

The gelling properties of *Dillenia indica* mucilage in benzyl benzoate emulgel formulations

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The objective of the study was to evaluate the gelling properties of *Dillenia indica* mucilage in benzyl benzoate emulgel formulation. Mucilage was extracted from the fruits of *Dillenia indica* using established methods and characterized by rheology and swelling. Emulsion (F1) was prepared using the continental emulsification method. Gelling agents (2 %^w/v) were prepared by dispersing in distilled water with constant stirring at a moderate speed using a magnetic stirrer. F1 was added to the gel (0-75 %^w/w) to obtain emulgel formulations and evaluated using viscosity, globule size, pH, release profiles and kinetic modeling. Data were expressed as mean ± SD, and similarity factor (f_2) was used to compare all formulations. Formulation viscosity was significantly higher with carbopol than with *Dillenia*; globule sizes increased with concentration of gelling agents, and pH reduced as the concentration of *Dillenia* increased. All formulations showed controlled release properties with t_{80} ranging between 114 and 660 min. The release was governed by Korsmeyer-Peppas model. Formulation F5 prepared with 50 % *Dillenia* showed highest similarity to F4 prepared with 75 %^w/w carbopol. *Dillenia indica* demonstrated acceptable gelling properties comparable with that of carbopol and could be improved for use in emulgel formulations.

Keywords: *Dillenia indica* mucilage. Benzyl benzoate. Emulsion. Gelling agents. Emulgel formulations.

INTRODUCTION

Emulgel formulations have in recent years been developed for a number of drugs intended for topical or systemic action. When gels and emulsions are prepared in united form, the dosage forms are referred to as emulgels (Kapoor *et al.*, 2014). Emulsions are controlled release systems containing two immiscible phases in which one is dispersed into the other, with the use of an emulsifying agent to stabilize the system. Both oil-in-water and water-in-oil type of emulsions are used as vehicles to deliver various drugs to the skin. Emulgels are prepared by mixing an oil-in-water type or water-in-oil type of emulsion with

a gelling agent. Direct (oil-in-water) system is used to entrap lipophilic drugs, whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) system.

Emulgel for dermatological use has several favourable properties, such as improved application property in comparison to classical formulation as creams and ointments (Shankar *et al.*, 2018). They also have faster and more complete release of the drug from the vehicle to the skin, and they are convenient to apply on hairy skin due to the absence of greasiness and lack of residue upon application. They also permit the incorporation of both aqueous and oleaginous ingredients, hence hydrophobic or poorly water soluble drugs, such as antifungal agents, are easily incorporated in such type of vehicles through the proper choice of the oily phase (Shahin *et al.*, 2011). Emulgels are also bio-friendly, easily removable, possess longer shelf life and a pleasing appearance (Mulye *et*

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al., 2013). It has very simple and cost effective method of preparation basically, including three steps: first, the preparation of oil-in-water or water-in-oil emulsion where the drug is incorporated as per formulation requirement; then, the second step is to formulate the gel base, and finally the addition of emulsion to gel in continuous stirring to form emulgel (Haneefa, Mohanta, Nayar, 2013; Vats *et al.*, 2014).

Benzyl benzoate is an organic compound used as an acaricide, scabicide and pediculicide in veterinary care in many animals, apart from cats to which it is toxic (Knowles, 1991). It is also used as a repellent for chiggers, ticks and mosquitoes; it is used as a dye carrier, solvent for cellulose derivatives, plasticizer and fixative in the perfume industry (Maki, Takeda, 2000). The drug is also an effective and inexpensive topical treatment for human scabies. The main disadvantage of benzyl benzoate is skin irritation within minutes after its application (Walton, Myerscough, Currie, 2000; McCarthy *et al.*, 2004). For this reason, it cannot be applied directly on the skin and therefore requires formulation into appropriate dosage form.

Dillenia indica popularly known as elephant apple is an evergreen large shrub native to southeastern Asia, that is, India, Sri Lanka, east to southwestern China, Vietnam, Thailand, Malaysia and Indonesia (Lim, 2012). Different parts of the plant have shown anti-diabetic (Kumar, Kumar, Prakash, 2011); antimicrobial, antibacterial and anticancer (Kumar *et al.*, 2010); antidiarrheal (Niaz *et al.*, 2016); wound healing activity (Paul, Janick, 2008); astringent and prophylactic effects (Deshmukh *et al.*, 2019). The fruit contains mucilage which holds the seeds together. The mucilage has high swelling capacity, appreciable viscosity, biodegradability and biocompatibility. It was successfully used in the formulation of ibuprofen microbeads, and it conferred controlled release properties (Ajala, Silva, 2020). In the present study, benzyl benzoate was formulated into emulgel, using the mucilage obtained from *Dillenia indica*, thus harnessing the properties of emulsion and gel in one product. There is a need to prepare benzyl benzoate as emulgel formulation because it currently exists as lotion in the market. Lotions, like creams and ointments, are sticky; thus may cause uneasiness when applied; the

spreading coefficient is low compared to emulgels and requires rubbing in the application process which may cause dermatitis. Emulgel as a novel delivery system can be applied to hairy skin without any uneasiness in addition to all other properties earlier mentioned, and it will thus find additional application in veterinary care. It is expected that the emulgel formulation may demonstrate improved pharmaceutical properties; furthermore, the use of a natural gel can expand the worth of *Dillenia* and assist the development of small-scale industries.

MATERIAL AND METHODS

Material

The materials used include Benzyl benzoate obtained from Krishna chemicals, India; carbopol 910 (Lubrizol management, Shanghai, China); Tween 80 (Croda chemicals, Argentina); methyl paraben (AMSAR PVT. LTD, India); distilled water; Span 20 (Spak Orgochem (I) Pvt. Ltd, India); while *Dillenia indica* fruits were obtained from the Botanical garden, University of Ibadan, Ibadan. All other reagents used were of analytical grade.

