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Matrix forming excipients from natural origin for controlled release matrix type tablets

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Since excipients from renewable sources are attractive due to their sustainable mass production, this study aimed at investigating the use of gel and whole leaf materials from Aloe vera and Aloe ferox to produce controlled release mini-matrix type tablets. The flow properties of the aloe materials were determined by means of different tests. Matrix type tablets manufactured from each aloe material individually and in combination with other polymers were evaluated in terms of their physical characteristics, mucoadhesive properties, swelling behavior and drug release kinetics. The drug release from some of the formulations was sustained over an extended period of time and two of the formulations approached zero-order kinetics. This study confirmed that A. vera and A. ferox leaf materials showed high potential to be used as excipients in modified release matrix-type tablets prepared by direct compression.

Key words: Aloe gel – Aloe whole leaf – Controlled release – Powder flow – Matrix type tablet – Swelling – Mucoadhesiveness.

Disadvantages of conventional immediate release tablets include fluctuations of drug plasma levels over successive administrations and forgotten doses may result in larger fluctuations that increase the chance of side effects, emergence of resistance and/or treatment failure [1]. A modified release drug delivery system is capable of delivering the drug to the target site at a rate that is required by the therapeutic needs of the patient for the specified period of treatment [2]. A controlled release drug delivery system is one that specifically controls the release of the drug in such a way that constant drug levels are maintained in the systemic blood circulation, which usually requires delivery of the maintenance dose at a rate governed by zero-order kinetics [3, 4]. The matrix-type tablet is considered as one of the most preferred controlled release dosage forms because they can be manufactured by cost-effective methods such as direct compression on a tablet press and the risk of dose-dumping is low [5]. Mini-monolithic matrices are an attractive alternative for pellets or beads to be loaded into a single hard gelatin capsule to produce a multiple-unit dosage form with several advantages over single-unit dosage forms [6, 7].

Polymers used in dosage form design are often classified as synthetic, semi-synthetic and natural polymers [8]. Polysaccharides obtained from plant materials are often extracted from either mucilage (also referred to as gel) or gum. Many succulent plants such as those from the genus Aloe store water in the form of mucilage or gel-containing tissue in their leaves to survive under arid conditions [9].

Aloe ferox is a robust, single stemmed aloe growing up to two meters high, with broad dull green to grayish-green leaves. Although it is indigenous to South Africa with a relatively wide distribution throughout the country, it is more abundant in the Eastern and Western Cape provinces. *Aloe vera* (also known as *Aloe barbadensis* Mill.) is a xerophytic plant used over many centuries for its medicinal properties and grows in nutritionally poor soils. Since *A. vera* has naturalized throughout the warm regions around the world, it is difficult to correctly establish its origin [10]. The leaves of aloe plants can be divided into three sections namely the green rind or epidermis, the aloin-rich bitter sap or exudate and the inner, translucent and fleshy gel or inner pulp. The latter section is usually rich in amino acids, minerals, vitamins, polysaccharides, enzymes and lipids [11]. Acetylated polymannan (also referred to as acemannan or aloverose) is considered the main functional component of *A. vera* gel, which is a polysaccharide consisting of a long chain of acetylated mannose monomers [12-14].

Since polysaccharide rich aloe leaf materials showed potential as excipients for the production of controlled release monolithic dosage forms [15, 16], this study investigated different aspects of dried gel and whole leaf materials from two different aloe species alone and in combination with other polymers as matrix forming agents.

I. MATERIALS AND METHODS

1. Collection and preparation of aloe materials

A. ferox whole leaves and leaf fillets were donated by Organic Aloe (Albertinia, South Africa). *A. vera* whole leaf extract and gel powders were generous gifts from the International Aloe Science Council (IASC051309, United States) and *A. vera* dehydrated gel or Daltonmax 700 was donated by Improve USA, Inc. (United States).

A. ferox leaves were laterally cut on both the upper and lower sides to completely isolate the gel fillet or pulp inside the leaves. Thereafter, the gel fillets were rinsed with warm water to remove any exudate, liquidized in a kitchen blender, frozen and lyophilized (Virtis benchtop K, United States) to produce *A. ferox* gel powder. For the *A. ferox* whole leaf extract material, the leaves, including the gel and rind, but without exudate that was removed by means of rinsing in water, were liquidized in a kitchen blender, frozen and lyophilized. Each freeze dried powder was passed through a 250 μm sieve and stored in airtight containers.

2. Nuclear magnetic resonance fingerprinting of aloe materials

To record ^{1}H-NMR spectra of the aloe materials, approximately 50 mg of each of the dried aloe leaf materials and approximately 5 mg internal standard (nicotinic acid amide) were dissolved in 1 mL D_2O. The ^{1}H-NMR spectra of the aloe solutions were recorded with an Avance 300 MHz NMR spectrometer (Bruker, Karlsruhe, Germany). The resultant ^{1}H-NMR spectra were used to identify and quantify marker molecules (e.g. aloeverose or acemannan, glucose and whole leaf marker) for the *A. vera* materials and to fingerprint the *A. ferox* materials [15].

