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Full Length Research Paper

Formulation and evaluation of paracetamol tablets manufactured using the dried fruit of *Phoenix dactylifera* Linn as an excipient

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Dried and milled date palm fruit was evaluated for its binding properties in comparison with acacia and tragacanth. Characterization of the granules in addition to quality control tests that included uniformity of weight, hardness, friability, disintegration and dissolution were undertaken. The granules manufactured using the binders had good flow properties and compressibility. As the concentration of the binders increased, the binding ability improved producing tablets with good uniformity of weight and hardness. The tablets manufactured using dried date palm was found to be less friable than tablets manufactured using acacia and tragacanth. Although, the tablets did not disintegrate, the drug release from the tablets passed the USP and BP specification for dissolution of paracetamol. Therefore, dried date palm fruit may be explored as a pharmaceutical excipient.

Key words: Date palm, quality control tests, disintegration, dissolution, weight variation, paracetamol.

INTRODUCTION

Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost. Excipients are essential ingredients of a dosage form which are added to increase volume, aid flow, enable compactness and make a drug convenient to administer. They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug. Furthermore, they act as vehicles which transport the incorporated drug to the site of absorption and are expected to guarantee the stability of the incorporated drug, the precision and accuracy of the dosage, and also improve on the organoleptic properties of the drugs where necessary in order to enhance patient adherence (Pifferi et al., 1999). They should optimize the performances of dosage forms during manufacturing as well as when patients ingest them (Pifferi and Restani, 2003).

Date fruit is an edible fruit composed of amino acids and proteins, carbohydrates, fatty acids, salts and minerals, and dietary fibre (Al-shahib and Marshall, 2003). Carbohydrates make up to 44 - 88% of the fruit which include mainly reducing sugars such as fructose, sucrose, mannose, glucose and maltose in addition to small amounts of polysaccharides such as pectin (0.5 - 3.9%), starch and cellulose (Al-shahib and Marshall, 2003). The protein content is approximately 2.3 - 5.6% with 23 amino acids which include alanine, aspartic acid, serine, glutamic acid, threonine, proline and glycine. There are 15 types of fatty acids such as arachidic, palmitic, stearic, myristic, capric, lauric and behenic acids, which make up about 0.2 - 0.5% of the fruit. However, eight of the fatty acids are found in the fleshy part of the fruit. The mineral content includes iron, cobalt, calcium, potassium, fluorine, copper, magnesium, phosphorus, sodium and zinc. Some varieties of date palm can produce as much as 400 - 600kg fresh fruits per annum for a span of 60 years and these fruits are available 8 months of the year (Al-shahib and Marshall, 2003). The moisture content decreases as they ripen

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Table 1. Compositions of paracetamol tablets at different concentrations of the binder.

Ingredients	Batch I (%) 2% binder	Batch II (%) 5% binder	Batch III (%) 10% binder	Batch IV (%) 20% binder
Paracetamol	71.4	71.4	71.4	71.4
Lactose	19.6	16.6	11.6	1.6
Binder	2.0	5.0	10.0	20.0
Corn starch	5.0	5.0	5.0	5.0
Talc	1.0	1.0	1.0	1.0
Magnesium stearate	1.0	1.0	1.0	1.0

from 83.6% to as low as 12.7% in dried state. Date palm fruit has been studied for its antioxidative and antimutagenic activities (Vayalil, 2002). However, little is known of its use as a pharmaceutical excipient.

This study was undertaken to explore the ability of dried date palm fruit to act as a binder in tablet manufacturing. To evaluate the binding properties of date palm, characterization of granules and tablets and *in vitro* drug release studies were undertaken.

MATERIALS AND METHODS

Materials

Paracetamol BP (Zhengzhou United Asia Trading Co.,Ltd, Zhengzhou, Henan, China), corn starch (G Koepcek E and Co GMBH, Sachsenfeld, Hamburg, Germany), lactose (Milkaut, Rivadavia, Franck - Pcia. de Santa Fe), talc (Hopkins and Williams, Chadwell Health Essex, England), Magnesium stearate (Gurr Chemicals, Bell Sons and Co, Southport, England), acacia (BDH Chemical Ltd, Poole, England) and tragacanth (Steculia Gum Halewood Chemicals Ltd, Stanwell Moor, Staines, Middlesex, England). Hydrochloric acid was of analytical grade.

