(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2011 (13.10.2011)

PCT

(10) International Publication Number
WO 2011/124876 A2

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 9/20* (2006.01)

(21) International Application Number:
PCT/GB2011/000502

(22) International Filing Date:
31 March 2011 (31.03.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1005976.4 9 April 2010 (09.04.2010) GB

(71) Applicant *(for all designated States except US)*: **ASTON UNIVERSITY** [GB/GB]; Business Partnership Unit, Aston Triangle, Birmingham B4 7ET (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MOHAMMED, Afzal** [GB/GB]; 39 Moat House Road, Ward End, Birmingham B8 3NP (GB). **ALHUSBAN, Farhan** [JO/GB]; 405 Qubez, 10 Townsend Way, Birmingham B1 2RT (GB). **PERRIE, Yvonne** [GB/GB]; 28 Spring Lane, Hockley, Health B94 6QY (GB).

(74) Agent: **CHUNG, Hsu Min**; Boult Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: A FREEZE-DRIED TABLET

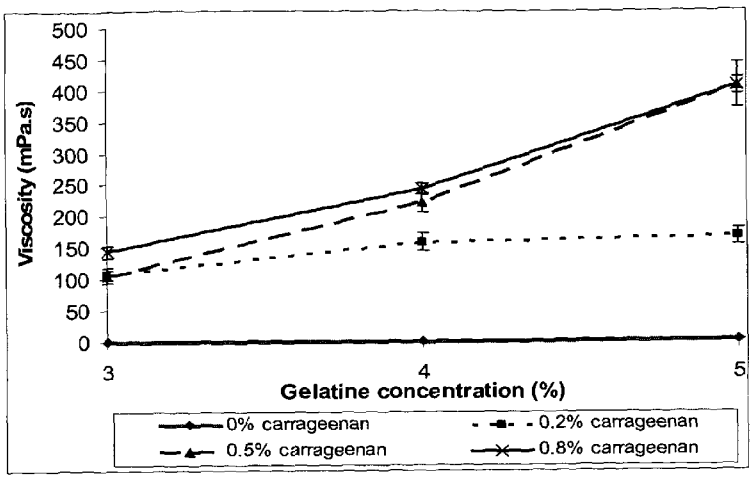


Figure 1

(57) Abstract: A freeze-dried tablet comprising particles comprising one more drugs, a binder comprising a proteinaceous material, and a viscosity modifying agent comprising a polysaccharide.

WO 2011/124876 A2

A Freeze-dried Tablet

The present invention relates to a freeze-dried tablet and its method of manufacture.

Swallowing difficulty or dysphasia affects a significant proportion of people, particularly in the geriatric and paediatric populations. In order to address this problem, orally disintegrating tablets have been developed.

Orally disintegrating tablets are solid unit dosage forms that disintegrate or dissolve in the mouth without chewing or the need for added water. Typically, the tablets remain solid until administered. However, once in the mouth, the tablets transform into a liquid within a short period of time, allowing the drug or pharmaceutically active agent to be swallowed by the patient.

Various methods of producing orally disintegrating tablets are known. For example, the pharmaceutically active agent may be dry-mixed with one or more excipients and the resulting mixture compressed to form a tablet. Alternatively, the tablet may be produced by freeze-drying a suspension or solution of the pharmaceutically active agent and excipients. However, not all forms of active agent are suitable for freeze-drying. For example, some active agents take the form of pellets or particles that are too dense to be adequately suspended in conventional freeze-drying media for the duration of the freeze-drying process.

Microparticles are known in the field of drug delivery and have been used to provide controlled or sustained release of a drug. Typically, these microparticles comprise drug(s)

in combination with polymers that modify the rate of release of the drug(s), protect the drug(s) from undergoing degradation before reaching its target absorption site and/or mask the bitter taste of drug(s). For example, the microparticles may each comprise a drug-containing core encapsulated or coated by one or more layers of a rate-controlling polymer(s). The polymer layer(s) may be selected to provide extended, delayed or pulsed drug delivery, allowing the rate of release of the drug to be tailored as required. Alternatively or additionally, the microparticles may each comprise a drug-containing core surrounded by an enteric coating. Such coatings are stable under the highly acidic pH conditions of the stomach. However, under the less acidic conditions of the small intestine, the coatings degrade rapidly, allowing the drug to be released and absorbed in the small intestine. By targeting the release of the drug in this manner, the drug is protected from the highly acidic conditions of the stomach and this reduces the risk of the drug being degraded before its reaches its site of absorption.

