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The Release Profiles of *Baccaurea angulata* Extract from Various Gelling Agents

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Abstract
This study investigates the release profiles of *Baccaurea angulata* extracts incorporated in carbopol, guar gum, and konjac gum. Franz cell diffusion was run for 24h for finite dosing, and 6h for infinite dosing. From finite dosing, carbopol had the highest cumulative amount permeated, (75.75±1.18% content release) compared to guar gum and konjac gum ($p<0.05$). Carbopol exhibited the fastest release profile with the highest mean flux (29.04±0.74µg/cm^2/h) ($p<0.05$) permeated within the first 0.75h. Konjac gum had faster release behavior compared to guar gum. However, the amount of content release by guar gum was higher compared to konjac gum for the total of 24h ($p<0.05$). For infinite dosing, the cumulative amount of content released by carbopol was the highest (4095.97±38.70µg) compared to guar gum and konjac gum ($p < 0.05$). Steady state flux of carbopol was the highest (379.26±3.58 µg/cm^2/h) compared to guar gum and konjac gum ($p<0.05$). Carbopol showed the highest permeability coefficient: 6.20×10^{-2}cm/h compared to guar gum and konjac gum ($p<0.05$). Guar gum had higher values in all calculated elements compared to konjac gum, except that its content release was slower. Therefore, it is concluded that carbopol has the best release profile to be developed as *Baccaurea angulata* dental gel.
Keywords: gels, Franz cell, release profile , *Baccaurea angulata*, drug delivery

INTRODUCTION

Topical medication is a favorable drug delivery route for wound healing due to its benefits of avoiding first pass metabolism, patient compliance [1] and direct delivery of the active ingredient to the target site. However, there are some limitations of this route such as low permeability across stratum corneum or membranes. Gel formulation is one of the preferred vehicle for topical drug delivery [2]. Gels was believed to give cooling effect to the site of application, long term and significant therapeutic efficacy, fast onset action, have better safety profile and improved patient compliance [3]. Human skin has two main layers, which are dermis and epidermis. The dermis is highly vascular while epidermis is the outermost layer called stratum corneum. It contains keratin and dead layer cells known as corneocytes embedded in matrix rich in lipid. Stratum corneum is the main barrier in the topical mediation since it reduces the permeation of certain compounds, especially water soluble compound [4]. Skin layers and oral mucosa have comparable histological structure with slight differences, where oral mucosa has epithelial layer, basal lamina, followed by lamina propria, and submucosal layer. In some locations like at the mucosa or hard palate, lamina propria is attached directly to bones. The epithelium can be keratinized such as at the gingiva or palate, or non-keratinized such at the area which needs flexibility for chewing purposes. Both skin and oral mucosa have comparable extracellular matrix (ECM) composition except that ECM of oral mucosa have more elastic structure [5, 6, 7, 8].

Release profile of drug from a topical gel is affected by several factors. These include physiological factors (such as hydration status, skin integrity, anatomic location, temperature and age of an individual) and drug factors (molecular size, nature of chemical of a drug, thermodynamic activity of drug in the donor sites, and partition coefficient) [9]. The physicochemical properties of gelling polymers and active pharmaceutical ingredients result in different release rates. The gel rigidity depends on the network structures and the forces responsible to maintain the interlinking structure of the gel [10]. That is why, in certain circumstances, polymers were mixed in different ratios in order to develop a stable gel that is capable of producing the best release profile and has the combination of advantages from each of the polymers constitutes [4, 9].

For *in vitro* release profile study, vertical diffusion cell specifically Franz cell method is commonly used. Simon et al. [3] investigated the permeation of rivastigmine in a transdermal system using Hanson Research (a Franz cell system). The cumulative permeated rivastigmine amount was successfully calculated and the result illustrated that the use of synthetic membrane could predict the drug diffusion profile *in vivo*. The use of synthetic membrane is suitable for study basis that aimed to investigate the drug release behavior [11, 12]. Basically, carbopol is synthetics polymer, whereas guar gum and konjac gum were considered as natural polymers [9]. Carbopol has different grades and each of them differs in term of their molecular weight, particle size, rheological profiles, and distribution of cross links [13]. Carbopol consists of polyalkenyl ether cross-linked with acrylic acid [14]. It was found to be safe with no effect of hypersensitivity towards human topical use due to its non-irritant and non-toxic properties [15]. Konjac gum in the other hand is a carbohydrate mainly konjac glucomannan [16]. It is approved for use and consumption by food industry in United States of America and Europe [17]. Commercially, konjac gum was used as stabilizing and thickening agent as well as a component in noodles, jellies, tofu, and others [16, 18]. Guar gum is galactomannan (a gel forming polymers) derived from endosperm portion of *Cyamopsis tetragonolobus* [19, 20]. The industrial application of guar gum includes stabilizers and thickeners due to its ability to form hydrogen bonding with water molecule [20].

