk of Parkinson's disease by its inhibitory action on adenosine receptor. With the aim of masking the bitter taste of caffeine, increasing the compliance and convenience in elderly patients, and achieving better therapeutic purpose, the orally dissolving films (ODFs) were developed in this research. Six formulation of caffeine ODFs (CA1-CA6) with increasing caffeine concentrations, 5, 10, 15, 20, 25 and 30% w/v; were prepared by solvent casting method. All of the caffeine ODFs, CA1-CA5 (except CA6), exhibit good film forming capacity and were peelable. The *in-vitro* disintegration time for CA1-CA5 were in the range of United States Pharmacopoeia's (USP) criteria (5-30s) and their surface pH is ~7, which suggested administration of ODF is not expected to cause irritation and discomfort.

INTRODUCTION: Caffeine is a natural alkaloid and present in the form of white powder [1]. Caffeine is naturally obtained from the seeds, nuts or leaves of different plants such as coffee, tea, cola, cocoa bean and guarana [2]. Caffeine is commonly found in carbonated drinks and energy drinks or over-the-counter drugs, such as painkillers, dietary supplements, migraine drugs, appetite suppressants and stimulants [3]. It enhances the therapeutic effect of some drugs, such as ergotamine tartrate which is used to relieve migraine headaches [4-5]. Caffeine acts as a stimulant which can increase one's energy and alertness of an individual as it has the ability to block adenosine subtypes receptor, A1 and A2A [6].

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Caffeine can improve alertness and maintain low levels of arousal even with low caffeine concentration of about one cup of coffee [6-7]. Besides that, caffeine inhibits phosphodiesterase enzyme and induces wakefulness effect in the central nervous system [2]. In addition, some researchers have found that caffeine can reduce the risk of Alzheimer's disease by preventing the production of β-amyloid and reducing memory deficits of mice models with Alzheimer's disease [2, 8].

Meanwhile, some researchers found that caffeine has an antagonistic effect on the A2A adenosine receptor which will reduce the risk of developing Parkinson's disease. Some studies have shown that caffeine can be used to prevent motor symptoms and dopaminergic neurons loss in Parkinson's disease [2]. Caffeine exhibits lipolytic property as it inhibits the activity of phosphodiesterase enzyme, thus, it is used to prevent fat accumulation in cells [9]. In addition, it is often found in the formulation of

cosmetic products as it has the function to protect the skin from photodamage and ultraviolet radiation as it exhibits antioxidant characteristics [9, 10]. The United States Food and Drug Administration (FDA) defines ODF as a soluble film, while European Medicines Agency (EMA) calls it as the or dispersible film or oral thin film [11, 12]. When ODF is placed on the tongue, it quickly hydrates and adheres to the tongue and immediately disintegrate and dissolve. Thus, the active pharmaceutical ingredients and bioactive compounds such as caffeine is released from ODF rapidly [13, 14].

Caffeine ODFs have been extensively studied by formulating with hydroxypropylmethyl cellulose (HPMC) [15] and HPMC E15 polymers [5]. Besides that, Hughes Medical Corporation, Dow Chemical Company and ODF Technologies Inc. are those pharmaceutical companies which marketed the caffeine ODF [16]. Caffeine ODFs were sold as energy strips to improve the mental alertness and wakefulness, especially when patient experienced feel fatigue or tired [16, 17]. Caffeine ODF can be used to improve athletes' performance in the terms of the speed, power, mental and aerobic capacity of an athlete [17]. In addition, there are caffeine sports drinks being marketed to provide hydration and better performance to athletes [18]. Hence, caffeine ODF can target on athletes, fatigue people, people in gymnasiums and for people to boost up their mental concentration. In this research, caffeine ODFs were developed by optimising the ratios of hydrophilic polymer, CMC, and plasticiser, PEG 400. Next, the film-forming capacity, disintegration time and uniformity of caffeine ODFs were evaluated.