Drug microparticles can be administered in tablet form. To produce such tablets, the microparticles are typically mixed with excipients and compressed. However, to produce a tablet with good structural integrity, relatively high compression pressures are required. These high pressures can cause damage to the polymer layers of the microparticles, and, as a result, compromise the microparticles' e.g. rate-controlling, taste-masking and/or protective properties.

The present inventors have developed a novel way of incorporating these microparticles into tablet form.

According to a first aspect of the present invention, there is provided a freeze-dried tablet comprising

particles comprising one or more drugs,

a binder comprising a proteinaceous material, and

a viscosity modifying agent comprising a polysaccharide.

According to a further aspect of the present invention, there is provided a method of manufacturing the tablet above, which comprises:

forming a suspension of particles comprising one or more drugs in a medium comprising (i) the binder comprising a proteinaceous material, (ii) the viscosity modifying agent comprising a polysaccharide and (iii) a solvent,

freezing the suspension, and

lyophilizing the frozen suspension.

In the method of the present invention, particles comprising one or more drugs are suspended in a medium comprising (i) a binder comprising a proteinaceous material, (ii) a viscosity modifying agent comprising a polysaccharide and (iii) a solvent. Without wishing to be bound by any theory, the present inventors have found that the proteinaceous material interacts with the polysaccharide to form a polymer network that allows the particles to be suspended in the medium in an effective manner. In a preferred embodiment, the polysaccharide (e.g. carrageenan) is polyanionic and the proteinaceous material (e.g. gelatin), polycationic below its isoelectric pH. Under suitable pH conditions, these oppositely charged species form coacervates and gel to provide a suspending medium with desirable viscosity characteristics. As a result, the drug particles remain suspended in the medium during the freezing step, allowing the suspension to be lyophilized to form the tablet.

The associative interaction between the proteinaceous material and the polysaccharide allows relatively high viscosities to be achieved even at relatively low binder (e.g. proteinaceous material) and/or viscosity modifying agent (e.g. polysaccharide) concentrations. As a result, the tablet's ability to disintegrate in the oral cavity is substantially uncompromised, making it ideally suited as an orally disintegrating tablet.

The tablet of the present invention is preferably an orally disintegrating tablet. Such tablets disintegrate in the mouth without the need for chewing and/or the need for added water. In the tablet of the present invention, the binder and viscosity modifying agent provide the tablet with sufficient structural integrity, so that it can be stored and administered in solid form. However, once in contact with saliva in the oral cavity, the freeze-dried tablet dissolves and/or disintegrates, allowing the particles of the drug to be swallowed by the patient.

Preferably, the freeze-dried tablet is an orally disintegrating tablet that meets the US Department of Health and Human Services, Food and Drug Administration's guidance on orally disintegrating tablets (see "Guidance for Industry: Orally Disintegrating Tablets", December 2008). In this Guidance, orally disintegrating tablets are considered to be solid oral preparations which disintegrate rapidly in the oral cavity with an *in vivo* disintegration time of approximately 30 seconds or less, when based on the USP disintegration test method or alternative (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.

pdf) and USP 29, <701> Disintegration, pp. 2670-2672. In a more preferred embodiment, the freeze-dried tablet of the present invention is an orally disintegrating tablet that dissolves and/or disintegrates in the mouth of a user in less than 20 seconds, less than 15 seconds, less than 10 seconds, or more preferably less than 5 seconds.

As mentioned above, the binder employed in the present invention is a proteinaceous material. The binder and, in particular, the proteinaceous material is preferably water-soluble and/or has a glass transition temperature close or at body temperature to facilitate disintegration. Suitable glass transition temperatures range from, for example, 35 to 38 degrees C, preferably about 37 degrees C. Suitable proteinaceous materials include fibroin, elastin, keratin, a collagen-based polymer and combinations thereof. In a preferred embodiment, the proteinaceous material is a collagen-based polymer, such as gelatin. Low bloom strength gelatin, high bloom strength gelatin or a combination thereof may be used. However, low bloom strength gelatin is preferred.

The binder and, in particular, the proteinaceous material, may form 10 to 60 weight % of the freeze-dried tablet. Preferably, the binder and, in particular, the proteinaceous material forms 20 to 45 weight %, more preferably 30 to 40 weight % of the freeze-dried tablet. In a preferred embodiment, the freeze-dried tablet comprises gelatin in an amount of 20 to 45 weight %, preferably 30 to 40 weight % of the freeze-dried tablet.

