Nigerian Journal of Pharmaceutical Sciences
Vol. 23, No2, 2024, ISSN: 0189-823X

CHARACTERIZATION AND EVALUATION OF THE BINDING PROPERTY OF THE MUCILAGE EXTRACTED FROM THE FRUIT OF *PHOENIX DACTYLIFERA* IN PARACETAMOL TABLET FORMULATIONS

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ABSTRACT

The search for new pharmaceutical excipients with comparable or better properties than the existing ones remains an integral part of research in Pharmaceutics. This study is aimed at extracting, characterizing and investigating the binding property of *Phoenix dactylifera* fruit mucilage in the formulation of paracetamol tablets. The dried date palm fruit was kept in the shade for two days and the seeds were removed before grinding the fruit in a blender. The resulting powder (500 g) was then hydrated in 15 L of distilled water and allowed to stand for 12 h before filtering through multiple layers of muslin cloth. The resulting mucilage was precipitated with 6 L of acetone. The organoleptic and physicochemical properties of the mucilage were determined by standard methods. Paracetamol granules were prepared by wet granulation method and were thereafter characterized before compressing into tablets. The tablets produced were evaluated for weight uniformity, tablet thickness and diameter, hardness and friability, disintegration and dissolution times in a quality control analysis. The mucilage exhibited a characteristic odour, colour and taste and is moderately coarse in texture. The mucilage also exhibited temperature dependent water solubility but was however insoluble in acetone and ethanol. The powdered mucilage exhibited good flow when characterized by density measurements using Hausner's ratio (1.13), Carr's index (13.59 %) and the angle of repose (33.03 ^{0}). The formulated tablets conformed to the required specifications as stated in the official compendium except at 2.5 % w/w binder concentration which failed the friability test. All the tablets disintegrated within 5 min and passed the dissolution test. The results of this study showed that *Phoenix dactylifera* mucilage has good flow and binding properties thus, it can be used as an alternative binder in tablet formulations.

Keywords: Binder, Flowability, Mucilage, *Phoenix dactylifera*

INTRODUCTION

Phoenix dactylifera L. originated from Mesopotamia and all parts of the plant are used for some purposes (Al-Snafi and Thuwaini, 2023). *Phoenix dactylifera* L. is an important crop in the arid and semi-arid regions of the world (Metoui *et al*., 2018). The tree of dates has played an important role as a food crop in the Middle East and North Africa region, providing valuable food for people for the last 5000 years (Ghnimi *et al*., 2017). The name of the species dactylifera means "finger-bearing" which refers to the fruit clusters produced by this plant. "Dactylifera" is a grouping of the Greek word "dactylus" which means finger, and the Latin word "ferrous" which means bearing (Ashraf and Hamidi-Esfahani, 2011). Currently, about 100 million trees are cultivated globally out of which approximately 90 % are in the Middle East and North Africa region (Ghinmi *et al*., 2017). Worldwide production of date fruit has increased almost threefold over the last 40 years, reaching 7.68 million tons in 2010 (Parvin *et al*., 2015). *Phoenix dactylifera* is not only a food substance but a raw material in many industries. The edible part of the date palm tree has been recognized to possess many medicinal properties when consumed alone or in mixture with other medicinal herbs

(Al-Alawi *et al*., 2017; Ajani *et al*., 2019; Al-Snafi and Thuwaini, 2023).

According to the Indian Pharmacopoeia, Pharmaceutical tablets are solid, flat or biconvex unit dosage forms, prepared by compressing a drug or a mixture of drugs, with or without excipients (Sahu *et al*., 2024). Tablets are the most widely used dosage form because of ease of administration, lower price of production, and elegance (Gaikwad and Kshirsagar, 2020). Excipients used in tablet preparation include diluents, binders, disintegrants, glidants and lubricants. Tablet binders or binding agents are the substances that are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets (Khairnar *et al*., 2024). Binders ensure that the tablets remain intact after compression (Ghatage *et al*., 2014). Examples of tablet binders include microcrystalline cellulose, starches, lactose, sugar alcohols like mannitol and polymers like polyvinyl pyrrolidone (Karandule *et al*., 2023).

