Evaluation of *Dacryodes edulis* (Burseraceae) exudate as a binding agent in paracetamol matrix tablet formulation.

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ABSTRACT

The binding ability of the stem bark exudate of *Dacryodes edulis* (Buseraceae) in paracetamol matrix tablet formulation was compared with that of Eudragit L-100. Crude exudates were purified by differential precipitation with water in acetone and petroleum ether and air-dried. Varying concentrations (1-10 %w/v) of the purified exudate or Eudragit L-100 were dissolved in acetone and used to form paracetamol matrix granules while 15 % w/v maize starch was used to form conventional granules by wet granulation. Drug excipient compatibility was carried out and the granules compressed into tablets. Tablet properties were evaluated and the data analyzed statistically using the student t-test ($p < 0.05$). Results showed a 71 % yield of the purified exudate. The exudate functioned perfectly as binder in the formulation of tablets at concentrations > 2.5 %w/v and compared favourably with Eudragit L-100. Tablets formed did not disintegrate within 15 min except for those formed with maize starch mucilage. The dissolution data fitted into the Higuchi equation with r^2-values ≥ 0.95. *Dacroydes edulis* exudate extended the release profile of paracetamol up to 70 % within 5 h.

Keywords: *Dacroydes edulis*, exudate, binder, Eudragit L-100, tablets

INTRODUCTION

An excipient is a natural or synthetic inert substance formulated alongside the active ingredient of a medicament intended for some specific functions such as stabilization, bulking up solid dosage formulation that contain potent active ingredients (i.e. fillers or diluents), conferring a therapeutic enhancement on the final dosage form, as binders, disintegrants or as lubricants to assist the flow properties of particulate systems [1, 2]. Substances used as pharmaceutical excipients are often assessed from studies carried out on their physicochemical characteristics. Material properties of drugs or excipients are evaluated from their behavioral characterization when formulated into a specific dosage form. Binders are usually included in tablet formulation to impart plasticity and hence enhance inter-particulate bonding strength within the compact [3]. When employed at optimal amounts, binders hold the ingredients in a tablet together and ensure that tablets and granules can be formed with an acceptable mechanical strength. In addition, binders act as adhesives to bind powders together and form granules with better flow properties [4]. Synthetic polymers such as polyvinylpyrrolidone, methylcellulose and carboxymethyl cellulose have been used extensively as excipients in the formulation of solid dosage forms as binders. However the high cost of these polymers which are often not locally available makes manufacturing of pharmaceuticals very expensive.

In recent times, emphasis has increasingly shifted to the extraction and development of natural products as pharmaceutical excipients in the formulation of various dosage forms. Natural products are cheap, locally sourced and readily available. They do not require sophisticated and expensive techniques for extraction. Above all, they are inert and biocompatible with drugs and bioactive substances of natural origin. Naturally occurring polysaccharides or gums which are obtained from woody and non-woody plant parts such as *Cissus populnea* have been investigated earlier as binders in pharmaceutical formulation of solid dosage

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forms and they have demonstrated potential applications as excipients [5]. *Dacryodes edulis*, commonly known as pear, is a medium sized evergreen tree grown in the rural tropical communities by peasant farmers for its fruits. It grows up to 18 m in height and exudes an odouriferous gummy substance from injured or excised portions of stem [6]. The objective of the present investigation was to explore the potential application of the exudates obtained from *Dacryodes edulis* as a binder in the formulation of matrix granules. The outcome of this investigation will be the identification of a potential substitute for the water insoluble polymers used in the formulation of matrix tablets for controlled release delivery systems of drugs.

EXPERIMENTAL

Materials

Dacryodes edulis (Family Bursaeraceae) tears/exudate was obtained from incisions made on tapped trees located at the Nigerian Institute for Oil Palm Research (NIFOR), Edo State, Nigeria. Paracetamol powder was obtained from Halewood Chemicals, UK and was used in this study as the drug model. Eudragit L-100 (Rohm GmbH & Co. KG, Darmstadt, Germany) was used in the study as a standard polymeric substance used in the formulation of matrix granules for modified release. Other reagents employed in the study were of analytical grade.