The viscosity modifying agent employed in the present invention is a polysaccharide. The viscosity modifying agent

and, in particular, the polysaccharide is preferably water-soluble and/or has a glass transition temperature close or at body temperature to facilitate disintegration. Suitable glass transition temperatures range from, for example, 35 to 38 degrees C, preferably about 37 degrees C. Suitable polysaccharides include carrageenan, agar, maltodextrin, pectin and alginate. In a preferred embodiment, the viscosity modifying agent is carrageenan. Carrageenan is preferred because of its solubility in water and its ability to protect the drug from damage during the freeze-drying step (cryoprotectant properties). Lambda, Iota, Kappa carrageenan may be used, although Lambda carrageenan is preferred.

The viscosity modifying agent and, in particular, the polysaccharide, may form 0.8 to 10 weight % of the freeze-dried tablet. Preferably, the viscosity modifying agent and, in particular, the polysaccharide forms 1 to 6 weight %, more preferably 1.5 to 4 weight % of the freeze-dried tablet. The total amount of viscosity modifying agent and, in particular, the polysaccharide in the freeze-dried tablet is preferably less than 6 weight %, more preferably less than 4 weight %. In a preferred embodiment, the freeze-dried tablet comprises carrageenan in an amount of 1 to 6 weight %, preferably 1.5 to 4 weight %. The total amount of carrageenan in the freeze-dried tablet is preferably less than 6 weight %, more preferably less than 4 weight %.

For the avoidance of doubt, the binder and viscosity modifying agent are preferably separate or distinct components of the freeze-dried tablet of the present invention. In other words, it is preferable for the binder and viscosity modifying agent not to consist solely of a single component, such as Gum Arabic. By using distinct binder and viscosity modifying

components, the relative concentrations of the binder and viscosity modifying agent can be controlled to provide the medium with the desired properties. This cannot be achieved if the binder and viscosity modifying agent consists solely of one component, such as Gum Arabic.

The weight ratio of the binder to the viscosity modifying agent may be 3-50:1, preferably 15-40:1, more preferably 20-30:1. In one embodiment, the weight ratio of the proteinaceous material to the weight ratio of polysaccharide is 3-50:1, preferably 15-40:1, more preferably 20-30 1. In a preferred embodiment, the freeze-dried tablet comprises gelatin and carrageenan in a weight ratio of 3-50:1, preferably 15-40:1, more preferably 20-3 :1. It has been found that, in the presence of a solvent, such as water, gelatin and carrageenan interact to form a polymer network that is particularly effective for suspending and cryoprotecting drug particles. As a result, the particles remain intact and suspended in the medium during the freezing step, allowing the suspension to be lyophilized to form tablets that, advantageously, disintegrate quickly upon contact with saliva. This allows the drug particles to be released in the oral cavity and then easily swallowed and transported to the site of absorption.

The particles comprising one or more drugs may each comprise at least one drug and at least one excipient. The excipient may mask the taste of the drug, modify the rate of release of the drug and/or protect the drug from possible degradation. In one embodiment, the particles each comprise a drug-containing core encapsulated and/or coated by one or more layers of polymer. The polymer may control the rate of release of the drug, protect the drug from possible

degradation and/or simply mask the taste of the drug. Where the polymer layer(s) are intended to control the rate of release of the drug, the polymer layer(s) may be selected to provide immediate, extended, delayed or pulsed drug delivery, allowing the rate of release of the drug to be tailored as required. Where the polymer layer(s) are intended to protect the drug from possible degradation, the polymer layer(s) may be enteric coatings. Such coatings are stable under the highly acidic pH conditions of the stomach. However, under the less acidic conditions of the small intestine, the coatings degrade rapidly, allowing the drug(s) to be released and absorbed in the small intestine. By targeting the release of the drug(s) in this manner, the drug(s) is protected from the highly acidic conditions of the stomach and this reduces the risk of the drug being degraded before its reaches its site of absorption in the small intestine.

Examples of polymers that can be used to coat the drug(s) include cellulosic and/or acrylic polymers. Specific examples include Aquacoat®, Surelease® and/or Eudragit®. The coating may be applied by known fluidized bed coating techniques, such as those described in US 4,623,588.

The particles comprising one or more drugs may take the form of pellets or pellet cores. Each pellet/pellet core may comprise at least one drug, at least one excipient and at least one polymer. The pellets/pellet cores may be prepared by any suitable technique including extrusion/spheronisation, dry or wet granulation, spray drying and freeze drying.

The drug particles incorporated into the tablet of the present invention may be any suitable size. Preferably, the particles are microparticles. Such microparticles have

diameters of 1 to 2000 microns, preferably 100 to 1000 microns, more preferably 300 to 800 microns.

