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(54) Title: WATER-DISPERSIBLE TABLETS

(57) Abstract

A water-dispersible tablet comprises an active compound such as acyclovir or lamotrigine and a dispersing agent. The dispersing agent is a swellable clay such as a smectite, e.g. Veegum F or bentonite, and is generally present within the granules of the tablet to provide a tablet which is capable of dispersing in water within 3 minutes to provide a dispersion which will pass through a 710μm sieve. The tablet can be optionally film-coated in which case the dispersion time is less than 5 minutes.

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WATER-DISPERSIBLE TABLETS

The present invention relates to a water-dispersible tablet formulation containing a therapeutically active compound.

Therapeutically active compounds or drugs are frequently administered to patients in tablet form where the drug is intended for oral administration since tablets are an especially convenient pharmaceutical form for manufacture, storage and generally usage. However, problems, may arise with the administration of such tablets to patients who have difficulty in swallowing the tablets (for example, children or more seriously ill patients) especially if the tablets are large in size arising from the amount of drug required in each tablet. A solution to such problems is to formulate the tablets in a form whereby they can be dispersed in water to form a dispersion containing the drug which can then be drunk by the patient.

Known water-dispersible tablets include effervescent formulations which rely on the formation of a gas to quickly break up the tablet, but these involve expensive methods of manufacture and strict regulations for such manufacture. Other known water-dispersible tablets use disintegrating agents such as microcrystalline cellulose used in Feldene R dispersible tablets. We have tested well-known disintegrating agents (incorporated both internally and externally to the preformed granules) such as sodium starch glycollate (e.g. Explotab), cross-linked povidone (e.g. Kollidon CL) and a cross-linked sodium carboxymethylcellulose (e.g. Starch, Avicel PH102, and Ac-Di-Sol) in an acyclovir tablet, but found that they did not provide a satisfactory water-dispersible formulation. We furthermore tested an ion exchange resin (Amberlite 1RP88) as a disintegrating agent and incorporated surface active agents (e.g. sodium lauryl sulphate and sodium docusate) in an attempt to improve tablet wetting and penetrating of water during dispersion, but in all cases the disintegration time was high.

After considerable research and investigation, we have now suprisingly found that the use of a swellable clay within the granulate of a tablet formulation provides a tablet which has good dispersibility in water to provide a dispersion which can be drunk by a patient.

Swellable clays such as Veegum^{R} and other magnesium aluminium silicates have previously been studied and proposed for use as disintegrating agents, binders and lubricants in the manufacture of tablets, but such studies and proposals were exclusively with respect to tablets intended for swallowing and not for water-dispersible tablets (Rubenstein, Pharmaceutics - The Science of Dosage Form Design (1990) for disintegrants see p 312 and 314). Moreover, there has never been any suggestion that a clay would be suitable to meet the more stringent requirements for dispersible tablets. Tablets for swallowing need only have a disintegration time in water of less 15 minutes and be able to form particles on disintegration in water that can pass through a 2.00mm mesh aperture (British Pharmacopia test for swallowable tablets). Such long disintegration times and large particle sizes are entirely unsuitable for a dispersible tablet.

Even when swellable clays have been proposed as disintegrating agents for swallowable tablets, they are not regarded as very suitable for such use because their off-white appearance can often discolour the tablet and because they are not as effective as other disintegrating agents (Banker and Anderson - Theory and Practice of Industrial Pharmacy p 328 (1986) and Bhargava et al - Drug Development and Industrial Pharmacy, 17(15), 2093-2102(1991)). In fact, bentonite is identified in Marshall and Rudnic, Modern Pharmaceutics (1990) p 374, as the least swellable of the ten disintegrants listed. There is no mention in the above text-book references of how the swellable clay should be incorporated - i.e. by intra-granular addition or by extra-granular addition. In the former case, the clay would be included in the mixture from which the granulate is formed; in the latter case the clay would be added to the pre-formed granulate.

In J. Pharm. Sci, 55, 1244 (1966), Wai et al. reviewed the following papers relating to swellable clays such as Veegum and bentonite as disintegrating agents: Wai et al., J.Pharm.Sci, 55, 1215(1966); Granberg et al., J.Am.Pharm.Assoc.Sci, 38, 648(1949); Gross et al., J.Am.Pharm.Assoc.Sci, 41, 157(1952); Firouzabadian et al., J.Am.Pharm.Assoc.Sci, 43, 248(1954); Ward et al., Drug Cosmetic Ind, 91, 35(1962); Nair et al., J.Am.Pharm.Assoc.Sci, 46, 131(1957); and Patel et al., Indian J.Pharm., 19, Jan.1957. Wai et al., then compared three grades of Veegum evalulating both extra-granular and intra-granular addition and concluded that "the clays were not good disintegrating agents when wet granulated" (i.e. intra-granular addition), and then went on to recommend extra-granular addition. Furthermore R.T.Vanderbilt and Co. (Manufacturers of Veegum) in their publication "Veegum - The Versatile Ingredient for Pharmaceutical Formulations" at p 19 describe a tablet formulation in which Veegum is added after granulation (tablet No.2). There is no reference in the publication to a formulation of a tablet in which Veegum is added during granulation.

In contrast to the above recommendations, we have found that a swellable clay such as Veegum must be added during granulation to meet the British Pharmacopoeia (B.P.) standard for dispersible tablets (presently set at a dispersion time of 3 minutes or less). If the swellable clay is added only after granulation the dispersion time is too high to meet the above standard.

By using Veegum and other swellable clays in the manner described above, we have been able to prepare water-dispersible tablets containing a variety of therapeutically active compounds. The resulting tablets can readily be dispersed in water to form a dispersion which can be drunk by a patient.

According to the present invention there is provided a water-dispersible tablet comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a

tranquillising benzodiazepine, an anti-viral nucleoside derivative (for example acyclovir), an anti-protozoal napthoquinone, allopurinol, oxopurinol, anti-convulsant 1,2,4 triazine derivative (for example lamotrigine) and trimethoprim (optionally in combination with sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay to provide a tablet which is capable of dispersing in water within a period of 3 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710μm in accordance with the test for dispersible tablets defined in the British Pharmacopoeia, 1988, Volume II, page 895.

The above-defined therapeutically active compound employed in the tablet according to the invention is hereinafter referred to as "the active compound".

The present invention further provides a process for the preparation of a water-dispersible tablet comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an anti-viral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol, anti-convulsant 1,2,4 triazine derivative and trimethoprim (optionally in combination with sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay which comprises bringing the said active compound into association with the said swellable clay to provide a water-dispersible tablet which is capable of dispersing in water within a period of 3 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710μm in accordance with the test for dispersible tablets defined in the British Pharmacopoeia, 1988, Volume II, page 895.

Preferably said process comprises the steps of:

a) admixing in dry, finely-divided form the active compound with an effective amount of a pharmaceutically acceptable swellable clay, optionally with the addition of one or more other pharmaceutical carriers or excipients;

b) addition of a quantity of a pharmaceutically acceptable liquid sufficient to moisten the dry mixture;

c) granulation of the resulting moist mixture to form granules;

d) drying the granules and optionally blending the granules with other optional carriers or excipients such as lubricants, glidants, flavouring agents and disintegrating agents; and

e) compression of the granules to form a tablet which is capable of dispersing in water within a period of 3 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710μm in accordance with the above defined British Pharmacopoeia test for dispersible tablets.

A tablet according to the invention, as well as being quickly dispersible in water, has the added advantage that it meets the British Pharmacopoeia (B.P.) test for dispersible tablets in respect of dispersion times and dispersion quality (i.e. passage through a 710μm sieve).

Preferably the dispersion time of a tablet according to the invention is less than 2 minutes, more preferably less than 1.50 minutes and most preferably less than 1 minute.