MATERIALS AND METHODS:

Chemicals: Caffeine anhydrous was purchased from Sigma-Aldrich (United States). CMC (medium viscosity), PEG 400, sodium chloride, potassium chloride and calcium chloride dehydrate and were purchased from Chem Soln (Malaysia). Magnesium chloride hexahydrate was purchased from Systerm (Malaysia), dibasic potassium phosphate was purchased from Friendemann Schmidt (Malaysia).

Pre-formulation Study of Polymeric Orally Dissolving Film: The polymeric films, C1-C6, were prepared from CMC hydrophilic polymer by using the ratio of CMC to PEG 400 in 5:1. The concentration of CMC was adjusted to 1.0 - 4.0% w/v using distilled water and the total composition of the mixture was adjusted to 1.2-4.8%, respectively **Table 1**. 700 µL of the homogeneous solution was pipetted and cast on a microscope slide. The glass slide was dried at room temperature.

TABLE 1: PRE-FORMULATION STUDY OF CMC POLYMERIC FILMS WITH CMC: PEG RATIO OF 5: 1 IS ADJUSTED TO DIFFERENT CONCENTRATION OF CMC

Formulation code	Concentration of CMC (% w/v)	Total Composition (%)
C1	1.0	1.2
C2	2.0	2.4
C3	2.5	3.0
C4	2.8	3.4
C5	3.0	3.6
C6	4.0	4.8

Formulation of Caffeine Orally Dissolving Film: Caffeine ODFs were prepared by different ratios hydrophilic polymer CMC, plasticiser PEG 400 and caffeine anhydrous **Table 2**. Distilled water was added to the mixture to adjust the total composition of the mixture to 3.4%. The following development for caffeine ODFs were employed by solvent casting method at room temperature as described in the development of pre-formulation study.

TABLE 2: FORMULATION OF CAFFEINE ODFSBY VARYING DIFFERENT RATIO OF CMC, PEG 400 AND CAFFEINE ANHYDROUS

Formulation code	The concentration of caffeine anhydrous (% w/v)	The ratio of CMC: PEG 400: caffeine anhydrous
CA1	5	8.0: 1.5: 0.5
CA2	10	7.5: 1.5: 1.0
CA3	15	7.0: 1.5: 1.5
CA4	20	6.7: 1.3: 2.0
CA5	25	6.3: 1.2: 2.5
CA6	30	5.8: 1.2: 3.0

Evaluation of Polymeric Films and Caffeine Orally Dissolving Film:

Visual Inspection: All of the films were visually inspected in the aspects of film-forming capacity, peelability, appearance and colour of the films.

Film Weight: Three small sizes (2 × 2 cm^2) of the polymeric film from different batches of formulation were weighted individually in analytical balance (Mettler-Toledo, United States) and the weight variations were calculated.

***In-vitro* Disintegration Time Test:** The simulated saliva is prepared by mixing 14.4 mM of sodium chloride, 16.1 mM of potassium chloride, 1.3 mM of calcium chloride dehydrate, 0.55 mM of magnesium chloride hexahydrate and 2 mM of dibasic potassium phosphate were mixed and made up to 1 L.

The pH value of the solution was adjusted to 6.84 with hydrochloric acid[19]. *In-vitro* disintegration of ODFs was performed by petri dish method. The 2 × 2 cm^2polymeric film was placed into the petri dish which contains 20 mL of simulated saliva fluid (37±1 ℃, pH = 6.84). A stopwatch timer was used to record the time needed for film breakage. All of the experiments were carried out in triplicates[19].

Surface pH Test: The 2 × 2 cm^2 polymeric film was dissolved completely in 20 mL of simulated saliva fluid. pH meter (CyberScan pH 510, Eutech Instruments) was used to measure the surface pH of the film. All of the experiments were carried out in triplicates.

Fourier-transform Infrared Spectroscopy (FTIR) Analysis: The spectral analysis of films was carried out by placing the film on the sample plate. The FTIR spectra of CMC, PEG 400, caffeine anhydrous, the polymeric films containing CMC and PEG 400 and the polymeric films containing CMC, PEG 400 and caffeine anhydrous were recorded by using a FTIR spectrum spectrometer (Perkin Elmer, United States). The FTIR test was carried out where the wavenumber in the range of 650 to 4000 cm^{-1}.