Paracetamol (acetaminophen) is the most widely used analgesic worldwide both over the counter and on prescription (Alchin *et al*., 2022). It has a unique clinical pharmacological profile that includes potent analgesic and antipyretic effect (Freo *et al*., 2021). Paracetamol crystals exhibit poor compressibility, poor flowability and hence it is used as a model drug for evaluating the binding property of many excipients (Govedarica *et al*., 2011). The study aims to harness the potential of the fruit mucilage of *Phoenix dactilyfera* as a pharmaceutical excipient with specific emphasis on its binding property in tablet formulations.

MATERIALS AND METHODS

Equipment

Tableting machine (Erweka AR 400, Germany), UV spectrophotometer (UV/Vis-1700 Shimadzu, Japan), blender (Kenwood, England), Oven (Gallenkamp, England), Moisture analyser (Sartorius, Germany), disintegration tester (Erweka Z T3, Germany), dissolution apparatus (Nr 43041, Germany), Hardness tester (TBH 100, Germany), friabrilator (TA3R, Germany), beakers, measuring cylinders, volumetric flasks cuvettes, Dessicator.

Reagents

paracetamol powder, talc, starch, magnesium stearate, lactose, acetone, (BDH England), ethanol, HCl (Merk, Germany), date palm fruit.

Preparation

The dried *Phoenix dactylifera* fruit was purchased from a local market in Maiduguri and air dried for two days. The seeds were removed and the fruit ground in a blender. The ground powder was then sifted through a 1 mm sieve and kept intact for extraction.

Extraction of Mucilage

The method of Ahad *et al*. (2012) was used with modification. A 500 g weight of the powdered date palm fruit was hydrated in 15 L of distilled water and allowed to stand for 12 h. It was filtered through a multiple-layered muslin cloth and the resulting filtrate was collected in a plastic bucket. The mucilage was precipitated with 6 L of acetone and then air dried for 5 days and stored in an air tight container for use throughout the study.

Characterization of the Mucilage

Organoleptic Properties

The colour, odour, texture, and taste of the mucilage extracted were observed using the organoleptic senses of look, smell, feel, and taste.

Solubility Test

The solubility analysis of the mucilage extract was done using standard methods as described by Evans (2009). One gram of the extracted mucilage was dissolved in 2 ml of cold distilled water, hot distilled water, ethanol and acetone, the solubility profile of the mucilage was determined and recorded.

Determination of Moisture Content

This was done using a digital moisture analyzer (Sartorius, Germany). Three gram (3 g) of the mucilage powder was put into the moisture content analyzer. The machine was then set to 130 °C ± 1°C for 5 min. The readings were noted when the machine automatically stopped. The procedure was done in triplicate and the mean was determined (Mu'azu *et al*., 2013).

Determination of Hydration Capacity

The method of Mu'azu *et al.* (2014) was adopted. One gram of the mucilage powder was placed in a tarred 20 ml stoppered centrifuge tube. The weight of the tube was noted; 10 ml of distilled water was added and shaken vigorously for 2 min. It was then allowed to stand for 10 min during which it was mixed by inverting the tube three times at the end of 5 and 10 min. The sample was centrifuged at 1000 revolutions per minute for 10 min. The aqueous supernatant was then carefully removed and the tube with the sediment was re-weighed. The hydration capacity was calculated as the ratio of the weight of the sediment to the initial weight of dry powder. The procedure was done in triplicate and the mean was calculated.

Determination of Swelling Power

The method of Mu'azu *et al.* (2014) was used and the tapped volumes occupied by 5 g of the mucilage was noted. The mucilage was then dispersed in 85 ml of distilled water and the volume made up to 100 ml with more distilled water. It was allowed to stand for 24 h. The volume of the sediment was then determined and the swelling capacity was calculated from the difference in volumes.