Baccaurea angulata is a forestry plant normally found in Southeast Asia, specifically Indonesia and Malaysia (Borneo) [21]. The fruit brown color indicates the high content of antioxidant and flavones [22]. *Baccaurea angulata* has high potential to be developed into antioxidant gels and has high possibility to be formulated as herbal gel to sooth and speed up wound healing in topical application. Theoretically, biochemical pathway plays important part in regulating the process of wound healing. This includes the functions of reactive oxygen species (ROS). A balanced and low amount of ROS in body's biochemical system is important to speed up wound recovery [23]. However, healing process might be inhibited if ROS is presence excessively since high ROS level can cause oxidative stress, thus impairing the pathway of wound healing [24]. High antioxidant compounds contained in many herbal plants including *Baccaurea angulata* were expected to help reducing the ROS level, thus reversing the negative effect of high ROS level. By the help of antioxidants, ROS can be maintained low, thus contributing to promotes recovery of wound [25]. Based on previous study, the high level of antioxidants found in *Baccaurea angulata* had open up a new possibility for it to be developed as herbal preparations that has high potential to deliver nutraceutical benefits towards our health [26, 27]. Therefore, it is hypothesized that *Baccaurea angulata* can be a good dental gel that promotes wound healing in tooth extraction. According to Ahmed et al. [27], who studied antioxidants content of *Baccaurea angulata*, significant and strong relationship was found between total phenolic content and the antioxidant capacity of this fruit.

In developing *Baccaurea angulata* herbal extract gel for dental use, the release profile kinetics should be considered. Different release kinetics are expected to be exhibited by different gelling agents. In this study, various gelling polymers, which are carbopol, guar gum and konjac gum, were used as vehicle to formulate the *Baccaurea angulata* extract gel. The ability of the gelling agents to deliver the active ingredients were studied based on the release profiles. Phenolic content was measured as the content released from the *Baccaurea angulata* extract gel. Gelling agent with the best release profile will be chosen to be developed into oral dental gel containing *Baccaurea angulata* extract for further evaluation.

MATERIALS AND METHODS

Materials

Gelling polymers include polyacrylic acid polymer (Carbopol 940) from Acros Organics (Geel, Belgium). Guaran composed of polysaccharides sugar galactose and mannose (guar gum), and konjac glucomannan (konjac gum), are both from Modernist Pantry (Massachusetts, Unites States). Propylene glycol, methanol, methyl and propyl paraben as well as triethanolamine all were from Sigma Aldrich (Missouri, United States).

Plant Source

Baccaurea angulata fruits were collected fresh from the plant by the native farmers in Bau Sarawak Malaysia. This is among the only place where this plant and fruit were available. The fruit is only available for the duration of approximately 1 month each year during its ripening season (February to March). The fruits were couriered and packed via airmail right after being harvested from the plants to International Islamic University Malaysia, Kuantan Campus. The fruits were directly unpacked and washed upon arrival for the temporary storage purpose, in -20 °C freezer. For long term preservation, the fruits were oven dried to remove all the water content in the fruit in order to make sure the active content of the fruits can last longer. Whole fruits were peeled and cut into small pieces before being dried in 50 °C. After 2 days of drying, they were then grounded until small granules-powder form before being kept again in -20 °C freezer until further research activity.