A further advantage of the tablets according to invention is that because a relatively fine dispersion is formed the tablet will have a lower dissolution time and thus the drug may be absorbed into the blood stream much faster. Furthermore the fast dispersion times and relatively fine dispersions obtained with tablets according to the

invention are also advantageous for swallowable tablets. Thus tablets according to the invention can be presented both for dispersion in water and also for directly swallowing. Those tablets according to the invention that are intended for swelling are preferably film-coated to aid swallowing. Such film-coating however increases the dispersion time up to 5 minutes determined in accordance with the above-mentioned B.P. test.

According to a further feature of the present invention therefore we provide a water-dispersible film-coated tablet comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an antiviral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol, an anti-convulsant 1,2,4-triazine derivative and trimethoprim (optionally in combination with sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay to provide a film-coated tablet which is capable of dispersing in water within a period of 5 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710μm in accordance with the above-defined British Pharmacopoeia test for dispersible tablets subject to the variation of the said period specified in the test from 3 minutes to 5 minutes. The references herein to tablets according to the invention include both film-coated and non-film-coated tablets.

After the dispersion has passed through the 710μm mesh screen, there should be substantially no residue, except fragments of undissolved tablet coating or shell, remaining on the screen or adhering to the lower surface of the disc, if a disc optionally has been used; and if any residue remains, it should consist of a soft mass having no palpably firm, unmoistened core.

The particle size distribution of the dispersion particularly when the active compound is acyclovir are set out in the following table with the increasingly preferred values being quoted from left to right.

Particle Size (μm)*	BP Standard	Preferably	More Preferably	Most Preferably
<710	<100%	100%	100%	100%
<300	-	>50%	>70%	>80%
<200	-	-	>50%	>70%
<150	-	-	-	>50%

* (equivalent spherical volume diameter)

Examples of active compounds which have been employed in the tablets according to the invention are listed below together with respective patent publications, (in appropriate instances) which teach how to make them and infections or medical conditions which can be treated by them (incorporated by reference): acyclovir (UK No.1523865), lamotrigine (EP Nos. 021 121 and 247 829), diazepam, paracetamol, (both commercially available), 1-(β-D-arabinofuranosyl)-5-propy-1-ynyl-uracil (EP No. 0272 065), 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy- 1,4-naphthoquinone (EP No. 0123 238), allopurinol (G.B. No. 1445 983).

Examples of other active compounds include: 3'-azido-3'-deoxythymidine (EP No. 0196 185), 5-prop-1-ynyl-1-(5-trimethylacetyl-β-D-arabinofuranosyl)uracil (EP No. 0375 164), 2-(2-amino-1,6-dihydro-6-oxo-9H(purin-9-yl)methoxy)ethyl-valinate (EP No. 0308 065), 2',3'-dideoxy-5-ethynyl-3'-fluorouridine (EP No. 0356 166), 5-chloro-1-(2,3-dideoxy-3-fluoro-β-erythropentofuranosyl)uracil (EP No. 0305 117 and EP No. 0317 128), penciclovir, i.e. 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (EP No. 141927), famciclovir, i.e. 2-amino-9-[4-acetoxy-3-(acetoxymethyl)butyl] purine (EP No. 0182024) and E-5-(2-bromovinyl)-1-β-arabinofuranosyluracil (EP No. 0031 128), dextromethorphan, pseudophedrine, acrivastine, triprolidine, guaiphenesine, dihydrocodeine, codeine phosphate and ascorbic acid.

Preferably the active compound is lamotrigine, i.e.(3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, more preferably acyclovir or pharmaceutically acceptable salts of these compounds which have acceptable dispersibility in water. Thus, for example, a suitable salt of lamotrigine is the isethionate salt (i.e. 2-hydroxymethanesulphonate).

It will be appreciated that reference to any active compound also includes any pharmaceutically acceptable salts thereof.

The term "swellable clay" as used herein includes layered clays (such as smectites), porous fibrous clay minerals, and synthetic clay materials related in structure to layered clays and porous fibrous clays.

The term "layered clays" as used herein includes substantially homogeneous layered clays and mixtures thereof, and interstratified or mixed layered clays. Substantially homogeneous layered clays includes the smectite group for example dioctahedral and trioctahedral types. Examples of dioctahedral smectites are the montmorillonite group (montmorillonoids); magnesium and other (e.g. calcium) aluminium silicates such as Veegum in its various grades e.g. Veegum, Veegum HV, Veegum F, and Veegum WG); almasilate; fullers earth (e.g. Surrey finest); American fullers earth; bentonite; beidellite; cheto montmorillonite, Wyoming montmorillonite, Utah montmorillonite; Tatalia and Chambers montmorillonites; and iron rich smectites such as nontrite (e.g. Garfield nontronite) and ferrian smectites.

Examples of triocatahedral smectites (also known as saponites) are Swinefordite, hectorite, stevensite. Examples of smectites containing more unusual elements are Volkhonsite, Medmontite, Sauconite, nickel smectites and vanadium smectites. As well as the montmorillonite group, related smectites such as vermiculites may also have application.

The term "interstratified or mixed layer clays", as used herein includes clays involving different layers arranged in a regular or irregular structure. The most common examples of such clays have generally two components in substantially equal proportions and have been given mineral names such as rectorite (mica-smectite), hydrobiotite (biotite-vermiculite), correnslten (chlorite-smectite) allettite (talc-saponite). More irregular arrangements include illite-smectite, chlorite-smectite, and kaolinite-smectite. Further examples of interstratified clays are tosudite, tarasovite, allevardite, Japanese bentonite ("acid clays"), AWAZU acid clay, and kaolinite-smectite. Other mixed layer clays may include one or more of the following minerals: clinchlore, chamosite, nimite, thuringite, sudoite, and cookeite. Mixed layer smectities are also known e.g. interdispersed montmorillonite and beidellite layers. The layers of mixed layer clays may be homogeneous or non-homogeneous.

The term "porous fibrous clays" includes palygorskite and sepiolite such as, for example attapulgite and American fuller's earth.

The term "synthetic clay materials" as used herein includes materials related in structure to layered clays and porous fibrous clays such as synthetic hectorite (lithium magnesium sodium silicate) for example laponite ^{R}.

It will be appreciated that within the scope of the invention the following classes of clays have application alone or in combination and in mixed layer clays: kaolinites, serpentines, pyrophyllites, talc, micas and brittle micas, chlorites, smectites and vermiculites, palygorskites and sepiolites. Other phyllosilicates (clay minerals) which may be employed in the tablets according to the invention are allophane and imogolite.

The following references describe the characterisation of clays of the above types: Chemistry of Clay and Clay Minerals. Edited by A.C.D. Newman. Mineralogical Society Monograph No. 6, 1987, Chapter 1; S.W.

Bailey; Summary of recommendations of AIPEA Nomenclature Committee, Clay Minerals 15, 85-93; and A Handbook of Determinative Methods in Mineralogy, 1987, Chapter 1 by P.L. Hall.

Suitably the swellable clay is a pharmaceutically acceptable crystalline mineral clay having a lattice structure which expands upon hydration, preferably a pharmaceutically acceptable smectite or attapulgite clay, especially a montmorillonoid, more preferably yet a montmorillonoid chosen from the group consisting of montmorillonite, sauconite, vermiculite, bentonite and hectorite, still more preferably an aluminium magnesium silicate and most preferably Veegum^{R}.

The term "smectite" as used herein in relation to tablets of the present invention includes the smectites as exemplified herein and with reference to O'Brian P. and Williamson C.J., in "Clays and Clay Minerals vol. 38 No. 3 pp322-326, 1990" and the other clay nomenclature references set out hereinbefore.