Determination of Bulk Density

The method of Sumedha *et al*. (2015) was adopted. Fifty grams of the powder was weighed and poured into a 100 ml measuring cylinder. The volume occupied by the powder is noted and recorded. It is expressed in g/ml and is given by,

$$\text{Bulk density} = \frac{\textit{weight of powder}}{\textit{volume of loose powder}} \text{ .. Eq 1}$$

Determination of Tapped Density

The method of Sumedha *et al*. (2015) was adopted. Fifty grams of the weighed powder in the cylinder was tapped gently by lifting it up to a height of about 2 cm and allowing it to fall freely onto a wooded base. Continue tapping until no further reduction in volume is detected (after about 50 taps). Calculated the tapped density using the formula

$$\text{Tapped density} = \frac{\textit{weight of powder}}{\textit{volume of packed powder}} \text{ .. Eq 2}$$

Determination of Hausner′s ratio

The Hausner′s ratio was calculated using the values of tapped and bulk density:

$$\text{Hausner′s ratio} = \frac{\textit{tapped density}}{\textit{bulk density}} \text{ .. Eq 3}$$

Determination of Carr′s index

The Carr′s index was calculated using the formula

$$\textit{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}} \text{ .. Eq 4}$$

Measurement of Angle of Repose

This was determined using the drained angle of repose. An open-ended cylinder was constructed with a white plain sheet of paper. 50 g of the powder was introduced into the constructed cylinder which is positioned vertically. The constructed cylinder was raised up slowly to allow the powder flow out to form a conical heap on the base. The height h, diameter d, and hence the radius, r of the cone formed by the heap of the powder was determined. The angle of repose was determined using the formula;

$$\Theta = \tan^{-1}\frac{h}{r} \text{ .. Eq 5}$$

The experiment was repeated two times for each and the mean was recorded (Sumedha *et al*., 2015).

Preparation and Evaluation of Paracetamol Granules

Paracetamol granules were prepared as described in Table I

Table I: Formula used for preparing the *Phoenix dactylifera* Mucilage and Corn Starch Tablets

Percentage (%)	PCM (mg)	lactose (mg)	Corn starch(mg)	binder (mg)	talc (mg)	magnesium stearate(mg)	tablet wt(mg)
PD 2.5	500	62.25	65	16.25	3.25	3.25	650
PD 5	500	46.0	65	32.5	3.25	3.25	650
PD 7.5	500	29.75	65	48.75	3.25	3.25	650
PD 10	500	13.5	65	65.00	3.25	3.25	650
CS 5	500	46.0	65	32.5	3.25	3.25	650

Key: PD =*Phoenix dactylifera* mucilage (2.5 %, 5 %, 7.5 % and 10 %), CS 5= Corn Starch (5 %.)

Formulation of Granules by Wet Granulation

Five batches of tablets were produced. Four batches for *Phoenix dactylifera* L. mucilage and a batch for corn starch as standard. The mucilage was prepared by dispersing the *Phoenix dactylifera* in 10 ml of distilled water at binder concentrations of 2.5 %, 5 %, 7.5 % and 10 % w/w for *Phoenix dactylifera* and 5 %w/w for corn starch as the standard. The mucilage was added to 50 g paracetamol powder and the calculated amounts of lactose in Table I (which were previously triturated in geometric order) in the mortar and dampened thoroughly. The granules were then obtained by forcing the damp mass through a 1.7 mm screen and dried in a drying cabinet at 60 ºC for 30 min. The dried granules were screened through a sieve carrying a 1 mm mesh and bottled. The granules were then mixed with the corn starch (i.e. the disintergrant) talc (glidant) and magnesium stearate (lubricant) in a bottle for 5 min before compressing into tablets (Onunkwo *et al*., 2004).

Tablet Quality Control Tests

Weight Variation

Twenty (20) tablets were randomly selected from each batch and each tablet was weighed and the weight recorded. The mean weight of the twenty tablets per batch was calculated (Wadkar *et al*., 2017).

Crushing Strength

The Erweka hardness tester (TBH 100, Germany) was used in measuring the crushing strength of the tablets. Ten (10) tablets were randomly selected from each batch. Each of these tablets was in turn placed between the anvil and the spindle of the Erweka hardness tester (Germany) and subjected to increasing pressure by turning the knurled knob in a clockwise direction at constant rate until the tablet was crushed. The value of the pressure applied at this point gives a measure of the tablet hardness in Kilogram Force (KgF). The mean of the ten determinations was taken for each batch (Wadkar *et al*., 2017).