Plant Extraction

Baccaurea angulata were being extracted using methanol extract method as described by Lailuma et al., with slight modifications [28]. About 20 g *Baccaurea angulata* dried coarse powder was mixed with 200 mL of methanol in conical flask. The conical flask is wrapped with aluminium foil to prevent sunlight degradation of the extract content. The mixture was stirred using incubator shaker New Brunswick™ Scientific Innova (New Jersey, USA) 4000 at 250 rpm, 37 °C temperature for duration of 24 h. Later, the methanol extract mixture were filtered using vacuum pump and Whatman® Grade 1 filter papers followed by ultracentrifugation using Supra 22K Ultracentifuge (Gwangju, Korea) at 9000 g at 4° C temperature for duration of 15 min [22, 27]. The supernatant was pipetted out, leaving the coarse content at the base of nalgene tube. The supernatant was then separated between the pure extract and the solvents using Ika RV8 rotary evaporator (Wilmington, USA) until dryness. The dried *Baccaurea angulata* extract was then stored in an airtight amber container and kept inside -20 °C freezer.

Preparation of gel

Three different gelling agents were used in this study, based on the outcome of previous research done by the same research team. It was found that 4% w/w carbopol 940, 5% w/w guar gum, and 5% w/w konjac Gum were of the best preparation among them to be incorporated with *Baccaurea angulata* extract. A gel with total weight of 50g was prepared, containing 3% w/w *Baccaurea angulata* extract. The gels were mixture of several excipients including 5% w/w propylene glycol [29] as solubilizer, 0.1% w/w methyl paraben, and 0.013% w/w propyl paraben both as preservatives. A total weight of 2.5g of propylene glycol, 0.05g of methyl paraben, and 0.15g of propyl paraben were used in all gel preparations. Two grams of carbopol 940 powder and 4.8g of triethanolamine (for carbopol 940 gel), 2.5g guar gum powder (for guar gum gel), 2.5g of konjac gum powder (for konjac gum gel) and 1.5g of *Baccaurea angulata* extract together with all other excipients were weighted using electronic balance. Specifically for carbopol, triethanolamine were dropped with triethanolamine dropwise until a total of 4.8g to transform the pH of the preparation from acidic to neutral (approximately pH 6.8), because carbopol will only become gel networks very well at this pH [30]. All the gels were quantity sufficient until weight of 50g for each gel using deionized water and stirred using Labortehnik RW20n overhead mechanical stirrer (Wilmington,USA) for duration of 60 mins (duration where most of the gel will become homogenous). After stir, the gels were left to stabilize at room temperature of 37 °C (to reform the gel network properly after being sheared with high shear stress using overhead mechanical stirrer) for 1 day, before further use for Franz Cell diffusion test [31].

Vertical Diffusion Cell

Vertical Diffusion Cell was performed using Franz Cell System. The three gels, namely carbopol, guar gum, and konjac gum were tested to investigate the difference in the release rate of active ingredients from *Baccaurea angulata* extract. The Franz Cell system was Hanson Research model (Chatsworth, USA), with 7 mL capacity of receptor capacity, and total of 1.8 cm^2 diffusion area. The receptor medium was phosphate buffered saline (PBS) with pH of 7.4 [32]. The system was set to mimic the body temperature of 37 ± 0.5 °C [33] using water jacket connected to circulated water bath. Cellulose acetate membrane was purchased from PolyScience (Illinois, USA) with diameter of 25 mm, pore size of 0.45 µm and thickness of 110 µm. The membrane was

allowed to swell before use by soaking in PBS for 30 min at 37 °C [34, 35]. The cellulose acetate membranes were mounted on the cells using tweezers right before starting the test. The receptor medium which is the phosphate buffer saline was filled until a curvy meniscus formed towards the outside area of the cell in order to ensure that the receptor chamber were completely filled when covered and in touch with the cellulose acetate membrane.
Cylindrical magnetic bars with pivot ring (12 × 6 mm) were placed into each cell, and speed of about 300 rpm was used to stir the receptor medium without making a vortex that may affect the static fluid layer surface underneath the membrane [36]. Both finite and infinite dosing Franz Cell tests were used, where a total of 18 mg for finite dosing and 400 mg for infinite dosing were spread on the cellulose acetate surface located at dosage wafer space, which is equivalent to 10 mg/cm^2 (for finite dosing) and 222.22 mg/cm^2 (for infinite dosing). Finite dosing test was run for 24 h [35] with sampling intervals of 0.5, 1, 2, 4, 6, 8, 12, 24 h, while infinite dosing test was run for 6 h with sampling intervals of 0.5, 1, 2, 4, and 6 h. At each sampling interval, 0.5 mL of receptor solution was collected and directly measured for total phenolic content.