Preparation of dried powdered date palm

Date palm fruits were bought from a local market in Jos, Nigeria. The fruits are usually sold partially dried. The seeds were extracted from the fruit and discarded while the fleshy fruits were further dried over 24 h and milled to powder for use as a binder.

Manufacture of tablets employing wet granulation method

Wet granulation method of tablet manufacturing was employed with milled date palm as a binding agent and water as the granulating liquid. Batches of paracetamol tablets were formulated using 2, 5, 10 and 20%$^{w}/_{w}$ of date palm powder. Paracetamol, lactose, date palm mucilage and corn starch were blended to form a damp coherent mass which was screened through a sieve No 10 and dried at 60°C for one hour. Corn starch was divided into two and incorporated during wet blending and after drying of granules to act as an intragranular and extragranular disintegrant. For comparative purposes, acacia and tragacanth gums were also used as binders at the same concentrations as date palm. The compositions of the batches are shown in Table 1.

Evaluation of granules

Particle size distribution of the granules

Particle size distribution of the granules was determined by mesh analysis employing a stack of sieves after granules had been weighed (34 g) and the granules were shaken for 10 min. The quantities of granules on each sieve were obtained gravimetrically.

Evaluation of bulk and tapped densities of the granules

The volume of a known quantity of the granules from each batch was obtained before and after tapping. The volume before tapping was used to determine the bulk density while the volume after tapping was employed to determine the tap density mathematically. Furthermore, Hausner's quotient and Carr's compressibility index used to determine the flow and compressibility properties of granules were obtained from the equations:

$$\text{Hausner's quotient} = \frac{\text{Tapped density}}{\text{Bulk}} \quad (1)$$

$$\text{Carr's compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (2)$$

Assessment of rate of flow and angle of repose

A simple method whereby weighed quantity of granules from each batch was allowed to flow through an orifice (funnel) at a fixed height was used to determine flow rate. The time taken for the weighed granules to flow out completely from the orifice was recorded. This was performed in triplicate. Flow rate was obtained by the equation below:

$$\text{Flow rate} = \frac{\text{Weight of granules}}{\text{Time (sec)}} \quad (3)$$

Furthermore, the angle of repose was determined by calculating tan θ from the height and radius of the cone formed by the granules as they flowed out of the orifice and subsequently obtaining the inverse of tan θ.

Compression of granules

The granules were blended with the disintegrant (corn starch), glidant (talc) and lubricant (magnesium stearate). The blend was

compressed using a single punch tableting machine (Manesty Type F3, Liver Poole, England) with a punch diameter of 0.75 cm set at 933 Pa (N/m^2) compression pressure. The die volume was to correspond to the weight of the tablet to ensure that 500 mg paracetamol is obtained.

Evaluation of the batches of tablets

Compendial and non-compendial tests were undertaken to assess the quality and performance of the batches with different binders in comparison with one another. These tests include uniformity of weight and diameter, hardness, friability, disintegration time and dissolution.

Uniformity of weight and diameter of tablets

Twenty tablets were randomly selected from each batch and assessed gravimetrically on an individual tablet basis. The mean weight as well as standard deviation were calculated. The diameters of the tablets were determined by employing a micrometer screw gauge (Sterling Manufacturing Company, India).

Mechanical strength of tablets

Although, the crushing strength test is non-compendial, it is undertaken to determine the ability of the tablets to withstand pressure during handling, packaging and transportation. A monsanto tablet hardness tester (Copley Scientific Ltd, Nottingham, United Kingdom) was employed to determine the mechanical strength of the tablets. The average force required to crush the tablets from each batch was obtained.

Friability testing of tablets

To evaluate the degree of friability of the tablets from each batch, ten tablets were randomly selected, dusted and weighed. The tablets were placed in a Roche friabilator (Erweka Gmbh, Germany) and subjected to its tumbling actions at 25 revolutions per minute for four minutes. Afterwards, the tablets were once again dusted and reweighed to determine the percentage loss of weight.

Disintegration studies on the tablets

Six tablets from each batch were utilized for disintegration studies in distilled water at 37°C using an Educational Sciences Disintegration Apparatus (Es Eagle Scientific Limited, Nottingham, United Kingdom). The disintegration time was taken to be the time no granule of any tablet was left on the mesh of the apparatus.

