EFFECT OF GRANULE SIZE, COMPACTION PRESSURE AND CONCENTRATION OF MALVA VERTICILLATA MUCILAGE ON THE IN VITRO PROPERTIES OF TABLETS

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ABSTRACT

Objective: To evaluate the effect of binder concentration, granule size and distance between punches on mechanical strength and drug release properties of tablets containing Malva verticillata mucilage (MVM) as a binder.

Methods: Paracetamol and lactose were converted into wet coherent masses by a liquid solution containing 1-3% w/w MVM as a binder. Granules containing 2% w/w binder was used to investigate the effect of granule size and distance between punches. Compressed tablets were evaluated for crushing strength, disintegration time and in vitro drug release using pharmacopeial methods.

Results: Granules containing MVM were found to be free-flowing and compatible with paracetamol. Mechanical strength and drug release properties of mucilage tablets significantly correlated with the amount of MVM binder. Tablet crushing strength was 3.54-7.12 kg/cm² while disintegration time 7.13-16.67 min. Compression pressure and granule size had no significant effects on drug release properties of mucilage tablets. Crushing strength of mucilage tablets were higher and significantly different (t(26) = 7.9631, p<0.05) from acacia tablets in the tested variables. The cumulative drug release rate of mucilage tablets was also lower than that of acacia tablets in tested concentrations.

Conclusion: Properties of tablets containing 2.5% w/w MVM matched the prescribed pharmaceutical limits and hence M. verticillata root mucilage has a great potential to become a new source of tablet binder.

Keywords: Malva verticillata, Mucilage, Acacia gum, Binder, Dissolution, Paracetamol

INTRODUCTION

Tablets remain one of the most important dosage forms of presenting pharmaceutically active ingredients. Common problems encountered during manufacturing and use of tablets include incompatibility, poor flow, mechanical strength and poor drug release rates [1, 2]. Incompatibility due to chemical and intergranulate interactions compromises stability, efficacious and viability of drug content. Also, the type and amount of binder, granules size and compression pressure influence mechanical strength and bioavailability of the formulated tablet. This calls for optimization of stated variables in order to strike a balance between the properties of compressed tablets.

Binders are included in a tablet formulation to improve granule flow, promote cohesiveness and strengthen intra-granular bonds. High concentration of binder leads to the formation of stronger tablets but with poor drug release rates [3]. The choice of a binder depends on compatibility with other ingredients, ability to improve mechanical strength and release of the drug to achieve its intended purposes [1, 4, 5]. Properties of aggregates and tablets vary with granule size [6]. It was earlier reported that decrease in granule size before compression corresponds to an increase in tablet strength [7], however, it has since been established that there is no correlation [8, 9]. The magnitude of compression force affects deformation of granules which subsequently alter tablet hardness and disintegration time with or without significant effect on dissolution rate [10-12].

Mucilage obtained from a number of plant species have been evaluated as tablet binders, thickening agents and as the polymer in sustained release tablets [10, 13-15]. However, these efforts have yielded few potential tablet binders with some being reported to demonstrate inferior performance as compared to the commercially available binders [15].

Malva verticillata L. (Cluster mallow, Malvaceae) is often used as a vegetable and as a herb in traditional medicine. The plant grows as a herb with alternate leaves that have five to seven lobes. It is an annual plant that grows in well-drained moist soil with moderate fertility into variable size ranging from low lying to 1.7 m tall [16, 17]. The roots of M. verticillata when peeled or soaked in water releases a sticky slippery fluid which can be exploited as a tablet binder. The aim of this study was to optimize the potential of MVM as a tablet binder by assessing the effect of binder concentration, granule size and distance between punches on the in vitro properties of the formulated tablets.

MATERIALS AND METHODS

Paracetamol IP, lactose BP, acacia gum BP, talc and magnesium stearate were sourced from the pharmaceutical manufacturing company. Other reagents used were of analytical grade. M. verticillata roots were collected from Eastlands, Nairobi County-Kenya after authentication by a taxonomist. Sample specimen was preserved at The University of Nairobi herbarium, voucher number, PCK2015/01.