3. Powder flow properties

The flow properties of the following powders were tested: *A. vera* gel (AVG), *A. vera* whole leaf extract (AVWL), *A. vera* dehydrated gel (Daltonmax700 or AVDG), *A. ferox* gel (AFG), *A. ferox* whole

leaf extract (AFWL), Carbopol (CBPL) and hydroxypropyl methyl cellulose (HPMC) as well as combinations of each of the aloe materials with CBPL and HPMC in three different ratios (i.e. 25:75, 50:50, 75:25). The bulk and tapped densities of the powders were determined to calculate Carr's index values as well as Hausner ratio values and the angle of repose values were measured to characterize the powders in terms of their flow properties.

3.1. Bulk and tapped powder densities

All bulk and tapped density tests were conducted using a mass of 33.3 g of each powder, which was poured into a 250 mL graduated glass measuring cylinder. The initial volume (V_0) of the powder was recorded and the cylinder was placed in an auto-tap apparatus and the volume of the powder was recorded again after 2500 taps (V_{2500}). The bulk density (ρ_{bulk}) was calculated as the ratio of the powder weight (m) to the initial powder volume (V_0) as described by the following equation [17]:

$$\rho_{bulk} = m/V_0 \quad \textbf{Eq. 1}$$

The tapped density was calculated as the ratio of powder weight (m) to the final volume (V_{2500}) of powder after tapping as described by the following equation:

$$\rho_{tap} = m/V_{2500} \quad \textbf{Eq. 2}$$

The bulk and tapped densities of each material were measured in triplicate to obtain the mean and standard deviation values.

3.2. Carr's index and Hausner ratio values

Carr's index (or percentage compressibility) and Hausner ratio values were calculated using the following equations [18]:

$$\text{Carr's index} = (\rho_{bulk} - \rho_{tap})/\rho_{bulk} \quad \textbf{Eq. 3}$$

$$\text{Hausner ratio} = \rho_{tap}/\rho_{bulk} \quad \textbf{Eq. 4}$$

3.3. Angle of repose

A quantity of each powder (33.3 g) was poured through a funnel placed at a fixed height (7 cm from the surface) to form a powder cone or heap for which the height and base diameter were measured. These values were used to calculate the angle of repose by means of the following equation:

$$\text{Tan}\theta = T/A \quad \textbf{Eq. 5}$$

where T is the transverse (height) and A is the adjacent (radius) sides of the angle of repose (θ). The angle of repose of each material was measured in triplicate to obtain the mean and standard deviation values.

4. Manufacture and evaluation of mini-matrix type tablets

4.1. Composition of the mini-matrix type tablets

The model drugs for this investigation that were included in the mini-matrix type tablets were: a freely soluble drug, diltiazem [(2S,3S)-3-acetyloxy-5-[2-dimethyl-amino]-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one hydrochloride] (particle size: 161 μm) and a poorly soluble drug, ibuprofen [2-(4-isobutylphenyl)-propionic acid] (particle size: 28 μm).

The same powders and combinations of powders as described for the powder flow property measurements (refer to 2.3) were used in the formulations of the mini-matrix type tablets, which each included ibuprofen or diltiazem as a model drug compound. These formulations were prepared by mixing the ingredients for direct compression, however, the aloe materials with poor flow properties were dry granulated first and then compressed with 6 mm concave punches on a multi-station rotary press (Cadmach CM 03-16). This relatively small tablet diameter was chosen to produce matrix type tablets that can be loaded into size 0 hard gelatin capsules to produce mini-tablet-in-capsule systems [19]. Only those powder formulations that showed compressibility into acceptable tablets, in other words those that did not laminate or cap or stick to the punches were further investigated, which constituted a total of 25 formulations. The composition of these formulations that compressed successfully into mini-matrix type tablets (F1 - F25) and that were investigated further is shown in *Table I*. These mini-matrix type tablets were characterized in terms of their physical properties, mucoadhesive properties, swelling behavior and dissolution kinetics.

4.2 Weight variation

The weight variation test was conducted by weighing 20 randomly selected mini-matrix type tablets from each of the final 25 formulations individually and comparing the individual weights to the average weight. For tablets with an average weight < 0.08 g, the specification of weight variation is that every tablet's weight should be within 10 % of the average weight [20].

4.3. Hardness and friability

The Erkewa hardness tester was used to determine the hardness of 10 randomly selected mini-matrix type tablets form each formulation. Each selected tablet was placed between two anvils, force was applied and the crushing strength was recorded.

Friability was tested using the Erkewa friabilator by randomly selecting 10 mini-matrix type tablets from each formulation, which were consequently weighed together (= weight before) and placed in the plastic chamber which then revolved at 25 rpm for 4 min, dropping the tablets at a distance of about 12 cm with each revolution. The mini-matrices were then brushed lightly to get rid of dust and weighed again (= weight after). The percentage friability was determined from

Table I - Composition of the different mini-matrix type tablet formulations (F1-25) that were successfully produced by direct compression.