The particles may form 5 to 60 weight %, preferably 20 to 40 weight % of the freeze-dried tablet.

Preferably, the weight ratio of the total weight of binder and viscosity modifying agent to the total weight of the particles comprising the one or more drugs is 0.3-4:1, more preferably 1-2:1.

The freeze-dried tablet of the present invention may include further excipients. These include fillers, disintegrants, thickening agents, stabilizers, surfactants, antioxidants, sweeteners, flavouring agents, preservative, taste-masking agents, absorption enhancers, pH modifying agents, bacteriostatic agents and colouring agents. Mixtures of two or more of these excipients may also be employed.

These further excipients may form 0 to 10 weight %, preferably 2 to 6 weight % of the freeze-dried tablet.

In one embodiment, the tablet additionally includes alanine and/or mannitol. These act as matrix-supporting or disintegration-enhancing agents, respectively. They may also act as crystallising agents to provide extra stability during and after freeze drying process. Alanine, in particular, is preferred, as it can help to improve the structural integrity (e.g. hardness) of the resulting tablet.

In one embodiment, the freeze-dried tablet comprises 10 to 60 weight %, preferably 20 to 50 weight % mannitol. In

another embodiment, the freeze-dried tablet includes 10 to 60 weight % alanine, preferably 20 to 50 weight % alanine.

The freeze-dried tablet of the present invention may be used in a method of treatment of the human or animal body by therapy. For example, the freeze-dried tablet may be used in the treatment of constipation, depression, drug addiction, diabetes, diarrhoea, epilepsy, fungal infection, headache, heart burn, gout, GORD, hypertension, malaria, migraines, Parkinson's disease, cancer, viral infections, bacterial infections, eczema, local or systemic pain, elevated cholesterol, inflammation, insomnia, protozoal infections, tapeworm infection, arrhymia, thrombosis, angina, allergic reaction, thyroid imbalance, water retention gastro-intestinal infection, erectile dysfunction, motion sickness, irritable bowel syndrome, Alzheimer's, psychotic diseases, osteoporosis, heart failure, autoimmune diseases, endocrine disorder, and/or obesity.

Any suitable drug may be present in the particles of the freeze-dried tablet of the present invention. For example, the drug(s) may be selected from an analgesic or anti-inflammatory agent, an anthelmintic, an anti-arrhythmic agent, an anti-coagulant, an anti-depressant, an anti-diabetic agent, an anti-epileptic agent, an anti-fungal agent, an anti-gout agent, an anti-hypertension agent, an anti-malarial, an anti-migraine agent, an anti-muscarinic agent, an anti-neoplastic agent, an anti-protozoal agent, an anti-thyroid agent, an anxiolytic, a sedative, a hypnotic agent or a neuroleptic agent, a corticosteroid, a diuretic, an anti-Parkinsonian agent, a gastro-intestinal agent, a histamine H1-receptor antagonist, a lipid regulating agent, an anti-anginal agent, a thyroid agent, a nutritional agent, an antipyretic agent, an

antibacterial agent, an immunosuppressant, an antiviral agent, hypothalmic or a pituitary hormone, a sex hormone, a prostaglandin, a vaccine, a cough suppressant, a local anaesthetic, an antisera, an opioid analgesic, a stimulant, a viral vector for gene therapy, an anti allergic agent, a cardio protective agent, an anti obesity agent, an oral contraceptive, an anti dementia, a fertility agent, a cholinesterase inhibitor, and an anti cholinergic agent or a therapeutic mixture thereof.

Examples of drugs or pharmaceutically active agents which may be used in the present invention include the following:

Analgesics and anti-inflammatory agents: aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac.

Anthelmintics: albendazole, bephenium hydroxynaphthoate, dichlorophen, ivermectin, mebendazole, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate, thiabendazole.

Anti-arrhythmic agents: amiodarone HCl, disopyramide, quinidine sulphate.

Anti-bacterial agents: benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine,

sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim.

Anti-coagulants: dicoumarol, dipyridamole, nicoumalone, phenindione.

Anti-constipation: docusate sodium, sodium picosulphate, sennosides, tegaserod maleate.

Anti-depressants: amoxapine, maprotiline HCl, trimipramine maleate.

Anti-diabetics: acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, insulin tolbutamide.

Anti-diarrhoea: loperamide HCL, Bismuth subsalicylate.

Anti-epileptics: beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, valproic acid.

Anti-fungal agents: amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid.

Anti-gout agents: allopurinol, probenecid, sulphin-pyrazone.