Friability Test

Ten (10) tablets were randomly picked from each batch and weighed accurately. They were then placed inside the drum of Erweka friabilator (Erweka, Germany) and operated for four (4) min at a speed of 25 rpm. Thereafter, the intact tablets were removed from the drum, dusted and weighed. The percentage loss of weight was recorded as the friability value for that batch (Wadkar *et al*., 2017).

Disintegration Test

The disintegration time of the tablets was determined using the Erweka disintegration tester. Distilled water was thermostatically maintained at 37 °C ± 1 °C was used as the disintegration medium. The disintegration time for three tablets from each batch was determined by recording the time taken for the last tablet or its fragment to pass through the mesh into the disintegration medium was recorded. The experiment was done in triplicate and the mean value and standard deviation determined (Wadkar *et al*., 2017).

Dissolution Time Test

The method of Mishra *et al*. (2012) was adopted with modifications. The Erweka dissolution test apparatus was used to determine the dissolution time of the paracetamol tablets from the different batches using the procedure as stated by the British Pharmacopoeia (BP, 2009). The dissolution medium used was 900 ml 0.1 M HCl thermostatically maintained at 37 °C ±0.5 °C. The basket which was adjusted 25 mm away from the base of the glass jar was set to rotate at 50 rpm. One tablet was placed into the glass jar. Samples of the dissolution medium (5ml) were then withdrawn at specified time intervals of 5, 15, 30, 45, and 60 min respectively and spectrophotometrically analyzed for paracetamol at 245.3 nm. After each withdrawal of the sample, the same volume of the dissolution medium was replaced.

Statistical Analysis

One-way Analysis of variance (ANOVA) test was performed in the various batches of the tablets to see if there is any statistically significant difference in the various tablet properties.

RESULTS AND DISCUSSION

The percentage yield of *Phoenix dactylifera* mucilage was found to be 38.46 %. This however could vary in different species of date palm or due to geographical location of the plant and also the method of extraction and solvent used. Pasha *et al*. (2022) obtained a yield of 58.4 % using ethanol as extraction solvent. The mucilage powder obtained is dark-brown colour; it has a pleasant odour and is tasteless with a fine texture (Table II). The solubility of the extracted mucilage in water was observed to be temperature dependent (Table III). The mucilage was however insoluble in acetone and ethanol which explains their use as precipitating solvents in the extraction process.

The flowability of powders can be compared by their bulk and tapped densities (Wells and Aulton, 2007). Date palm mucilage had a bulk density of 0.60 and tapped density of 0.68 g/ml (Table IV). The results differ slightly from that obtained by Pasha *et al*. (2022) for the crude date palm mucilage (0.74 and 0.85g/ml respectively for bulk and tapped density). *Phoenix dactylifera* L. has a Carr′s index of 13.59 %, similar result was obtained by Pasha *et al*. (2022) (14.4) which is indicative of good flow. The Hausner′s ratio of *Phoenix dactylifera* L. has a value of 1.13 which also signifies good flow (Aulton, 2013). Angle of repose is a characteristic related to the inter-particulate friction or resistance to the measurement between powder particles. It can be used in evaluating the flow properties of powders. *Phoenix dactylifera* L has an angle of repose of 33.04 º which signifies good flow (Aulton, 2013). This result is similar to that of Pasha *et al*. (2022) who obtained a value of 32.1 º.

Table II: Organoleptic Properties of *Phoenix Dactylifera* Mucilage

Parameters	Date palm
Odour	Characteristic odour
Colour	Dark brown
Taste	Characteristic taste
Texture	Fine

Table III: Solubility Profile of *Phoenix Dactilifera* Mucilage in Different Solvents

Solvent	Solubility
Cold distilled water	Sparingly soluble
Hot distilled water	Soluble
Ethanol	Insoluble
Acetone	Insoluble

Swelling which is an indication of tablet disintegration ability can be assessed by the determination of hydration capacity, swelling capacity/power and moisture sorption profile (Bakre *et al*., 2009). *Phoenix dactylifera* L has a hydration capacity of 1.02 which suggests a potential disintegrating ability.