Methods

Collection and purification of *Dacryodes edulis* tears/exudate

The tears/exudate, an odoriferous gummy substance, was obtained as nodules and tears from tree trunks by making incisions and bleeding the trees over three weeks; a process known as tapping. Extraneous matter was removed by hand from the crude exudate prior to hardening the exudate by air drying for seven days. The dried exudate (300 g) was weighed into a clean stainless steel jar and dissolved completely in 400 ml of acetone. The solution was strained to remove any undissolved materials. The resulting solution was precipitated with excess water, and the precipitated exudate was scooped out and washed with more water. Further purification was carried out by defatting the exudate with petroleum ether and precipitating with water. The resulting mass was washed with excess water and air dried for 2 weeks at room temperature and the percentage yield of the pure exudate calculated.

Physicochemical characterization of the purified exudate

Organoleptic properties: The texture, colour and odour of the exudate were noted.

Solubility: The solubility profile of a 100 mg quantity of the purified exudate was determined in 2 ml of water, acetone, chloroform and ethanol at ambient temperature.

Solid state characterization of the purified exudate

DSC characterization of the purified exudate was carried out using the Netzsch DSC 204F1 Phoenix® apparatus (Netzsch, Germany). Four mg of the sample was weighed into an aluminium pan. The seal was pierced and calibration of the calorimeter was done with indium and the purge gas was nitrogen. The sample was heated at the rate of 10 °C per min from 30 to 350 °C under nitrogen at a flow rate of 70 ml/min. FTIR analysis of the sample was done using a Fourier Transform Infrared Spectrophotometer (Spectrum BX, Perkin Elmer, England) on a KBr disc at a range of 4000 - 1000 cm^{-1}.

Preparation of binding solutions

Varying concentrations (1, 2.5, 7.5 and 10 % w/v) of binder solutions of *Dacroydes edulis* and Eudragit L-100 were prepared by dissolving the required amounts of binder in 20 ml of acetone and allowing the mixture to stand overnight to form a solution. The maize starch mucilage (15 % w/v) was prepared by dispersing 15 g of maize starch powder in 20 ml of water in a beaker and making it up to 100 ml with sufficient boiled water. The mixture formed was then stirred into a gel-like mucilage.

Granulation

The wet granulation method of massing and screening was used in preparing all the batches of paracetamol granules using the calculations shown in Table 1. Nine batches of granules (E1-E9) were prepared consisting of four batches of test binder *Dacryodes edulis* (E1-E4), four batches of Eudragit L-100 (E5-E8) and one batch (E9) of maize starch mucilage.

Paracetamol powder and lactose were weighed into a mixer and dry mixed for 5 min. Sufficient quantities of the binder solution or mucilage required to form a wet mass was gradually added to the dry powder mix. The wet mass was passed through a 2.80 mm mesh screen and the resulting granules air dried (batches E1-E8) or in the case of batch E9 dried at 60 ºC for 30 min in a hot air oven (Gallenkamp, UK). The dry granules were rescreened through a 710 µm aperture sieve to obtain the final granules. The calculated amounts of lubricant were weighed and added to the granules in geometric proportion and mixed vigorously. Batches of the granules were compressed into tablets using a single punch tableting machine (F-3 Manesty Machines, UK) at a compression pressure of 30 arbitrary units. The die volume was adjusted to compress tablets of uniform weight by using granules weighing 555 mg. The tablets made were then kept in air-tight containers and stored in a desiccator until evaluation.

Table 1: Formula of prepared paracetamol granules and tablets

Ingredients	Quantity/Tablet	Quantity/Batch
Paracetamol	500 mg	50 g
Lactose	50 mg	5 g
Binder solution*	q.s	q.s
Talc	1 % w/w	1 % w/w

*Binder solution, *Dacroydes edulis* or Eudragit L-100 (1, 2.5, 7.5 and 10 % w/w) or maize starch BP (15 % w/w)

Compatibility studies

DSC and FTIR compatibility studies were carried out on the tablet granules of *D. edulis* exudate and paracetamol powder.

Characterization of tablets [7].

Uniformity of weight: The individual weights of 20 tablets from each batch was determined using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed.

Hardness test: The hardness of each of ten tablets per batch was determined using a hardness tester (Campbell Electronics, Model HT-30/50, India). The mean hardness was calculated.

Friability test: The weight of ten tablets was determined on the electronic balance. The tablets were then placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm. After 4 min, the tablets were reweighed. The weight was then recorded and friability calculated as percentage loss in weight.

Disintegration time: The disintegration times of six tablets per batch were determined in distilled water at 37 ± 0.5 ºC using the BP disintegration tester (MK IV, Manesty Machines, UK).