Anti-gastro-oesophageal reflux disease (GORD): rabeprazole sodium, esomeprazole magnesium, famotidine, Omeprazole magnesium.

Anti-heart burn: Omeprazole magnesium, famotidine, Cimetidine, Ranitidine HCl.

Anti-headache: Paracetamol/metoclopramide hydrochloride.

Anti-hypertensive agents: amlodipine, diazoxide, felodipine, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, prazosin HCl, reserpine, benazepril, Verapamil hydrochloride.

Anti-malarials: amodiaquine, chloroquine, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine, quinine sulphate.

Anti-migraine agents: dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate.

Anti-muscarinic agents: atropine, benzhexol HCl, biperiden, hyoscyamine, mepenzolate bromide, tropicamide.

Anti-neoplastic agents and Immunosuppressants: aminoglutethimide, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, tamoxifen citrate, testolactone.

Anti-protazoal agents: clioquinol, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furzolidone, metronidazole, nitrofurazone, tinidazole.

Anti-thyroid agents: carbimazole, propylthiouracil.

Anxiolytic, sedatives, hypnotics and neuroleptics: alprazolam, amylobarbitone, barbitone, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clozapine, diazepam, droperidol, ethinamate, fluanisone, flunitrazepam, fluopromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol, lorazepam, lormetazepam, medazepam, meprobamate, methaqualone, midazolam, nitrazepam, oxazepam, pentobarbitone, perphenazine pimozide, prochlorperazine, sulpiride, temazepam, thioridazine, triazolam, zopiclone.

β-Blockers: nadolol, pindolol.

Cardiac Inotropic agents: digitoxin, digoxin, lanatoside C, medigoxin.

Corticosteroids: beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.

Diuretics: acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene.

Anti-parkinsonian agents: bromocriptine mesylate.

Gastro-intestinal agents: bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine, omeprazole, sulphasalazine.

Histamine H,-Receptor Antagonists: astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, meclozine HCl, oxatomide, terfenadine.

Lipid regulating agents: bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol, atorvastatin calcium, ezetimibe, simvastatin.

Nitrates and other anti-anginal agents: amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, pentaerythritol tetranitrate.

Nutritional agents: betacarotene, vitamin A, vitamin B2, vitamin D, vitamin E, vitamin K.

Opioid analgesics: codeine, dextropropyoxyphene, diamorphine, dihydrocodeine, meptazinol, morphine, pentazocine.

Sex hormones: clomiphene citrate, danazol, ethinyl estradiol, medroxyprogesterone acetate, mestranol, methyltestosterone, norethisterone, norgestrel, estradiol, conjugated oestrogens, progesterone, stanozolol, stibestrol, testosterone, tibolone.

Stimulants: dexamphetamine, dexfenfluramine, mazindol, nicotine.

The viral vector may be a retrovirus (such as Moloney murine leukaemia virus), a lentivirus, an adenovirus, an adeno-associated virus (AAV) or a nanoengineered substance such as Ormosil.

Anti allergic agent: promethazine HCl, Chlorpheniramine maleate, diphenhydramine HCl, loratadine.

Cardio protective agent: aspirin, dexrazoxane.

Anti obesity agent: orlistat, sibutramine HCl, methamphetamine HCl, phentermine HCl.

Oral contraceptive: levonorgestrel, norgestrel, ethinyl estradiol, drospirenone.

Anti dementia: donepezil HCl, rivastigmine tartrate, memantine HCl.

Cholinesterase inhibitor: donepezil hydrochloride, galantamine hydrobromide.

Anti cholinergic agent: Benzhexol, ipratropium bromide.

Vaccine: typhoid Vaccine, OPV (oral polio vaccine).

Pharmaceutically acceptable salts, isomers and derivatives thereof may be substituted for the drugs listed above. Mixtures of drugs may be used.

The drug is preferably present in the tablet in a pharmaceutically effective amount. Preferably, the tablet comprises from 0.0001% to 55% by weight of the drug based on

the total weight of the tablet. More preferably, the tablet comprises from 5% to 50%, from 10% to 40%, or from 20% to 30% by weight of the drug based on the total weight of the tablet.

To produce the freeze-dried tablets of the present invention, the particles comprising one or more drugs are first suspended in a medium comprising (i) the binder comprising a proteinaceous material, (ii) the viscosity modifying agent comprising a polysaccharide and (iii) a solvent. Any suitable pharmaceutically acceptable solvent may be used to form the tablets. Suitable solvents include water, isopropanol, glycol and/or acetone.