In vitro drug release studies

In vitro drug release studies were undertaken using USP apparatus I (basket method). The dissolution medium was 1000 mL of 0.1 N HCl at 37°C for 30 min to depict the gastric medium where the tablets will disintegrate. In all experiments, 5 mL of sample was withdrawn at 5 min interval and replaced with fresh medium to maintain sink condition. Samples were filtered and assayed spectrophotometrically at 230 nm.

Data analysis

Simple statistical analysis was utilized for content uniformity of weight, uniformity of diameter and uniformity of thickness while dissolution efficiency (DE) was used for the *in vitro* dissolution studies.

RESULTS AND DISCUSSION

The powder obtained from milling dried fruit of *phoenix Dactylifera* was brown in colour. On hydration, rapid swelling was observed which generated viscous mucilage that was utilized as a binder for wet granulation method. Granulation is employed in pharmaceutical manufacturing due to the poor flow and compaction of powders (Krycer et al., 1983). Wet granulation is a pharmaceutical process of tabletting which provides better uniformity of content especially for low drug concentrations, controls product bulk density as well as compaction of even high drug contents (Faure et el., 2001). Furthermore, it improves flow and handling, appearance, mixture's resistance to segregation and reduces variation in tablet dissolution (Kristensen and Schaefer, 1987; Westerhuis and Coenegracht, 1997; McConville et al., 2004). The type of binder used in granulating influences the properties of the granules as well as the quality of the tablets produced (Becker et al., 1997). Wet granulation is basically the addition of a binder solution or a solvent to a powder mixture; sieving to generate granules and subsequent granule drying.

Evaluation of granules

Particle size distribution of granules is evaluated due to the impact of granule size on flowability, uniformity of weight and content, compression, dissolution and subsequently, drug release (Yalkowsky and Bolton, 1990; Fichtner et el., 2005; Rohrs et al., 2006; Virtanen et al., 2010). Particle size and particle size distribution affects the compatibility and rearrangement of particles (Virtanen et al., 2010). Though, there are exceptions, the flow properties of granules are improved when the particles are large and the particle size distribution is narrow. However, larger particles lead to less strong tablets due to the fact that they have lesser surface areas for bond formation as compared to smaller particles (Sun and Himmelspach, 2006). Hence, an optimal particle size and size distribution will be required to obtain good flow properties, compaction and hardness.

The particle sizes of the paracetamol granules increased as the concentration of the binders increased as shown in Figure 1. This applied for both date palm and tragacanth; however for acacia, particle size increased as concentration increased to 10% and then a decrease in particle size was observed at 20% concentration of acacia. It may be an indication that the binding mechanism of acacia changes above 10% (Becker et al., 1997). There were much less fine particles which implied that the granules may have good flow properties. However, less fine particles may indicate that there would be more unfilled voids during the process of compression