Dissolution studies: The dissolution profiles of the paracetamol matrix tablets were determined for batches E2-E4 and E6-E9 using the BP paddle method. (Caleva ST7, UK). The test was carried out for 60 min with batch E9 tablets and 6 h for the other batches. Dissolution media comprised 900 ml of 0.1 N HCl solution for the first 2 h and phosphate buffer solution pH 7.4 for the subsequent 4 h. The dissolution medium was thermostated at 37 ± 0.5 °C and the apparatus operated at speed of 50 rpm. Aliquots of 5 ml were withdrawn at predetermined intervals and

replaced with equivalent volumes of fresh dissolution medium maintained (37 ± 0.5 °C). The samples were filtered and diluted serially with the dissolution medium. The absorbances of the resulting solutions were measured at the λmax of 244 nm on a UV-Vis spectrophotometer (T70, PG Instruments Ltd, UK). The concentration and percentage of drug released at each time interval was determined from the standard calibration plot obtained using pure paracetamol. Triplicate determinations were carried out.

Release kinetics: Data from the dissolution studies was fitted into different equations to determine the release kinetics of paracetamol from the matrix tablets. The kinetic equations used were zero order, first order, Higuchi and Korsmeyer-Peppas models [8,9].

Statistical analysis: All data obtained were subjected to student t-test ($p < 0.05$) to test for significance of difference using GraphPad InStat software version 3.10.

RESULTS AND DISCUSSION

Physical properties of *Dacroydes edulis* purified exudate

The purified exudate of *Dacroydes edulis* was colourless and transparent, aromatic in odour and smooth in texture against its dark-brown, wet and sticky nature on collection. It was insoluble in water but soluble in acetone, chloroform and ethanol indicating a hydrophobic nature. The percentage yield obtained from the purification process was 71.77 %.

The DSC characterisation of the purified exudate (Figure 1 (a)) revealed a broad trough between 50-100 °C followed by a primary degradation phase between 150-200 °C. A secondary degradation phase was observed from 200 °C leading to the formation of product with exothermic transition above 350 °C. The broad trough between 50-100 °C suggests that the purified exudate is an amorphous compound with no definite melting point. The trough is also indicative of the presence of two or more complex constituents in the purified exudate. The FTIR analysis of the purified exudate (Figure 2 (a)) showed the characteristic absorption spectra for -OH or -NH (3400 - 3550 cm^{-1}), CH stretching of CH_2 and CH_3 (2924 cm^{-1}), C≡C or C≡N triple bond (2500-2100 cm^{-1}), carboxylic acid C=O stretch (1730 cm^{-1}), H-O-H bending of absorbed water (1648 cm^{-1}), carbonyl stretching with aromatic ring (1634 cm^{-1}) and CH_2 bending (1430 cm^{-1}). The absorption bands appearing between 1000 and 1200 cm^{-1} indicate CO stretching of ether linkage (1250 cm^{-1}) COC antisymmetric bridge stretching (1166 cm^{-1}), and CO symmetric stretching of a primary alcohol (1062 cm^{-1}). These absorption bands further confirms the presence of many compounds in the exudate such as alcohols, carboxylic acids, carbonyl compounds and ethers. Previous studies on the possible phytochemical composition of the exudate confirms that it contains proteins, fats or oils and carbohydrates [10-12].

Compatibility studies

Thermal analysis: Figure 1 shows the DSC thermograms of pure paracetamol powder (b) and the paracetamol granules prepared from *D. edulis* as the binder (c). Paracetamol thermogram shows a sharp endothermic peak, corresponding to its melting point (169 °C). This sharp peak which appears as a spike is indicative of the purity and crystallinity of paracetamol. On the other hand, the thermogram of the granules containing *D. edulis* as excipient and paracetamol together (c) showed two sharp peaks and one broad endothermic peak with the characteristic peak of pure paracetamol. The broad trough manifested by the sample could be the result of decomposition.

FTIR: The FTIR spectrum of pure paracetamol (Figure 2 (b)) powder showed characteristic peaks at 1227.00 cm^{-1}, 1636.42 cm^{-1} and 3171.00 cm^{-1}. These peaks observed for paracetamol remained unchanged when compared with the spectral data of the granules (Figure 2 (c)). This observation ruled out the possibility of chemical interaction and complex formation between paracetamol and *D. edulis* excipient during the mixing process.

