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(54) Title: LIQUID AND SOLID DOSAGE FORMULATIONS CONTAINING DATES (PHOENIX DACTYLIFERA)

(57) Abstract: Oral liquid and solid dosage formulations comprise a homogeneous dispersion of date material in a finely divided form. The formulation may be of nutritional and/or therapeutic value. Alternatively, the processed dates in the liquid and solid form may function purely as an excipient, in particular as an agent capable of improving the palatability of a pharmaceutically active substance with an unpleasant taste. The liquid formulation may be prepared by dispersing stoned, but otherwise whole date material in water, and subjecting the dispersion to homogenisation. The solid dose formulation preferably takes the form of granules, a tablet or a lozenge, and is preferably prepared by a process that involves the formation of a homogeneous dispersion of the date material in water, mixing of the date dispersion with some or all of the further ingredients of the formulation, and drying to remove excess water.

Title - Liquid and solid dosage formulations containing dates (*Phoenix dactylifera*)

The present invention relates to liquid and solid dosage oral formulations containing processed dates (*Phoenix dactylifera*). The formulations for oral use containing processed dates are useful as nutriceutical and/or pharmaceutical compositions. The invention also relates to a process for the preparation of such formulations.

Dates, the fruit of the date palm (*Phoenix dactylifera*), are virtually fat, cholesterol and sodium free fruits. They provide essential vitamins and minerals – such as B-complex vitamins, magnesium and iron. They also contain fibre as an insoluble component. The fruit of the date palm (*Phoenix dactylifera*), because of its tannin content, has been used in traditional medicines as a detersive and astringent in the treatment of intestinal disorders. Dates have also been used in the form of an infusion, decoction, syrup or paste to alleviate the symptoms of sore throat, colds and bronchial catarrh. Dates have also been said to counteract alcohol intoxication

Such traditional extemporaneous preparations of dates were unlikely to possess the characteristics expected of modern medicines, such as elegance, consistency, reproducible quality, safety, physical, chemical and microbiological stability and bioavailability. There is no clinical evidence of efficacy or reports of any clinical trials carried out to demonstrate efficacy of dates in the aforementioned or any other ailments. One possible reason for the lack of clinical trials is that there are, at present, no reliable, stable, safe, convenient and pharmaceutically acceptable preparations of dates. There are no reports that dates have ever been successfully and satisfactorily formulated into any oral liquid and solid dosage forms.

Dates are of course also widely used as foodstuffs, and it is known to produce date pastes and date preserves, e.g. for use in bakery products and confectionery. However, the fibrous nature of the date material, and the presence of insoluble material within the dates, means that such preparations are generally rather

inhomogeneous, have a poor mouth feel, and are difficult to formulate into a pharmaceutically acceptable liquid or compress into a tablet, for example. Dates have been used to produce various date juice products. These are often clear or clarified liquids, containing only soluble components of the date. However, such products have found little use, due to their rather poor and bland taste. Attempts have also been made to prepare date-based beverages. Some of these beverages have been carbonated, some not, but generally they have required reinforcement with organic acids and additional flavours in order to produce acceptable tasting products. Dates syrups have also been produced, but again they comprise substantially only the soluble components of the dates, and are produced by extraction of the date juice, clarification and concentration. Date spread is also known, and fits between date paste, made of the whole date flesh, and date syrup, from which all non-solubles have been removed.

It has surprisingly now been found that liquid and solids date-based formulations with acceptable properties for nutriceutical or pharmaceutical use can be prepared.

Thus, according to the invention, there is provided a liquid or solid formulation suitable for nutriceutical or pharmaceutical use by oral administration, which formulation comprises processed dates.

Liquid preparations according to the invention are in the form of homogeneous aqueous suspensions using the whole date (without the stone). Such formulations have acceptable taste and mouthfeel, as well as offering certain other advantages over the prior art. The solid formulations according to the invention may have various forms, eg compressed tablet forms and lozenges. Fundamental to both solid and liquid formulations according to the invention is the preparation of a fine and homogenous dispersion of processed dates

By "homogeneous" in this context is meant that the particles of date material present in the formulation are sufficiently fine and uniform that the formulation feels smooth in the mouth when presented as liquid or in a solid dose form.

Furthermore, because of the uniformity and fineness of the dispersion, there is a greater degree of contact between the date particles and the papillae on the tongue. Therefore, the dates dispersion of this invention exhibits "roundness" of taste particularly for a liquid product. This unique property will also apply to the dried dispersion presented in the form of solid dosage form such as chewable or dispersible tablets.

Any suitable variety of date may be of utility in the present invention. Dates are grouped generally into three varieties: soft, semi-soft and dry or bread dates. Some commonly available dates are as follows:

- Deglet noor: A semi-dry date, originally imported from Algeria, possesses a delicate flavour, and is firm-textured in appearance, with a colour range from light red to amber or straw.
- Halawy: A soft date, thick flesh, caramelly and sweet, somewhat wrinkled in appearance, with a yellow colour ripening to a light amber and then to a golden brown. Originally this date was imported from Iraq.
- Khadrawy: A soft date originally imported from Iraq, it has many desirable qualities. It cures well; it ripens to amber, and then cures to a reddish brown, with a caramel-like texture and a sweet flavour.
- Zahidi: A semi-dry date from Iraq, distinguished by its large seed in proportion to the fruit itself. This date lends itself well to processing and softening by steam hydration.
- Thoory: Often called "Bread Date". Driest date variety, with firm skin, less sticky; flesh chewiest and is the staple diet of the Nomadic tribes of the desert countries of the world.
- Medjool: 'Medjool' dates most likely exist as a landrace variety at its location of origin, the Tafilalt region of Morocco. Another possibility is that 'Medjool' date may have a very high mutation rate.

Dates ripen in stages. The khalal stage is when it reaches maximum size and identifying colour. The rutab stage is when the fruit begins to soften at the tip. The tamar stage is when the date is fully cured or dried. For the purposes of this

invention, it may be possible to use dates at all stages of ripening, but it is preferred to use rutab or tamar dates.

One group of formulations according to the invention are in liquid form.

Thus, according to a first specific aspect of the invention, there is provided a liquid dosage formulation, in the form of a homogeneous dispersion in water of date material in finely divided form.