The term "magnesium aluminium silicate" as used herein in relation to tablets of the present invention should be understood to include the Aluminium Magnesium Silicate defined in the British Pharmacopoeia, volume 1, pages 27-28, 1988 and the Magnesium Aluminium Silicate defined in the United States Pharmacopoeia, National Formulary XVI, pages 1943-1944, 1990. Advantageously, said silicate is in the form of a microfine powder having a No. 325 US Standard mesh particle size, a viscosity of 250 cps (± 25%) for a 5.5% (w/v) aqueous dispersion and an acid demand (the volume in ml. of 0.1N hydrochloric acid required to reduce the pH of one gram to 4) of 6-8: such a material is available as VEEGUM F (R.T. Vanderbilt Co., New York, N.Y., U.S.A.; K & K-Greeff Chemicals Ltd., Croydon, Surrey CR9 3QL, England).

The amount of swellable clay employed in the tablet according to the invention generally depends on the weight of the tablet. Experiments with acyclovir indicate for a 100mg tablet, amounts as low as 0.25% w/w of tablet can be used whereas for tablets of about 1000mg to

1200mg up to 60% w/w, advantageously up to 50% w/w preferably up to 40% w/w could be used to give a satisfactory dispersible tablet in accordance with the invention. Other practical considerations such as poor flow and compression properties may, however, limit the maximum percentage weight of clay which can be incorporated within any given weight of tablet. In our experiments up to 40% w/w of swellable clay was used for a tablet having a total weight of 1100mg and gave fine dispersions and fast dispersion times.

Thus for a dispersible tablet containing an active compound defined hereinbefore such as acyclovir or lamotrigine, the intra-granular amount of swellable clay such as a crystalline mineral clay for example, magnesium aluminium silicate is suitably present in the following general ranges 0.25 to 60% w/w, preferably 0.25 to 50% w/w, more preferably 0.5 to 50% w/w, more preferably still 1 to 50% w/w, more preferably still 1 to 40% w/w, more preferably still 2 to 20% w/w, more preferably still 2.5 to 20% w/w, still more preferably 3 to 10% w/w, and most preferably 5 to 10%, most desirably about 5% w/w.

The tablets according to the invention will generally contain a pre-determined amount of the active compound, depending on the identity of the compound, the desired dosage and the total weight of the tablet.

When the active compound is acyclovir, the tablets generally contain 100 to 1000mg, preferably 200 to 800mg, such as 400 to 800mg of the compound. Such dosage units may be administered one or more times, for example up to five times, per day, at the discretion of the physician, according to the age and condition of the patient and the particular condition being treated. For an acyclovir tablet having a total weight about 1000 to 1200mg and containing about 750 to 850mg of acyclovir, the swellable clay e.g. Veegum F, is preferably present in an amount of 40 to 120 mg intragranularly.

When the active compound is lamotrigine or a pharmaceutically acceptable salt thereof the tablets according to the invention conveniently contain 2.5 to 500 mg. desirably 5 to 250 mg. of lamotrigine calculated as lamotrigine base. Preferred said unit doses include 5 mg., 12.5 mg., 25 mg., 50 mg., 100 mg., 150 mg., 200 mg. and 250 mg., calculated as the base. For tablets having a total weight of about 55 to 65mg and containing about 5mg lamotrigine, the swellable clay, e.g. Veegum F, is preferably present in an amount of 2 to 4mg, especially about 3mg. Similarly for a tablet having a weight of about 220 to 350mg and containing about 80 to 120mg, preferably 100mg of lamotrigine, the swellable clay, e.g. Veegum F, is preferably present in amount of 5 to 20mg, especially about 12mg.

In general the tablets according to the invention contain the active compound in the following percentage proportions:-

Acyclovir - 20 to 90% w/w, preferably 45 to 85% w/w

Lamotrigine - 3 to 90% w/w, preferably 5 to 40% w/w

1-(β-D-arabinofuranosyl)-5-propynyl-1-ynyluracil - 10 to 90% w/w, preferably 65 to 80% w/w

Paracetamol - 50 to 90% w/w, preferably 60 to 75% w/w

2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone - 50 to 85% w/w, preferably 60 to 75% w/w

Allopurinol - 25 to 80% w/w, preferably 45 to 65% w/w

Diazepam - 4 to 30% w/w, preferably 8 to 16% w/w

Pseudoephedrine - 5 to 50% w/w, preferably 15 to 30% w/w

Dextromethorphan - 2 to 20% w/w, preferably 5 to 15% w/w

Triprolidine - 10 to 50% w/w, preferably 20 to 30% w/w
Codeine phosphate
Dihydrocodeine
Ascorbic Acid

Acrivastine - 1 to 10% w/w, preferably 2 to 5% w/w

Guaiphenesine - 10 to 40% w/w, preferably 15 to 30% w/w

Ibuprofen - 20 to 90% w/w, preferably 65 to 85% w/w

When the active compound (such as acyclovir) is present in an amount of at least 60% w/w in tablets according to the invention, we have suprisingly found that the dispersion time remains substantially constant over a range of tablet hardnesses. This is a considerable quality control advantage since in industrial manufacture it is essential to maintain a constant tablet hardness. Tablets according to the invention can thus be produced with sufficient hardness and friability so that they can easily be film-coated. A tablet according to the invention should desirably have a friability of about 2% or less, preferably 0.5% or less.

Based on experiments that we have carried out, it has been found that in addition to the amount of swellable clay present within the granules of the tablet, a further amount of swellable clay may be present outside the granules. At very low intra-granular amounts (such as 1% w/w or below), higher extra-granular amounts (such as about 10% w/w or more) may decrease the dispersion time, but in general extra-granular addition has little or no effect on the dispersion time. The maximum percentage(s) of the clay present within the granules and, optionally outside the granules, may be limited by other practical considerations such as poor flow and compression properties.

Other excipients suitable for inclusion in the tablets according to the invention include the following:

a) Binders and Adhesives: we have found e.g. with acyclovir tablet formulations that if there is sufficient amount of swellable clay such as Veegum F present within the granules, then a separate binder is not required (i.e. the clay also acts as a binder). Preferably however a separate binder is present in a sufficient amount to provide a tablet having a satisfactory tablet hardness and satisfactory dispersion characterstics. The amount of binder will vary depending on the overall tablet formulation and type of binder used but general functional limits for most tablets of the invention are 0 to 25% w/w. The following binders and amounts are suitable for inclusion in a tablet according to the invention. The concentration of the binder in the granulation fluid (% w/v) is given (% w/w in tablet will vary according to the volume of granulating solution used to form a satisfactory tablet): Examples of binders are: acacia mucilage 0 to 25% w/v, preferably 1 to 5% w/v, alginic acid 0 to 20.0% w/v, preferably 1 to 5% w/v, polyvinylpyrrolidone (povidone) 0 to 15.0% w/v, preferably 0.5 to 5% w/v, gelatin 0 to 20.0% w/v, preferably 1 to 5.0% w/v, sucrose 0 to 70.0% w/v, preferably 2.0 to 20.0% w/v, starch mucilage 0 to 10.0% w/v, preferably 0.5 to 5.0% w/v, pregelatinised starch 0 to 10.0% w/v, preferably 0.5 to 5.0% w/v, starch paste 0 to 10.0% w/v, preferably 5.0 to 10.0% w/v, sodium alginate 0 to 5.0% w/v, preferably 1.0 to 3.0% w/v, sorbitol 0 to 10.0% w/v, preferably 3.0 to 10.0% w/v, tragacanth 0 to 20% w/v, preferably 5.0 to 10.0% w/v, glucose 0 to 50%, preferably 5 to 25% w/v, hydroxypropylmethyl cellulose (HPMC) 0 to 10% w/v, preferably 1.0 to 5.0% w/v, magnesium aluminium silicate 0 to 40% w/v, preferably 2 to 10% w/v, starch paste 0 to 25% w/v, preferably 5 to 15% w/v, polyvinylpyrrolidone 0 to 15% w/v, preferably 3 to 10% w/v, carboxymethylcellulose sodium 0 to 10% w/v, preferably 1 to 6% w/v, dextrin 0 to 50% w/v, preferably 5 to 25% w/v, ethyl cellulose 0 to 10% w/v, preferably 1 to 6% w/v,

polyethylene glycol 0 to 5% w/v, guar gum 0 to 10% w/v, preferably 1 to 5% w/v, zein 0 to 30% w/v, preferably 1 to 10% w/v, hydroxyethyl cellulose 0 to 5% w/v, preferably 2 to 4% w/v, hydroxypropyl cellulose up to 5% w/v, preferably 2 to 4% w/v, methyl cellulose up to 20% w/v, preferably 1 to 10% w/v, polymethacrylates up to 25% w/v, preferably 5 to 10% w/v, carboxymethylcellulose calcium 0 to 20% w/v, preferably 5 to 10% w/v.