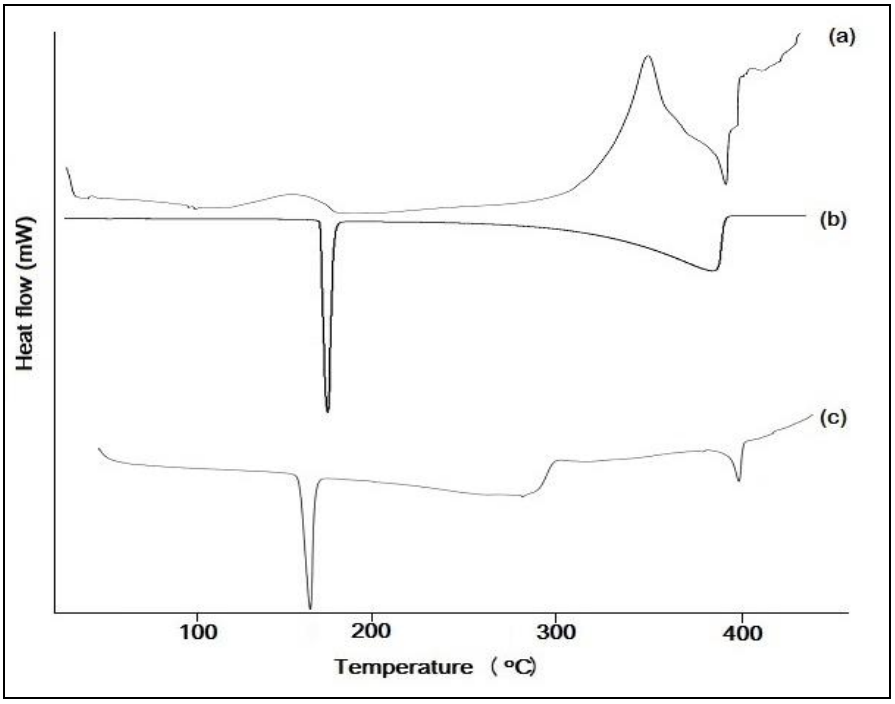

Figure 1: DSC of (a) *Dacroydes edulis* purified exudate, (b) paracetamol and (c) paracetamol granules prepared with *Dacroydes edulis* purified exudate

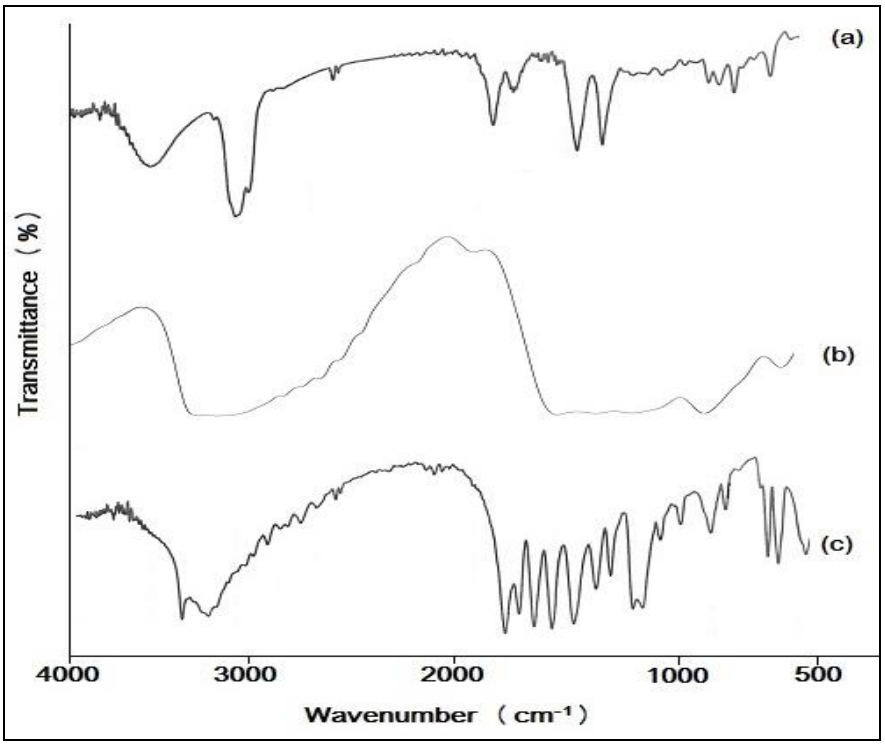

Figure 2: FTIR of (a) *Dacroydes edulis* purified exudate, (b) paracetamol and (c) paracetamol granules prepared with *Dacroydes edulis* purified exudate

Tablet properties

Table 3 shows the mean weight of the various batches of the matrix tablets prepared. The weights of all the tablets complied with the British Pharmacopoeia (2003) specifications for weight uniformity [7].