RESULTS AND DISCUSSION:

Evaluation of Polymeric Film: The CMC polymeric films, C1-C3, with 1.0, 2.0 and 2.5% w/v of the concentration of CMC and the total composition ranged from 1.2 - 3.0% could not be peeled off due to poor film forming capacity. Also, when the concentration of CMC was 4% w/v and total composition of CMC and PEG 400 was 4.8% w/v, it cannot form a film (C6). Hence, these results demonstrated that only C4 and C5 formed CMC polymeric films, where the total composition of CMC and PEG 400 were optimum at 3.0-4.8 w/v% **Table 3.**

The appearance of CMC polymeric films C1-C5 were transparent. The average weight of C4 and C5 small size films was in the range of 7.3 - 8.8 mg. The average surface pH value of C4 and C5 films in simulated saliva fluid (pH = 6.84) were ranged from 6.4-6.7, thus, C4 and C5 films did not ionised in the oral cavity as CMC is ionised when the pH value is 2-6 [20]. Therefore, CMC polymer is not expected to cause mucosal irritation, because it is at neutral pH value. Lastly, the average disintegration time of C4 and C5 films ranged from 8.8-13.0s, which met with the standard of USP (5-30s).

TABLE 3: SUMMARY OF FILM FORMING CAPACITY, PEELABILITY, APPEARANCE, AVERAGE WEIGHT, DISINTEGRATION TIME AND SURFACE PH FOR CMC POLYMERIC FILM

Formulation code	Total Composition (%)	Film forming capacity	Peelability	Appearance	Average weight (mg)	Disintegration time (s)	Surface pH value
C1	1.2	Poor	No	Transparent	-	-	-
C2	2.4	Poor	No	Transparent	-	-	-
C3	3.0	Average	No	Transparent	-	-	-
C4	3.4	Excellent	Yes	Transparent	8.67 ± 0.06	9.33 ± 0.58	6.48 ± 0.02
C5	3.6	Excellent	Yes	Transparent	7.47 ± 0.15	12.00 ± 1.00	6.61 ± 0.05
C6	4.8	Very poor	No	-	-	-	-

Note: '-'Not determine due to poor film forming capacity.

FTIR Analysis for Polymeric Film: The FTIR results of C4 **Fig. 1** and C5 **Fig. 2** polymeric films were very similar. The peaks with frequency of ~3400 cm^{-1} and ~2870 cm^{-1} were resulted from

CMC hydrophilic polymer. The four peaks at 1593, 1416, 1324, and 1060 cm^{-1} resulted from CMC and PEG 400. It could be concluded that the CMC polymeric films contained CMC and PEG 400.