b) Disintegrating agents: Tablets according to the invention can be formulated in the absence of separate disintegrating agents although their inclusion may be advantageous for their disintegration in water as an adjunct to the dispersion afforded by the clay above. Examples of suitable disintegrating agents which can optionally be incorporated into a tablet according to the invention are: microcrystalline cellulose (e.g. Avicel R) 0 to 30% w/w, preferably 5 to 10% w/w, Sodium carboxymethyl cellulose (e.g. Nymcel R) 0 to 5% w/w, preferably 1 to 2% w/w, calcium carboxymethyl cellulose 0 to 20% w/w, preferably 1 to 5% w/w, modified cellulose gum (e.g. Ac-Di-Sol R) 0 to 10% w/w, preferably 1 to 5% w/w, cross-linked povidone 0 to 10% w/w, preferably 2 to 6% w/w, alginic acid and alginates 0 to 10% w/w, 2 to 5% w/w, pregelatinised starch 0 to 10% w/w, preferably 0.5 to 5% w/w, sodium starch glycollate (e.g. Explotab R, Primojel R) 0 to 10% w/w, preferably 0.5 to 5% w/w, modified corn starch (e.g. starch 1500 R) 0 to 20% w/w, preferably 1 to 10% w/w, starch (e.g. potato/maize starch) 0 to 15% w/w, preferably 0.2 to 10% w/w, ion exchange resin such as polacrin potassium (e.g. Amberlite IRP-88) up to 5% w/w, preferably 0.5 to 2.0% w/w.

Work with lamotrigine and other active compounds is supportive of the view that if LHPC is used a suitable dispersion can be obtained without the need for a separate wetting agent/surfactant.

c) Fillers: These serve the purpose of bulking up the tablet to a suitable size and aiding compressibility especially in lower dosage tablets. The amount of filler depends on its type, size of tablet and amount of active compound. When the concentration of active compound is below 60% w/w, more preferably 45% w/w and most preferably below 30% w/w, an inorganic water-insoluble filler is advantageously used. Examples of water-soluble fillers (which can be used in general quantities of 0 to 95% w/w) are: soluble lactose, compressible sugar, confectioners sugar, dextrose, mannitol, sodium chloride, sorbitol, xylitol, sodium chloride F. Examples of water-insoluble fillers (which can be used in general quantities of 0 to 93% w/w) are: calcium carbonate, magnesium carbonate, calcium phosphate (e.g. di and tri basic calcium phosphate), calcium sulphate, kaolin, microcrystalline cellulose, powdered cellulose, pregelatinized starch 5 to 75%, starch, barium sulphate, magnesium trisilicate, aluminium hydroxide.

Inclusion of a filler having a negative heat of solution in water, for example mannitol, sorbitol and xylitol, provides tablets which, in addition to being water-dispersible, are especially suitable for chewing in the mouth, the dissolving of such an excipient in the saliva producing a cool, pleasant sensation.

d) Lubricants: Generally lubricants are used in as low an amount as possible. Examples of lubricants with percentage weights which are suitable for a tablet are: stearates (e.g. magnesium or calcium stearate) 0.2 to 5% w/w, preferably 0.25 to 1% w/w, talc 0.19 to 5% w/w, preferably 1 to 2% w/w, polyethylene glycol 0.19 to 5% w/w, preferably 2 to 5% w/w, liquid paraffin 0.18 to 5% w/w, preferably 2 to 5% w/w, sodium lauryl sulphate 0.19 to 5% w/w, preferably 0.5 to 2% w/w, magnesium lauryl sulphate 0.12 to 5% w/w, preferably 1 to 2% w/w, colloidal silicon dioxide 0.1 to 5% w/w, preferably 0.1 to 1.0% w/w, palmitostearate 0.01 to 5%

w/w, preferably 1 to 3% w/w, stearic acid 0.01 to 5% w/w, preferably 1 to 3% w/w, zinc stearate 0.01 to 2% w/w, 0.5 to 1.5% w/w, hydrogenated vegetable oil 0.5 to 5% w/w, preferably 1 to 3% w/w. More suitably the lower value is 0.25%.

e) Wetting agents/surfactants: examples with suitable amounts are: sodium dodecyl sulphate 0 to 10% w/w, preferably 0.5 to 2% w/w, sodium lauryl sulphate 0 to 10% w/w, preferably 0.1 to 3.0% w/w, polyoxyethylene sorbitan fatty acid esters (Tweens) 0 to 3% w/w, preferably 0.05 to 1.0% w/w, polyoxyethylene stearates 0 to 2% w/w, preferably 0.05 to 1.0% w/w, sorbitan fatty acid esters (Spans) 0 to 3% w/w, preferably 0.05 to 1.0% w/w.

f) Glidants: for example, talc 0 to 5% w/w, preferably 1 to 2% w/w, starch 0 to 15% w/w, preferably 2 to 10% w/w, magnesium stearate up to 5%, preferably 0 - 2.0% w/w, silica derivatives generally 0 to 1% w/w, preferably 0.2 to 0.5% w/w, such as colloidal silica (e.g. Aerosil) 0 to 0-5% w/w, preferably 0.25 to 3% w/w, pyrogenic silica 0 to 2% w/w, preferably 0.25 to 1% w/w, hydrated sodium silicoaluminate 0 to 2% w/w, preferably 0.5 to 1% w/w, colloidal silicon dioxide 0 to 0.5% w/w.

g) Flavouring agents: are used in for example approximate quantities of 0 to 5% w/w, preferably 0.25 to 2% w/w, orange, cherry and strawberry, raspberry, grape and passion fruit.

h) Sweetening agents: for example sodium saccharin 0 to 10% w/w, preferably, 0.5 to 5.0% w/w, aspartame 0 to 10% w/w, preferably 0.25 to 5.0% w/w, confectioners sugar 0 to 30% w/w, preferably 5 to 20% w/w, sorbitol 25 to 90% w/w, preferably 0.5 to 10% w/w, sucrose 0 to 85% w/w, preferably 0.5 to 20% w/w, xylitol 0 - 20% w/w, preferably 0.5 to 10% w/w.

Such materials may be incorporated at the appropriate stage(s) of the manufacturing process together with any other agents (e.g. colourants).

Based on the teachings and principles set out herein, the following general formulations are illustrative of tablets of the invention, and the skilled man given these teachings and principles will be able to make specific tablet formulations in accordance with the invention.

INGREDIENT	CONCENTRATION (% w/w) in Tablet
Active compound	5 to 90
Swellable clay	0.25 to 60 (preferably 0.25 to 50)
Binder	0 to 25
Disintegrating agent	0 to 20
Water-soluble filler	0 to 95
Water-insoluble filler	0 to 95
Wetting agent	0 to 5
Lubricant	0.1 to 5
Colours, flavours, sweeteners	0 to 10
Approximate Tablet weight:	50-2000mg

Other aspects of the tablet preparation will now be discussed.

Suitably the dry mixing is effected with a mixing time of 5 minutes to 25 minutes preferably about 10 minutes.

The swellable clay can be dry mixed with the active compound and other excipients and then granulating solution added, or the clay and other excipients can be dispersed firstly in the granulating solution and then added to the active compound and any other excipients prior to granulation.