Advantageously, the medium has a viscosity that allows the particles to be suspended for the duration of the freeze-drying process. While highly viscous suspending media can reduce the risk of settling or sedimentation, they can also lead to tablets that do not readily disintegrate in the oral cavity. With the present invention, however, the specific binder and viscosity modifying agents employed allow relatively high viscosities to be achieved even at relatively low binder and/or viscosity modifying agent concentrations. Thus, although the drug particles remain suspended in the medium for the duration of the freeze drying step, the disintegration characteristics of the resulting tablet remain uncompromised. Accordingly, the resulting tablets not only contain drug particles are homogenously dispersed, but also disintegrate readily, for example, when placed in the oral cavity.

The viscosity of the medium is desirably from 50 to 500 mPa.s, more preferably from 100 to 300 mPa.s. The desired viscosity of the medium may vary, depending on the size of the

drug particles and their densities. However, by varying the relative amounts of e.g. the binder, viscosity modifying agent and/or solvent, the viscosity of the medium may be tailored to meet a range of applications.

Any suitable method of measuring viscosity may be used. For example, viscosity measurements may be made with a Brookfield LVT viscometer with its spindle number 3 rotating at speed of 20 rpm at room temperature in a 100 mL beaker with the spindle guard.

The amount of solvent in the medium may be 60 to 95 weight %, preferably 70 to 90 weight %, more preferably 80 to 90 weight %.

The amount of binder and, in particular, the proteinaceous material, in the medium may be 10 to 60 weight %, preferably 20 to 45 weight %, more preferably 30 to 40 weight %. As mentioned above, the preferred binder is gelatin.

The viscosity modifying agent and, in particular, the polysaccharide, may form 0.8 to 10 weight % of the medium. Preferably, the viscosity modifying agent and, in particular, the polysaccharide forms 1 to 6 weight %, more preferably 1.5 to 4 weight % of the medium. The total amount of viscosity modifying agent and, in particular, the polysaccharide in the medium is preferably less than 6 weight %, more preferably less than 4 weight %. As mentioned above, the preferred viscosity modifying agent is carrageenan.

The weight ratio of solvent to binder to viscosity modifying agent may be (1500 - 2200):(20 - 80): (2 - 2), preferably (1800 - 2000): (30 - 50):(2 - 2).

The amount of drug added to the medium may be varied as required to provide the desired concentration in the tablet.

Once the particles are suspended in the medium, the suspension is frozen and, preferably, maintained at a low temperature then annealed for a period of time. Preferably, the frozen solution or suspension is annealed at a temperature of from -70°C to -5°C for at least 5 hours. More preferably, the frozen solution or suspension is annealed at a temperature of from -40°C to -10°C for at least 5 hours. Preferably, the frozen solution or suspension is annealed at a temperature of from -30°C to -10°C for at least 10 hours. Annealing the frozen solution or suspension leads to the formation of an improved product.

Prior to freezing, a crystallising excipient may be added to the solution or suspension. Adding the crystallising excipient to the solution or suspension modifies the thermal profile of the frozen material. The modified thermal profile allows freeze-drying at higher temperatures and consequently decreases the primary drying time. The resulting tablet may also have better structural integrity, reducing the risk of it disintegrating or crumbling prior to being administered.

As mentioned above, the crystallising excipient may be selected from alanine and mannitol. Alternatively or additionally, glycine, cysteine, lactose, asparagine and/or serine may be employed. The crystallising excipient may form

10 to 60 weight %, preferably 20 to 50 weight % of the final tablet.

These and other aspects of the present invention will now be described with reference to the following Examples and Figures, in which:

Figure 1 is a graph showing how the viscosity of a suspending medium varies with gelatin and carrageenan concentrations.

Example 1

Solutions were prepared by dissolving gelatin in 100 ml of double distilled water at about 40 degrees C to obtain gelatin concentrations of 3, 4 and 5% (w/v), respectively. Carrageenan was then added to each of the solutions at concentrations of 0.2, 0.5 and 0.8 weight %. The viscosities of the solutions were measured before and after the addition of carrageenan using a Brookfield LVT viscometer (spindle 3 rotating at a speed of 20 rpm at room temperature in a 100 ml beaker with a spindle guard). Figure 1 shows the average of the viscosity readings of the three independent batches.

As can be seen from the Figure, a significant increase in viscosity is observed even at carrageenan concentrations of 0.2 weight %. Without wishing to be bound by any theory, this is believed to be caused by the associative interaction between gelatin and carrageenan.