Extraction and purification of mucilage

Air dried root bark of M. verticillata was grounded into 250-500 µm size particles. These were then pre-treated with 95% ethanol in a boiling-water bath for 1 h to remove pigments and organic compounds. Distilled water containing 1% sodium metabisulphite was added to the pre-treated root bark at the ratio of 20:1 (ml/g) and stirred regularly at 50 °C for 3 h to arrest oxidation, microbial growth and enzymatic activity. The mixture was strained through a fourfold muslin cloth and centrifuged at 3000 rpm for 10 min to remove fine insoluble fibre. The supernatant was deprotonated with 1M hydrochloric acid and centrifuged at 3500 rpm for 10 min to remove the precipitate. The resulting filtrate was concentrated to near dryness and freeze dried to obtain the mucilage. No significant effect on dissolution rate was observed in different concentrations of mucilage [10].
was then mixed with 95% ethanol at equal volumes to dissolve the mucilage. The obtained mucilage was then dried at 45 °C in an oven dryer, ground and passed through British standard sieve (BSS) no. 60 (250 µm) before storing in airtight bags at room temperature.

Preparation of granules
The model drug (paracetamol) and diluent (lactose) were homogeneously dry-mixed in a pestle and mortar. This blend was converted into a wet coherent mass by adding 15 ml of a liquid suspension containing 1.0 to 3.0 % w/w of tablet binder (table 1). The wet mass was forced through a BSS no.18 (1000 µm), dried in a hot air oven at 50 °C to obtain granules with a moisture content below 2.9 % w/w. These were then mixed with 1 % talc as an internal lubricant and stored in airtight bags. The lubricant was added after granulation as wet lubricants interfere with the disintegration of tablets. In this study, disintegrants were not included in the formulations.

| % w/w of binder per tablet | Tablet ingredients | Lactose (mg) diluents | Talc (mg) lubricant | Tablet weight (mg) |
|---------------------------|--------------------|-----------------------|-------------------|-------------------|
| 1.0                       | Binder (mg)        | Paracetamol (mg)      | 3.0               | 300               |
| 1.5                       | 3.0                | 250                   | 44.0              |                   |
| 2.0                       | 4.5                | 250                   | 42.5              | 300               |
| 2.5                       | 6.0                | 250                   | 41.0              | 300               |
| 3.0                       | 7.5                | 250                   | 39.5              | 300               |

Table 1: Formulation of tablets with different amounts of binder

Compressibility

 Granules containing 1.0 to 3.0 % w/w binder were passed through BSS no. 25 (710 µm) and compacted into 300 mg circular tablet by a single punch press and stored over silica gel to allow for elastic recovery. Granules containing 2% w/w binder were divided into two portions. The first portion was shaken through a nest of sieves to give three fractions viz. 149–250 µm, 250–500 µm and 500–707 µm. Each fraction was compacted at fixed amplitudes between punches. The second portion was passed through BSS no. 25 and compacted at different amplitudes (3–5 cm) between punches. Above procedure was repeated using acacia gum (AGC) as the standard binder.

Evaluation of granules

Bulk density, Tap density, Hausner’s ratio and Carr’s index
Granules (149-707 µm) weighing 20 g and containing 1.0 to 3.0 % w/w MV M was transferred into 50 ml graduated cylinder and tapped at a height of 5 × 10⁻² m from the bench. The volume was noted after three tapings and also at equilibrium (constant volume). Bulk density (Dₙ) and tap density (Dₜ) were determined based on the three tapings and at equilibrium. Flow properties and cohesiveness of mucilage granules were determined by Hausner index (Dₜ/Dₙ) and Compressibility index (1-Dₜ/Dₙ) 100 [18].