Methods

Extraction of Dillenia mucilage

The method of Ajala, Silva, (2020) was used in the extraction of the mucilage. Fruits of *Dillenia indica* were cut open, and the inner part containing the mucilaginous material was scooped out and soaked for 24 h in chloroform water. Straining was done through a muslin cloth to remove extraneous materials and then precipitated, using ethanol (96 %v/v). The precipitated mucilage was filtered and then washed with diethyl ether before drying at 50 °C for 48 h. It was then pulverized and kept in air-tight containers.

Determination of morphology and swelling profiles for Dillenia indica mucilage

The morphology and surface characteristics of *Dillenia indica* mucilage particles were determined

using the scanning electron microscope (Hitachi Model S, 2460N, Tokyo, Japan).

Dillenia indica mucilage (5 g) was transferred to a 100 mL cylinder (V1); 50 mL distilled water was added and the slurry was shaken for 5 min and then made up to 100 mL. The suspension was allowed to stand for 24 h and the sedimentation volume (V2) was measured at different time intervals. The swelling index was calculated using the equation below, and appropriate plots were made.

$$\text{Swelling index} = \frac{V2-V1}{V1} \quad \text{Eqn 1}$$

Preparation of emulgel formulations

The emulsion was prepared using the continental emulsification method which involves the formation of a pre-emulsion. The pre-emulsion was prepared by heating the aqueous phase (85 °C) and pouring it into the oil phase at nearly the same temperature. The aqueous phase contained 2.5 %_{w/w} Tween 80 (hydrophilic surfactant), methyl paraben (0.1 %_{w/w}) and distilled water (69.9 %_{w/w}), while the oil phase contained 2.5 %_{w/w} span 20 (hydrophobic surfactant) and 25 %_{w/w} benzyl benzoate (oily active ingredient). The

obtained mixture was homogenized under high stirring intensity, using a heavy duty laboratory mixer (Model L2R, Silverson Machines Limited, Chesham Bucks, England) for 1 minute to obtain the emulsion (F1).

The gelling agents (2 %_{w/v}) were prepared by dispersing in distilled water with constant stirring at a moderate speed using a magnetic stirrer (SHC-1 Maple Scientific Instruments, Staffordshire, England) until a homogenous gel was obtained. The emulsion (F1) earlier prepared was added to the gel to obtain different gel concentrations (50 -75 %_{w/w}) of the gel in the emulgel formulations. Table I showed the details of the ingredients in the formulations. The minimum effective concentration (MEC) or minimum inhibitory concentration (MIC) was predetermined using antimicrobial assay on dermatophytes. The concentrations used were 5.0, 2.5, 1.25, 0.625, 0.3125 %_{w/w}, and 1.25 %_{w/w} was the MIC. The data are not shown in this study. When the emulsion was diluted with the gel, the concentration of the active ingredient was reduced but did not go below the MIC. At 1:1 mixture of emulsion and gel, the active ingredient reduced to 12.5 %_{w/w}; at 2:1, it reduced to 8.3, and at 3:1, it comes to 6.25 %_{w/w}.

TABLE I - The Details of gelling agents and their concentrations in the formulations

Formulation code	Gelling agents	Concentration of gelling agent (% _{w/w})	Concentration of emulsion (% _{w/w})	Dosage form
F1	-	0	100	Emulsion
F2	Carbopol	50	50	Emulgel
F3		67	33	Emulgel
F4		75	25	Emulgel
F5	<i>Dillenia</i>	50	50	Emulgel
F6		67	33	Emulgel
F7		75	25	Emulgel

Viscosity determinations for gelling agents and formulations

The viscosity of the gelling agents and formulations was measured at 2, 2.5, 4, 5, 10, 20, 50 and 100 revolutions per minute with spindle size 04 using a rotational

viscometer (Brookfield Viscometer® VT 181, Haake, Karlsruhe, Germany). About 50 g of each sample was transferred at 25 ± 2 °C into a beaker, and the viscosity was measured. Appropriate plots were prepared to describe the viscosity profiles.

pH determinations for gelling agents and formulations

The pH of the gelling agent and respective formulations was determined using Jenway model 3520 pH meter (Barloworld Scientific Ltd., Dunmox Essex CM63LB). The measurement was done in triplicate and the mean determined.

Globule size and photomicrographs of the formulations

The globule size of the internal phase of the formulations was measured using an optical microscope (Olympus Light Microscope) fitted with a camera and computer software- (Motic MC 1000, Motic Group Co.Ltd., China) for image analysis transmitted on the monitor. One hundred particles were measured from each preparation, and photomicrographs were documented.

Effect of storage on formulation appearance

The formulations were stored for 4 months at 30 ± 2 °C and observed weekly for creaming, coalescence and phase separation.

In vitro release measurements

The release measurements in 900 mL phosphate buffer (pH 7.4) was conducted in a Dissolution test apparatus using a seamless high retention cellulose dialysis tubing (Sigma Aldrich Co. St Loius, MO63176 USA) having molecular weight of 13,000 g/mol to serve as the permeation cell. The dialysis tubing was soaked in distilled water for 30 min before use, sealed at one end, and the formulations (2.0 mL) were placed inside it, while the other end was attached to the rotating paddle. The medium in the receptor compartment was maintained at 37 ± 1 °C and rotated at 100 rpm. Samples (5 mL) of the receptor compartment fluid were withdrawn at various time intervals (2, 5, 10, 15, 30, 60, 90, 120, 180, 240 min), and the percentage of benzyl benzoate released was analyzed using UV-Visible Spectrophotometer (Spectrum Lab 752s UV-VIS Spectrophotometer, China) at 256 nm. The volume withdrawn each time was replaced with drug-free receptor fluid. The cumulative percentage drug

released at various intervals of time was calculated and plotted against time.