In such formulations, the nutritional principles are better assimilated, which is of particular importance for formulations intended for dietetic and/or nutritional products, especially for children. The fineness and uniformity of the dispersion may also lead to significantly improved physical stability. The dispersion is physically stable over a long period and is not prone to separation. If some separation does occur, the homogenised product redisperses easily by simple shaking and reverts to its original homogeneous appearance. There is also a significant reduction or attenuation of the typical "collar" effect (separation and also floating of some suspended particles above the separated fluid, and also be some sediment at the bottom part of the bottle) that is commonly observed with suspension formulations, such as extemporaneously prepared dispersions of fruit juices.

In quantitative terms, "homogeneous" may mean that all or substantially all of the date material is present in the form of particles having a particle size of less than 500µm, and more preferably less than 100µm. For instance, more than 90% w/w of the date material is preferably present in the form of particles with a size less than 100µm, or a size less than 80µm, or a size less than 50µm. It may well be that the majority of the date material, e.g. more than 90% w/w or more than 95% w/w, is present in the suspension in the form of particles with a size in the range 1-50µm.

Obviously, for use in the invention the dates must be stoned, but otherwise it is preferred that the date material used in the present invention is whole date

material, i.e. substantially the whole of the material that constitutes the flesh of the date, and not just certain components of the date. Soluble components of the date material may dissolve in the aqueous carrier medium, while insoluble components are held in suspension.

In this aspect of the invention the amount of dates, on dry basis, will generally be at least 5% w/w, and up to 50% w/w, of the weight of the formulation, preferably between 5% w/w and 35 % w/w, e.g. about 30% w/w of the final weight of the formulation.

The liquid dosage formulation of the invention may be prepared by dispersing date material in water, and subjecting the dispersion to homogenisation. Such a process represents a further aspect of the invention.

Homogenisation of the date dispersion can be achieved by means of a high shear mixer such as a Silverson, which is well known to those skilled in the art. Other forms of colloid mill, fluid energy mill or high pressure homogenisation may also be suitable. Conventional techniques such as wet milling, spray-drying and freeze-drying may also be used as part of the process. Additional ingredients of the formulation may be added either before or after homogenisation.

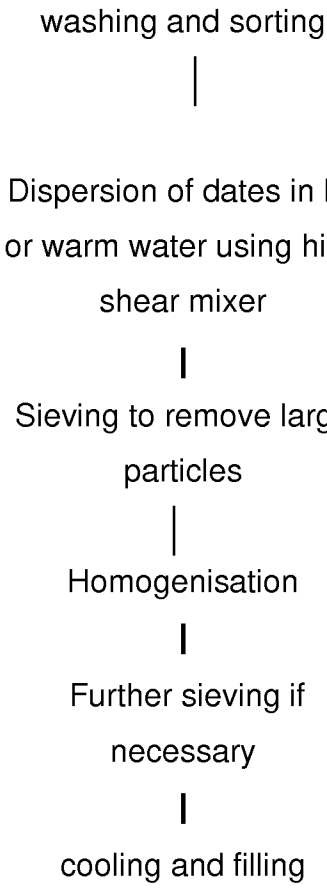
High pressure homogenisation is an entirely mechanical process, in which the product is forced by a high pressure piston pump through a homogenising valve. The commercially available Niro Soavi homogeniser is an example of a suitable high pressure homogeniser.

In the process of homogenisation, however performed, the dimensions of the suspended particles of date material are reduced. At the end of the process, the suspension commonly presents a uniform distribution, according to a “Gaussian” curve, although such a particle size distribution may not be essential. The particle size distribution will vary with the operating conditions. The temperature at which dates are dispersed in water prior to or after homogenisation and the

homogenisation pressure may require careful adjustment to achieve a commercially viable, stable, safe and elegant dispersion.

The yield and quality of the dispersion prepared from the dates by homogenisation will depend on the variety, ripeness and dimensions of the dates, as well as on the degree of integrity of dates, the manner in which they have been stored, and the preparation technique.

Typically, the steps involved in the production process for homogenisation are as follows:



The liquid dosage formulation according to the invention represents a balanced nutritional source and may be used for that purpose. Formulations for such use may additionally contain one or more additional nutritional components such as fats, carbohydrates, proteins, vitamins, drugs and minerals.

Fats or lipids that may be incorporated into the liquid formulation include, but are not limited to, coconut oil, soy oil, corn oil, olive oil, safflower oil, high oleic safflower oil, MCT oil (medium chain triglycerides), sunflower oil, high oleic sunflower oil, structured triglycerides, palm and palm kernel oils, palm olein, canola oil, marine oils, cottonseed oil and combinations thereof. Carbohydrates that may be incorporated into the formulation may be simple or complex, lactose-containing or lactose-free, or combinations thereof. Non-limiting examples of suitable carbohydrates include hydrolysed corn starch, maltodextrin, glucose polymers, sucrose, corn syrup, corn syrup solids, rice-derived carbohydrate, glucose, fructose, lactose, high fructose corn syrup and indigestible oligosaccharides such as fructooligosaccharides, and combinations thereof.

The liquid formulation may further comprise any of a variety of vitamins, non-limiting examples of which include vitamin A, vitamin D, vitamin E, vitamin K, thiamine, riboflavin, pyridoxine, vitamin B12, niacin, folic acid, pantothenic acid, biotin, vitamin C, choline, inositol, salts and derivatives thereof, and combinations thereof.

The liquid formulation may further comprise any of a variety of electrolytes, non-limiting examples of which include calcium, phosphorus, magnesium, iron, selenium, manganese, copper, iodine, sodium, potassium, chloride, and combinations thereof.

Another significant aspect of this invention relates to use the processed dates dispersion to manufacture solid dosage forms. This is particularly surprisingly because fibrous and adhesive materials such as dates are very difficult to compress into tablets and the fibrous materials are also not suitable for formulating into lozenges.

Thus, according to a second specific aspect of the invention, there is provided a solid formulation suitable for nutriceutical or pharmaceutical use by oral administration, which formulation comprises processed dates.