Angle of repose
Granules (149-707 µm) weighing 20 g were allowed to flow through a funnel to form a heap that just touched the tip of the funnel. The height of the heap (θ) and the diameter of the base (D) were used to calculate the Angle of repose (θ) [19].

\[
\theta = \tan^{-1} 2hD^{-1}
\]

Strength of granules
Granules (0.250-0.707 µm) weighing 6.5 g were run for 100 revolutions in a friabilitator and sieved through a 60-mesh screen. The oversize granules were weighed and strength of granules determined [20].

\[
\text{% strength of granules} = \frac{\text{weight of granules-oversize}}{\text{weight of granules}} \times 100
\]

Drug-excipient compatibility
A portion of the sample weighing 100 mg was mixed with KBr and compressed into discs by applying pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the IR spectra of MVM, paracetamol and granules mixture were obtained and compared to check for interaction, shift or loss of functional peaks [13].

Evaluation of tablets

Crushing strength
One tablet at time (n = 6) was placed in between the jaw of Monsanto hardness tester and force required to diametrically break the tablet was determined.

Friability
Twenty tablets were rotated 100 times in a Roche friabilitator @. Tablets were then removed dusted, weighed and friability calculated as percentage weight loss [20].

Disintegration time
One tablet was placed into each of the six tubes of disintegration apparatus (Model ED-2 Electrolab, Mumbai) and suspended in 900 ml of 0.1M HCl medium at 37±1 °C. The time taken by each tablet to break into small particles was noted [21].

Dissolution rate
The Paracetamol in vitro release profiles were determined in 900 ml phosphate buffer (pH 5.8) at 37±1 °C using basket apparatus no. 2 at 50 rpm. 10 ml samples were drawn after 5 min and subsequently after every 10 min for 1 h. The samples were filtered, diluted and the absorbance determined at 243 nm. Amount of drawn sample was replaced by equivalent volume of buffer solution [21].

Evaluation of in vitro properties
Tablet in vitro properties are usually evaluated using variables that include crushing strength (CS), friability ratio (FR) and disintegration time (DT). The in vitro properties evaluated were mechanical strength and drug release. Crushing strength-friability ratio (CS/FR) was used to evaluate mechanical strength of tablets while drug release was measured by CS/FR: DT ratio. Stronger tablets have higher CS/FR ratio while high CS/FR: DT ratio indicates a better balance between mechanical strength and disintegration properties of tablets [22].

Data analysis
Multivariate analysis including analysis of variance (ANOVA), correlation, regression and t-test were used to test for significant effect of binder concentration, granule size and distance between punches on mechanical and drug release properties of tablets. Graphs were plotted in Microsoft Excel and data analyzed by IBM SPSS. All values were expressed as means±SD. Values of P<0.05 and P<0.01 were considered to be statistically significant.

RESULTS AND DISCUSSION

Properties of granules
The decrease in bulk and tap density with increase in the amount of mucilage (table 2), indicated the capability of MVM to enlarge granules and concentrate binding bridges. High values of tap density showed the existence of particle attraction and interlocking property. The registered CI (<15 %) and HI (<1.25) values in all formulations signified that mucilage granules were cohesive, free-flowing, compressible and possessed desirable packing characteristics (table 2). The significant difference in granule flow between 2.5 % and 3 % w/w mucilage formulations was due to increase in density and saturation of the binding forces [23]. The angle of repose was less than 30° within the tested formulations. This illustrated good flow and uniform distribution of bridging forces [19]. Decrease in percentage...
Friability and fines with an increase in binder concentration (table 2) signified capability of the mucilage to bind particles and form granules with satisfactory properties. The observed negative correlations (r<1) with the micrometric properties and mucilage concentration showed that densification, ability to flow and cohesiveness of the granules were dependent on mucilage concentration.