Released Content Quantification

Baccaurea angulata was found rich in phenolic content [22, 27]. Therefore, the total phenolic content was selected as release marker to be quantified from *Baccaurea angulata* extract gels. The phenolic content were quantified using Folin Ciocalteau reagent test [37]. Briefly, 50 µL of Folin ciocalteau Reagent (diluted 1:4 with water) was pipetted into 96-well plate. Then 10 µL of receptor solution was added and incubated for 5 min. After that, 50 µL of 40% w/v sodium carbonate (40% w/v) was added and further incubated for another 2 h at 37° C. The absorbance was then read at 725 nm using microplate reader of TECAN Infinite 200 PRO (Mannedorf, Switzerland) operated by Tecan i-control software version 1.6.19.2. The calibration curve was made using Gallic Acid as standard. All the absorbances were of triplicate readings, where the results is expressed as standard Gallic Acid equivalence in µg/mL [27]. For finite dosing, the amount of applied gel was 18 mg, which contains a total of 275.48 ± 2.45 µg of total phenolic content (gallic acid equivalent). The amount of phenolic quantified from receptor solution will be compared with this original content from the applied gel at the dosage wafer. Whereas for infinite dosing, the amount of applied gel was 400 mg, which contains a total of 6.12 ± 0.05 mg of total phenolic content (gallic acid equivalent). A large dose was used for infinite doses to apply the concept of infinity dosing where any depletion of the compound from the dosage wafer due to diffusion into the receptor chamber, or evaporation can be negligible since the applied dose is very large at the dosage wafer [38].

Statistical Analysis

The data were analyzed with the application of ANOVA (one-way analysis of variance) followed by Tukey test of multiple comparison using Minitab 17. The data were conducted in triplicate and the results were expressed as mean ± standard deviation. The significance of the differences between mean values of each data measured was determined based on p value, where P value < 0.05 is considered statistically significant.

RESULTS

Finite Dosing

As illustrated in Fig 1, cumulative amount of *Baccaurea angulata* extract released at sampling intervals of 0.5 h from carbopol gel was the highest with the value of 58.08 ± 1.48 µg/cm^2 followed by konjac gum with the value of 37.13 ± 0.44 µg/cm^2 and guar gum with the value of 3.62 ± 0.11 µg/cm^2 ($p < 0.05$). At the end of 24 h period, carbopol exhibited the highest cumulative release of 115.92 ± 1.81 µg/cm^2, equivalent to mean of 208.66 ± 3.26 µg for the 1.8 cm^2 total surface area of the receptor chamber) followed by guar gum (56.21 ± 0.68 µg/cm^2, equivalent to 101.12±1.22 µg) and konjac gum (49.48 ± 0.47µg/cm^2, equivalent to 89.06 ± 0.85 µg) ($p < 0.05$). The equivalent percentage of content released from the extract gel was found as 75.75 ± 1.18% for carbopol, 36.71 ± 0.44% for guar gum and 32.33 ± 0.31% for konjac gum ($p < 0.05$). The cumulative compound release from carbopol started to become plateau fashion at the 8th hours, for guar gum was at 12th hours, and konjac gum was at 1 hour.
The mean flux value (as illustrated in fig 2) has shown that carbopol had the highest mean flux value at 0.25 h with the value of 29.04 ± 0.74 µg/cm^2/h followed by konjac gum with the value of 18.57 ± 0.22 µg/cm^2/h and lastly guar gum with the value of 1.81 ± 0.06 µg/cm^2/h ($p < 0.05$). At the end of the experiment (midpoint of sampling interval at 18th h), the mean flux for guar gum was the highest with the value of 3.6 ± 0.13 µg/cm^2/h, followed by 0.26 ± 0.11 µg/cm^2/h and carbopol with the value of 0.75 ± 0.21 µg/cm^2/h.