In solid formulations according to the invention, the processed dates may themselves be of nutritional and/or therapeutic value. For instance, the processed dates may have a demulcent effect. Alternatively, the processed dates may function purely as an excipient, in particular as granulating agents, or as an agent capable of improving the palatability of a pharmaceutically active substance with an unpleasant taste. The formulations offer a commercially acceptable, stable, economic, simple, consistent and convenient dosage form for the oral administration of processed dates, either alone or in conjunction with pharmaceutically active agents. Tablets that are dispersed in water prior to administration (e.g. dispersible and effervescent tablets), and also chewable tablets, as are widely used by patients and in particular children, who have difficulty in swallowing conventional tablets or capsules, often contain active ingredients with an unpleasant taste, such as some vitamins and analgesics (e.g. paracetamol). The processed dates used in the present invention have a long-lasting flavour and are capable of masking the after taste of such drugs, either alone or in conjunction with other suitable flavours and sweeteners.

The formulation according to the invention may take any one of numerous forms. Most preferably, however, the formulation takes the form of a tablet or lozenge. The formulation may be swallowable, disintegratable, effervescent, chewable or suckable, and may be intended for buccal or sub-lingual administration.

Similar to the preparation of the liquid oral dosage form, there may be many methods by which processed dates, usually in finely divided form, may be incorporated into solid dosage forms according to the invention. A particularly preferred method, which represents a further aspect of the invention, involves the formation of a homogeneous dispersion of the date material in water, mixing of the date dispersion with some or all of the further ingredients of the formulation, and drying to remove excess water.

Homogenisation of the date dispersion can be achieved by means of a high shear mixer such as a Silverson, or high pressure homogenisation which is well known

to those skilled in the art. Other forms of colloid mill and fluid energy mill may also be suitable.

A typical process for the preparation of tablets in accordance with the invention is set out in the following flow diagram;

washing and sorting of date material

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Dispersion of date material in hot or warm water and homogenization or high shear mixing followed by sieving

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Further homogenization and final sieving if necessary

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Granulation (massing) of tablet excipients with homogenised dates granulating agent (dates dispersion)

The process of wet massing is carried out in a suitable mixer such as a planetary, high shear mixer or in a fluid bed granulator

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Sieving and drying of granules

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Further granulation (massing) if necessary with homogenised dates granulating agent (dates dispersion)

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Further sieving and drying of granules

|

Mixing with lubricants, disintegrants and flow aids etc

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Compression

In this process, the tablet diluents are granulated with a fine dispersion of dates in water prepared by homogenisation and/or milling.

If soluble diluents are required to achieve desired tablet characteristics, then diluent bases such as glucose, sucrose, maltose, lactose, arabinose, xylose, ribose, fructose, mannose, galactose, sorbose, trehalose, sorbitol, xylitol, mannitol, maltitol, lactitol, isomaltol, maltodextrin, hydrogenated starch hydrolysis products and mixtures thereof, and sorbitol are employed for oral, suckable, dispersible, swallowable or chewable tablets.

Alternatively, insoluble diluents, or a mixture of soluble and insoluble excipients, may be granulated with the date dispersion in the manufacturing processes as necessary to achieve the desired properties. Suitable insoluble materials include starches, water-insoluble cellulose derivatives, microcrystalline cellulose or an alkaline earth metal carbonate, sulphate or phosphate.

Lozenges may be prepared by combining sucrose and corn syrup in a ratio of 50:50 to 70:30, and incorporating a suitable amount of a dispersion of dates in water. In this case, the liquid sucrose syrup and corn syrup and dates are cooked, eg at 125°C. Final heating is performed, e.g. at 148°C, under vacuum. Any drugs or herbal ingredients such as liquorice are mixed with other ingredients such as flavours and benzyl alcohol. Any acids, such as citric or tartaric acid, are then mixed. There are many ways of adding the drug and flavours. However the most common method is to add the drug / flavour mixture and other constituents and additives (such as menthol etc) on the mixing table. The candy base containing dates is then formed, rope-sized, moulded, cooled and sized.

Chewable tablets may be prepared as follows. The formulation containing the drug and other excipients is granulated using the dates dispersion as granulating agent to granulate all or some of the ingredients of the formulation. Another option is to produce base granules containing one or more diluents produced by granulating with the dates dispersion. The base granules are then used for

blending and compression with the drug, flavours, sweeteners and other excipients similar to the process used for direct compression.

In some cases, if the ingredients are not moisture- and/or heat-sensitive, the drug and other components of the formulation may also be granulated with water containing a binder and/or dates dispersion. These may then sieved, dried and tabletted.

In this aspect of the invention the amount of dates, on dry basis, will generally be at least 5% w/w, and up to 50% w/w, of the weight of the solid formulation, preferably between 5% w/w and 35 % w/w, eg about 30% w/w of the final weight of the solid formulation. The aqueous dispersion of dates may be used to granulate (where present) diluents, excipients such as disintegrants, flavours, and wetting agents, and the pharmaceutically active agents.

Surprisingly, in some compositions of the invention, the dates act as an efficient binder, aiding compaction of granules and obviating the need to include a conventional binding agent such as Povidone (PVP), as is typically used in tablets prepared by moist granulation.

The formulations according to the invention are also of utility for the delivery of pharmaceutically active agents, and in particular are of benefit in the delivery of pharmaceutically active agents that have an unpleasant taste. The longer-lasting taste profile of the homogenised date dispersion is capable of masking the unpleasant taste of a wide range of active agents.

Thus, according to another aspect of the invention, there is provided a liquid or solid dosage formulation comprising one or more pharmaceutically active agents, wherein the formulation further comprises processed dates.

The taste-masking effect of the formulation may be further enhanced by the inclusion of additional viscosity enhancing agents, flavours and/or sweeteners.

Flavouring agents that may be used in the present invention include, but are not limited to, natural flavours, natural fruit flavours, artificial flavours, artificial fruit flavours, flavour enhancers or mixtures thereof. The natural flavour may be selected from apple essence, pear essence, peach essence, berry essence, wildberry essence, date essence, blueberry essence, kiwi essence, strawberry essence, raspberry essence, cherry essence, plum essence, pineapple essence, and apricot essence, natural mixed berry flavour, citric acid, malic acid, vanilla, vanillin, cocoa, chocolate, and menthol. In addition, the flavours may be selected from one or more of the group consisting of anise oil, cinnamon oil, peppermint oil, oil of wintergreen, clove oil, bay oil, anise oil, eucalyptus oil, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds, cassia oil, lemon oil, orange oil, lime oil, grapefruit oil, grape oil and combinations thereof.