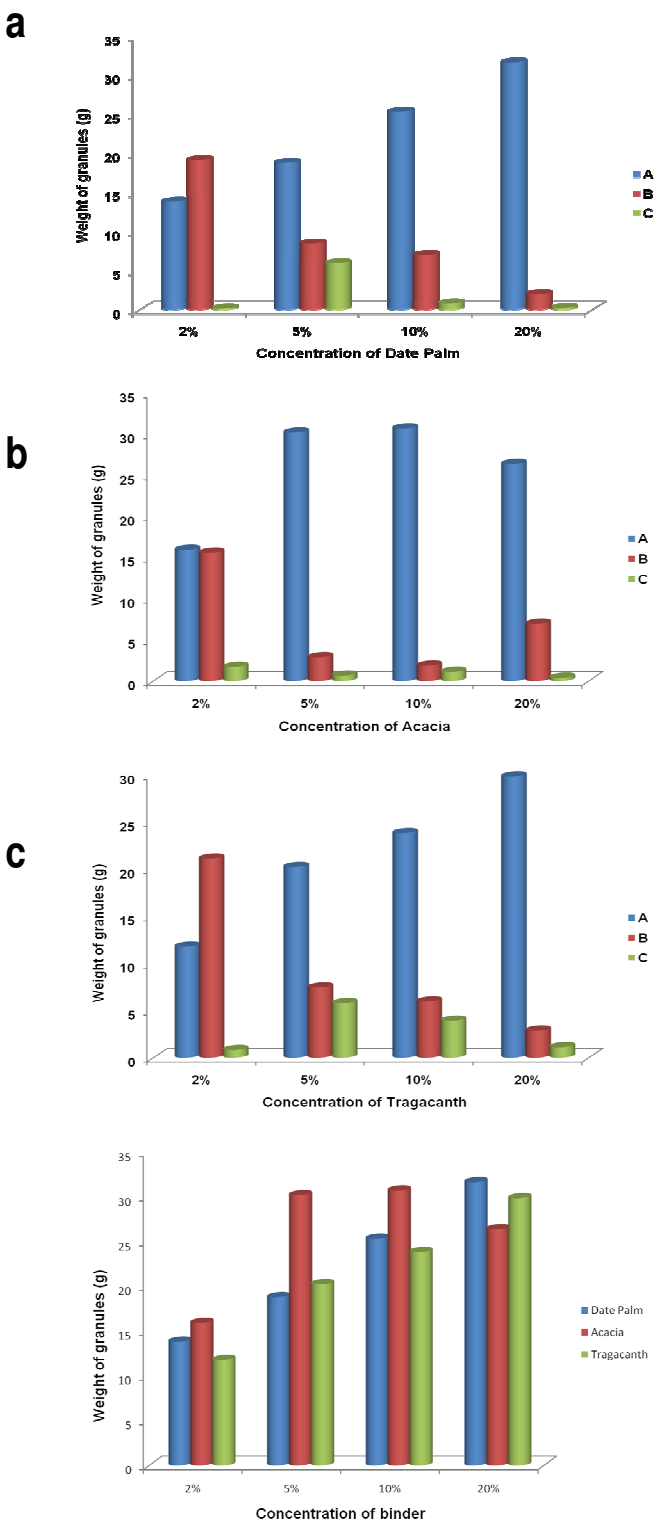

Figure 1. (a) Particle size distribution of granules employing date palm as a binder at different concentrations. NB: A, B, C depicts the weights of the granules on each sieve: A is for sieve with mesh number 60; B – mesh number 80 and C is 100. (b) Particle size distribution of granules employing acacia as a binder at different concentrations. (c) Particle size distribution of granules employing tragacanth as a binder at different concentrations. (d) comparative particel size distribution of the date palm, acacia and tragacanth at mesh number 60.

which may lead to less hard and friable tablets. Granules prepared with date palm as a binder compared more measurably with those prepared with acacia and more specifically with tragacanth.

Other parameters for assessing the properties of granules which include flow rate, angle of repose, bulk and tapped densities, Hausner quotient and Carr's compressibility are shown in Table 2. Compressibility of granules is determined so as to assess the ability of the granules to compact and decrease in volume when pressure is applied. This is needed to ensure that the suitability of the granules for tabletting in order to produce strong tablets which can withstand pressure. Compressibility index is also an indicative of the flow properties of granules while Hausner quotient relates to the cohesiveness of the granules (Mohammadi and Harnby, 1997). When the percentage compressibility is below 15% the granules have excellent flow properties while cohesive granules have percentage compressibility above 25% indicating poor flow properties (Endale et al., 2008; Bacher et al., 2008). Granules with Hausner ratio below 1.25 have good flow properties (Panda et al., 2008) and granules with angle of repose below 40° Cbut preferably below 30° Cexhibit good flow (Reddy et al., 2003) while granules with 50° would flow with difficulty (Reus-Medina et al., 2004).

Therefore, granules prepared by using different binders - date palm, acacia and tragacanth - exhibited good flow properties and satisfactory compressibility. Carr's compressibility and Hausner ratio were below 15% and 1.25, respectively, for the different concentrations of the binders while angle of repose was below 40°C for the different binder concentrations except 2% tragacanth. The flow properties of granules are determined due to its effect on the uniformity of weight of tablets. Hence, it is envisaged date palm as a binder would exhibit less variation in the uniformity of weight of tablets.

Evaluation of tablets

A summary of the properties of the tablets formulated for the batches employing the different binders are shown in Table 3 (Ferrari et al., 1996). Uniformity of weight, thickness and diameter are indication of the amount of active pharmaceutical ingredient (API) in the tablets, however, it is not a guarantee that the API is uniform in all tablets especially in formulations with low dose concentrations.

Furthermore, should weights, thickness or diameter of tablets in a batch vary, there will be variations in disintegration and dissolution. The compendial specification for uniformity of weight states that for tablets weighing more than 324 mg, weights of not more than two tablets should deviate from the average weight by more than 5% (USP, 1995). The tablets from the different batches which had different binders and at different

Table 2. Characterization of the granules prepared by the different binders.