The liquid employed to moisten the dry mixture, prior to the granulation step, is preferably aqueous, for example water or a mixture of water and a suitable alcohol such as ethanol or isopropanol.

Wet mixing or granulating times which are suitable (depending on the type of mixer used) are 5 to 20 minutes.

Suitable granule drying times and conditions (which will vary according to the type of equipment used and batch size of granules) are about 50 to 80^{o}C, (using a dryer such as with a tray or fluid bed dryer) to obtain a moisture content generally below about 4%.

Generally suitable compression weights and final table hardness will vary according to the size of tablet, but generally suitable values are as follows:

Approximate Tablet weight (mg)	Approximate Tablet diameter (mm)	Approximate Target tablet hardness (Kp)
60	5.6	1-2
80	6.4	3-4
125	7.4	4-5
250	8.6	5-6
330	9.4	6-8
500	11.0	10-12
600	11.8	10-14
1000	14.0	12-16

The tablets may optionally be film-coated, for example with hydroxypropylmethyl cellulose, polyethylene glycol or titanium dioxide, and/or may be scored and/or may be polished, for example with polyethylene glycol 8000. If the tablets are film-coated, this makes them easier to swallow or chew (i.e. the tablets are suitable for either dispersion in water or for direct swallowing or chewing), but the dispersion time is increased.

The present invention also provides:

a) Granules containing an active compound and a pharmaceutically acceptable swellable clay, suitable for use in the preparation of a water-dispersible tablet according to the invention.

b) Use of granules as defined above in the preparation of a water-dispersible tablet according to the invention. Optionally, a further amount of swellable clay may be added after granulation and before compression;

c) Use of a pharmaceutically acceptable swellable clay as a dispersing agent in the preparation of a water-dispersible tablet containing an active compound (as defined above);

d) Use in human medicinal therapy of a water-dispersible tablet comprising an active compound (as defined above), together with an effective amount of pharmaceutically acceptable swellable clay within the granules of the tablet.

Suitably the swellable clay of the invention is a pharmaceutically acceptable crystalline mineral compound, such as aluminium magnesium silicate (e.g. Veegum).

The therapeutic use of a tablet of the invention includes both treatment and prophylaxis.

The invention has been found to have particular application with lamotrigine because of the long term instability of lamotrigine in aqueous media. Furthermore dispersible tablets containing lamotrigine have been found to give a finer dispersion than tablets using more common disintegrating agents such as Explotab.

Further aspects of the invention illustrated with respect of lamotrigine are:

e) Granules, suitable for use in the preparation of a water-dispersible compressed tablet, comprising lamotrigine or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable crystalline mineral clay as dispersing agent;

f) Use of granules as defined above in the preparation of a water-dispersible compressed tablet which may involve the addition of a further amount of crystalline mineral clay compound after granulation and before compression; and

g) Use of a pharmaceutically acceptable crystalline mineral clay as dispersing agent in the preparation of a water-dispersible compressed tablet containing lamotrigine or a pharmaceutically acceptable salt thereof.

h) A water-dispersible tablet comprising lamotrigine or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable crystalline mineral clay having a lattice structure which expands upon hydration as dispersing agent. The lamotrigine or a pharmaceutically acceptable salt thereof together with the mineral clay are comprised within the tablet in granulated form.

i) A method for the preparation of a lamotrigine water-dispersible tablet which comprises the steps of

admixture in dry, finely-divided form of lamotrigine or a pharmaceutically acceptable salt thereof and the pharmaceutically acceptable crystalline mineral clay which may be chosen from the group consisting of attapulgite, smectite and montmorillonoid clays or magnesium aluminium silicate,

optional addition of other pharmaceutical ingredients such as fillers (eg lactose, avicel or mannitol), disintegrants, binders, etc.

addition of a quantity of a pharmaceutically acceptable liquid sufficient to moisten the mixture,

granulation of the resulting moist mass,

drying of the granules and blending of the granules with optional lubricants, glidant, flavours, disintegrants etc., and

formation of the blend into a tablet.

j) Use in human medicine of a water-dispersible compressed tablet comprising lamotrigine or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable crystalline mineral clay as dispersing agent, and

k) A method for the treatment in a human being of a disorder of the central nervous system which comprises administration of a water-dispersible compressed tablet comprising lamotrigine or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable crystalline mineral clay as dispersing agent.

Especially preferred tablets are those wherein the lamotrigine is present as the base.

The said tablets may be employed in human medicine in the treatment of disorders of the central nervous system and in particular in the treatment of epileptic seizures. They may be administered one or more times per day, for example up to five times per day, at the discretion of the attendant physician and dependent upon the age and condition of the patient, the particular disorder being treated, the unit dose adopted and the total dose required. A suitable daily dose for the treatment of epileptic seizures will generally lie in the range of 5 to 500 mg., more often in the range of 25 to 400 mg., calculated as the base.

The physical size of the said tablets is desirably such as to permit their dispersion, prior to oral ingestion, in an acceptably small volume of water. Thus, for example, a tablet containing 5 mg. (calculated as the base) of lamotrigine or a salt thereof, a dose especially suitable for paediatric use, is advantageously small enough to disperse in the volume of water held in a standard 5 ml. medicine spoon.

Tablets of the invention containing lamotrigine (or a salt thereof) advantageously include a magnesium aluminium silicate such as Veegum F as the swellable clay together with further optional pharmaceutical carriers or excipients referred to above such as binders, lubricants, fillers, disintegrating agents etc.

In such tablets the ingredients are advantagously present in the following proportions: lamotrigine: 2% w/w to 90% w/w preferably 5% w/w to 40% w/w; swellable clay: 0.25% w/w to 40% w/w preferably 0.25% w/w to 10% w/w.

A suitable formulation of a dispersible tablet containing 25 to 200mg lamotrigine would be:

Lamotrigine	30% w/w to 50% w/w, preferably 35-45%
Calcium carbonate	26% w/w to 46% w/w, preferably 31-41%
LHPC-LH11 or microcrystalline cellulose (e.g. Avicel PH101)	5% w/w to 30% w/w, preferably 5-15%
Magnesium aluminium silicate Veegum F or bentonite	0.25% w/w to 30% w/w, preferably 0.25-10%
Povidone	0.25% w/w to 5.0% w/w, preferably 0.5-2%
or pre-gelled starch	1.0% w/w to 8.0% w/w, preferably 2-5%
Sodium starch glycollate	0% w/w to 8% w/w, preferably 0-5%
Magnesium stearate	0.25% w/w to 2% w/w, preferably 0.25-1%

and if optionally film coated:

Opadry	0.1% w/w to 2% w/w, preferably 0.25-1%
Polyethylene glycol 8000	0.1% w/w to 0.5% w/w, preferably 0.1-0.2%

A suitable formulation of a dispersible tablet containing 5mg to 50mg of lamotrigine would be as follows, (values being in % w/w).

Lamotrigine	3-13	preferably 5-11
Lactose or calcium carbonate	50-60	preferably 53-59
Microcrystalline cellulose (e.g. Avicel PH101) or LHPC-LH11	20-35	preferably 24-30
Sodium starch glycollate	0-8	preferably 0-5
Magnesium aluminium silicate Veegum F or bentonite	0.25-30	preferably 0.25-10
Povidone K30	0.25-5.0	preferably 0.5-2.0
or pregelled starch	1.0-8.0	preferably 2-5
Sodium docusate	0-0.5	preferably 0.5-0.15
Sodium saccharine	0-3	preferably 0.5-2
Magnesium stearate	0.25-2	preferably 0.25-1

and if optionally film coated

Opadry	0.1-2.0	preferably 0.25-1
Polyethylene glycol 8000	0.1-0.5	preferably 0.1-0.2

As referred to above, the present invention is particularly applicable to the formulation of water-dispersible tablets containing acyclovir as the active compound.