The bulk density of granules is primarily dependent on particle size, particle size distribution and particle shape. It is an indirect measure of granule flow and determines the die fill volume. From the results obtained, the bulk density of the granules varies from 0.53- 0.67 (g/ml). The bulk density of the granules increased with increasing binder concentration (Table V). From the bulk and tapped densities of the different granules batches, *Phoenix dactylifera* L has a Carr′s (compressibility) index of less than 15 %, thus indicating good flow. The Hausner′s ratio of the granules falls within the range of 1.09-1.16 which is also an indication of good flow. The angle of repose of the granules was observed to be between the ranges of 20-30 (^{0}) which indicates excellent flow property (Aulton, 2013).

Table IV: Physicochemical Properties of *Phoenix dactylifera* Mucilage

Parameter	PD
Hydration capacity	1.02
Moisture content (%)	6.02
Angle of repose (^{0})	33.04
Bulk density (g/ml)	0.60
Tapped density (g/ml)	0.68
Carr index (%)	13.59
Hausner ratio	1.13

Key: PD=*Phoenix dactylifera*

Table V: Physicochemical Properties of the Granules

Parameters	PD 2.5	PD 5	PD7.5	PD 10	CS 5
Bulk density (g/ml)	0.52	0.63	0.66	0.63	0.62
Tapped density (g/ml)	0.58	0.69	0.74	0.78	0.67
Hauner′s ratio	1.09	1.23	1.75	1.16	1.13
Carr′s index (%)	8.6	13	14	14	11.75
Angle of repose (^{o})	20.2	22.6	34.1	30.3	22.2

Key: PD=*Phoenix dactylifera*, CS =Corn Starch; 2.5, 5, 7.5 and 10 refer to the respective binder concentrations.

Table VI: Tablet Properties

Batch	Weight variation (mg±SD)	Diameter (mm±SD)	Thickness (mm±SD)	Friability (%)	Crushing strength (KgF±SD)	Disintegration time (min)
PD 2.5	617±9.02	11.55±0.03	3.74±0.02	4.99	4.48±0.70	1.15±0.08
PD 5	678±10.51	12.56±0.04	3.66±0.01	0.84	5.44±0.51	1.24±0.09
PD 7.5	642±13.32	12.05±0.04	3.75±0.07	0.22	5.50±0.33	1.43±0.90
PD 10	609±8.11	11.45±0.04	3.55±0.05	0.11	5.94±0.34	4.17±1.90
CS 5	660±5.0	12.55±0.02	3.76±0.25	0.81	6.42±0.30	4.76±1.50

Key: PD=*Phoenix dactylifera*, CS =Corn Starch; 2.5, 5, 7.5 and 10 refer to the respective binder concentrations.

The tablet diameter for all the tablets from all the batches produced falls within the range of 11.45-12.56 mm, a feature of good (consistent) die fill secondary to good powder flow. Tablet thickness should be controlled within ± 5 % variation of standard (Odeku *et al.*, 2008). The physical dimension of the tablet and the density of the material in the tablet formulation and their proportion determine the weight of the tablet. The hardness of a tablet provides information on the tablets resistance to capping, abrasion or breakage under condition of storage, transportation and handling from production to usage. It also predicts the absorption and the bioavailability from solid oral dosage form. If a tablet is too hard, it may not disintegrate in the required time to meet dissolution specifications, if it is too soft, it may not be able to withstand handling stress (Odeku *et al*., 2008).

From the results (Table VI), all the tablets fall within the range of 3-5 kgF for crushing strength. It can also be observed that the crushing strength increases with increasing binder concentration (Figure 1a) and this is due to the increasing binding capacity of binders at high concentration leading to a greater bonding force among granules during compression. Higher values were obtained by Abbas-Aksil *et al*. (2016) with matrix tablets from Algerian Lyophilized berries and date palm fruit.

The friability test is closely related to tablet hardness and is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. A maximum weight loss of not more than 1 % of the weight of the tablets being tested during the friability test is considered generally acceptable (Alderborne, 2013). From the results obtained, all the batches fall within the required range except the 2.5 % and this is likely due to the low concentration of the binder. Tablet friability decreased with increase in the binder concentration (Figure 1b).

Disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mm mesh screen. For most uncoated tablets, it is required that the tablets disintegrate in 15 min (Alderborne, 2013). From the result obtained (Table VI) all the formulations disintegrated in less than 5 min, similar result was obtained by Alanazi, (2010) with date syrup as a tablet binder, this could be due to the high hydration capacity and swelling power previously observed, thus it could serve as a disintegrant. However, when the whole dry fruit was used as a binder instead of extracting the mucilage, it shows a high binding property (Ngwuluka *et al.,* 2010). Disintegration time increased with increase in the binder concentration (Figure 1c).

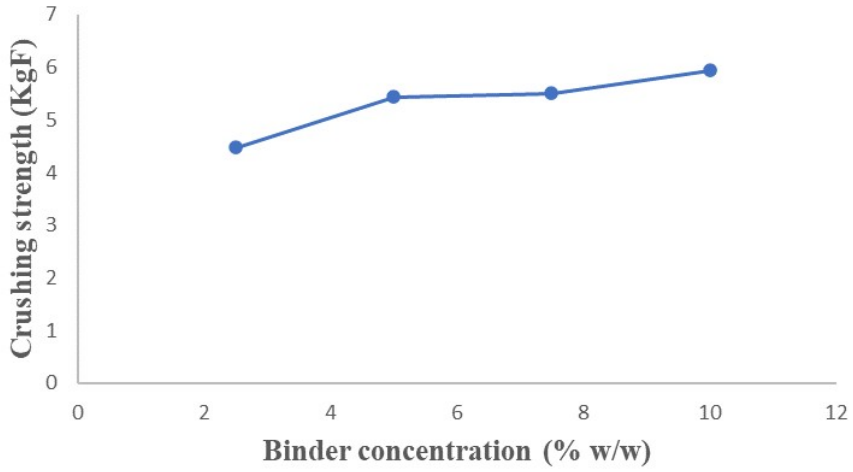

Figure 1a: Effect of Binder Concentration on Tablet Crushing Strength

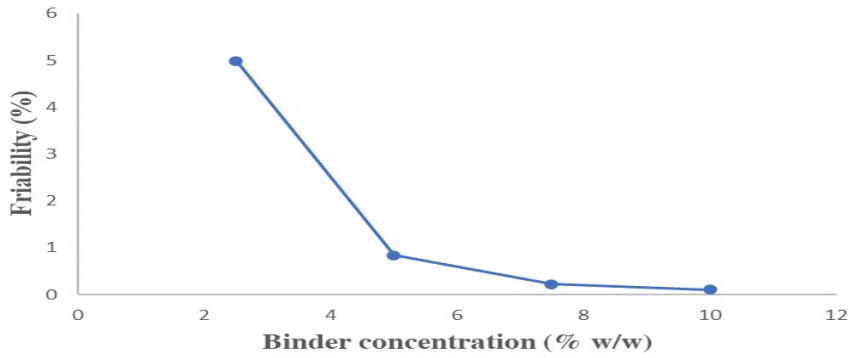

Figure 1b: Effect of Binder Concentration on Tablet Friability

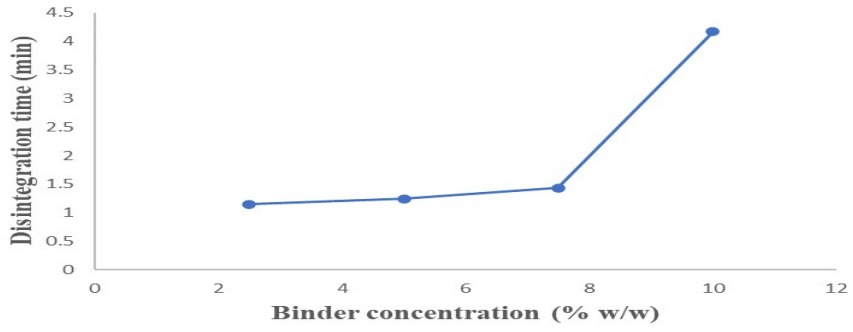

Figure 1c: Effect of Binder Concentration on Tablet Disintegration Time

The dissolution test measures the time required for a percentage of the drug substance in a tablet to go into solution under a specified set of conditions. It describes a step toward physiological availability of the drug substance, but is not a measure of the safety or efficacy of the tablet being tested (Odeku *et al.