Modeling of release profile

Data obtained from the *in vitro* release studies were fitted to various kinetic equations to determine the kinetics and mechanism of drug release from the emulgel formulations. The results of the drug release for the formulations were fitted to zero order, first order, Higuchi, Korsmeyer – Peppas and Hixson-Crowell equations. The model of best fit was identified by comparing the values of correlation coefficients. The various kinetic equations used are itemized below:

Zero-order equation (Gibaldi, Feldman, 1967)

$$Q = Q_0 + K_0 t \quad \text{Eqn.2}$$

Where Q is the amount of drug released at time t, and k_0 is the apparent dissolution rate constant or zero order release constant and Q_0 is the initial concentration of the drug in the solution resulting from a burst effect.

First-order equation

$$\ln Q = \ln Q_0 + K_1 t \quad \text{Eqn.3}$$

Where k_1 is the first order release constant, in this case the drug released at each time is proportional to the residual drug inside the dosage form.

Higuchi equation (Higuchi, 1961)

$$Q = k_H t^{\frac{1}{2}} \quad \text{Eqn. 4}$$

Where- Q is the amount of drug released at time t, and k_H is the Higuchi release constant. This is the most widely used model to describe the drug release from pharmaceutical matrices.

Korsmeyer – Peppas equation (Korsmeyer *et al.*, 1983)

$$\frac{Q_t}{Q_a} = k_k t^n \quad \text{Eqn.5}$$

Where k_k is the release rate constant which considers the structural and geometric characteristics of the tablet, and n is the diffusional exponent or release exponent, indicative of the drug release mechanism. The value of $n = 0.5$ indicates Fickian Diffusion (Higuchi Matrix), $0.5 < n < 1.0$ indicates anomalous (non-Fickian) diffusion, $n = 1.0$ indicates Case-II Transport (zero-order release) and $n > 1.0$ indicates Super Case-II transport.

Hixson - Crowell equation (Hixson, Crowell, 1931)

$$Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = k_s t \quad \text{Eqn 6}$$

where Q_0 is the initial amount of drug in the matrix tablet, Q_t is the amount of drug remaining in the pharmaceutical dosage form at time t , and k_s is a constant incorporating the surface/volume ratio.

Data presentation and analysis

The tests were conducted in triplicate, and the mean and standard deviations were determined. The similarity factor (f_2) was used to determine whether formulations prepared using *Dillenia indica* mucilage were similar to that prepared using the standard gelling agent (carbopol). Level of significance ($p \leq 0.05$) was considered significant.

RESULTS

The properties of *Dillenia indica* mucilage

The particle shape and surface morphology of *Dillenia* mucilage are shown in Figure 1 with the scanning electron micrograph. The particle shape of the mucilage is irregular, and the surface is somehow granular in outlook. The irregular shape of *Dillenia* mucilage particles is similar to that of *chrysophyllum albidum* mucilage (Ajala *et al.*, 2016). Irregularly shaped particles do not pack well, but the arrangement gives more room to the penetration of water to enhance easy dispersion and hastening of production process. In addition, irregularly shaped particles may exhibit a high specific surface area, thus increasing the number of particle-particle interactions and any associated chemical interactions. Even at lower volume fractions, higher particle roughness or shape irregularity can lead to increased viscosity as the liquid flow is deviated around them.

Some other material and physicochemical properties of *Dillenia indica* mucilage were previously reported in our study where the mucilage was used as a polymer in the preparation of microbeads (Ajala, Silva, 2020).

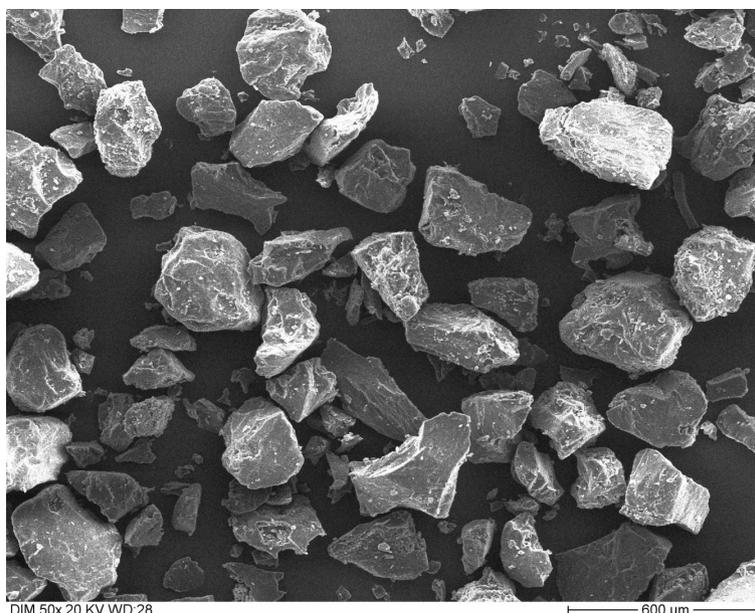


FIGURE 1 - Scanning electron micrograph (SEM) of *Dillenia indica* mucilage particles.

pH, viscosity and swelling profiles of *Dillenia* mucilage and carbopol

Gelling agents are used in emulgel formulations to improve the properties of the dosage form. From our previous study, *Dillenia indica* mucilage showed a weakly acidic pH. The carbopol -a standard gelling agent used here-has a basic pH. The pH of both gelling agents were considered acceptable for use in the formulations since the stratum corneum of the skin can accommodate pH ranges between 3 and 9 (Isa *et al.*, 2000).