Acyclovir is a compound which has been found to have potent activity against viruses of the herpes family, particularly herpes simplex and herpes varicella zoster. Such activity has been demonstrated by the outstanding success of acyclovir in the therapeutic treatment of clinical conditions such as genital herpes caused by the herpes varicella zoster virus.

In the treatment of certain conditions, it may be necessary to administer acyclovir to the patient in relatively large dosages to achieve the effective therapeutic levels of drug in the plasma, particularly when oral administration is desired. For example, in the treatment of shingles, it is recommended to administer acyclovir at a dosage regime of 800mg five times per day. A tablet formulation containing 800mg of acyclovir is currently available but its relatively large size sometimes renders it difficult to swallow by elderly patients, such patients being particularly susceptible to shingles. This problem is obviated by the water-dispersible tablets according to the invention which enable relatively high doses of acyclovir to be administered in a drinkable dispersion by the oral route.

The advantageous water-dispersibility of tablets according to the invention containing acyclovir as the active compound is especially surprising in view of the poor water-dispersibility demonstrated by tablets containing conventional disintegrating agents such as sodium starch glycollate, cross-linked povidone and cross-linked sodium carboxymethylcellulose.

Yet further aspects of the invention with respect to acyclovir are as follows:

l) A granulate comprising acyclovir together with a pharmaceutically acceptable magnesium aluminium silicate compound;

m) Use of a granulate according to e) above for the manufacture of a water-dispersible tablet formulation.

n) Use of magnesium aluminium silicate in the manufacture of a water-dispersible tablet formulation of acyclovir.

o) A water-dispersible pharmaceutical tablet formulation comprising acyclovir together with a pharmaceutically acceptable magnesium aluminium silicate compound.

p) A process for the preparation of a pharmaceutical tablet formulation which comprises admixing acyclovir with a magnesium aluminium silicate compound and optionally one or more further pharmaceutical carriers or excipients, granulating the resulting mixture with a pharmaceutically acceptable liquid, drying the resulting granulate, optionally mixing the dried granulate with one or more further pharmaceutical carriers or excipients, and subsequently compressing the dried granulate to form tablets. The liquid employed in the above granulation step is advantageously aqueous, for example, an aqueous ethanol mixture. The resulting tablets may be subsequently film coated for example with hydroxypropylmethyl cellulose, titanium dioxide or polyethylene glycol and, if desired, polished for example with polyethylene glycol 8000.

Tablets according to the invention containing acyclovir advantageously include a magnesium aluminium silicate such as Veegum F as the swellable clay optionally together with further pharmaceutical carriers or excipients referred to above such as disintegrating agents, binders, fillers, lubricants etc.

In such tablets the ingredients are advantageously present in the following proportions: acyclovir 40 to 98% w/w, preferably 75 to 85% w/w, swellable clay 0.5 to 40% w/w, preferably 0.5 to 10% w/w.

A suitable formulation of an acyclovir dispersible tablet containing from 200mg-800mg acyclovir would be:

Acyclovir	70% w/w to 90% w/w, preferably 75-85% w/w
Povidone or pregelled starch	0.25% w/w to 5% w/w, preferably 0.5-2% w/w
Magnesium aluminium silicate Veegum F or bentonite	0.5% w/w to 30% w/w, preferably 0.5-10% w/w
Microcrystalline cellulose Avicel PH101 or LHPC-LH11	5% w/w to 25% w/w, preferably 5-15% w/w
Sodium starch glycollate	0% w/w to 8% w/w, preferably 0-5% w/w
Magnesium stearate	0.25% w/w to 2% w/w, preferably 0.25-1.0% w/w

and if optionally film coated:

Opadry	0.1% w/w to 2% w/w, preferably 0.25-1.0% w/w
Polyethylene glycol 8000	0.1% w/w to 0.5% w/w, preferably 0.1-0.2% w/w

The following Examples illustrate the present invention.

Examples 1 to 6 and 29 are comparative examples while examples 7-28, 30 and 31 describe the preparation of tablets according to the invention in which the active compound is acyclovir.

Example Number	1 mg/tablet	2 mg/tablet	3 mg/tablet	4 mg/tablet
Intra-granular:				
Acyclovir *	848.0	848.0	844.0	844.0
Avicel PH101	60.0	NIL	101	NIL
Lactose	120.0	NIL	NIL	NIL
Starch (maize)	NIL	NIL	50	NIL
Explotab	NIL	75.0	50	NIL
Primogel	NIL	NIL	NIL	75.0
Ac-Di-Sol	83.0	NIL	23	NIL
Kollidon CL starch	NIL	NIL	NIL	NIL
Saccharin sodium	20.0	10.0	NIL	NIL
Sodium lauryl sulphate	5.0	NIL	3.0	NIL
Sodium docusate	NIL	1.0	NIL	0.5
Dicalc.phosph.dihyr.	NIL	NIL	NIL	200.0
Povidone K30	NIL	10.0	22	11.2
Extra-granular:				
Ac-Di-Sol	40.0	NIL	NIL	NIL
Avicel PH102	60.0	94	NIL	NIL
Amberlite 1RP88	NIL	NIL	NIL	50.0
Kollidon CL	NIL	NIL	60.1	NIL
Mg stearate	12.0	10.0	10.1	11.0
Tablet weight (mg)	1248.0	1048.0	1163.2	1191.7

* In the following examples except examples 13, 14 and 15, the actual quantity of acyclovir used is calculated from a factor so as to provide 800mg of acyclovir per tablet. (The factor for acyclovir is typically 105.5 equivalent to 100 acyclovir). In examples 13, 14 and 15, the actual quantity of acyclovir used was adjusted from the factor so as to provide 800mg of acyclovir per tablet.

Example Number	5 mg/tablet	6 mg/tablet	7 mg/tablet	8 mg/tablet	9 mg/tablet
Acyclovir	844.0	848.0	844.0	848.0	848.0
Avicel PH 101	101.0	83.46	100.0	89.0	89.0
Veegum F	NIL	NIL	53.0	53.0	53.0
Sodium starch glycollate (Explotab)	90.0	39.37	42.0	42.0	42.0
Povidone K30	11.0	10.27	NIL	11.0	11.0
Magnesium stearate	9.5	8.85	9.4	9.4	9.4
Film coat composite 1:					
Opadry	NIL	NIL	NIL	NIL	7.86
Film coat composite 2:					
Polyethylene glycol 8000	NIL	NIL	NIL	NIL	2.097
Tablet weight (mg)	1055.5	989.95	1048.4	1052.4	1062.4

In accordance with the invention, to illustrate that the disintegration time remains substantially constant at different tablet hardnesses, the formulation of Example 7 was compressed at approximately 8 kp (7a), 12 kp (7b) and 18 kp (7c) and the results noted hereafter.

Example Number	10 mg/tablet	11 mg/tablet	12 mg/tablet
Acyclovir	848.0	848.0	848.00
Avicel PH 101	118.5	71.1	86.8
Veegum F	26.5 *	53.0	53.0
Primojel	42.0	42.0	42.0
Povidone K30	NIL	20.9	5.2
Magnesium stearate	9.4	9.4	9.4
Tablet weight (mg)	1044.4	1044.4	1044.4

* Veegum added as a paste - example contains no PVP-K30 as a binder.