The hardness test is not an official test. However, a minimum hardness of 4 kp is

generally considered desirable [13]. From the results in Table 3, only batches E1 and E2 exhibited unsatisfactory hardness, having values of 2.35 and 3.87 kp, respectively. An increase in tablet hardness was observed with increase in binder concentrations. This increase in hardness might be due to the adhesive nature of the binder, leading to increased bond formation between the granules as a result of formation of plastic and elastic deformation and asperity melting of the particles during compaction [14]. Binders also promote plastic deformation of particles, thereby increasing the area of contact for interparticulate bonding [15] and subsequently leading to the formation of more solid bonds in the tablet.

The friability values of the matrix tablets are also shown in Table 3. Five (E3, E4, E7, E8 and E9) out of the nine batches met had acceptable friability values (< 1%) for tablets. The friability values of the tablets decreased with increasing binder concentrations. This was expected since like hardness, friability is dependent on interparticulate bonding and bridges in tablets [16]. Increased binder concentration will lead to a reduction in the size of the capillary spaces between the particles [17] by filling up of the interparticulate spaces, thereby increasing the area of contact between the particles leading to the formation of additional solid bonds, eventually confering resistance to tablet fracture and abrasion.

Table 3: Physicochemical characteristics of paracetamol tablet batches

Binder	Batch	Binder Concentration (% w/w)	Mean Weight (g) (SD)	Hardness (kp) (SD)	Friability (%)	Disintegration Time (min) (SD)
Dacroydes edulis	E1	1	0.549 (0.01)	2.35 (0.50)	38	8:34 (0.62)
	E2	2.5	0.550 (0.01)	3.87 (0.09)	9.8	31:29 (0.25)
	E3	7.5	0.540 (0.01)	8.40 (0.10)	0.9	146 (1.11)
	E4	10	0.545 (0.08)	10.55 (0.12)	0.8	169 (1.50)
Eudragit L-100	E5	1	0.548 (0.03)	7.91 (0.11)	2.2	3:36 (0.81)
	E6	2.5	0.556 (0.01)	7.92 (0.11)	1.7	16:54 (0.70)
	E7	7.5	0.555 (0.01)	10.82 (0.04)	0.9	104 (1.17)
	E8	10	0.550 (0.01)	11.24 (0.04)	0.8	175 (1.25)
Maize starch BP	E9	15	0.549 (0.011)	5.60 (0.22)	0.8	0.75 (1.91)

SD = Standard deviation

Most of the formulated tablet batches did not disintegrate within 15 min except for batches E1, E5 and E9, thus indicating that the tablets were matrix tablets. The results showed an increase in the disintegration time with increase in binder concentration. The reduction of capillary spaces between the particles, coupled with the hydrophobic nature of the binder and the consolidation of the formed matrix structure of the tablet as a result of the increase in the concentration of binder is expected to reduce the penetration of water into the tablet, thus leading to longer disintegration times. Moreover, matrix tablets are not expected to disintegrate over a long time because of their matrix structure.

Figure 4 show the release profiles of paracetamol from the selected batches of tablets. From the dissolution plots, it was observed that the matrix tablets formulated from batches with higher binder concentrations showed a slower release of the drug especially when compared with batch E9, the conventional tablet, with 100 % drug release in less than 1 h. A comparison of the empirical release data obtained from these plots are presented in Table 4. It can be observed that batches E4 and E8 with the highest amount of binders gave the best results in terms of delayed release of the drug and had similar release profiles. These two formulations release 70 % of the drug over a period of 5 h, an indication of delayed or prolonged release. The results of the release mechanism and kinetics of the drugs from the matrix tablets is shown in Table 5. Drug release was generally most consistent with the Higuchi model ($r^2 \geq 0.95$) indicating that drug release was diffusion mediated [18].