### Table 2: Micrometric properties of granules vs. amount of MVM

| Binder concentration (% w/w) | Bulk density (g/ml) | Tap density (g/ml) | Hausner’s index | Compressibility index (%) | Angle of repose (θ) | % Friability |
|-----------------------------|---------------------|-------------------|----------------|---------------------------|---------------------|-------------|
| 1.0                         | 0.665±0.006         | 0.770±0.002       | 1.16±0.006     | 13.70±0.006               | 27.32±1.52           | 19.42±0.5   |
| 1.5                         | 0.65±0.005          | 0.740±0.004       | 1.14±0.002     | 12.46±0.002               | 27.52±1.01           | 18.75±0.12  |
| 2.0                         | 0.62±0.003          | 0.712±0.004       | 1.130±0.002    | 12.46±0.002               | 28.35±1.08           | 18.41±0.5   |
| 2.5                         | 0.62±0.003          | 0.690±0.007       | 1.123±0.007    | 11.79±0.006               | 30.19±0.64           | 18.13±0.3   |
| 3.0                         | 0.60±0.007          | 0.655±0.007       | 1.088±0.003    | 10.96±0.003               | 29.55±0.59           | 17.24±0.7   |

n=3, data presented as mean±SD and p<0.01

### Drug-mucilage compatibility

*M. verticillata* mucilage was found to be compatible with paracetamol because all individual characteristic and functional vibrational peaks associated with the active principle were observed in the FTIR spectra of granules mixture (fig. 1). The observable functional peaks include O-H, N-H, C=O and C-N stretching bands at 3326.98, 3413.77, 1654.81 and 1259.43 cm⁻¹ respectively. Decrease in IR absorption intensity of hydroxyl functional group of paracetamol in the granule mixture illustrates the possibility of formation of hydrogen bonds [13, 24]. Absence of peak shifting and retention of functional peaks indicated that there was no chemical interaction in the mixture.

![Fig. 1: FTIR spectrum of granule mixture](image)

### Mechanical strength of tablets

Effect of the amount of MVM and ACG on the mechanical strength of tablets are presented in table 3 below. Friability was observed to decrease with increase in the concentration of binder. During the test, none of the tablets cracked, peeled or smashed. This indicated the potential of MVM and ACG to enhance formation of adhesive bridges which resist abrasion, shock and capping tendencies, common with substances which undergoing fragmentation [25].

The significant correlation (r=1, P<0.01) between the amount of mucilage and crushing strength, signifies ability of MVM to form a thick mucilaginous film which contributes to tablet strength [26]. Increase in mucilage concentration by 1.0% w/w had a significant effect (p<0.05) on the hardness of tablets. This indicated that the binding potential of MVM was concentration-dependent. Mechanical strength of the tablets obtained from mucilage formulation was found to be superior to those of acacia gum at 2-3% w/w concentration as depicted by high CS/FR ratio [22]. This was supported by high regression coefficient of 1.78 in MVM as compared to 1.43 of acacia tablets. Tablets containing 1% w/w mucilage were weaker than corresponding acacia tablets because of high bulk density which reduces space for deformation while ACG increases packing per unit space [27].

### Table 3: Mechanical strength of tablets containing different amount of binders

| Binder concentration (% w/w) | Crushing strength (kg/cm²) | Friability (%) | Crushing strength-friability ratio (CS/FR) |
|-----------------------------|----------------------------|---------------|------------------------------------------|
|                             | MVM                        | ACG           | MVM                                      | ACG                      | MVM                             | ACG                      |
| 1.0                         | 3.54±0.27                  | 3.58±0.34     | 0.66±0.04                                | 0.64±0.04                | 4.12±0.30                       | 5.38±0.166               |
| 1.5                         | 5.07±0.14                  | 4.18±0.16     | 0.55±0.01                                | 0.54±0.02                | 9.16±0.14                       | 7.70±0.21                |
| 2.0                         | 6.15±0.06                  | 5.12±0.04     | 0.51±0.02                                | 0.43±0.03                | 12.07±0.42                      | 11.81±0.69               |
| 2.5                         | 6.78±0.25                  | 5.94±0.33     | 0.38±0.01                                | 0.42±0.02                | 17.85±0.20                      | 14.80±0.67               |
| 3.0                         | 7.12±0.21                  | 6.26±0.25     | 0.35±0.03                                | 0.33±0.01                | 17.0±0.25                       | 15.67±0.59               |