Examples of Acyclovir formulations

Example Number	13 mg/tablet	14 mg/tablet	15 mg/tablet
Component (mg/tablet)			
Acyclovir	800.0	800.0	800.0
Avicel PH 101	100.0	89.0	89.0
Veegum F	53.0	53.0	110.0
Sodium starch glycollate	42.0	42.0	42.0
Povidone K30	NIL	11.0	11.0
Magnesium stearate	9.4	9.4	9.9
Tablet weight (mg)	1004.4	1004.4	1061.9

Example Number	16		17		18		19	
	% w/w	mg/ tablet	% w/w	mg/ tablet	% w/w	mg/ tablet	% w/w	mg/ tablet
Acyclovir	79.95	848.0	75.54	795.00	65.47	689.00	55.00	583.00
Avicel PH101	8.86	89.0	8.86	89.00	8.86	89.00	8.86	89.00
Veegum F	5.28	53.0	10.00	106.00	20.00	212.00	30.00	318.00
Explotab	4.18	42.0	4.18	42.00	4.18	42.00	4.18	42.00
Povidone K30	1.09	11.0	1.09	11.00	1.09	11.00	1.09	11.00
Magnesium stearate	0.94	9.4	0.94	9.40	0.94	9.40	0.94	9.40
Tablet weight (mg)	100.0	1052.4	100.0	1052.4	100.0	1052.4	100.0	1052.4

Example Number		20		21		22
	% w/w	mg/ tablet	% w/w	mg/ tablet	% w/w	mg/ tablet
Acyclovir	45.32	477.00	84.3	890.00	44.93	848.00
Avicel PH101	8.86	89.00	8.86	89.00	8.86	157.76
Veegum F	40.00	424.00	1.00	10.60	40.00	712.22
Explotab	4.18	42.00	4.18	42.00	4.18	74.43
Povidone K30	1.09	11.00	1.09	11.00	1.09	19.41
Magnesium stearate	0.94	9.40	0.94	9.40	0.94	16.74
Tablet weight (mg)	100.00	1052.4	100.00	1052.4	100.00	1828.56

Example Number	23		24		25		26	
	% w/w	mg/ tablet	% w/w	mg/ tablet	% w/w	mg/ tablet	% w/w	mg/ tablet
Acyclovir	65.47	689.00	55.00	583.00	45.32	477.00	79.65	848.00
Avicel PH101	8.86	89.00	8.86	89.00	8.86	89.00	8.86	89.0
Veegum F	*20.00	(106.00 (106.00	*30.00	(159.00 (159.00	*40.00	(212.00 (212.00	5.28	53.0
Explotab	4.18	42.00	4.18	42.00	4.18	42.00	4.18	42.0
Povidone K30	1.09	11.00	1.09	11.00	1.09	11.00	1.09	11.0
Magnesium stearate	0.94	9.40	0.94	9.40	0.94	9.40	0.94	9.4
Tablet weight (mg)	100.00	1052.4	100.00	1052.4	100.00	1052.4	100.00	1052.4

* In these examples the Veegum is distributed equally both intra-granularly and extra-granularly.

Example Number	27		28		29		30	31
	% w/w	mg/ tablet	% w/w	mg/ tablet	% w/w	mg/ tablet	mg/ tablet	mg/ tablet
Acyclovir	84.43	848.00	84.68	848.00	84.93	848.00	848.0	840.0
Avicel PH101	8.86	83.95	8.86	83.70	8.86	83.46	89.0	89.0
Veegum F	0.50	4.74	0.25	2.36	0.00	0.00	-	-
Bentonite	-	-	-	-	-	-	53.0	NIL
Attapulgite	-	-	-	-	-	-	NIL	53.0
Explotab	4.18	39.60	4.18	39.49	4.18	39.37	42.0	42.0
Povidone K30	1.09	10.32	1.09	10.30	1.09	10.27	11.0	11.0
Magnesium stearate	0.94	8.91	0.94	8.88	0.94	8.85	9.1	9.1
Tablet weight (mg)	100.00	995.53	100.00	992.73	100.00	989.95	1052.1	1044.1

Examples 32-40 describe the preparation of tablets according to the invention in which the active compound is lamotrigine.

Example Number	32 mg/ tablet	33 mg/ tablet	34 mg/ tablet	35 mg/ tablet	36 mg/ tablet	37 mg/ tablet	38 mg/ tablet
Lamotrigine	100	5.0	5.0	100	100	100	100
Calcium carbonate	95	NIL	NIL	NIL	95	NIL	NIL
Lactose	NIL	34	35.0	15	NIL	98.1	84
L HPC-LH11	25	NIL	NIL	NIL	25	NIL	NIL
Veegum F	12	3.0	3.0	7.5	12.0	16.0	12
Povidone K30	3.0	0.6	0.6	1.5	3.0	3.2	3
Explotab	10.0	2.0	1.2	6.0	NIL	12.8	10.0
Sodium Saccharin	2.5	0.5	0.5	NIL	NIL	NIL	NIL
Aspartame	NIL	NIL	NIL	4.0	7.5	NIL	7.5
Microcrystalline cellulose (Avicel PH101)	NIL	17	17	15	NIL	89.6	23
Sodium docusate	NIL	0.05	NIL	NIL	NIL	0.26	0.2
Magnesium stearate	2.5	0.4	0.4	1.5	2.5	3.2	2.5
Tablet weight (mg)	250	62.55	62.70	150.5	245	323.16	242.2

Example Number	39	40
Lamotrigine	100.0	100.0
Calcium carbonate	95.0	90.0
Lactose		
L HPC-LH11	25.0	25.0
Veegum F	12.0	12.0
Povidone K30	3.0	3.0
Explotab	-	10.0
Sodium Saccharin	-	-
Aspartame	7.5	7.5
Microcrystalline cellulose (Avicel PH101)	-	-
Sodium docusate	-	-
Magnesium stearate	2.5	2.5
Flavour	-	1.24
Tablet weight (mgs)	245.0	251.24

Examples of Tablet Formulations
containing other Active Compounds

Example Number	41	42	43	44	45
Active compound * (mg)	200.0	300.0	758.0	500.0	5.0
Avicel PH101	50.0	64.0	83.0	-	17.0
Explotab	12.3	21.0	40.0	27.0	2.5
L-HPC-LH11	50.0	-	41.0	87.0	-
Lactose	-	110.0	-	-	34.0
Veegum F	16.7	27.0	50.0	71.0	3.0
Citric acid monohydrate	-	-	0.8	-	
Na docusate	-	-	0.8	-	-
Saccharin sodium	-	-	0.5	-	-
Povidone K30	3.3	10.8	20.0	20.0	0.7
Magnesium Stearate	1.0	2.7	5.0	2.0	0.4
Flavour (Pineapple)	-	-	2.0	-	-
Tablet Weight (mg)	333.3	535.5	1001.1	707.0	62.6

* The active compound for each Example is as follows:-

Example 41 - 1-(β-D-arabinofuranosyl)-5-propynyluracil

Example 42 - Allopurinol

Example 43 - 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4,naphthoquinone

Example 44 - Paracetamol

Example 45 - Diazepam

Method of Preparation

The tablets described in Examples 1-45 above were prepared according to the following general method:

(a) A dry mixture was made of all components except Povidone/PVP K30, sodium docusate (if present) and magnesium stearate;

(b) The Povidone/PVP K30 and sodium docusate (if present) were dissolved in 50% aqueous alcohol to form a granulation solution;

(c) The granulation solution was added to the dry mixture to form granules;

(d) The wet granules were dried in a fluid bed dryer;

(e) The granules were then sifted through a 1000μm diameter mesh sieve; and

(f) The dried granules were blended with the magnesium stearate and compressed to form tablets.

Flavouring agents where present were added at blending step (f) above.

This general method is illustrated with respect to the following specific examples.

Example 8 : Uncoated Tablets

(a) A dry mixture was made of all components except Povidone/PVP K30 and magnesium stearate using a Diosna P100 (high shear mixer - granulator) for 3 minutes.

(b) The Povidone/PVP K30 was dissolved in 50% aqueous alcohol to form a granulation solution.

(c) The granulation solution was added to an approximate quantity of 300ml per kg dry weight to the dry mixture to form granules. Wet mixing was carried out for approximately 5 minutes.

(d) The wet granules were dried in an Aeromatic T3 fluid bed drier at a temperature of 70°C for approximately 30 minutes. The moisture content of the granules was approximately 4%.