Formulation	Ingredients*	Quantity (%)
F1	AVG:diltiazem	81.2:18.8
F2	AVG:ibuprofen	81.2:18.8
F3	AVWL:ibuprofen	81.2:18.8
F4	CBPL:diltiazem	81.2:18.8
F5	CBPL:ibuprofen	81.2:18.8
F6	HPMC:ibuprofen	81.2:18.8
F7	AFG:CBPL:diltiazem	40.6:40.6:18.8
F8	AFG:CBPL:diltiazem	20.3:60.9:18.8
F9	AFG:CBPL:ibuprofen	40.6:40.6:18.8
F10	AFG:CBPL:ibuprofen	20.3:60.9:18.8
F11	AVDG:CBPL:diltiazem	40.6:40.6:18.8
F12	AVDG:CBPL:diltiazem	20.3:60.9:18.8
F13	AVDG:CBPL:ibuprofen	20.3:60.9:18.8
F14	AVDG:CBPL:ibuprofen	40.6:40.6:18.8
F15	AVDG:HPMC:diltiazem	20.3:60.9:18.8
F16	AVG:CBPL:diltiazem	40.6:40.6:18.8
F17	AVG:CBPL:diltiazem	20.3:60.9:18.8
F18	AVG:CBPL:ibuprofen	60.9:20.3:18.8
F19	AVG:CBPL:ibuprofen	40.6:40.6:18.8
F20	AVG:CBPL:ibuprofen	20.3:60.9:18.8
F21	AVWL:CBPL:diltiazem	20.3:60.9:18.8
F22	AVWL:CBPL:ibuprofen	60.9:20.3:18.8
F23	AVWL:CBPL:ibuprofen	40.6:40.6:18.8
F24	AVWL:HPMC:ibuprofen	60.9:20.3:18.8
F25	AVWL:HPMC:ibuprofen	20.3:60.9:18.8

*AVG: *A. vera* gel; AVWL: *A. vera* whole leaf extract; AVDG: *A. vera* dehydrated gel (Daltonmax700); AFG: *A. ferox* gel; AFWL: *A. ferox* whole leaf extract; CBPL: Carbopol; HPMC: hydroxypropyl methyl cellulose

the results by the following equation:

friability (%) = {[weight before (g) - weight after (g)]/weight before (g)} × 100 % **Eq. 6**

Mini-matrix type tablets with a friability of less than 1 % were considered acceptable [17].

4.4. Mucoadhesive properties

The evaluation of the mucoadhesion properties of the mini-matrix type tablets involved the measurement of the force required to detach a mini-tablet from the mucosal surface of excised pig intestine with a TA.XT plus texture analyser (Stable Micro Systems, United Kingdom). The pig intestines were obtained from a slaughterhouse (R&R abattoir, Pretoria North) immediately after slaughtering the animal. The excised piece of intestine was cleaned by running cold Krebs Ringer bicarbonate buffer through the lumen and stored in ice cold buffer during transport. The excised intestinal tissue was cut open and cut into rectangular sections which were stored in a fridge at -25 °C until use.

A mini-matrix type tablet was attached to the cylindrical probe of the texture analyser by using double-sided tape. A piece of pig intestine was equilibrated in Krebs Ringer bicarbonate buffer at 37 ± 0.5 °C for approximately 1 min. A section of the pig intestinal tissue was then clamped into the holder stage of the mucoadhesion rig of the TA.XT plus texture analyser. The probe with the tablet attached was allowed to move down at a pre-test speed of 0.5 mm/s until it touched the mucous layer of the tissue at a force of 2 N. The contact time with the tissue was set at 30 s and then the tablet was withdrawn at a speed of 0.1 mm/s for a distance of 7 mm. The graph obtained of detachment force plotted as a function of time was used to identify the maximum detachment force and the area under the curve (or work of adhesion) for each mini-matrix type tablet formulation.

4.5. Swelling behavior of the mini-matrix type tablets

Swelling of the mini-matrix type tablets was evaluated by immersion of three mini-matrix type tablets in a dissolution flask containing 900 mL phosphate buffer solution (pH 6.8) in triplicate per formulation batch. The mini-matrix type tablets were removed from the flasks at pre-determined time intervals (0, 30, 60, 90, 120, 150, 180, 240, 300, 360, 540 and 720 min), weighed and placed back as quickly as possible.

The degree of swelling or swelling index (SI) was calculated according to the following equation [21]:

$$SI = [(W_S - W_D)/W_D] \times 100 \quad \textbf{Eq. 7}$$

where W_S is the swollen mini-tablet weight and W_D is the dry mini-tablet weight.

4.6. Dissolution study

The USP paddle method was used for all the *in vitro* drug release studies in a six station dissolution apparatus (TDT-08L, Electrolab, India). The rate of stirring was 50 rpm in 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C. At pre-determined time intervals (0, 30, 60, 90, 120, 150, 180, 240, 300, 360, 540 and 720 min), 5 mL samples were taken and filtered through a 0.45 µm Millipore filter. The samples removed were each replaced by 5 mL of fresh dissolution medium to maintain a constant volume in the dissolution flask. The concentration of dissolved drug in the medium was determined with a spectrophotometer at 239 nm for diltiazem and 265 nm for ibuprofen. The wavelength of maximum UV absorption for ibuprofen and diltiazem was obtained by scanning solutions (1 mg/mL in phosphate buffer, pH 6.8) over a wide range of wavelengths (200-400 nm). The linearity of the spectrophotometric analysis method for each of the model drugs over the concentration range of the dissolution test was determined by constructing a standard curve. A stock solution of each model drug was prepared by weighing 100 mg of the drug accurately and dissolving it in 100 mL of phosphate buffer (pH 6.8) to produce a 1 mg/mL solution. The two stock solutions were further diluted to produce a series of solutions with concentrations ranging from 0.03125 mg/mL to 1.00000 mg/mL for ibuprofen and from 0.015625 µg/mL to 0.50000 µg/mL for diltiazem. The absorbance of each solution was measured and plotted as a function of concentration for which the least squares best fit or regression was determined (i.e. R^2 value) as well as the equation describing the straight line. This equation for each model drug was used to calculate their concentrations in the dissolution samples after the absorbance was determined spectrophotometrically.