Example 2

Solutions were prepared by dissolving gelatin in 100 ml of double distilled water at about 40 degrees C to obtain gelatin concentrations of 3, 4 and 5% (w/v), respectively. Carrageenan was then added to each of the solutions at concentrations of 0.2 and 0.5 weight %. Once clear, alanine was added at concentrations of 2 and 5% (w/v). The compositions of the solutions are shown in Table 1.

Table 1

Sample No.	Gelatin (wt%)	Carrageenan (wt %)	Alanine (wt%)
i	3	0.2	5
ii	4	0.5	2
iii	5	0.2	2
iv	5	0.2	5

The viscosities of the solutions were measured using the procedure described in Example 1 above. These measurements are shown in Table 2.

1.5 g of each solution was poured into a tablet mould (13.80 mm diameter, 8.50 mm height), frozen at -80 degrees C for about 60 minutes and freeze-dried (ADVANTAGE Freeze-dryer, VITRIS) according to an optimized regime (primary drying for 24 hours at a shelf temperature of -40 degrees C and secondary drying for 4 hours at a shelf temperature of 20 degrees C and a vacuum of 50 mTorr).

The disintegration properties of the tablets were measured using a USP disintegration tester (Erweka, ZT3). In this apparatus, each tablet was placed in a basket that was

dipped into distilled water (800 ml) at 37 degrees C. The time to disintegration was recorded and shown in Table 2.

The hardness properties of the tablets were investigated with a texture analyser (QTS 25 Brookfield, Essex, UK) equipped with a 25 kg load cell. The instrument was calibrated by standard weights of 500 g and 5 kg. The tablet was placed in a holder and the hardness was taken as the peak force after 1 mm penetration of a 5 mm diameter probe travelling at a speed of 6 mm/min.

Table 2

Sample No.	Viscosity (mPa.s)	Disintegration time (s)	Hardness (N)
i	97.5	28	8.79
ii	210.3	28	11.27
iii	170.5	8	15.94
iv	156.4	24	21.38

The results show that gelatin and carrageenan can be used to produce solutions that have good suspending properties by virtue of their viscosities. The solutions can also be freeze-dried to form tablets that are reasonably hard, but at same time readily disintegrate in water.

Example 3 (Comparative)

Example 2 was repeated with compositions comprising gelatin and 30% alanine (w/w of the dried materials).

Gelatin concentration (%w/w)	Viscosity (mPa.s)	Disintegration time (s)	Hardness (N)
2	0.5 ± 0.1	8 ± 1	1.6 ± 0.2
5	1.5 ± 0.1	6 ± 0.6	14.9 ± 1.1
7.5	1.9 ± 0.2	52 ± 6	31.9 ± 4.8
10	2.9 ± 0.2	96 ± 11	53.1 ± 2.9

The results show that increasing the concentration of gelatin increases the viscosity of the solution slightly. However, this increase was accompanied by a significant deterioration in the disintegration properties of the freeze-dried tablet. This suggests that gelatin alone cannot be used to produce a sufficiently viscous suspending medium for formulating a fast-disintegrating tablet.

Example 4

Gelatin (0.5g), carrageenan (0.02g) and alanine (0.3g) were dissolved in 10 ml of distilled water to form a suspending medium having a viscosity of 172 ± 21.3 mPas. The medium was used to suspend enteric coated omeprazole pellets having the following characteristics:

Drug content% (w/w)	Density (g/cm^3)	Drug recovery %	Size (μm)
8.27 ± 0.29	1.439 ± 0.006	91.24 ± 1.22	710 ± 40

The drug recovery of the pellets was determined by placing the pellets in a gastric solution for 1 hour. 91.24% of the pellets were recovered, showing that the enteric

coating remained substantially intact under the low pH conditions of the gastric solution.

The resulting suspension was poured into a mould, frozen at -80 degrees C for about 60 minutes and freeze-dried (ADVANTAGE Freeze-dryer, VITRIS) according to an optimized regime (primary drying for 24 hours at a shelf temperature of -40 degrees C and secondary drying for 4 hours at a shelf temperature of 20 degrees C and a vacuum of 50 mTorr).

The resulting tablet had a disintegration time of 14 seconds and a hardness of 17.2 ± 21.3N. The latter was investigated with a texture analyser (QTS 25 Brookfield, Essex, UK) as described in Example 2 above.

The drug recovery of the tablet was determined by placing the tablet in a gastric solution for 1 hour. 93.14 ± 1.22 % of the pellets were recovered, showing that there was no damage to the pellets during tablet manufacture.

Claims

1. A freeze-dried tablet comprising particles comprising one or more drugs, a binder comprising a proteinaceous material, and a viscosity modifying agent comprising a polysaccharide.