Natural flavours, artificial flavours or mixtures thereof include mint (such as peppermint or spearmint), menthol, cinnamon, vanilla, artificial vanilla, chocolate, artificial chocolate or bubblegum. Natural fruit flavours, artificial fruit flavours or mixtures thereof include, but are not limited to, cherry, grape, orange, strawberry or lemon. Flavour enhancers include, but are not limited to, citric acid. Although flavouring agents are generally provided as a minor component of the formulation, the addition of at least one flavouring agent is preferred. However, up to two flavouring agents may generally be employed.

The taste masking composition may further comprise an effective amount of a sweetener, at least one flavouring agent, and an artificial sweetening agent.

Optional sweetening agents include, but are not limited to, sugar sweeteners such as monosaccharides, disaccharides and polysaccharides. Examples of suitable sugar sweeteners include, but are not limited to, xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolysed starch (such as maltitol syrup) or corn syrup, and sugar alcohols such as sorbitol, xylitol, mannitol, glycerin and combinations thereof. Artificial sweeteners include, but are not limited to, aspartame, acesulfame potassium, cyclamate, saccharin, saccharin sodium, sucralose and mixtures thereof.

The amount of additional sugars, optional and artificial sweetener used in the formulation will vary depending on the degree of sweetness and palatability desired.

The liquid formulations according to the invention are preferably formulated with a certain degree of viscosity, which may be imparted by the date material. Alternatively, additional viscosity enhancing agents may be included to achieve the optimum viscosity, taste masking and desired physical and/or chemical characteristics throughout product shelf life.

Examples for suspending agents are poly(vinylpyrrolidone); poly(vinyl alcohol); methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and mixtures thereof; sodium alginate; polyacrylamides; polyacrylic acids; collagen; polyethylene glycol; polysaccharides and carbohydrates such as starch, cellulose, dextrans and derivatives; thixotropic media; and the like. Other suspending agents include natural gums such tragacanth, acacia or xanthan gum, guar gum, and gelatin, as well as clays such as veegum, bentonite, and hectorite.

A preservative system is also generally required for an oral liquid such as the liquid formulations of the invention, and this may be selected from those conventionally employed in oral medicines. These usually consist of benzoic acid, sodium benzoate, potassium sorbate, ascorbic acid, sorbic acid, domiphen or other suitable preservatives and their mixtures.

As the liquid formulations of the invention may be thermodynamically unstable dispersed systems, in which the solid particles of the internal phase tend to aggregate and form sediment, the use of a coadjuvant may be required to improve dispersion, viscosity and other aspects so that a stable product is obtained.

An effective quantity of a wetting agent may be required if relatively insoluble drugs or ingredients are present in the composition. Such wetting agents may be selected from the group consisting of surface active agents, (eg anionic, non-ionic

and cationic surfactants), glycerol, propylene glycol, liquid polyethylene glycols, sorbitol and mixtures thereof.

Pharmaceutically active compounds that may be incorporated into the solid dosage forms of the present invention include antihistamines, decongestants, antitussives, expectorants, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesic drugs, such as paracetamol (acetaminophen) and phenacetin.

Antihistamines that may be mentioned (along with their preferred salt form) are chlorpheniramine (maleate), brompheniramine (maleate), dexchlorpheniramine (maleate), dexbrompheniramine (maleate), triprolidine(HCl), diphenhydramine (HCl), doxylamine (succinate), tripelennamine (HCl), cyproheptatine (HCl), bromodiphenhydramine (HCl), phenindamine (tartrate), pyrilamine (maleate, tannante) and azatadine (maleate).

Antitussives that may be mentioned (along with their preferred salt form) are caramiphen (edisylate), dextromethorphan (HBr), codeine (phosphate, sulfate), and pholcodeine.

Decongestants that may be mentioned (along with their preferred salt form) are pseudoephedrine (HCl), phenylpropanolamine (HCl) and phenylephrine (bitartrate, tannate, HBr, HCl).

Expectorants that may be mentioned (along with their preferred salt form) are terpin hydrate, guaifenesin (glyceryl guaiacolate), potassium (iodide, citrate) and potassium guaicolsulfonate, and salbutamol and others

Non-steroidal anti-inflammatory drugs (NSAIDs) for use in the formulations of the invention may be selected from any of the following categories:
(1) propionic acid derivatives;(2) acetic acid derivatives;(3) fenamic acid derivatives; (4) biphenylcarboxylic acid derivatives; and (5) oxicams.

Of the propionic acid derivatives, ibuprofen, naproxen, ketoprofen, flurbiprofen, fenoprofen, suprofen, fenbufen, and fluprofen may be mentioned as preferred compounds. Of the acetic acid derivatives, tolmetin sodium, zomepirac, sulindac and indomethacin may be mentioned. Of the fenamic acid derivatives, mefenamic acid and meclofenamate sodium are examples. Diflunisal and flufenisal are biphenylcarboxylic acid derivatives. The oxicams include piroxicam, sudoxicam and isoxicam. Other analgesic compounds useful in the practice of the present invention include acetominophen (parecetamol) and phenacetin.

Active pharmaceutical ingredients are incorporated into the solid dosage forms in amounts governed by their physicochemical characteristics, and shall be in compliance with applicable regulatory guidelines.

Compositions according to the invention that contain conventional pharmaceutical actives may be of utility in the treatment of any conditions that are conventionally treated with the actives concerned. In addition, the compositions, either with or without conventional pharmaceutical actives, may be useful in the treatment of conditions that may be ameliorated by the demulcent properties of dates. Thus, the formulations of the present invention may be used to treat individuals suffering from the mucosal irritation associated with mucositis. The formulations may also be suitable for the treatment of microbial infections such as influenza, rhinoviruses, or other microbial infections that can irritate the throat and tonsils.

The formulation may also contain demulcents additional to the date material, such as liquorice (Glycyrrhiza), to further enhance the demulcent properties of the formulation.