The presence of friction or internal resistance within the molecules of a system occurs due to attractions between the molecules as one layer moves in relation to the next; this resistance is called viscosity (Rawlins, 2004). When viscosity is high, it means that the attractive forces which may be Vander Waals forces or dipole interactions are quite strong between the molecules; when the forces are weak, then the viscosity will be low (Rawlins, 2004). The viscosity profiles of *Dillenia* mucilage and carbopol are presented in Figure 2. The results showed that carbopol is significantly more viscous than *Dillenia* mucilage. The profiles also showed that, for the two gelling agents, the viscosity reduced as shear rate increased demonstrating pseudoplastic rheology. Since the viscosity of both gelling agents was high, it shows that strong interactions existed between the molecules of the materials. The Non-Newtonian and pseudoplastic rheological profiles of both gelling agents imply that

when used in preparing rheological pharmaceutical formulations, such as emulsions, suspensions, semi solid dosage forms and emulgels, they will offer shear thinning to the product and enhance pourability. Pseudoplasticity is the flow property of plastic dispersions of hydrocolloids (Kumar, Gupta, 2012) and it will enhance the physicochemical profiles of the emulgel formulations.

Swelling power has been described as the maximum increase in volume and weight which a material undergoes when allowed to swell freely in water. For dosage forms that require disintegration, materials with high swelling power would be expected to disintegrate faster, thus releasing the active ingredient. Swelling power usually depends on the ability of the molecules of a material to hold water through hydrogen bonding. The swelling profiles of the gelling agents as seen in Figure 3 showed that *Dillenia* has significantly higher swelling compared to carbopol. As time progressed, the swelling of *Dillenia* increased while that of carbopol reduced. The differences observed in the swelling of carbopol and *Dillenia* mucilage also indicate structural variances as the presence of a strongly bonded micellar network poses a great influence on the behaviour of pharmaceutical materials (Tang, Mitsunaga, Kawamura, 2005). The reduction in the swelling of carbopol over time may be attributed to dissolution of the particles, meanwhile, instead of dissolving; *Dillenia* mucilage maintained its swelling consistently showing that both materials have different swelling behaviour.

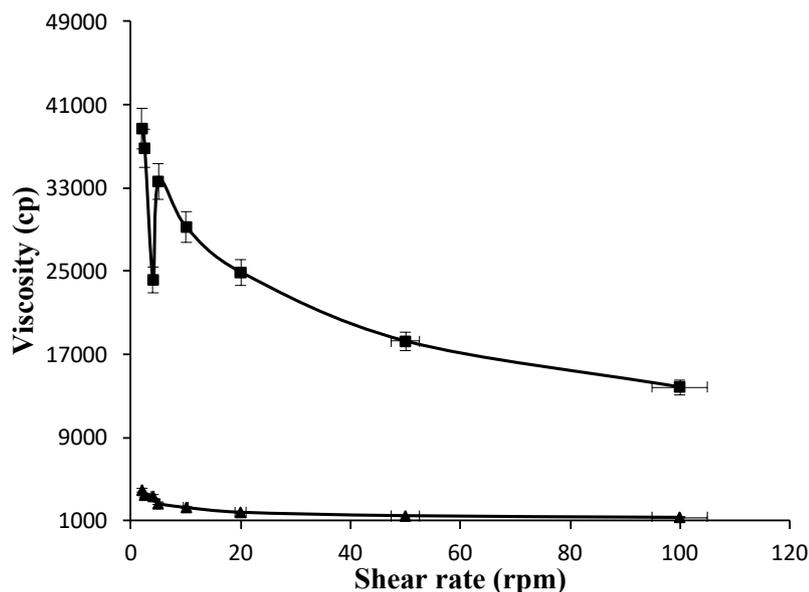


FIGURE 2 - Viscosity profiles of the gelling agents (Δ -*Dillenia indica* mucilage, \blacksquare - Carbopol).

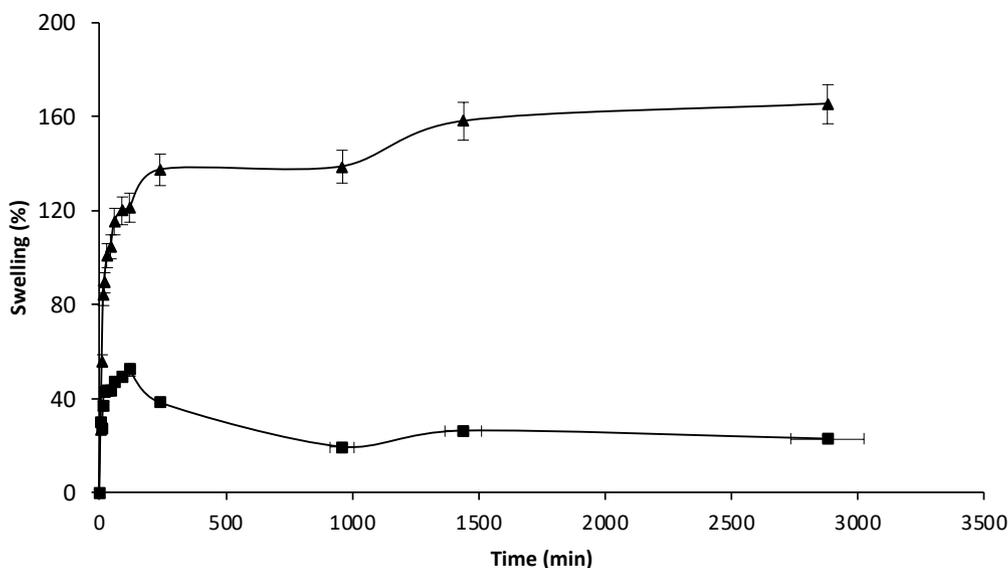


FIGURE 3 - The swelling profiles of the gelling agents (Δ -*Dillenia indica* mucilage, \blacksquare - Carbopol).