	Date palm powder				Acacia gum				Tragacanth gum			
	2%	5%	10%	20%	2%	5%	10%	20%	2%	5%	10%	20%
Angle of repose (^{o})	29.74	28.02	26.66	29.62	32.25	31.56	31.27	31.51	42.73	28.90	26.72	28.99
Flow rate (g/sec)	5.90	5.63	5.86	5.37	6.99	5.01	5.67	5.05	0.86	7.05	5.84	5.52
Bulk density (g/mL)	1.06	0.69	0.51	0.49	0.85	0.43	0.48	0.62	1.26	0.59	0.51	0.44
Tapped density (g/mL)	1.15	0.74	0.55	0.52	0.94	0.45	0.51	0.67	1.33	0.65	0.54	0.47
Hausner quotient	0.92	0.94	0.92	0.94	0.90	0.94	0.94	0.93	0.94	0.91	0.94	1.07
Carr's compressibility (%)	8.47	6.52	8.94	6.06	11.11	6.00	5.97	7.84	5.88	9.52	6.35	6.85

Table 3. Compendial and non-compendial tests for tablets prepared by the different binders.

	Date palm powder				Acacia gum				Tragacanth gum			
	2%	5%	10%	20%	2%	5%	10%	20%	2%	5%	10%	20%
Uniformity of weight (g)	0.703	0.693	0.694	0.700	0.699	0.697	0.693	0.699	0.690	0.692	0.673	0.697
Std. dev.	0.008	0.014	0.015	0.007	0.007	0.004	0.010	0.006	0.010	0.019	0.024	0.024
Uniformity of diameter (mm)	0.954	0.956	0.965	0.985	0.964	0.966	0.967	0.965	0.967	0.966	0.965	0.966
Std. dev.	0.002	0.002	0.002	0.003	0.005	0.004	0.003	0.002	0.007	0.006	0.007	0.006
Uniformity of thickness (mm)	0.28	0.28	0.29	0.29	0.29	0.23	0.21	0.26	0.27	0.20	0.21	0.22
Std. dev.	0.003	0.002	0.002	0.002	0.004	0.004	0.003	0.003	0.005	0.006	0.007	0.006
Hardness (kg)	6.00	8.50	8.50	> 14	> 3.50	4.00	8.50	8.50	1.00	4.50	6.25	> 14
Friability (%)	24.89	11.34	7.22	0.93	23.18	12.44	18.52	26.65	-	9.89	11.15	24.89
Disintegration (min)	> 30	> 30	> 30	> 30	23	27	> 30	> 30	5	7	11	14

concentrations met the compendial specification.

Crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It is the property of a tablet that is measured to assess its resistance to permanent deformation. Furthermore, the mechanical strength of a tablet determines the disintegration time and the rate of dissolution. As the concentration of the binder increases, the mechanical strength increases. This was obtainable for date palm and tragacanth while there was no further increase in mechanical strength when 20% acacia was used. For the mechanical strength of a tablet to be satisfactory, the minimum requirement is 4 kg (Allen et al., 2004). As shown in Table 3, 2% acacia and tragacanth did not comply with the specification. All the concentrations of date palm met the specifications implying that date palm produced tablets with good mechanical strength.

Friability is another mechanical property of a tablet with compendial (USP, 1995) specification not more than 1%. While crushing strength test is a bulk deformation of the tablet, friability is a surface deformation which may be enhanced by the morphology of the tablet (Riippi et al., 1998). The rougher the surface of the tablet, the more friable it will be. It was observed that paracetamol tablets prepared with acacia and tragacanth were friable though hard as the concentration of the binder increases. 2% tragacanth could not withstand the friability test due to its softness. On the contrary, the friability of the tablets prepared with date palm decreases as the concentration of the binder increases. However, only 20% date palm met the compendial specification for friability.