Embodiments of the invention will now be described in greater detail, by way of illustration only, with reference to the following Examples, in which dates from which the stones had been removed were used. These dates were readily available in the local market as rectangular 250g blocks and those used were either Babylonian or Algerian dried (tamar) dates. Typically these contain 99% dates in a hydrated form. The formulations described below are specific to the

dates from these origins. Some adjustment to the formulation and the process may be needed to achieve the desired properties for compression and palatability if dates of other origin are used. The formulations given below are for pharmaceutical oral liquid products containing drugs. Formulations of dates for nutritional use may require different criteria for palatability (e.g. sweetness, flavour), viscosity, preservation, taste and mouthfeel.

In the following Examples 1 to 8, which relate to liquid dosage forms, the following general preparative method was used:

1. The dates were mixed with hot de-ionised water and the blend was passed through a high shear mixer or homogenized, sieved and then passed through a homogenizer (e.g Silverson) until a very fine homogeneous dispersion with an acceptable mouth feel was achieved . Dates dispersions were also prepared with a high pressure homogeniser (Niro Soavi 2K) at a range of pressures and using one and two passes to produce optimum dispersion characteristics

2. To water, ingredients were added in the following order: preservatives, citric acid, Xantural (xanthan gum), dates, ibuprofen, and stirred using a Silverson mixer or high pressure homogeniser until a homogeneous suspension was obtained. For Example 8, ibuprofen was first sieved to remove agglomerates then added to the suspension.

The moisture content of the dates used was determined using a moisture balance (Mettler PE360/LP15, setting 7) and the dates were heated for 45 minutes at 110°C. The dates used had 12% water content.

Example 1

Dates Hydrated	25% (as supplied)
Dried basis	22.5%
Water	75%

This formulation did not have sufficient viscosity or sweetness with the dates used. Sweetening agents and viscosity enhancing agents can be used to adjust the viscosity and sweetness

Example 2

Dates Hydrated	25%
Dried basis	22 %
Water	74.5%
Xantural 180	0.5%

This formulation was not sufficiently sweet.

Example 3

Dates Hydrated	35.0%
Dried basis	30.8%
Water	65%.

Suspension was too viscous although sweetness appeared satisfactory.

Example 4

Dates Hydrated	30.3%
Dried basis	26.6%
Water	69.7%

The sweetness and viscosity were acceptable.

Example 5

Dates Hydrated	30%
Dried basis	26.4 %

Water	69.7%

Sweetness and viscosity were acceptable.

Example 6

Dates Hydrated	30%
Dried basis	26.4%
Water	68.35%
Xantural 1800.	0.25%
Preservatives**	0.4%
Citric acid	1.0%

** paraben system:

Methyl hydroxybenzoate 0.1%w/w

Propyl hydroxybenzoate 0.05%w/w

Sodium benzoate 0.25%w/w

Acceptable product with respect to sweetness and viscosity.

Example 7

Dates Hydrated	30.85%
Dried basis	27%
Water	67.5%
Xantural 180	0.25%
Preservatives**	0.4%
Citric acid	1.0%

** paraben system:

Methyl hydroxybenzoate 0.1%w/w

Propyl hydroxybenzoate 0.05%w/w

Sodium benzoate 0.25%w/w

Acceptable sweetness and viscosity.

Example 8

Dates Hydrated	27%
Water	66.98%
Xantural 1800.	0.25%
Citric acid	0.98%
Preservatives**	0.392%
Ibuprofen	2.0%

** paraben system:

Methyl hydroxybenzoate 0.1%w/w

Propyl hydroxybenzoate 0.05%w/w

Sodium benzoate 0.25%w/w

Acceptable sweetness, viscosity, taste and mouthfeel.

Examples 9 to 18 relate to solid dosage forms.

Example 9

Tablets containing 18.2% processed dates

An aqueous date dispersion was prepared by using dates from which the stones had been removed. A 40% dispersion of these stoned dates in water was prepared (40g of dates containing 12% moisture in 100g of water). The 100g of dispersion contained 40g of hydrated dates, i.e. 35.2g on dried basis.

The moisture content of the dates used was determined using a Moisture balance (Mettler PE360/LP15, setting 7) and the dates were heated for 45 minutes at 110°C.

Table 1 - formulation composition with 1 18.2 % dates

Excipient	Amount used / g	% on dried basis
Lactose	105	80.8
40% Dates dispersion	67 (26.8 g of dates)	18.2
Magnesium stearate	-	1.0

Process :

1 The 40% w/w date dispersion in hot water was prepared using a homogeniser (Silverson).

2 Massed lactose (105g) with date dispersion in a planetary mixer.

3 Passed the mass through a sieve and dried the granules for 30 minutes at 50℃ in an oven.

4 Placed the granules again in the mixer and massed with additional amount of the date dispersion.

5 Passed the mass again through a sieve.

6 Dried the granules in a hot air oven and added 1% w/w magnesium stearate, which was passed through a sieve to deaggregate.

7 Compressed the tablets on a tablet machine using 10x21mm pillow shaped tooling.

The tablets produced were robust and there was no indication of any compressional problems or any sign of capping during and following compression.

Tablet weight uniformity

Mean	317.1mg
Min	310.0mg

Max	326.0mg
Relative standard deviation	1.45 %

Tablet Hardness

Mean	16 kp
Minimum	13kp
Maximum	19 kp

Example 10

Tablets containing 25% dates

An aqueous date dispersion was prepared by using a block of dates from which the stones had been removed as described in Example 1.

A 40% dispersion of these stoned dates in water was prepared (40 g of dates containing 12% moisture). The 100 g of dispersion will contain 40g of dates and 35.2g on dried basis.

Table 2 - formulation composition with 25%dates

Excipient	Amount used / g	%
Lactose	67.1	74
Dates (40% w/w dispersion)	63.9 (25.5 g of dates)	25
Magnesium stearate	1.76	1.0

Process :

1 The 40% w/w date dispersion was prepared using hot water and a homogeniser as described in Example 1 to achieve a fine dispersion.

2 Massed lactose (105g) with date dispersion in planetary mixer.

3 Dried for 180 minutes at 50°C in a hot air oven.

4 Placed the granules again in the planetary mixer and massed with additional amount of the date dispersion to achieve the desired concentration of dates in the blend.