The physicochemical properties of the formulations

The formulations prepared in this study were coded F1 to F7 as presented in Table I. The globule size, viscosity, pH and colour of the formulations are presented in Table II. The formulations had globule size range between 9.763 ± 3.415 to 34.519 ± 31.381 μm . F1 which contained only emulsion without any gelling agent

had the least globule size and this was significant ($p < 0.05$) when compared with the other formulations containing the gelling agents.

Generally, the globule sizes were lower for emulgel formulations prepared with *Dillenia* mucilage (F5-7), compared to that of carbopol (F2-4). In both cases, the globule sizes increased with increase in the concentration of gelling agent. A measurement of the

size of dispersed globules in an emulgel formulation is a great tool to determining how much penetration it can offer when applied to the skin. The globule sizes of the formulations were lower than 50 μm , hence lower than that of conventional creams which are around 100 μm . Conventional creams have been reported to have poor penetration into deep skin layers, especially when loaded with drugs. The emulgel formulations will therefore be expected to have improved penetration into skin layers to effect its therapeutic efficacy. Furthermore, a previous study reported particle size of 138.8 ± 4.09 nm for optimized fisetin-loaded glycosomes gel formulation (Moolakkadath, Agili, Ahad, 2020). Imam *et al.* (2015) also investigated the effects of formulation variables on the development of risperidone proniosomal formulations as potential transdermal delivery systems. The size of the vesicles was found to range between 437.76 and 614.12 nm. The difference in the results of these studies to that obtained from our current study could be due to variance in formulation type and active drug. For example, emulgel

formulations are microparticles, while nanovesicles are nanoparticulate systems.

The viscosity of the formulations as shown in Table II was generally high, and it increased with increase in the concentration of gelling agents. In addition, the viscosity of the emulgel formulations was generally higher than that of the emulsion, and emulgel formulations containing carbopol showed significantly higher ($p < 0.05$) viscosity than *Dillenia*. The high viscosity of the formulations is advantageous in that when they are applied to the skin, they will adhere due to their pseudoplastic rheologic behaviour and this will prevent run off from the skin surface. Furthermore, the high viscosity will confer prolonged activity on the skin surface since they will cling as a film until washing off is done (Adeyeye *et al.*, 2002). In addition, the viscosity profiles of the formulations are presented in Figure 4. The viscosity reduced with increased shear rate. The formulations therefore followed the rheological pattern of the gelling agents which are also pseudoplastic and shear thinning in nature.

TABLE II - The physical properties of benzyl benzoate formulations (mean \pm SD, n=3)

Formulation code	Globule size (μm)	Viscosity (cP)	pH	Colour
F1	9.76 ± 3.42	453.3 ± 46.2	6.49 ± 0.14	White
F2	22.76 ± 23.42	2240.3 ± 80.1	7.77 ± 0.22	White
F3	34.52 ± 21.38	4666.7 ± 46.2	8.67 ± 0.15	White
F4	35.27 ± 26.91	6053.3 ± 122.2	9.08 ± 0.12	White
F5	19.79 ± 22.93	406.7 ± 11.5	5.84 ± 0.40	Off-white
F6	20.81 ± 9.74	566.7 ± 57.7	4.94 ± 0.06	Off-white
F7	22.45 ± 12.91	2880.2 ± 80.4	4.16 ± 0.07	Off-white

The pH of the formulations ranged from 4.16 - 9.08 and *Dillenia* showed least values while carbopol had higher. The emulsion (F1) was slightly acidic; emulgel formulations prepared with carbopol (F2-4) were basic,

while those prepared with *Dillenia* were slightly acidic. The formulations prepared with carbopol became more basic as the concentration of carbopol increased, while those prepared with *Dillenia* increased in acidity as the

concentration of *Dillenia* also increased. Carbopol is basic, hence its presence increased the basicity of the emulgel system.

Generally, the pH of skin is between 4 and 6 (Rippke, Schreuner, Schwanitz, 2002), which is weakly acidic. As reported in our previous study on *Dillenia* mucilage, the pH is 4.120 ± 0.181 which is within the range for

skin. With respect to pH, therefore, *Dillenia* has more compatible attribute with the skin compared to carbopol. However, because the stratum corneum has been reported to tolerate a wider range (3-9) of pH (Isa *et al.*, 2000), then the basic pH of carbopol is acceptable as well. Therefore, the basicity or acidity of all the formulations lies within the range useful for skin formulations.