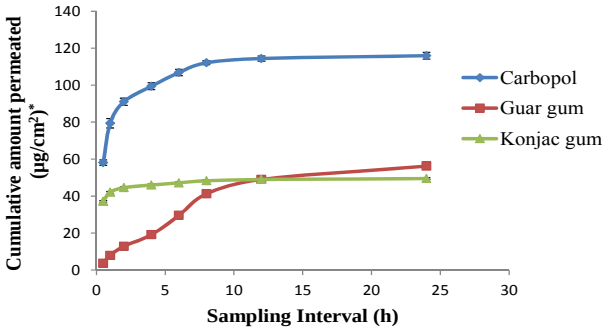

Fig 1: Cumulative amount of content released from various gel containing *Baccaurea angulata* extract for finite dosing test. *Values were expressed as mean ± S.D.

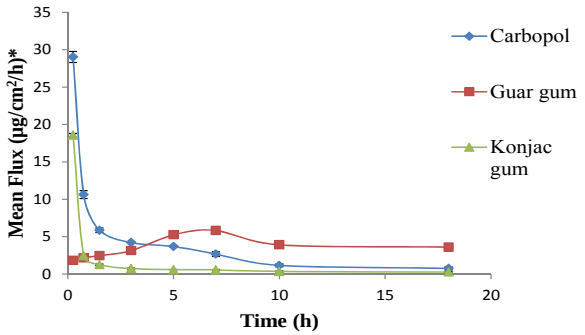

Fig 2: Cumulative amount of content released from various gel containing *Baccaurea angulata* extract for finite dosing test. *Values were expressed as mean ± S.D.

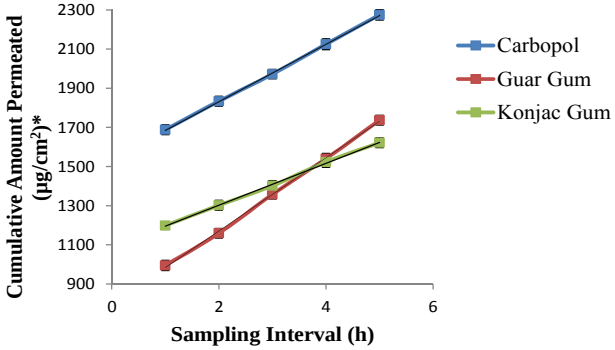

Fig 3: Cumulative amount of content released from various gels cotaining Baccaurea Angulata Extract for infinite dosing test. Values were expressed as mean ± S.D.

Infinite Dosing

Fig 3 illustrated the cumulative amount permeated for all three gels in infinite dosing test. At sampling interval of 0.5 h, carbopol was found to release the highest cumulative amount (1688.86 ± 16.91 µg/cm^2) followed by konjac gum (1198.68 ± 10.35 µg/cm^2) and guar gum (994.99 ± 8.02 µg/cm^2) ($p < 0.05$). At sampling interval of 6 h, carbopol was found to release the highest content with the value of 2275.54 ± 21.50 µg/cm^2 followed by guar gum with the value of 1737.05 ± 13.97 µg/cm^2 and konjac gum with the value of 1621.59 ± 16.75 µg/cm^2 ($p < 0.05$). The equation for regression for carbopol gel was y = 146.5x + 1539.3, while for guar gum was y =186.52x + 798.47 and last for konjac gum was y = 106.73x + 1089.4. The regression for all the three gels developed for this infinite dosing test had acceptable regression values of 0.9997 for carbopol, 0.9991 for guar gum, and 0.9990 for konjac gum.

Table 1: Permeation Rate Flux, Permeability Coefficient and Regression Value (Infinite Dosing)

Gel polymers	Steady State Flux (J_{ss}, µg/cm^2/h)*	Permeability Coefficient (K_p, cm/h x 10^{-2})	R^2 value
Carbopol	379.26 ± 3.58^a	6.20	0.9997
Guar gum	289.51 ± 2.33^b	4.72	0.9991
Konjac gum	270.27 ± 2.79^c	4.41	0.9990

*Values were expressed as mean ± S.D. Different alphabetical superscripts in the same column are significantly different ($p < 0.05$) based on multiple comparison using Tukey's HSD test.