*, 2008). It is considered as one of the most important quality control tests performed on pharmaceutical dosage forms as it controls the absorption, bioavailability, onset of action, duration of action and efficacy from tablets. This parameter is affected by the type and concentration of binder used, hardness of the tablet, surface area, and distance of diffusion, solubility of the drug, manufacturing process (wet granulation or direct compression) and diluents (Ngwuluka *et al.*, 2010). All the formulations released up to 70 % of the drug within 30 min (Figure 2) which suggest good release property of the drug from the dosage form.

Statistical analysis (One-way ANOVA) on the tablet properties of the various batches gave a calculated p-value of 0.99, this shows that there is no statistically significant difference between the various batches and the standard ($p>0.05$).

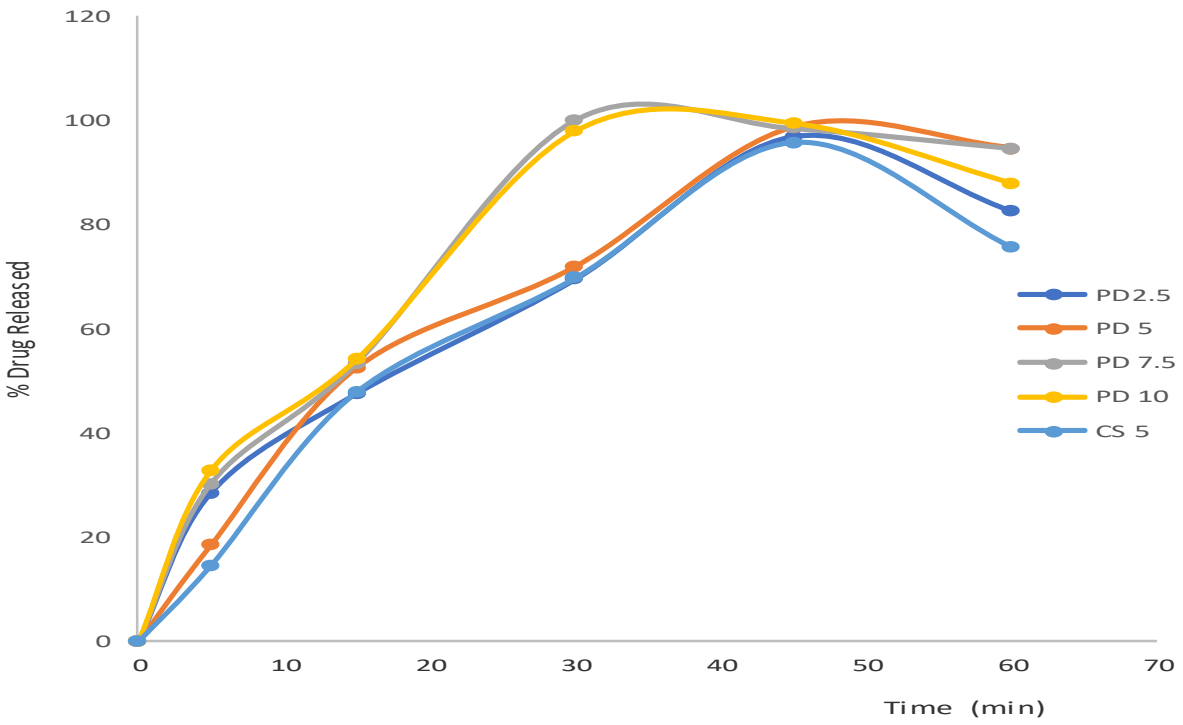

Figure 2: Dissolution Profile of *Phoenix Dactilifera* Mucilage and Corn Starch (5% Binder Concentration) Tablets

CONCLUSION

Phoenix dactylifera mucilage produced tablets which met all the requirements (weight and content uniformity, hardness, friability, disintegration and dissolution time) as specified in official compendia. This study therefore shows that *Phoenix dactylifera* has a good binding property and could be used as cost-effective and available alternative binder.

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