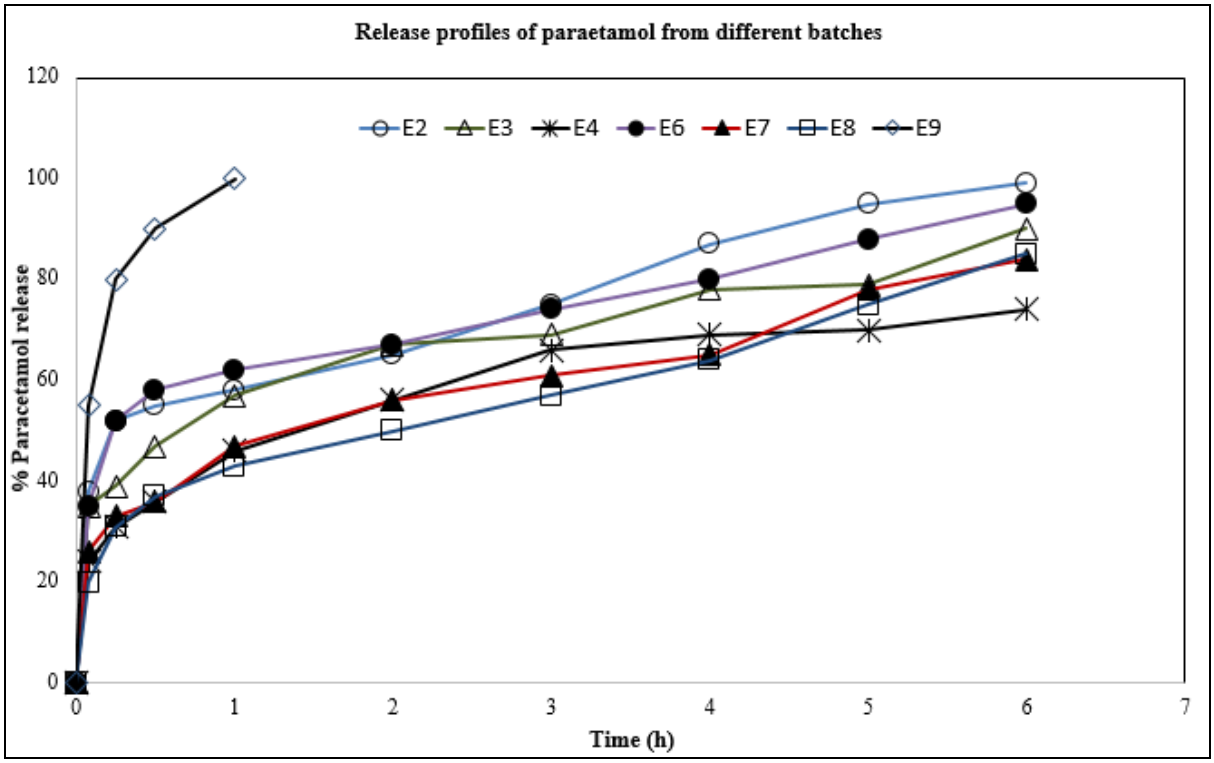

Figure 4: Release profiles of paracetamol from different tablet batches.

E2 = *D. edulis* (2.5 % w/w), E3 = *D. edulis* (7.5 % w/w), E4 = *D. edulis* (10 % w/w), E6 = Eudragit L-100 (2.5 % w/w), E7 = Eudragit L-100 (7.5 % w/w), E8 = Eudragit L-100 (10 % w/w), E9 = Maize starch BP (15 % w/w).

Table 4: A comparison of the empirical release data of paracetamol tablets

Parameter Evaluated	Batch						
	E2	E3	E4	E6	E7	E8	E9
m_∞ (%)	99	90	74	95	84	85	100
$t_{50\%}$ (h)	0.25	1	2	0.25	1	2	0.08
$t_{70\%}$ (h)	2.5	3	5	3	4	5	0.25

Table 5: Correlation coefficient (r^2) of the dissolution studies

Batch	Release Kinetic				
	Zero order	First order	Higuchi	Korsmeyer-Peppas	
		r^2			N
E2	0.7676	0.7676	0.8629	0.8907	22.452
E3	0.7631	0.7446	0.9530	0.9095	18.434
E4	0.8104	0.7994	0.9563	0.7508	7.051
E6	0.6953	0.8793	0.9083	0.8538	24.315
E7	0.8374	0.8374	0.9576	0.9492	12.919
E8	0.8689	0.8219	0.9578	0.8843	10.912
E9	0.6135	0.6127	0.9988	0.8710	16.597

CONCLUSION

Paracetamol tablets formulated with *Dacroydes edulis* exudate as binder exhibited extended release of paracetamol with formulation E4 releasing 70 % of the drug within 5 h. This result compared favourably with the standard Eudragit L-100 frequently employed in controlled release formulations. As such *D. edulis* exudate can be used in the

formulation of a sustained release tablet which will enhance patient compliance by reducing the frequency of administration of the drug.

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