In order to eliminate the possibility of any interference by the excipients on absorbance when spectroscopically analyzing the model drugs, all the excipients (i.e. different aloe materials, Carbopol and hydroxypropyl methyl cellulose) were scanned over a range of wavelengths between 200-400 nm to identify any absorbance peaks that may overlap with those obtained for the model drugs.

4.7. Kinetic analysis of drug release data

Drug release from simple swellable and erosion matrix type drug delivery systems is described by the well-known power law expression and is defined by the following equation [22]:

$$M_t/M_\infty = K_1 t^n \quad \textbf{Eq. 8}$$

where M_t/M_∞ is the fractional drug release, M_t is the amount of the drug released at time t, M_∞ is the overall amount of the drug released, K_1 is the release constant and n is the release exponent.

The release exponent (n) can be used for the interpretation of release mechanisms from swellable controlled release drug delivery systems. For the case of cylindrical tablets, $n \leq 0.45$ corresponds to Fickian diffusion release (case I diffusional), $0.45 < n < 0.89$ to anomalous (non-Fickian) transport, $n = 0.89$ to zero-order (case II) release kinetics, and $n > 0.89$ to supercase II transport [22].

4.8. Statistical analysis of data

The results were statistically analysed by means of a single factor one-way repeated analysis of variance (ANOVA) to determine if differences between the experimental groups and Carbopol alone in terms of Carr's index values, maximum force of detachment and swelling are significant. Differences were considered significant if $p \leq 0.05$.

II. RESULTS AND DISCUSSION

1. ^{1}H-NMR characterization of the aloe materials

The ^{1}H-NMR spectra obtained for *A. vera* gel and *A. ferox* gel are shown in *Figures 1 and 2*, respectively.

Fresh *A. vera* gel consists of three main components namely aloverose (partly acetylated polymannan or acemannan), glucose and malic acid, which are detectable by ^{1}H-NMR spectroscopy and serve as marker molecules for identification of aloe gel material. Presence of iso-citric acid (or whole leaf marker) is a marker molecule for indication of aloe whole leaf material. High quantities of lactic acid indicate bacterial degradation of the gel material, while succinic and fumaric acid are produced by plant's own enzyme system. Presence of acetic acid and formic acid are caused by hydrolysis of aloverose and thermal degradation of glucose during storage. It is evident from the ^{1}H-NMR spectrum in *Figure 1* that the *A. vera* gel material used in this study contains all three the main marker molecules namely aloverose, glucose and malic acid to positively identify it. The results also indicated the presence of low levels of lactic acid and succinic acid.

The ^{1}H-NMR spectrum of the *A. ferox* gel material in *Figure 2* shows a different chemical composition than that obtained for the

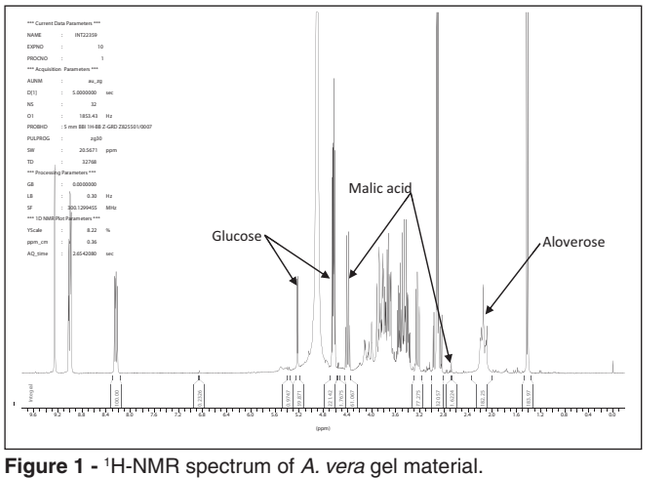

Figure 1 - ^{1}H-NMR spectrum of *A. vera* gel material.

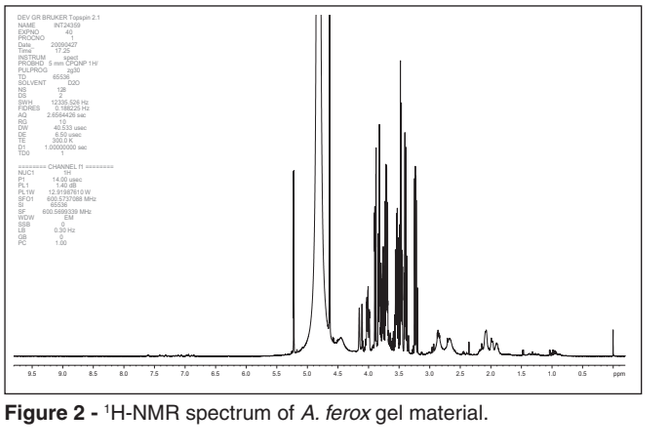

Figure 2 - ^{1}H-NMR spectrum of *A. ferox* gel material.