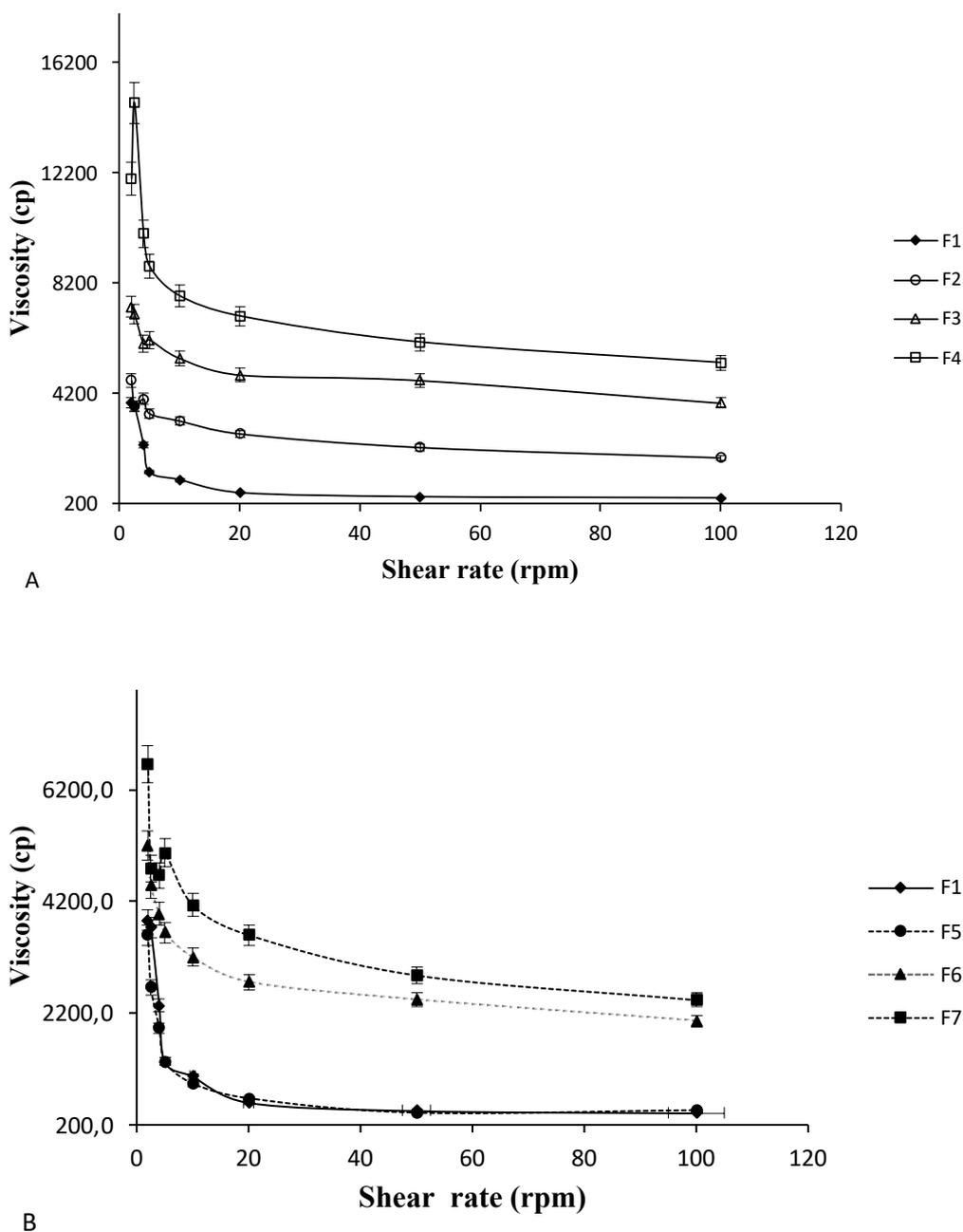


FIGURE 4 - Viscosity profiles of the emulgel formulations prepared using carbopol (A) and *Dillenia indica* mucilage (B) as gelling agents (NB: F1 is the emulsion and it contains no gel).

The determination of emulsion type, using microscopic method was done by staining with an aqueous dye and observing the globules. The photomicrographs of the formulations are presented in Figure 5. The results showed spherical globules with clear interior; the observation of globules with clear interior implied that the globules did not take up the dye. This suggests that they comprise oil dispersed in water, thus giving the formulations a

classification as being oil-in water. Generally, oil in water emulsions and emulgels are usually water-washable systems which are devoid of staining when applied on the skin, and this is considered an important quality of the formulations as well. Emulgels for dermatological use have been reported to be easily removable, greaseless and water washable; these properties are important considerations in percutaneous absorption (Stanos, 2007).