DISCUSSION

This study was conducted to investigate the release profiles of *Baccaurea angulata* extract from three different types of gel polymers; carbopol, guar gum and konjac gum. In some cases, finite dosing was conducted for 72 h (like in the case of transdermal patches)[39]. However, during the pilot study of this research, it was found that the maximum amount released from the gel was within less than 24 h. Therefore, the test was set to run for only 24 h.

In this study, a synthetic membrane was used. Synthetic membrane has advantage of being more consistent, eliminating the variability among different test cells. Natural membrane such as rat skin or human skin may vary based on sources of the membrane, area of the skin origin (anatomy location), and age [36, 40]. The drug thermodynamic solubility, pH, partition coefficient, drug-excipient interaction and other drug-vehicle relationship can be better explained by using synthetic membrane instead of natural membrane in Franz cell diffusion test [39]. Natural membranes might be advantageous when the study aims to correlate *in vitro* release data with *in vivo* one, which is not the objective of this study.

Various studies including organization for economic cooperation and development (OECD) guidelines suggested the use of application of formulation with variable weight, and normally it is within the range of 1-10 mg/cm^2 in the finite dosing test[38, 39, 41, 42, 43]. In this study, the highest dosage was chosen (10 mg/cm^2) because the released phenolic content from the gels was small to be detected by UV-Vis microplate reader. Fig 1 illustrates the cumulative release per surface area Q of the membrane (µg/cm^2) for finite dosing conducted for 24 hours in each cell, whereas Fig 3 illustrates the cumulative release per surface area Q of the membrane (µg/cm^2) for infinite dosing conducted for total of 6 hours each cell. The formula for Q is shown in Eqn. 1[34, 36, 44]:

$$Q = \{C_n V + \sum_{i=1}^{n-1}(C_i S)\}/A \qquad \text{Eqn. 1}$$

where Q is the cumulative release per surface area of the membrane (µg/cm^2), C_n is the concentration of the compound determined at nth sampling interval (µg/mL), V is the volume of the receptor chamber. $\sum_{i=1}^{n-1} C_i$ is the sum of the concentrations of the compound determined at sampling intervals 1 through n – 1 (µg/mL), S is the volume of sampling aliquot which is 0.5 mL and lastly A is the surface area of the sample well which is 1.8 cm^2. Fig 1 illustrates the cumulative amount permeates as a function of time, in hours [36, 44].

Besides that, mean flux which is also known as the rate of absorption denoted by unit (µg/cm^2/h) was calculated and illustrated in Fig 2 (for finite dosing). Mean flux is the average rate of amount passed through the membrane in a particular duration [44]. For example, the rate of content that being released between the 2nd hour to 4th hour is denoted as mean flux within this 2 hours gap, and reported as the rate of absorption at the mid-point of this duration which is the 3rd hour [45]. As illustrated in Fig 2, carbopol and konjac gum gels behaved differently from guar gum where both released the major contents within the early hours of gel application, while guar gum released the contents slowly to reach the highest mean flux to diffuse across the membrane in an increasing fashion. This might be due to the behavior of the guar gum which holds the *Baccaurea angulata* extract content longer due to its specific polymer networks, compared to carbopol and konjac gum which release their content faster. According to Deivasigamani et al. [46] guar gum is stable over wide pH range, non-ionic, and the viscosity is constant in the pH range of 1 - 10.5 [47]. This highly stable profile explains why guar gum does not break down and release its content easily. Guar gum and konjac gum were both considered as polysaccharides [9, 48]. However this study had shown that each of them behaves differently, specifically in term of releasing behavior of content from *Baccaurea angulata* extract. According to Pundir et al. [49], guar gum was identified as polymeric component that has function of major rate-controlling release. Some medicines (tablet dosage form) that contains constant sustained released matrix were normally developed consisting of polymers of guar gum. Besides, T. M. Aminabhavi et al. [50] also explained that guar gums were among the components used as matrix formulation in tablets for controlled released delivery of some anti-hypertensive, anti-inflammatory, and anti-infective drugs. This information supports the findings of why content from *Baccaurea angulata* extracts was released slowly in this study.