A. vera gel material. China acid was found to be the major compound (as elucidated by 2-D COSY) in the *A. ferox* gel material with no aloverose present. However, the presence of China acid could interfere with signals of acetyl groups and therefore prevented identification of aloverose in the *A. ferox* materials which may be present in small quantities because small amounts of mannose could be detected with high performance thin layer chromatography in hydrolysed *A. ferox* gel material. It was also shown that iso-citric acid or whole leaf marker was present in the *A. ferox* whole leaf material, which is characteristic of fresh aloe whole leaf extract material.

2. Powder densities, Carr's index and Hausner ratio values

The bulk density, tapped density, Carr's index and Hausner ratio values for the different powder formulations are shown in *Table II*.

A Hausner ratio value of less than 1.2 is indicative of good flowability of a powder, while a value of higher than 1.5 indicates poor flow. For Carr's index, a value of between 5 and 10 indicates excellent flow and the flowability decreases with increasing values where a value between 23 and 28 suggest poor flow. According to the Hausner ratio and Carr's index values obtained, none of the powders investigated in this study exhibited good flowability. Comparatively, *A. vera* whole leaf powder has the best powder flow properties of all the powders tested. *A. vera* gel also had relatively good comparative powder flow and it improved the powder flow properties of hydroxypropyl methyl cellulose and Carbopol when mixed with these polymers as compared to their individual flow properties. Hydroxypropyl methyl cellulose, Carbopol, *A. ferox* gel and *A. vera* dehydrated gel (Daltonmax700) powder each on their own exhibited extremely poor flow and, as expected, it reduced the flow of all powder mixtures that contained them. Furthermore, *A. vera* dehydrated gel, when mixed with Carbopol, had the worst comparative powder flow properties of all the powders investigated based on Hausner ratio and Carr's index values.

Table II - Hausner ratio and Carr's index values for the different individual powders and mixtures of powders.

Powder or mixture*	Bulk density	Tapped density	Hausner ratio	Carr's index
AFG	0.26	0.37	1.53	30.8#
AVDG	0.49	0.79	1.62	38.2#
AVG	0.64	0.88	1.44	26.9#
AVWL	0.69	0.98	1.37	29.2#
CBPL	0.20	0.33	1.41	40
HPMC	0.34	0.52	1.67	34.7#
AFG(75%)+CBPL(25%)	0.27	0.45	1.67	40
AFG(50%)+CBPL(50%)	0.25	0.44	1.72	41.8#
AFG(25%)+CBPL(75%)	0.22	0.38	1.71	41.6#
AFG(75%)+HPMC(25%)	0.27	0.41	1.55	35.6#
AFG(50%)+HPMC(50%)	0.29	0.48	1.64	38.9#
AFG(25%)+HPMC(75%)	0.31	0.49	1.60	37.4#
AVDG(75%)+CBPL(25%)	0.36	0.64	1.77	43.5#
AVDG(50%)+CBPL(50%)	0.27	0.50	1.87	46.4#
AVDG(25%)+CBPL(75%)	0.22	0.38	1.72	41.9
AVDG(75%)+HPMC(25%)	0.46	0.72	1.57	36.1#
AVDG(50%)+HPMC(50%)	0.40	0.64	1.60	37.6
AVDG(25%)+HPMC(75%)	0.36	0.59	1.65	39.6
AVG(75%)+CBPL(25%)	0.48	0.76	1.59	37.1
AVG(50%)+CBPL(50%)	0.30	0.52	1.73	42.2
AVG(25%)+CBPL(75%)	0.23	0.40	1.72	41.9#
AVG(75%)+HPMC(25%)	0.54	0.76	1.41	29.0#
AVG(50%)+HPMC(50%)	0.45	0.64	1.42	29.7#
AVG(25%)+HPMC(75%)	0.39	0.57	1.46	31.5#
AVWL(75%)+CBPL(25%)	0.47	0.76	1.61	37.7#
AVWL(50%)+CBPL(50%)	0.30	0.52	1.74	42.5#
AVWL(25%)+CBPL(75%)	0.22	0.38	1.70	41.0
AVWL(75%)+HPMC(25%)	0.57	0.79	1.40	28.4#
AVWL(50%)+HPMC(50%)	0.46	0.67	1.45	31.2#
AVWL(25%)+HPMC(75%)	0.38	0.59	1.55	35.4#

*AVG: *A. vera* gel; AVWL: *A. vera* whole leaf extract; AVDG: *A. vera* dehydrated gel (Daltonmax700); AFG: *A. ferox* gel; AFWL: *A. ferox* whole leaf extract; CBPL: Carbopol; HPMC: hydroxypropyl methyl cellulose. Carr's index values marked with # to indicate statistically significantly different from Carbopol alone.