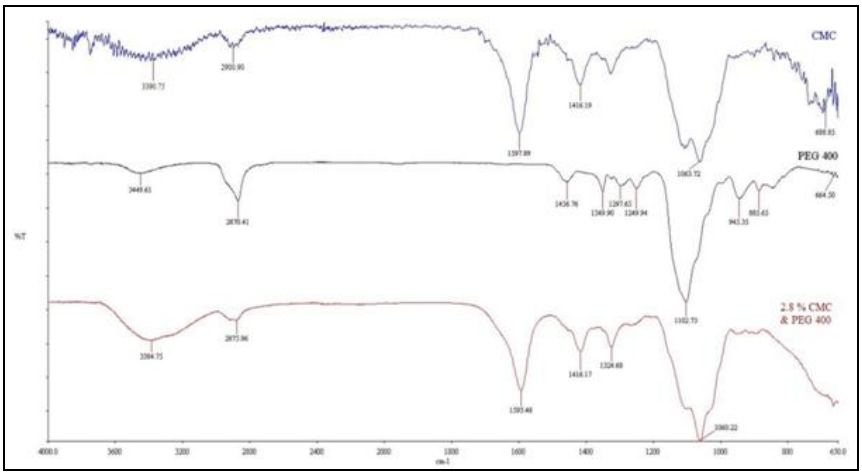

FIG. 1: FTIR SPECTRA FOR CMC, PEG 400 AND C4 POLYMERIC FILM

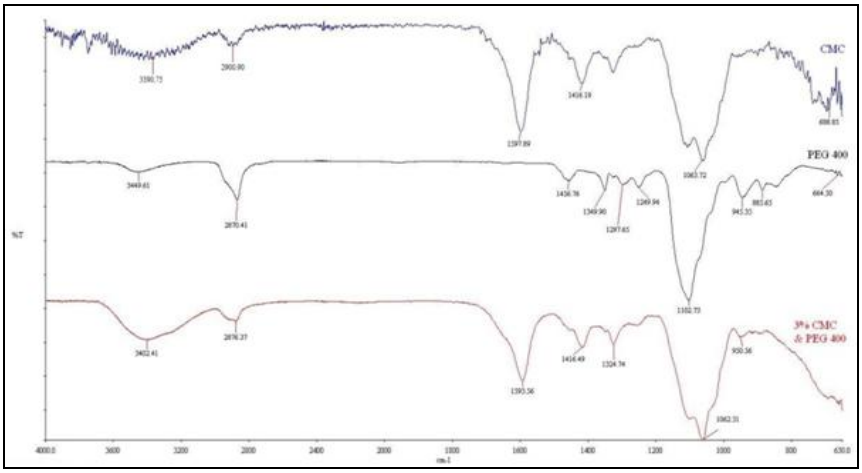

FIG. 2: FTIR SPECTRA FOR CMC, PEG 400 AND C5 POLYMERIC FILM

Evaluation of Caffeine Orally Dissolving Film: The total composition for all of the caffeine ODFs were fixed at 3.4% w/v since the pre-formulation study demonstrated where the total composition is optimum at the range of 3.0-4.8%. Besides that, all caffeine ODFs have excellent film-forming capacity, however, when the concentration of caffeine was 30% w/v, a film cannot be formed. It could be concluded that the maximum concentration of caffeine that can be added to the film was 25% w/v. The appearance of CA1 and CA2 ODF were translucent. When the concentration of caffeine increased, the appearance of the film turned into opaque white colour (CA5 and CA6) **Table 4.** The average weight for 2 × 2 cm^2 caffeine ODFs were in the range of 4.9-7.9 mg. The average surface pH value of caffeine ODF in simulated saliva fluid (pH = 6.84) was in the range of 6.4-6.8. Caffeine was partially ionised into cationic and anionic form, but it remained neutral in the pH range of 5.5-9[21]. Hence, caffeine could be formulated as ODF because it did not formed ions in the oral cavity and did not caused irritation to the mucosal lining. The disintegration time for all of the caffeine ODFs were ranged between 6-15s, which met the standard of USP **Table 4.**

TABLE 4: SUMMARY OF FILM FORMING CAPACITY, PEELABILITY, APPEARANCE, AVERAGE WEIGHT, DISINTEGRATION TIME AND SURFACE PH VALUE FOR CAFFEINE ODFS

Formulation code	Film-forming capacity	Peelability	Appearance	Average weight (mg)	Average disintegration time (s)	Average surface pH value
CA1	Excellent	Yes	Translucent	6.30 ± 0.27	6.67 ± 0.58	6.45 ± 0.02
CA2	Excellent	Yes	Translucent	5.43 ± 0.51	8.00 ± 1.00	6.75 ± 0.02

CA3	Excellent	Yes	Translucent with opaque	7.10 ± 0.17	8.33 ± 0.58	6.52 ± 0.07
CA4	Excellent	Yes	Translucent with opaque	6.67 ± 0.06	11.33 ± 0.58	6.50 ± 0.07
CA5	Excellent	Yes	Opaque	7.63 ± 0.38	13.67 ± 0.58	6.64 ± 0.03
CA6	Average	No	Opaque	-	-	-

FTIR Analysis for Caffeine Orally Dissolving Film: All of the spectra for caffeine ODFs (CA1-CA5) were similar and therefore the spectra of CA1 **Fig. 3A** and CA5 **Fig. 3B** are used for illustrations. The caffeine ODF contained CMC, PEG 400 and caffeine anhydrous as all of the prominent peaks were observed. However, as the concentration of caffeine increased, the spectra of caffeine ODF became sharper and more similar to that of the spectra of pure caffeine anhydrous. The weak peak at 2300-2400 cm^{-1} is results from C=O asymmetrical stretching in carbon [22].