For dental gel development, the pharmaceutical vehicle that suits the most is the one that can release its content in fast and short duration. The movement nature in the mouth might cause the gel to dissolve easily or to be eluted by the saliva. Carbopol and konjac gum showed fast release but the cumulative release of konjac gum (as illustrated in Fig 1) was less than that of carbopol and even less than guar gum. The gel with highest content release is the best choice to be formulated as dental gel. Therefore, from the finite dosing test, carbopol had the best release profile for *Baccaurea angulata* extract.

Fig 3 illustrates the cumulative amount of content released for infinite dosing test and Table 1 illustrates the permeation rate flux, permeability coefficient, and regression value for this test. Infinite dosing relies on the concept where the amount of compounds present on the surface of the skin remains effectively constant for a period of time and it is assumed that there is no reduction of active compound concentration in the donor solution (the gel at the dosage wafer) [1, 51]. Infinite dosing is used to determine the kinetic parameters including the permeation flux at steady state (J_{ss}, µg/cm^2/h), and permeability coefficient (K_p). The formula of K_p is shown in Eqn. 2 [52, 53].

$$K_p = \frac{\text{Experimental Permeation rate Flux}, J_{SS}}{\text{Initial Drug Concentration in the donor portion}, C_O}$$

Eqn. 2

The extract contents in infinite dosing test are not expected to be fully released, because this test is to measure the release kinetics and to develop the permeability coefficient and the steady state flux. That is why duration of 6 hours to run infinite dosing is normally suitable with the first 5 points of release profiles [54]. The steady state flux in infinite dosing test (which is known as mean flux for finite dosing) is expressed as the average rate of release of the content from the gel each hour, for 6 hours as a whole at steady state. However, the term of mean flux value expressed in finite dosing test refers to the average rate of release of the content for each of the time interval studied.

The cumulative amount of compound permeated into the receptor solution had increased with time, and it approached a constant trend of slope. The findings of this part was found to be as expected, according to assumptions that has been explained by De Salzer et al. [38]. The infinite dosing test results supported the findings in finite dosing test regarding the cumulative amount of permeant released (Q, $\mu g/cm^2$) at the end of the experiment. Both tests showed the ranking of cumulative released as follows: carbopol > guar gum > konjac gum. Referring to Table 1, it was shown that carbopol had the highest steady state flux (J_{ss}) followed by guar gum and konjac gum ($p < 0.05$). Regarding permeability coefficient (K_p), the same pattern occurred like the ranking of cumulative amount permeated (at the end of experiment for both tests), in which the highest permeability coefficient goes to carbopol, followed by guar gum and konjac gum. High permeability coefficient denotes that the gel polymer has good ability to release the content of *Baccaurea angulata* extract from the gel matrix. This illustrates the gel ability to release the phenolic content at the membrane around the alveolar bone (extracted tooth area).

According to Jain et al. [35], the release profiles of diclofenac from ethosome loaded 0.5% w/w carbopol gel was significantly different ($p < 0.05$) from ethosome formulation without carbopol. This denotes that incorporation of carbopol polymer had affect on the release profile of the diclofenac. Vadlamudi et al. [55] also found that naproxen incorporated in Aloe Vera gel which used the base of carbopol 934 had effective *in vivo* and *in vitro* release profiles (higher mean steady state flux, and permeability coefficient) compared to commercial products. However, since the present study used different grades of carbopol and different active pharmaceutical ingredients, the exact values of flux and permeability coefficient were different. Overall, this data justified that carbopol is actually a good gelling agent that can be a good vehicle to deliver pharmaceutical active ingredients.

CONCLUSION

The overall results of the release study suggest that carbopol is the best gelling polymer as the vehicle for *Baccaurea angulata* extract to be developed as dental gel. Carbopol had the best release profiles of *Baccaurea angulata* extract in the finite and infinite dosing test over konjac gum and guar gum. In finite dosing, carbopol released the highest percentage and cumulative amount of content from the extract, and had highest mean flux value, with fastest release. Same goes to infinite dosing test, where carbopol had the highest cumulative amount permeated, and highest permeation rate flux (J_{ss}), and highest permeability coefficient. The ranking was followed by guar gum and konjac gum. However, the time to reach the highest mean flux value for konjac gum is shorter compared to guar gum. Therefore, carbopol is the best candidate to be the developed into dental herbal gel containing *Baccaurea angulata* extract to be used at tooth socket after the extraction of tooth.

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