3. Angle of repose and flow rate

Figure 3 shows the angle of repose and flow rate values of the powder formulations, however, not all the powders successfully passed through the funnel and therefore the angle of repose for some of the powders formulations could not be determined.

In contrast to the Hausner ratio and Carr's index values, the angle of repose results indicated that the powders containing *A. vera* gel and *A. vera* whole leaf material alone as well as in combination with hydroxypropyl methyl cellulose have excellent flow (i.e. having an angle of repose below 20). On the other hand, the flow rate value for *A. vera* whole leaf material was very high indicating poor flow, which is in direct contrast with the angle of repose value. The powder formulations containing *A. vera* gel and *A. ferox* gel alone and in combination with other polymers exhibited very good flow properties according to the flow rate values (lower flow rate values indicate faster flow through the funnel).

These results confirm that powder flowability cannot be expressed as a single value or index and this is also the reason why the industry selects a specific powder flow test method for a given application [23].

4. Evaluation of mini-matrix type tablets

As mentioned before, only 25 of the powder formulations could successfully be compressed into acceptable mini-tablets. From the angle of repose results, it was expected that *A. vera* gel and *A. vera* whole leaf extract would be good candidates for direct compression,

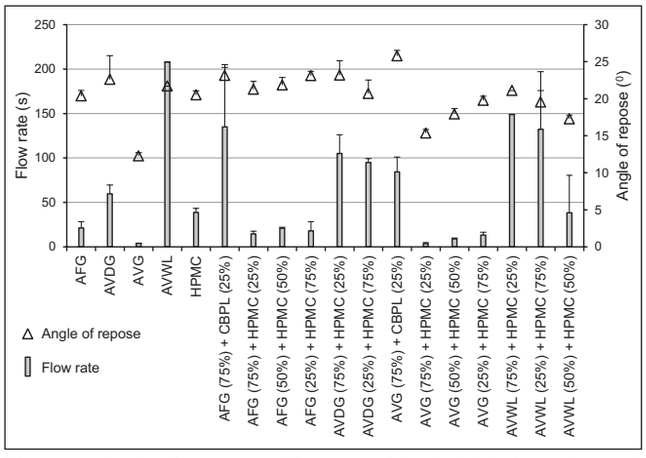

Figure 3 - Angle of repose and flow rate of the individual powders and mixtures of powders. Values represent the average ± standard deviations (error bars) of three replicates.

which were indeed the only two aloe materials that directly compressed into mini-tablets when used individually. *A. ferox* gel and *A. vera* dehydrated gel (Daltonmax700) could only form mini-tablets when mixed in different ratios with other polymers.

4.1. Physical properties of the mini-matrix type tablets

Table III shows the values obtained for the physical properties of the mini-matrix type tablets (F1-F25) including their hardness, friability and mass variation.

It is clear from the results that the inclusion of Carbopol in the formulation of the matrix type mini-tablets in addition to the aloe materials had a pronounced increase on their hardness. The friability of all 25 mini-matrix type tablet formulations showed a percentage friability < 1 %, which complies with the requirement of the USP and indicate that they would be able to resist abrasion during handling after manufacture. The mass variation within each mini-tablet formulation also complies with the USP requirement of < 10 % difference of each individual tablet mass from the average mass. An inter-formulation difference in average tablet mass was expected since the materials used as excipients showed different bulk and tapped densities, thereby influencing the mass of powder that could be accommodated in the die of the tablet press. For example, F1, with a relatively low bulk density had the highest mass of 102.8 mg, while F24, with a relatively high bulk density had the lowest mass of 85.1 mg.

Table III - Physical properties of the mini-matrix type tablet formulations that were successfully compressed.

Formulation	Hardness (N)	Friability (%)	Mass (mg)
F1	113 ± 22	0.14	102.8 ± 2.2
F2	92 ± 36	0.40	94.7 ± 2.2
F3	64 ± 19	0.43	90.0 ± 4.2
F4	108 ± 25	0.08	89.6 ± 2.3
F5	129 ± 19	0.19	93.0 ± 2.2
F6	97 ± 8	0.21	96.6 ± 2.7
F7	90 ± 29	0.06	95.6 ± 3.5
F8	106 ± 9	0.06	90.5 ± 2.0
F9	82 ± 19	0.04	94.4 ± 2.3
F10	84 ± 10	0.06	91.8 ± 4.9
F11	165 ± 14	0.14	88.7 ± 3.1
F12	96 ± 19	0.13	90.2 ± 2.5
F13	101 ± 11	0.16	87.8 ± 3.0
F14	108 ± 15	0.20	88.1 ± 2.4
F15	121 ± 8	0.16	90.9 ± 1.7
F16	133 ± 24	0.08	94.6 ± 3.0
F17	110 ± 41	0.07	95.4 ± 4.6
F18	71 ± 7	0.03	90.9 ± 5.1
F19	130 ± 24	0.23	85.6 ± 2.3
F20	105 ± 22	0.16	93.5 ± 4.0
F21	100 ± 23	0	88.0 ± 2.8
F22	91 ± 16	0.14	87.0 ± 2.1
F23	99 ± 24	0	88.6 ± 3.3
F24	84 ± 4	0.18	85.1 ± 2.7
F25	70 ± 7	0.07	95.5 ± 4.9

4.2. Mucoadhesive properties of the mini-matrix type tablets

Table IV shows the results for the maximum force required to remove a tablet from the mucosal surface of pig intestinal tissue, the work of adhesion (or area under the curve) and the separation distance. Carbopol, which is a known mucoadhesive polymer, was used as the reference standard of comparison for the mucoadhesive properties of the other formulations containing the individual aloe materials or mixtures with other polymers.