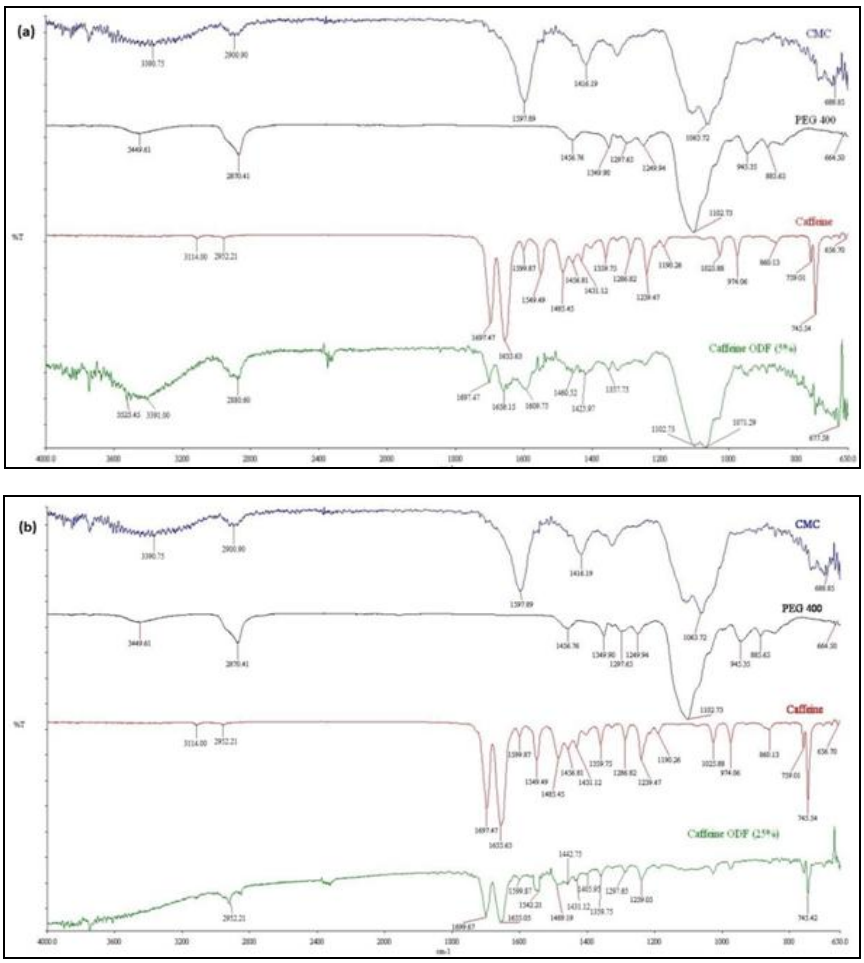

FIG. 3: FTIR SPECTRA FOR CMC, PEG 400, CAFFEINE ANHYDROUS AND (A) CA1 AND (B) CA5 ODF

CONCLUSION: Caffeine ODF could help to provide mental alertness and improve performance ability. It also helped to improve the bioavailability and patient compliance. Therefore, caffeine ODF can be used as an alternative delivery route and provide a beneficial innovation for future market. In conclusion, caffeine anhydrous could be delivered *via* buccal route in oral cavity. Caffeine ODFs was formulated by using CMC as the hydrophilic polymer and PEG 400 as the plasticiser. The pre-formulation studies demonstrated that to form a CMC polymeric film, the total composition of CMC and PEG 400 is optimum at 3.0-4.8 w/v%, C3-C5. Therefore, the total composition of caffeine ODFs was fixed at 3.4% w/v. In addition, most of the caffeine ODFs (CA1-CA5, except CA6) have acceptable physical properties such as film-forming capacity, peelability and appearance. The disintegration time for CA1-CA5 were complied with the USP

requirement (<30s) and the surface pH value is within the acceptable range, pH ~7.

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