Disintegration is a crucial step in release of drugs from immediate release dosage forms. The rate of disintegration is directly proportional to the rate of dissolution. The rate of disintegration is influenced by the rate of influx of water into the tablets which is also dependent on the porosity of the tablets. When the porosity is high, disintegration is hardly influenced by tablet formulation; otherwise, disintegration will be affected by the excipients (Bi et al., 1999). Although, the batches of the different types and concentrations of binders contained the same quantity of disintegrant (corn starch), only tragacanth at its different concentrations met the BP specification for disintegration which states that uncoated tablets should disintegrate within 15 min. Tragacanth in comparison with date palm and acacia produced relatively soft tablets which were friable and disintegrated rapidly. While, 2 and 5% acacia disintegrated in less than 30 min, none of the concentrations of date palm disintegrated in less than 30 min. The main mechanisms of disintegration proposed are swelling of disintegrant resulting in development of swelling force, capillary action and annihilation of intermolecular forces

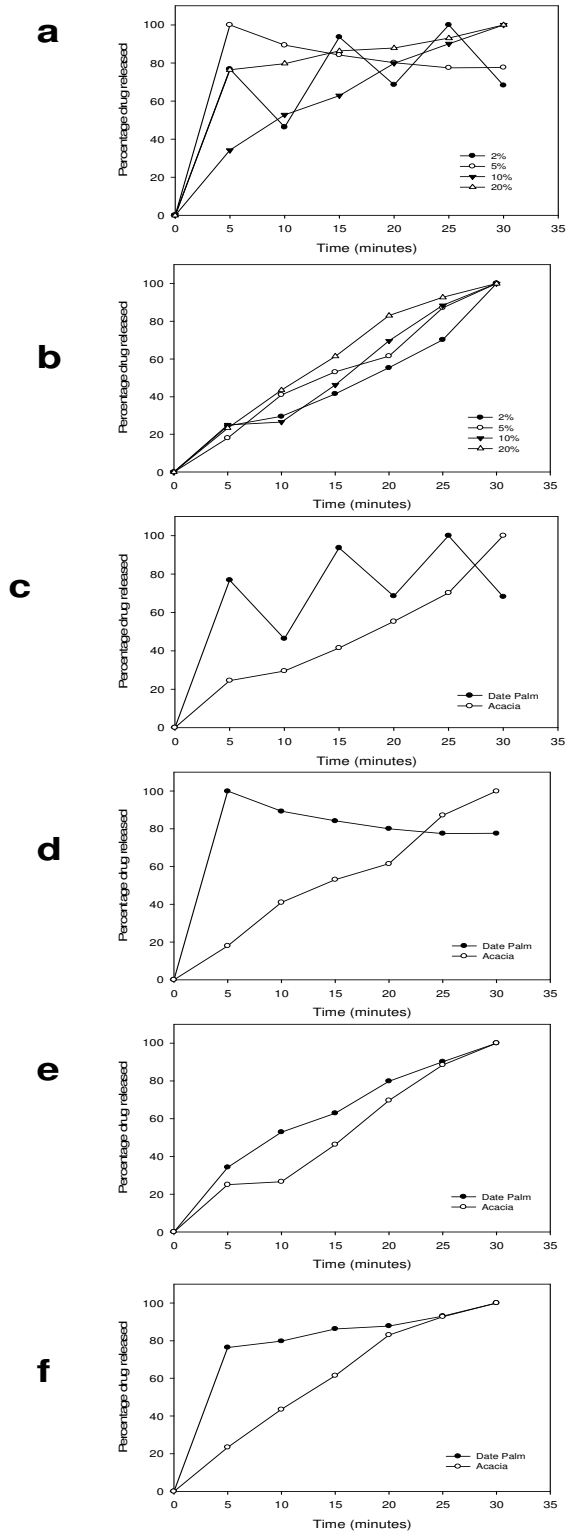

Figure 2. (a) Percentage drug release profiles of paracetamol tablets with date palm as the binding agent. (b) Percentage drug release profiles of paracetamol tablets with acacia as the binding agent. (c) Comparative drug release profiles of paracetamol tablets at 2% binder concentration. (d) Comparative drug release profiles of paracetamol tablets at 5% binder concentration. (e) Comparative drug release profiles of paracetamol tablets at 10% binder concentration. (f) Comparative drug release profiles of paracetamol tablets at 20% binder concentration.

resulting in development of a repulsive force between particles.

Some pharmaceutical excipients have inherent ability to disintegrate due to annihilation of bonds within which is enhanced by the penetration of a solvent (depending on its dielectic constant) that helps to weaken the bonds. The higher the dielectric constant of the solvent employed; the greater the weakening of bonds within the particles. Whichever the mechanism of disintegration in a given formulation, it should be adequate to overcome the impact of tablet hardness to disintegrating properties of a tablet. Basically, tragacanth did not produce very hard tablet and so the disintegrant, which employed swelling mechanism was able to induce disintegration. Perhaps increasing the quantity of disintegrant in the batches with date palm may enable disintegration of the tablets since it appeared that date palm may not be a self-disintegrating binder where annihilation of bonds is observed.