Based on the maximum force required to detach a mini-tablet from the mucosal surface of pig intestinal tissue, it is evident that *A. vera* whole leaf material alone with ibuprofen as active ingredient (F3) had a statistically significantly ($p < 0.05$) higher value compared to Carbopol alone with abuprofen as active ingredient (F5), while that of *A. vera* gel alone (F1 with diltiazem and F2 with ibuprofen) was higher compared to Carbopol alone with ibuprofen (F5) but not statistically significantly. Interestingly, when *A. vera* whole leaf was combined with hydroxypropyl methyl cellulose (F24 and F25) in a tablet formulation it increased the mucoadhesion of the hydroxypropyl methylcellulose. The type of active ingredient incorporated in the formulations did not have a clear effect on the mucoadhesion accept that diltiazem seemed to decrease the mucoadhesion properties in some cases.

4.3. Swelling behavior of the mini-matrix type tablets

Figure 4 shows the swelling index values of the mini-matrix tablet formulations (F1-F25) as determined over a period of 12 h.

Table IV - Mucoadhesive properties of the mini-matrix type tablets that were successfully compressed.

Formulation	Maximum force of detachment (N)	Work of adhesion (N/s)	Separation distance (mm)
F1	0.216	0.247	0.158
F2	0.133	0.178	0.198
F3	0.215#	0.245	0.196
F4	0.076	0.770	2.887
F5	0.123	0.416	1.184
F6	0.056	0.088	0.213
F7	0.166	0.340	0.312
F8	0.099	0.221	0.321
F9	0.155	0.392	0.330
F10	0.113	0.233	0.315
F11	0.155	0.137	0.140
F12	0.149	0.482	0.921
F13	0.149	0.471	1.166
F14	0.105	0.210	0.283
F15	0.100	0.209	0.350
F16	0.120	0.446	1.380
F17	0.079	0.595	2.227
F18	0.198	0.092	0.278
F19	0.061	0.356	2.891
F20	0.055	0.246	1.425
F21	0.141	0.122	0.102
F22	0.038#	0.090	3.668
F23	0.049	0.156	1.041
F24	0.086	0.143	0.314
F25	0.107	0.092	0.161

Maximum force detachment values marked with # are statistically significantly different from F5 (Carbopol alone containing ibuprofen as active ingredient).

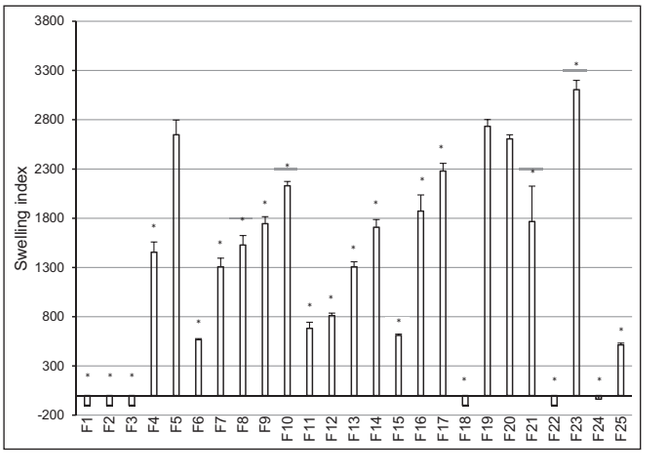

Figure 4 - Swelling index of the mini-matrix tablet formulations after 12 h. Statistically significant differences between experimental groups and Carbopol alone (F5) are indicated by *. Values represent the average ± standard deviations (error bars) of three replicates.

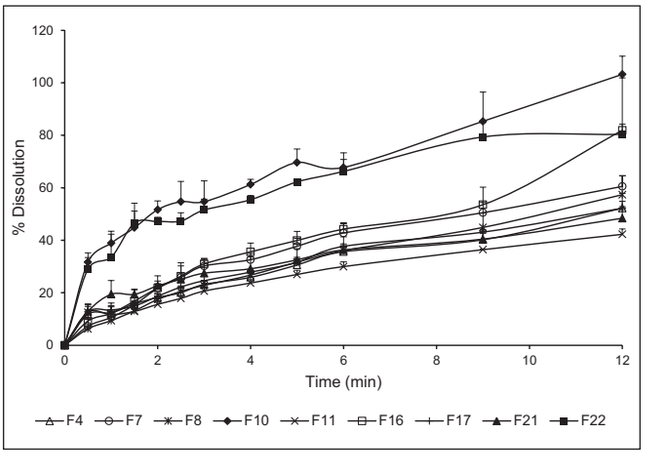

Figure 5 - Cumulative percentage dissolution of the selected mini-matrix type tablets. Values represent the average ± standard deviations (error bars) of three replicates.