5 Passed the mass through a sieve 10 mesh sieve size (2000 micrometer).

6 Dried the granules in a hot air oven.

7 Added 1% w/w magnesium stearate, which was passed through a sieve to deaggregate and blended with the dried granules.

8 Compressed the tablets on a tablet machine using 10x21mm pillow shaped tooling.

The tablets produced were robust and there was no indication of any compressional problems or any sign of capping during and following compression.

Tablet weight uniformity

Mean	317.1mg
Minimum	310.0 mg
Maximum	326.0 mg
Relative standard deviation	0.45 %

Tablet Hardness

Mean	19 kp
Minimum	18 kp
Maximum	21 kp

Examples 11 to 16

Date-based ibuprofen tablets

In Examples 11 to 16, ibuprofen has been used as a model drug to represent drugs with poor compressional properties. Formation of robust and hard tablets containing a poorly compressible drug such as ibuprofen used at a high dose would show that dates act as an effective binding agent. Those skilled in the art would be able adjust the tablet formulation by adding suitable tablet excipients such as disintegrants, wetting agents, dispersants and polymers to achieve desired physico-chemical properties (including chewability, rapid dispersability, mouthfeel, taste-masking, immediate or controlled release of the drug contained in the tablet). The robust tablets can also be coated satisfactorily using dry, film or sugar coating.

Example 11

Ibuprofen tablets using dates as a diluent and binder

Table 3 - Ibuprofen tablets prepared using dates at 5% w/w (used as granulating agent)

	Amount used / g	Solids in dried state / g	% w/w
Ibuprofen fine	500	500	79.10
Microcrystalline cellulose	100	100	15.83
30% w/w date dispersion	119.7	31.6	5.0

The block stoned dates contained typically 12% moisture. Therefore 31.6g on dried basis is equivalent to 35.9g of the hydrated dates.

Process :

1 The ibuprofen and microcrystalline cellulose were sieved and blended.

2 The date dispersion was prepared by adding stoned dates to hot water and homogenizing using a Silverson mixer.

3 The ibuprofen/microcrystalline cellulose blend was placed in a planetary mixer and the date dispersion was added as the granulating agent.

4 Additional water was added to achieve suitable heavy mass.

5 The wet mass passed through a sieve by hand.

6 The wet granules were dried in a hot air oven overnight.

7 The granules were passed through a 16 mesh sieve (1190 micrometer).

8 The dried granules were blended with magnesium stearate (1% w/w of the dried granules).

9 The lubricated granules were compressed using a tablet machine fitted with 10x21mm pillow shaped tooling.

Tablet weight uniformity

Mean	638.5mg
Minimum	615 mg
Maximum	656 mg
Relative Standard deviation	2.04%

Tablet Hardness

Mean	6.5 kp
Minimum	5.2 kp
Maximum	8.6 kp
Relative standard deviation	15.4%

Example 12

Ibuprofen tablets using dates as a diluent and binder

Table 4 - Ibuprofen tablets prepared using dates at 10% w/w (used as granulating agent)

	Amount used / g	Solids / g	% w/w
Ibuprofen	500.0	500.0	74.95
Microcrystalline cellulose	100.0	100.0	14.99
30% w/w date dispersion	254.0	67.1	10.06

Dates contain 12% moisture: 67.0g anhydrous = 76.2g hydrated.
To add 76.2g of dates in dispersion (30% w/w), need 254.g of 30% w/w dispersion

Process :

1 The ibuprofen and microcrystalline cellulose were sieved and blended.

2 The date dispersion was prepared by adding the dates to hot water and homogenised using a Silverson mixer.

3 The ibuprofen / microcrystalline cellulose blend was placed in a planetary mixer and the date dispersion was added as the granulating agent

4 Additional water was added as necessary to form a suitable (heavy) mass.

5 The wet granules were sieved through a 10 mesh sieve size (2000 micrometer) and dried in a hot air oven at 50°C overnight.

6 The dried granules were sieved through a 16 mesh sieve (1190 micrometer).

7 Magnesium stearate (1% w/w of the dried granules) and crosscarmellose sodium (4% w/w of the dried granules) were then added to the granules and blended.

8 The lubricated granules containing lubricant and disintegrant were compressed using a tablet machine fitted with 10x21mm pillow shaped tooling.

Tablet weight uniformity	
Mean	689 mg
Min	664 mg
Max	697mg
Relative standard deviation	1.4%

Hardness	
Mean	11.6 kp
Min	8.6 kp
Max	13.5 kp
Relative standard deviation	12.40%

Disintegration time : over 30 minutes (mean hardness 11.6 kp)

Disintegration time : 7 minutes 50 seconds (mean hardness 7.8kp)

Example 13

Ibuprofen tablets using dates as a diluent and binder

Table 5 - Ibuprofen tablets prepared using dates at 15% w/w (used as granulating agent)

	Amount used / g	Solids / g	% w/w
Ibuprofen	500.0	500.0	70.82
Microcrystalline cellulose	100.0	100.0	14.16
30% w/w date dispersion	401.7	106.0	15.01

Dates contain 12% w/w moisture: 106.0g anhydrous = 120.5g hydrated.

To add 120.5g of dates in dispersion (30% w/w), need 401.7g of 30% w/w dispersion

Process :

1 The ibuprofen and microcrystalline cellulose were sieved and blended.

2 The date dispersion was prepared by adding the dates to hot water and homogenised using a Silverson mixer.

3 The ibuprofen and microcrystalline cellulose blend was placed in a planetary mixer and the date dispersion added as the granulating agent.

4 Additional water was added to form a suitable (heavy) mass.

5 The wet mass were sieved through a 10 mesh size sieve (2000 micrometer) and dried in a hot air oven at 50°C overnight.

6 The dried granules were sieved through a 16 mesh size (1190 micrometer) sieve.

7 Magnesium stearate (1%. w/w of the dried granules) and crosscarmellose sodium were added to the granules and then blended.