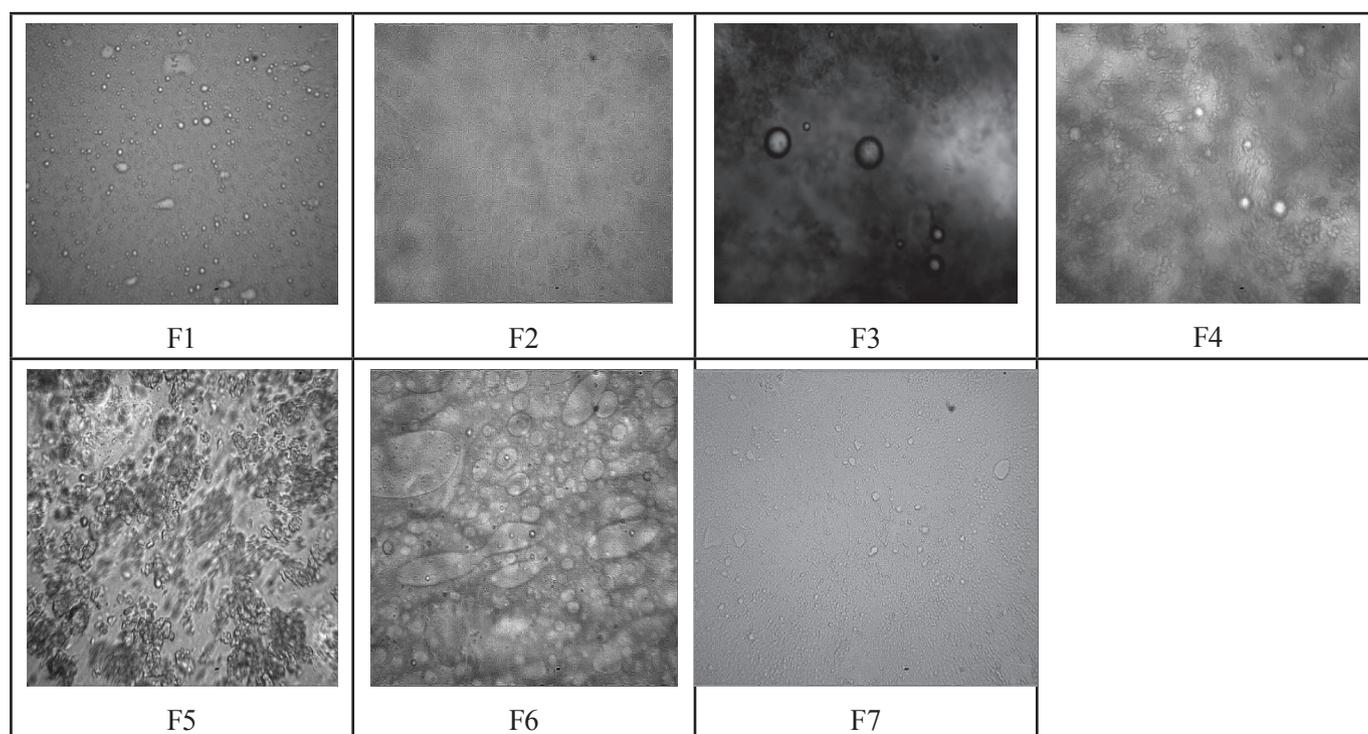


FIGURE 5 - Photomicrographs of the benzyl benzoate formulations (X100) {(F2-4, carbopol -50-75%) (F5-7, Dillenia-50-75 %; F1-0 % gel)}.

Weekly observation of the stored formulations for creaming, coalescence and phase separation showed that none of them creamed, coalesced nor had separated phases. Generally, none of the products also had offensive odour nor colour change and are thus considered acceptable. It was observed however in the photomicrographs that spherical globules were reduced in F6 compared to the others. In addition, signs of agglomeration were observed, and the microscopic structure of F6 showed disrupted outlook. An emulsion is a dynamic system which is vulnerable to

instability, such as flocculation and resultant creaming which represent potential steps towards complete coalescence of the internal phase (Reuter, Merfort, Schkemp, 2010). The addition of gelling agents to emulsions results in emulgel dosage forms which overcome the limitations of emulsions and gels to offer improved stability properties (Kapoor *et al.*, 2014). The agglomeration observed in the photomicrograph of F6 is a sign of instability, although in terms of physical appearance, the formulation was satisfactory. Generally, the formulations were found to be stable

after sixteen weeks of storage and observation, and this could be attributed to some factors. The small globule sizes of the formulations will enhance higher viscosity with consequent reduction in the rate of creaming or phase separation (Abdurahman, Rosli, 2006). This is because high viscosity also retards the movement of the dispersed droplets, thus enhancing stability (McClements, 1999). Furthermore, blends of emulsifiers were used in the preparation, and these usually produce emulsions of superior quality than single ones (Betageri, Prabhu, 2002). In general, small oil globules, high viscosity and use of a blend of emulsifiers contributed to the stability of the formulations (Huang, Kabuda, Cui, 2001).

The release properties of the formulations

The release profiles of the emulgel formulations are shown in Figure 6. The emulsion (F1) had the slowest release compared to the emulgels; this is shown by the fact that in 240 min, it has not released up to 50 % of the drug. Generally, the formulations showed controlled release profiles in the rank order of $F1 \ll F5 < F4 < F2 < F6 < F3 < F7$. The prolonged release is further confirmed by the release times (t_{80}) presented in Table III, which ranged from 112.54 to 669.24 min. Formulations prepared with carbopol showed cumulative amount released seemingly independent of the concentration of carbopol used, while formulations prepared with *Dillenia* had increased cumulative release as the amount of *Dillenia* in the preparations increased. Among formulations prepared with carbopol, F4 (75 % carbopol) showed longer release times, while F7 (75 %^{w/w} *Dillenia*) also showed longer release times among formulations prepared with *Dillenia* as gelling agent. Generally, gels have been shown to have faster release than emulsions but their inability to deliver hydrophobic drugs is a drawback. The addition of gelling agents to produce emulgels has offered the formulations longer release times with successful

delivery of the hydrophobic drug used (benzyl benzoate). Moolakkadath, Agili, Ahad, (2020) studied fisetin-loaded nanovesicles, and the optimized fisetin-loaded glycosomes formulation was converted into a Carbopol® gel matrix. The results showed that the optimized fisetin-loaded glycosomes gel formulation exhibited zero-order release kinetics. The release profiles of risperidone proniosomal formulations for transdermal delivery showed first-order kinetics with Fickian diffusion-controlled mechanism having an initial burst release phase followed by a prolonged release (Imam et al, 2015). Our study showed release kinetics optimal with Korsmeyer-Peppas model with an initial burst release in which t_{15} was less than 30 min for all formulations, but later followed by prolonged release.

Additionally, the mechanism of release was due to mass transfer following a non-Fickian anomalous diffusion. These results all showed that release kinetics vary for different formulations-gel, transdermal systems and emulgels all demonstrated varied patterns of release. It strengthens the knowledge that type of drug delivery system can be used to modify release patterns.