In vitro drug release studies

The rate of dissolution determines the rate and extent of absorption and subsequent therapeutic outcome of a drug. The factors that affect dissolution include type and concentration of binder, hardness, surface area, distance of diffusion, solubility of the drug, manufacturing process (wet granulation, dry granulation or direct compression) and diluents. The batches with date palm were compared with those of acacia for *in vitro* drug release studies. Although, tablets prepared with date palm as a binder did not disintegrate, the incorporated paracetamol was released from the tablets within 30 min. The drug release profiles of tablets with date palm was compared with those of acacia (Figure 2) and only tablets prepared with 10% date palm were comparable with tablets prepared with acacia producing a linear drug release profile. Tablets prepared with 2 and 20% date palm released over 70% of the drug in 5 min while 5% released 100% of the drug in 5 min as well. The rapid dissolution of paracetamol showed that date palm at 2, 5 and 20% did not control its rate of release. Furthermore, the drug release profile obtained from tablets with 2% date palm as a binder if utilized may produce erratic concentrations of paracetamol tablets in the plasma.

Solubility of paracetamol is 14 mg/mL and it is classified under the biopharmaceutical classification system, BCS class III – high solubility and low permeability, though, it may be said to have properties of BCS class I – high solubility and high permeability (Kalantzi et al., 2006). This indeed may explain the rapid release within 5 min from date palm batches though the tablets did not disintegrate which also attest to increased rate of hydration enabling rapid dissolution and diffusion out of the tablets. The USP and BP states that the quantity of drug released should not be less than 85% of the labelled amount of paracetamol in 30 min. Hence, all the batches of date palm and acacia complied with the

specification. Furthermore, FDA guidance for industry, for the dissolution testing of immediate release solid oral dosage forms suggests that in some cases for class III drugs, 85% drug release in 0.1 N HCl in 15 min ensures that there would be no bioavailability problems. Based on this, tablets with 5 and 20% date palm may not have any bioavailability problems. However, to compare and determine the similarities or dissimilarities between the binders' dissolution profiles, dissolution efficiency was employed. Dissolution efficiency is known as area under the dissolution curve within a time range (t_1- t_2) expressed as a percentage of the dissolution curve at maximum dissolution y_{100}, over the same time frame (Anderson et al., 1998; Costa and Sousa Lobo, 2001) and is represented by the equation:

$$\text{Dissolution Efficiency (DE)} = \frac{\int_{t_1}^{t_2} y.\,dt}{y_{100}(t_2 - t_1)} \times 100 \qquad 4$$

Where, y is the percentage dissolved at time t.

The integral of the numerator which is the area under the curve was calculated using the trapezoidal method:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})\,(y_{i-1} + y_i)}{2} \qquad 5$$

The dissolution efficiency is used to determine the dissolution performance of an individual formulation. The dissolution efficiencies of the different concentrations of date palm and acacia are shown in Table 4. The dissolution profiles of tablets formulated with date palm and acacia can only be said to be equivalent and be used interchangeably if the differences between them are within appropriate limits (± 10%, which is often used) (Anderson et al., 1998). The differences between the dissolution profiles from the binders for the same concentration exceeded by more than ± 10%; hence, the dissolution profiles are dissimilar. This is an indication of the paracetamol tablets formulated with date palm may be adjudged to be bio-inequivalent to those formulated with acacia.

Conclusion

Dried date palm fruit is a natural product which is non toxic, biodegradable and biocompatible that can be employed as a pharmaceutical binding agent for immediate release dosage forms. The granules manufactured with date palm had good flow properties and satisfactory compressibility which led to tablets with less variation in uniformity. The tablets had good uniformity of uniformity of weight, thickness and diameter, hard and less friable than acacia and tragacanth as its concentration increases; and a better binder than tragacanth.

Table 4. Dissolution efficiencies of the different concentrations of the binders.

Concentration of binder	Dissolution efficiency (%)
2% date palm	102.5
5% date palm	100.9
10% date palm	61.6
20% date palm	78.9
2% acacia	45.2
5% acacia	51.9
10% acacia	44.6
20% acacia	59.0

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