n=3, data presented as mean±SD, p<0.05.
This could be explained in terms of porosity. Larger decrease with increase in granule size. Large granules in the size range 500-700 µm disintegrated faster than small size disintegration time and tablets obtained by compressing time of tablets. The negative correlation (r<1, p<0.01) between granules form strong pores which do not collapse during compression while small sized granules of less than 250 µm form collapsible pores. Small pores reduce penetration and hence increase disintegration time. Earlier studies attributed disintegration to swelling and creation of other active disintegration mechanisms [26]. The poor disintegration of tablets obtained from the initial granule mixture (149-707 µm) was more pronounced in tablets containing 3% w/w mucilage that disintegrated after 16 min which is above the pharmacopoeial limit of ≤15 min [29]. This observation showed that mucilage at high concentration has strong binding properties which may hinder disintegration. Regression analysis showed that hardness of tablets had less influence on disintegration time than the amount of binder.

Results in table 3, fig. 2 and 3 above, showed that mechanical properties of mucilage tablets in all tested variables; concentration, granule size and distance between punches were high and significantly different from those of acacia tablets (F = 7.963, p<0.05). The following model equation was used to indicate that tablet hardness increased significantly with a decrease in granule size. Increase in the concentration of mucilage and increase in distance between punches.

\[ Y = 6.03 + 1.79X_1 - 1.76X_2 + 0.83X_3 \]

Where \( Y \) is hardness in kg/cm², \( X_1 \) is mucilage concentration (% w/w), \( X_2 \) is granule size in µm and \( X_3 \) is the distance between punches in cm. The negative coefficient (-1.760) signified that crushing strength decreased significantly (p<0.05) with an increase in granule size. The high correlation coefficient (1.79) indicated that binding potential of MVM was concentration-dependent. A low coefficient of \( X_3 \) implied the insignificant effect of distance between punches. Disintegration time

Table 4 shows the effect of increasing concentration of binder on the time of disintegration. The significant correlation (p<0.05) between the concentration of MVM and disintegration time was due to the formation of a mucilaginous viscous film which hindered penetration of water thus preventing disintegration [11]. This effect was more pronounced in tablets containing 3% w/w mucilage that disintegrated after 16 min which is above the pharmacopoeial limit of ≤15 min [29]. This observation showed that mucilage at high concentration has strong binding properties which may hinder disintegration. Regression analysis showed that hardening of tablets had little influence on disintegration time than the amount of binder.

Table 4: Disintegration time for tablets containing different amount of MVM and ACG as tablet binder

| Binder concentration (% w/w) | Disintegration time (min) | CSFR: DT |
|-----------------------------|--------------------------|---------|
|                             | MVM | ACG |       | MVM | ACG |       |
| 1.0                         | 7.1±0.51 | 3.35±0.13 | 0.58±0.06 | 1.61±0.02 |       |       |
| 1.5                         | 9.23±0.28 | 4.52±0.06 | 0.94±0.03 | 1.76±0.05 |       |       |
| 2.0                         | 12.17±0.53 | 5.71±0.57 | 1.6±0.04 | 1.23±0.07 |       |       |
| 2.5                         | 14.80±0.48 | 7.15±0.13 | 1.21±0.05 | 1.94±0.08 |       |       |
| 3.0                         | 16.67±0.59 | 7.35±0.20 | 0.97±0.01 | 1.84±0.15 |       |       |

n=3, data presented as mean±SD, p<0.05).
granule size was found to have no significant effect on drug release properties as shown by CSFR/DT values (fig. 4b).

**Fig. 4a:** Effect of granule size on disintegration time of tablets, mean±SD, n=3, p<0.01 ACG-DT disintegration time of tablets containing acacia gum and M. verticillata mucilage, respectively

**Fig. 4b:** Effect of granule size on drug release properties of tablets, mean±SD, n=3, p<0.01 AG-CSFR-DT is the crushing strength-friability, disintegration time ratio of tablets containing acacia gum and M. verticillata mucilage, respectively

Fig. 5 below shows the insignificant correlation (r >1, p>0.01) between the effects of increasing distance between punches on disintegration time. Wider distance between punches brings particles closer to each other resulting in a reduction in tablet porosity and hence increase in disintegration time.