8 The lubricated granules were compressed using a tablet machine fitted with 10x21mm pillow shaped tooling.

Tablet weight uniformity	
Mean	708.3 mg
Min	703 mg
Max	713 mg
Relative standard deviation	0.45%

Hardness	
Mean	10.0 kp
Min	9.3 kp
Max	11.5 kp
Relative standard deviation	6.6% kp

Disintegration time for tablets containing 4% w/w crosscarmellose

Greater than 30 minutes (hardness 10kp)

Greater than 30 minutes (hardness 12kp)

13 minutes (hardness 5kp)

11 minutes (hardness 7.6k)

Example 14

Ibuprofen tablets using dates as a diluent and binder

Table 6 - Ibuprofen tablets prepared using dates at 20% w/w (used as granulating agent)

	Amount used / g	Solids / g	% w/w	Qty Dispensed / g
Ibuprofen	500.0	500.0	66.67	100.0
Microcrystalline cellulose	100.0	100.0	13.33	20.0
Dates (30% w/w dispersion)	568.3	150.0	20.00	113.7

Dates contain 12% w/w moisture: 150.0g anhydrous = 170.5g hydrated.
To add 170.5g of dates in solution (30% w/w), need 568.3g of 30% w/w dispersion

Process :

1 The ibuprofen and microcrystalline cellulose were sieved and blended.

2 The date slurry was prepared by adding the dates to very hot water and homogenising using a Silverson mixer.

3 The ibuprofen / microcrystalline cellulose blend was placed in a planetary mixer and the date dispersion added as the granulating solution.

4 Additional water was added as necessary to form a suitable (heavy) granule.

5 The wet granules were sieved through a 10 mesh sieve (2000 micrometer) and dried in a hot air oven at 50°C overnight.

6 The dried granules were sieved through a 16 mesh sieve (1190 micrometer).

7 After blending with magnesium stearate (1% w/w of the dried granules), the granules were divided into two parts. The first part only contained magnesium stearate (1% w/w of the dried granules); the second part contained magnesium stearate (1% w/w of the dried granules) and crosscarmellose sodium.

8 The lubricated granules with and without the crosscarmellose sodium were compressed using a tablet machine fitted with 10x21mm pillow shaped tooling.

Tablet weight uniformity, hardness and disintegration times of tablet formulation without crosscarmellose sodium:

Tablet weight uniformity	
Mean	767 mg
Minimum	761 mg
Maximum	774 mg
Relative standard deviation	0.69%
Tablet Hardness (kp)	
Mean	11.5 Kp
Minimum	10.5 Kp
Maximum	12.5 Kp
Relative standard deviation	5.0%

Disintegration time: greater than 30 minutes

Tablet weight uniformity, hardness and disintegration times of tablet formulation with 4% w/w crosscarmellose sodium

Tablet weight uniformity	
Mean	756 mg

Minimum	744 mg
Maximum	767 mg
Relative standard deviation	0.91%

Tablet Hardness (kp)

Mean	6.7 kp
Minimum	5.4 kp
Maximum	8.0 kp
Relative standard deviation	12.81%

Disintegration time : 26 minutes

Tablet weight uniformity, hardness and disintegration times of tablet formulation with 4% w/w crosscarmellose sodium compressed at higher compressional pressure and hardness

Tablet weight uniformity

Mean	755 mg
Minimum	741 mg
Maximum	778 mg
Relative standard deviation	1.45%

Tablet Hardness (kp)

Mean	10.5 kp
Minimum	9.1 kp
Maximum	13.5 kp
Relative standard deviation	12.81%

Disintegration time : greater than 30 minutes

Example 15

Ibuprofen tablets using dates as a diluent and binder

Table 7 Ibuprofen tablets prepared using dates at 26% w/w (used as granulating agent)

	% w/w	mg/tablet
Ibuprofen	50.56	485.5
Microcrystalline cellulose	20.22	194.2
crosscarmellose sodium	2.53	24.3
Dates (30% w/w dispersion)	26.69	256.3
Magnesium stearate	1	9.7

Process :

1 The ibuprofen, microcrystalline cellulose and crosscarmellose sodium were sieved and blended.

2 The blend was placed in a planetary mixer and the dates dispersion added as granulating agent.

3 The wet granules were sieved and dried in a hot air oven at 50℃ .

4 The dried granules were then sieved using 16 mesh sieve (1190 micrometer).

5 The magnesium stearate was added and the granules blended.

6 Tablets compressed using tablet machine fitted with 10x21mm pillow shaped tooling as described in Example 6.

Tablet weight uniformity of the formulation:

Mean	973mg
Minimum	961mg
Maximum	980mg
Relative standard deviation	0.62%

Tablet Hardness (kp)	
Mean	18.7 kp
Minimum	17.6 kp
Maximum	19.8 kp
Relative standard deviation	3.9%

Disintegration time : greater than 30 minutes

Example 16

Ibuprofen tablets using PVP as a diluent and binder

Table 8 - Ibuprofen tablets containing PVP (Povidone), used as granulating solution (3.25% povidone w/w was dissolved in 100 g of water), as binder instead of dates

	% w/w	Amount used / g
Ibuprofen	67.02	100.0
Microcrystalline cellulose	26.81	40.0
crosscarmellose sodium	3.35	5.0
PVP	2.82	4.2

Process :

1 The ibuprofen, microcrystalline cellulose and crosscarmellose sodium were sieved and blended.

2 The blend was placed in a planetary mixer and the Povidone solution added.

3 The wet granules were sieved and dried in a hot air oven at 50°C.

4 The dried granules were then sieved using 16 mesh sieve (1190 micrometer).

5 The magnesium stearate was added and the granules blended.

6 Tablets compressed using tablet machine fitted with 10x21mm pillow shaped tooling as described in Example 6.

Tablet weight uniformity of the formulation

Mean	967 mg
Minimum	918mg
Maximum	1011mg
Relative standard deviation	4.0%

Tablet Hardness (kp)

Mean	11.3 kp
Minimum	9.9 kp
Maximum	12.4 kp
Relative standard deviation	7.2%

Disintegration time : greater than 30 minutes

Table 9 - Comparison of the strength of ibuprofen tablets containing 26% dates and 3.25% w/w Povidone

Formulation	Mean weight and Relative standard deviation	Mean hardness and Relative standard deviation
Dates formulation Example 7	973mg 0.62%	18.7 kp 3.9%
Povidone formulation Example 8	967 mg 4.0%	11.3 kp 7.2%

Example 17

Lozenges containing dates

The following formulation provides approximate quantities of the base ingredients.