TABLE III - Release times for benzyl benzoate Emulgel formulations

Formulation code	Release times (min)	
	t_{50}	t_{80}
F1	278.23	669.24
F2	64.47	198.96
F3	30.39	112.54
F4	79.87	252.56
F5	50.69	139.06
F6	46.14	134.76
F7	78.19	210.96

F1 is the emulsion

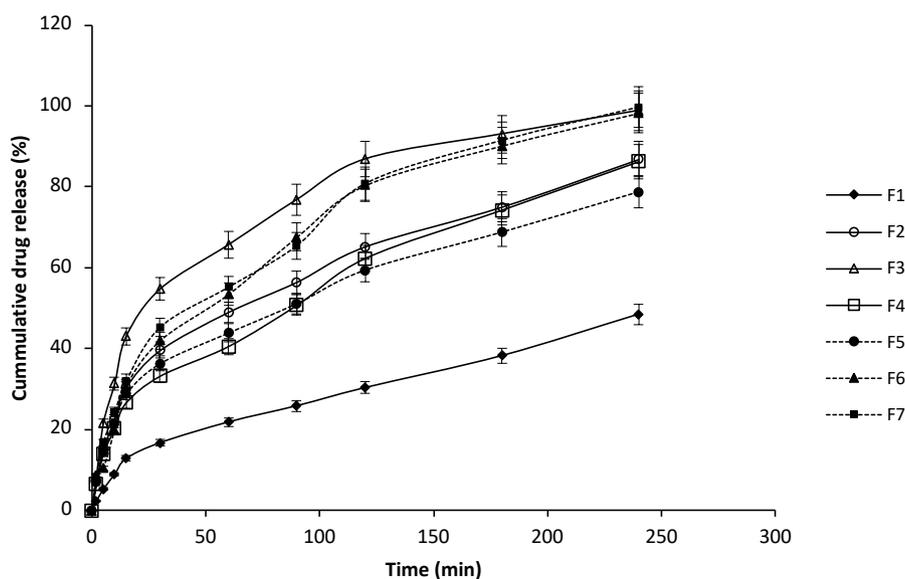


FIGURE 6 - The release profiles of benzyl benzoate from the formulations.

The kinetics of drug release from the emulgels containing the gelling agents fitted the Korsmeyer-Peppas model with r^2 ranging from 0.991-0.994 according to Table IV. The model also provides a release exponent 'n' which corresponds to the mechanism of the release. The n values obtained were 0.359-0.535. Generally, in this study, the drug release from the emulgel formulations was controlled by diffusion. The release mechanism using the n value for all the preparations therefore corresponds to mass transfer following a non-fickian anomalous diffusion in which $n < 1.0$. The kinetics of drug release is important due to

their influence on drug bioavailability, dosage intervals and occurrence of toxic or untoward side effects (Costa, Lobo, 2001). Korsmeyer-Peppas model of drug release is useful in describing release from polymeric systems (Korsmeyer *et al.*, 1983). The rate of release for the model is related to the structural and geometric properties of the drug delivery systems; in this case, the gelling agents serving as carriers. Emulgels from both gelling agents showed release kinetics which followed the same model. It further reveals the usefulness of *Dillenia* mucilage as a gelling agent which has similar properties to carbopol.

TABLE IV - Correlation coefficients obtained for benzyl benzoate emulgel formulations using different mathematical models (n=3)

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas		Hixson-Crowell
				r^2	n	
F1	0.833	0.899	0.989	0.991*	0.535	0.881
F2	0.617	0.892	0.978	0.994*	0.417	0.841
F3	0.401	0.939	0.922	0.979*	0.359	0.890
F4	0.597	0.852	0.974	0.994*	0.408	0.796
F5	0.708	0.974	0.987	0.989*	0.466	0.954
F6	0.661	0.954	0.985	0.993*	0.439	0.928
F7	0.746	0.923	0.993	0.994*	0.474	0.893

*Highest correlation coefficient of drug release kinetics

Dillenia offered release properties dependent of concentration of gelling agent, while carbopol seems independent of concentration, but optimal at 67 %. The concentration of *Dillenia* mucilage can thus be used to control the release properties of benzyl benzoate in emulgel formulations, but not that of carbopol. *Dillenia* mucilage also has significantly higher swelling compared to carbopol. As time progressed, the swelling of *Dillenia* increased while that of carbopol reduced. This showed that *Dillenia* has superior swelling properties and may thus strengthen the gel network within the formulation, thus enhancing formulation stability compared to carbopol which may go into solution leading to product breakdown with time.

The similarity of release profiles between the emulgel formulations is presented in Table V. The emulgels prepared with carbopol showed similarity of release profiles to those prepared with *Dillenia*, None of the emulgel formulations showed similarity to F1 which is the emulsion. Highest similarity was observed between F4 prepared with 75 % carbopol and F5 prepared with 50 % *Dillenia*. The similarity factor, f_2 is a measure of similarity between pairs of dissolution profiles. Values of $f_2 > 50$ (50 - 100) indicate resemblance or uniformity of the two dissolution profiles and values of 100 indicate same profiles. The similarity of release profiles between emulgels prepared with carbopol and *Dillenia* mucilage further strengthens the usage of *Dillenia* as gelling agent.

TABLE V - Similarity factors for preparations that showed similar release profiles

Formulation Pairs compared	Similarity Factor (f_2)
F2/F5	67.44
F2/F6	53.74
F2/F7	52.79
F3/F6	52.63
F3/F7	56.96
F4/F5	73.00

f_2 between 50-100 are similar

CONCLUSION

The formulations had pH within the range useful for skin application; the pseudoplastic rheological profiles offered by the emulgels would promote skin adherence while enhancing product pourability. Furthermore, both gelling agents offered longer release times which would prolong the activity of benzyl benzoate at application site. The formulations maintained also stability within the study period. *Dillenia indica* mucilage produced emulgel formulations similar to that obtained, using carbopol with f_2 values greater than 50. Thus, the improved property of emulgel over emulsion and gels was obtained using the gelling agents. *Dillenia indica* mucilage can therefore be improved for use as gelling agent in emulgel formulations.

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