The negative swelling index values indicate net erosion (or complete disintegration), which included the mini-tablets prepared from the individual *A. vera* gel and *A. vera* whole leaf materials. However, most of the formulations that showed net swelling did not return to their original tablet masses after drying of the mini-tablets, which indicates erosion has occurred in conjunction with swelling. Some of the formulations where *A. vera* gel was used in combination with Carbopol showed no or negligible mass loss meaning they have undergone swelling without erosion. The mini-tablet consisting of *A. vera* whole leaf (50 %) + Carbopol (50 %) with ibuprofen as model drug showed the highest swelling capability of all the formulations investigated, which was higher than the mini-tablet consisting of Carbopol alone. The mixture of *A. vera* gel with Carbopol also showed a higher swelling than the individual powders of this mixture on their own. These results therefore indicate that the individual aloe materials that could be compressed into mini-tablets are suitable for the manufacture of immediate release tablets that disintegrate but when combined with other polymers such as Carbopol they provide matrix forming excipients with excellent swelling properties.

4.4. Dissolution test and kinetic analysis

The UV scan of 100 mg/mL of each of the aloe materials and other polymers showed negligible absorbance at wavelengths ranging from 200 to 400 nm. It is evident that the excipients used in the study would therefore not interfere with the absorbance of both ibuprofen (peak at wavelength of 265 nm) and diltiazem (peak at wavelength of 239 nm).

The correlation coefficient (R^2 value) for both diltiazem and ibuprofen standard curves were 0.999, which indicates good linearity within the given range of concentrations tested.

Figure 5 shows the cumulative percentage dissolution of a selected nine out of the possible 25 formulations of the mini-matrix tablets that were chosen based on their ability to sustain drug release without exhibiting an initial burst release of the drug. These selected formulations also showed good correlation coefficient values (R^2 values) obtained with the power law model that was used to analyze the kinetics of their dissolution profiles. Those with burst release effects did not have good correlation coefficient values and were therefore excluded from further discussion because the aim was to investigate materials from natural origin as potential excipients specifically for matrix type tablets that can control drug release. All nine the selected formulations contained Carbopol, either alone or in combination with the aloe materials. This better performance of Carbopol over hydroxypropyl methyl cellulose in this regard can possibly be explained by its better swelling properties (*Figure 4*). From *Figure 5* it is clear that the following aloe materials showed the possibility to serve as functional excipients in combination with Carbopol for the manufacture of modified release matrix type tablets: *A. ferox* gel, *A. vera* dehydrated gel (Daltonmax 700), *A. vera* gel and *A. vera* whole leaf extract.

The only formulation that released 100 % of model compound over a period of 12 h was *A. ferox* (25 %) + Carbopol (75 %) containing ibuprofen as active ingredient, which can possibly be explained by the faster initial release of the drug compared to the other formulations possibly due to erosion in combination with swelling. The general faster release of ibuprofen compared to diltiazem in these formulations can possibly be explained by the alkaline nature of aloe gel materials, which creates a micro-environment that increases ibuprofen (weak acidic drug) dissolution and consequently, release, but this needs to be confirmed in a follow up study. Furthermore, the smaller particle size of the ibuprofen (28 μm) compared to diltiazem (161 μm) could have contributed to this phenomenon.

From the kinetic analysis of the dissolution data of the nine selected mini-matrix type tablet formulations it is clear that three of the mini-matrix type tablet formulations namely F10, F21 and F22 showed Fickian diffusion as release mechanism because they had release exponent (n) values < 0.45, while the other formulations from the selected group namely F4, F7, F8, F11, F16 and F17 showed anomalous drug release ($0.45 < n < 0.89$). The mini-matrix type tablets consisting of *A. ferox* gel ($n = 0.68$) and *A. vera* gel ($n = 71$) each in combination with Carbopol approached zero order kinetics (zero order prevails when $n > 0.89$ [21]. According to these results from the kinetic analysis, *A. ferox* gel and *A. vera* gel materials showed high potential to serve as functional excipients in matrix type tablets to control drug release when combined with a polymer such as Carbopol.

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In conclusion, it is clear, according to Hausner ratio and Carr's index values, that none of the individual aloe materials or combinations with other polymers has good powder flowability. On the other hand, both angle of repose and flow rate results indicated that *A. vera* gel powder has excellent powder flowability. *A. vera* whole leaf extract also showed very good powder flow properties based on the angle of repose value. Thus, from the powder flow results it was expected that out of all the aloe materials investigated *A. vera* gel and *A. vera* whole leaf extract would be good candidates for direct compression into tablets. Although a single powder flow indicator cannot be used to predict powder flowability for all applications, it was indeed found

that only *A. vera* gel and *A. vera* whole leaf extract could be directly compressed into mini-matrix type tablets when used alone as excipients. The individual aloe materials that could be compressed into mini-matrix type tablets showed relatively fast erosion and disintegration and therefore could be used to form immediate release tablets by means of direct compression. However, *A. vera* gel and *A. ferox* gel each in combination with Carbopol showed swelling and the drug release approached zero order kinetics indicating that this aloe material is a good candidate for use as an excipient in matrix type tablets for modified drug release. These formulations could probably be optimized by pre-processing of the aloe materials and or by addition of other excipients.

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