Sucrose	90- 100 parts
Glucose Syrup	60- 80 parts
Dates dispersion	10- 25 parts
Water	40-50 parts

Process :

The above blend is heated to around 140/145° C until the moisture is reduced to less than 4%. The mass is poured on to a hot plate. Any additional ingredients such as menthol, antiseptics, cough suppressants, antifungal agents, anaesthetics such as benzocaine, benzyl alcohol, dextromethorphane, zinc, flavours, buffers, preservatives, colours, acidulents or salts to adjust the pH may be added. The mass is then rolled and moulded and may be passed through a calendar to form lozenges which are then cooled and dried.

Example 18

Chewable tablets containing dates

Granules of microcrystalline cellulose are produced by granulating microcrystalline cellulose alone or with other diluents such as sweeteners lactose, sucrose or mannitol using the dates dispersion as the granulating agent. The granules are then sieved and dried. These dried granules are then blended with antacids such as calcium carbonate, aluminium hydroxide and magnesium carbonate or with vitamins, food and minerals, herbs, antihistamines, laxatives, cough suppressants and any other drug or combination for which the chewable form may be considered appropriate and/or convenient.

Other standard tablet diluents may be employed instead of microcrystalline cellulose, such as sugar or lactose, sucrose or mannitol, sorbitol and others listed as soluble or insoluble diluents in the detailed description of the invention given above.

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Claims

1. A liquid or solid dosage formulation suitable for nutriceutical or pharmaceutical use by oral administration, which formulation comprises processed date material in the form of a homogeneous dispersion of date in a finely divided form.

2. A formulation as claimed in Claim 1, which further comprises one or more pharmaceutically active agents.

3. A formulation as claimed in Claim 1 or Claim 2, wherein all or substantially all of the date material is present in the form of particles having a particle size of less than 500µm, and more preferably less than 100µm.

4. A formulation as claimed in Claim 3, wherein more than 90% w/w of the date material is present in the form of particles with a size less than 100µm, or a size less than 80µm, or a size less than1-50µm or 1-30 µm.

5. A formulation as claimed in any preceding claim, wherein the date material is prepared from khalal, rutab or tamar dates.

6. A formulation as claimed in any preceding claim, wherein the amount of dates, on dry basis, is at least 5% w/w and up to 50% w/w of the weight of the formulation.

7. A formulation as claimed in Claim 5, wherein the amount of dates, on dry basis, is between 5%w/w and 35% w/w of the weight of the formulation.

8. A formulation as claimed in any preceding claim, which further comprises one or more flavouring agents intended to further enhance the palatability of the formulation.

9. A formulation as claimed in any preceding claim, which comprises one or more flavouring agents selected from the group consisting of natural flavours, natural fruit flavours, artificial flavours, artificial fruit flavours, flavour enhancers or mixtures thereof.

10. A formulation as claimed in any preceding claim, which further comprises one or more sweetening agents.

11. A formulation as claimed in any preceding claim, which comprises an effective amount of a sweetener and/or an artificial sweetening agent.

12. A formulation as claimed in any preceding claim, which further comprises liquorice.

13. A formulation as claimed in any preceding claim, which further comprises one or more additional nutritional components selected from the group consisting of fats, carbohydrates, proteins, vitamins, drugs and minerals.

14. A formulation as claimed in any preceding claim, which comprises one or more vitamins selected from the group consisting of vitamin A, vitamin D, vitamin E, vitamin K, thiamine, riboflavin, pyridoxine, vitamin B12, niacin, folic acid, pantothenic acid, biotin, vitamin C, choline, inositol, salts and derivatives thereof, and combinations thereof.

15. A formulation as claimed in any preceding claim , which comprises one or more electrolytes selected from the group consisting of calcium, phosphorus, magnesium, iron, selenium, manganese, copper, iodine, sodium, potassium, chloride, and combinations thereof.

16. A formulation as claimed in any preceding claim, which comprises an effective amount of a preservative system.

17. A formulation as claimed in Claim 2, wherein the one or more pharmaceutically active agents are selected from the group consisting of antihistamines, decongestants, antitussives, expectorants, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesic drugs.

18. A formulation as claimed in any preceding claim, which is in the form of a homogeneous dispersion in water of date material in finely divided form.

19. A formulation as claimed in Claim 18, which further comprises one or more fats or lipids selected from the group consisting of coconut oil, soy oil, corn oil, olive oil, safflower oil, high oleic safflower oil, MCT oil (medium chain triglycerides), sunflower oil, high oleic sunflower oil, structured triglycerides, palm and palm kernel oils, palm olein, canola oil, marine oils, cottonseed oil and combinations thereof.

20. A formulation as claimed in Claim 18 or Claim 19, which comprises one or more carbohydrates selected from the group consisting of hydrolysed corn starch, maltodextrin, glucose polymers, sucrose, corn syrup, corn syrup solids, rice-derived carbohydrate, glucose, fructose, lactose, high fructose corn syrup and indigestible oligosaccharides such as fructooligosaccharides, and combinations thereof.

21. A formulation as claimed in any one of Claims 18 to 20, which comprises an effective amount of a viscosity enhancing agent.

22. A formulation as claimed in any one of Claims 1 to 17, which has the form of a powder, granules, tablet or lozenge.

23. A method of treatment of a condition that can be ameliorated by the demulcent properties of dates, which method comprises the administration of a formulation as claimed in any one of Claims 1 to 22 to a patient suffering from, or susceptible to, such a condition.

24. A process for the preparation of a formulation as claimed in any one of Claims 1 to 22, which process comprises the steps of dispersing date material in water, and subjecting the dispersion to homogenisation.

25. A process as claimed in Claim 24, wherein homogenisation of the date dispersion is achieved by means of a high shear mixer such as Silverson or high pressure homogeniser.

26. A process as claimed in Claim 24 or Claim 25, which is a process for the manufacture of a solid formulation for oral administration, which formulation comprises processed dates, and which process comprises

(a) the formation of a homogeneous dispersion of the date material in water;

(b) mixing of the date dispersion with some or all of the further ingredients of the formulation; and

(c) drying to remove excess water