2. A tablet as claimed in claim 1, wherein the binder is gelatin.

3. A tablet as claimed in claim 1 or 2, wherein the viscosity modifying agent is carrageenan.

4. A tablet as claimed in any one of the preceding claims, wherein the weight ratio of binder to viscosity modifying agent is 30-20:1.

5. A tablet as claimed in any one of the preceding claims, wherein the weight ratio of the total weight of binder and viscosity modifying agent to the total weight of the particles comprising the one or more drugs is 1-2:1.

6. A tablet as claimed in any one of the preceding claims, wherein the particles are coated and/or layered.

7. A tablet as claimed in any one of the preceding claims, wherein the particles comprise an excipient that controls the rate of release of the one or more drugs.

8. A tablet as claimed in any one of the preceding claims, wherein the particles are microparticles.

9. A tablet as claimed in any one of the preceding claims, which further comprises a disintegrant and/or a filler.

10. A tablet as claimed in claim 9, which further comprises mannitol and/or alanine.

11. A tablet as claimed in any one of the preceding claims, which is an orally disintegrating tablet.

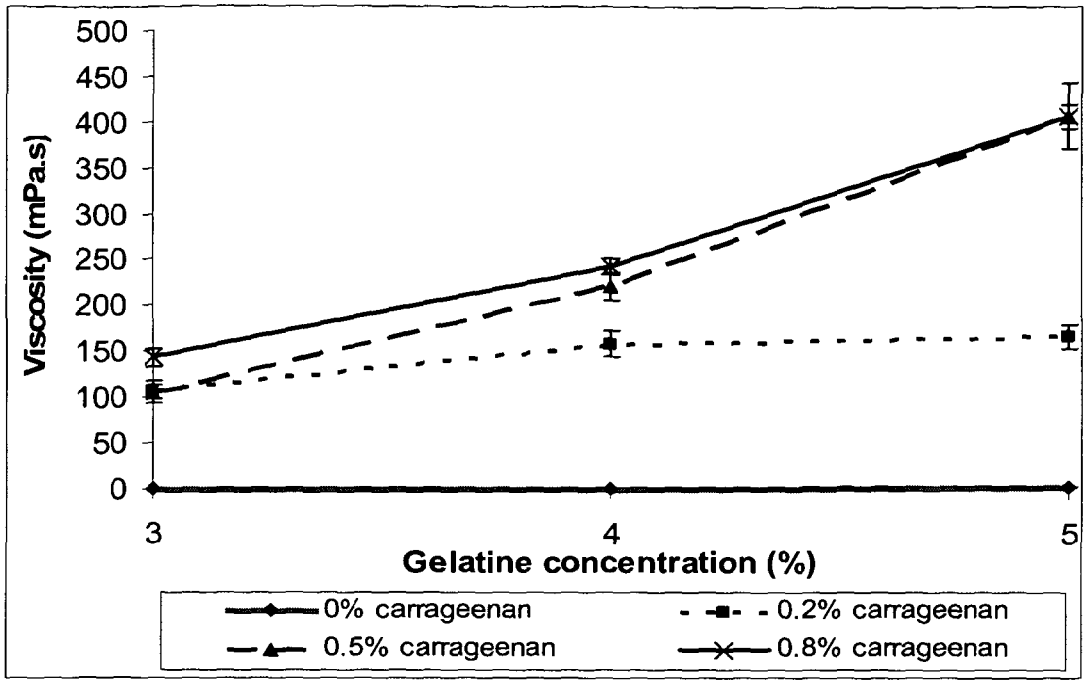
12. A method of manufacturing a tablet as claimed in any one of the preceding claims, which method comprises:
forming a suspension of the particles comprising one or more drugs in a medium comprising (i) the binder comprising the proteinaceous material, (ii) the viscosity modifying agent comprising a polysaccharide and (iii) a solvent,
freezing the suspension, and
lyophilizing the frozen suspension.

13. A method as claimed in claim 12, wherein the suspension further includes a disintegrant and/or a filler.

14. A method as claimed in claim 12 or 13, wherein the frozen suspension is annealed, optionally, at a temperature of -40 to -10 degrees C prior to the lyophilizing step.

15. A method as claimed in any one of claims 12 to 14, wherein the tablet is formed in the absence of a compression step.

Figure 1


500
450
400
350
300
250
200
150
100
50
0
Viscosity (mPa.s)
3
4
5
Gelatine concentration (%)
0% carrageenan
0.2% carrageenan
0.5% carrageenan
0.8% carrageenan