**Fig. 5:** Effect of pressure on drug release properties of tablets containing M. verticillata mucilage and acacia gum as tablet binder, mean±SD, n=3, p<0.01. AGM-CSFR: DT and MVM-CSFR: DT is the Crushing strength-friability, disintegration time ratio of tablets containing 2.0% w/w of acacia gum and M. verticillata mucilage as tablet binder respectively

Results in table 4, fig. 4 and 5 above shows that mucilage tablets were less superior and significantly different at all tested variables compared to those of acacia tablets (r 14 = -39.925, p<0.05). This was revealed by low values of CSFR: DT. The negative coefficient indicated that mucilage retarded disintegration time more than acacia gum. Decreasing granule size while increasing MVM concentration and distance between punches hindered disintegration thus increasing tablet disintegration time as shown by the following model equation.

\[ Y_2 = 13.18 + 4.77X_1 - 3.04X_2 + 2.29X_3 \]

Where \( Y_2 \) is disintegration time in minutes, \( X_1 \) is s concentration of mucilage (% w/w), \( X_2 \) is granule size in microns and \( X_3 \) is the distance between punches. High coefficient of concentration (4.77) indicates that it has more influence on disintegration time than other tested variables. The peak CS/FR: DT values for mucilage tablets was recorded at 25% w/w, 149-707 µm granule size and when compressed at low pressure (table 4, fig. 4 and 5). This observation are indicative of the optimum conditions for the formulation of mucilage tablets.

**DISSOLUTION**

Fig. 6 illustrates the cumulative amount of drug release against time for tablets containing 2.0 and 3.0% w/w MVM and ACG as a binder. The positive correlation (r=0.947) between the amount of drug released and time indicated a constant drug release. The gradient of the curves with a dipping slope at the initial stage was an indication of the ability of tablets to boost and maintain constant drug concentration in vivo. High dissolution rate of ACG tablets was through the enhancement of drug solubility [28]. Low release rate of mucilage tablets was due to hydration which leads to the formation of the mucilaginous and sticky film. The viscosity of the film and diffusional path length determines the release rate [12]. Cumulative amount of 68-94% for tablets containing 3.0% w/w mucilage at the end of 30 min was below the Pharmacopoeial limit (>80% after 30 min) and is an indication of tablet with slower release rates.

**Fig. 6:** Cumulative percentage of drug release Vs. time of tablets containing 2.0 and 3.0 % w/w M. verticillata mucilage and acacia gum as tablet binder, n=3 and p<0.01, ACG-2 and ACG-3 tablet containing g 2.0 and 3.0 % w/w acacia gum as tablet binder, MVM-2 and MVM-3 tablet containing g 2.0 and 3.0 % w/w M. verticillata mucilage as tablet binder

**CONCLUSION**

The in vitro properties of mucilage tablets varied in all the tested variables. M. verticillata mucilage is compatible with paracetamol and has the capability to improve granule flow. Small sized granules when compressed at high-pressure yields tablets with high mechanical strength and poor drug release properties. Compression pressure and granule size were found to have no significant effect on drug release properties of MVM tablets. Granules in the size range of 149-707 µm containing 2.0% w/w mucilage yield tablets with good mechanical strength and drug release rate properties comparable with those of acacia gum. This study has shown that M. verticillata mucilage at a higher concentration can be exploited as a binder in the formulation of slow release and mucoadhesive tablets.

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**AUTHORS CONTRIBUTIONS**

The conception and formulation of the research methodology were done by the first author who was also responsible for execution of the experiments and drafting of the manuscript. The four co-authors were jointly involved in the design of the work, supervision, conducting a literature search and writing of the manuscript.

**CONFLICT OF INTERESTS**

The authors declare that they have no conflict of interest.
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