(e) The granules were then sifted through a 1000μm diameter mesh sieve using a Jackson Crockatt No.7 sifter.

(f) The dried granules were blended with the magnesium stearate using a collette mixer for approximately 10 minutes and compressed to form tablets using a Manesty D3 Rotary tablet press fitted with caplet shaped punches of approximately 19.3mm length and 9.0mm breadth. Tablets were compressed to a weight of 1052mg ± 2%.

This granule can be used to make other strengths of acyclovir dispersible tablets, e.g. 200mg and 400mg, compressing the dried granules to a weight of respectively 263mg and 526mg, using round punches with diameters of respectively 11.0mm and 8.6mm.

Example 9 : Film Coated Tablets

Steps (a) to (f) described in Example 8 were repeated to form an uncoated tablet which was then film-coated by the following procedure.

The film-coating apparatus used was a Manesty Accellacota 10. The coating suspension was sprayed onto the tablet cores to a target weight increase of between 0.5 - 1.0% using suitable parameters of:

pan rotation speed (8.5 rpm)
spray (application rate (~20g per min)
inlet temperature (~75°C)
exhaust temperature (~53°C).

A polish coat of PEG8000 was then applied to the film-coated tablets, to a further weight gain of 0.1 - 0.2%.

Examples 13 to 15

In Example 13, Acyclovir, Avicel PH101, Sodium starch glycollate and Veegum F are dry mixed in a mixer. The mixture is then granulated after adding a sufficient volume of 50% aqueous alcohol (IMS). The resulting granules are dried, blended with the magnesium stearate and then compressed to form tablets.

Example 14

The procedure described in Example 13 for the preparation of the granules and formation of the tablets is employed except that granulation of the dry mixture is effected with the Povidone in a 50% aqueous alcohol solution. Film coating of the resulting tablets can be optionally effected by treating the tablets with a dispersion of Opadry white dispersion in purified water and drying the coated tablets which are subsequently polished with a solution of polyethylene glycol 8000, USNF in 50% aqueous alcohol (IMS).

For Example 15, the procedure described in Example 13 for the preparation of the granules and formation of the tablets is employed except that granulation of the dry mixture was effected with the Povidone in a 50% aqueous alcohol solution.

Example 33

(a) A dry mixture was made of all components except Povidone/PVP K30 and magnesium stearate using a Z-blade Morton Mixer, mixing for 10 minutes at a slow speed.

(b) The Povidone/PVP K30 was dissolved in 50% aqueous alcohol to form a granulation solution;

(c) The granulation solution was added to an approximate quantity of 350ml per kg dry weight to the dry mixture to form granules;

(d) Wet mixing was carried out for approximately 10 minutes. The wet granules were sieved through a 2000μm mesh sieve;

(e) The wet granules were dried in an Aeromatic fluid bed drier at a temperature of 70°C for approximately 25 minutes;

(f) The granules were then sifted through a 1000μm diameter mesh sieve;

(g) The dried granules were blended with the magnesium stearate using a Rotomixer rotary blender for 5 minutes and compressed to form tablets using a Manesty D3 Rotary press fitted with 5.6mm diameter round (normal curvature) punches and dies. Tablets were compressed to a weight of 62.55mg ± 2%.

Flavouring agents may be added at blending step (g) above.

For a 50mg tablet, the same procedure was used, except that a die of 11.8mm diameter was used and the tablets were compressed to a weight of 625.5mg ± 2%.

The lamotrigine tablets could be optionally film coated using the same procedure as described for Example 9.

The tablets prepared in accordance with the above Examples were then tested as follows.

Tablet Evaluation Methods

1. Average tablet weight. Twenty tablets were weighed on an analytical balance and the average tablet weight calculated.

2. Tablet breaking strength (kilo pond-kp). 5 tablets were individually tested using a Schleuniger crushing strength tester, and the average breaking strength calculated.

3. Friability (% loss). 10 tablets, accurately weighed, were subjected to 10 minutes friability testing using a Roche Friabilator. The tablets were dedusted, reweighed, and the weight loss due to the friability was calculated as a percentage of the initial weight.

4. Dispersion Disintegration time DT (BP 1988). 6 tablets were tested in accordance to the above-defined BP test (without discs) for dispersible tablets. This utilises water at a temperature of 19-21^{o}C.

5. Dispersion Quality. In accordance with the BP uniformity of dispersion test for dispersible tablets (BP 1988 Volume II page 895), two tablets were placed in 100ml of water at 19-21^{o}C and allowed to disperse. A smooth dispersion was produced which passed through a 710μm mesh sieve.

Granule Evaluation Methods

1. Loss on Drying (LOD). The residual moisture content of the granule (LOD) was determined on a 3-4g sample using a Computrac moisture analyser set to 90^{o}C operated in accordance with the manufacturer's procedure.

2. Weight Median Diameter (WMD). A 10g sample of granule was sifted for 2 minutes at suitable pulse and sift amplitudes in an Allen Bradley sonic sifter in accordance with manufacturer's instructions. Sieves of 710μm, 500μm, 355μm, 250μm, 150μm, 106μm and 53μm were used. The WMD was calculated from the cumulative percentage undersize size distribution using a computer programme.

Acyclovir Granule and Tablet Evaluation Results

Example Number	Actual Average Tablet Weight (mg)	Target Tablet Weight (mg)	Average Thickness (mm)	Average Breaking Strength (Kp)	Friability (%)	Disintegration time ** First Tablet	Disintegration time ** Last Tablet	Granule Properties Loss on Drying (% LOD)	Granule Properties Weight median diameter WMD (m)	Tablet shape/ maximum dia-meter
1	-	1248.0	-	11.0	-		12'17"	1.43	-	Caplet*
2	-	1048.0	-	11.6	-		7'26"	1.59	-	Caplet
3	1176	1163.2	-	10.7	-	>10'	>10"	2.28	-	Round 14.0mm
4	-	1191.7	-	13.7	-		4'50"	1.18	-	Round 14.0mm
5	1053	1055.5	-	15.0	-		4'21"	1.75	186	Round 14.0mm
6	983	989.95	5.46	10.8	0.34	6'27"	7'26"	1.43	315	Caplet
7a	1022	1048.4	-	7.2	2.74		0'33"	1.31	233	Caplet
7b	1046	1048.4	-	12.8	0.47		0'42"	1.31	233	Caplet
7c	1048	1048.4	-	17.1	0.19		0'44"	1.31	233	Caplet
8 (uncoated)	1049	1052.4	7.0	14.6	0.18		0'35"	4.06	138	Caplet
9 (coated)	1053	1062.4	6.99	16.1	negligible		1'05"	4.06	138	Caplet

** All dispersions passed through a 710 m sieve (BP uniformity of dispersion test).

Example Number	Actual Average Tablet Weight (mg)	Target Tablet Weight (mg)	Average Thickness (mm)	Average Breaking Strength (Kp)	Friability (%)	Disintegration time ** First Tablet	Disintegration time ** Last Tablet	Granule Properties: Loss on Drying (% LOD)	Granule Properties: Weight median diameter WMD (m)	Tablet shape/ maximum diameter
10	-	1044.4	-	14.4	0.11	-	0'32"	2.65	123	Caplet
11	-	1044.4	-	15.3	0.24	-	0'46"	1.46	196	Caplet
12	-	1044.4	-	13.3	0.73	-	0'27"	1.76	105	Caplet
13,14,15	***									
16	1051.24	1052.4	7.1	11.6	0.49	0'46"	0'49"	1.12	185	Caplet
17	1059.54	1052.4	7.0	11.8	0.46	0'28"	0'30"	2.18	125	Caplet
18	1060.79	1052.4	6.90	11.5	0.62	0'17"	0'19"	1.46	178	Caplet
19	1053.4	1052.4	6.70	11.6	0.71	0'19"	0'24"	2.00	73	Caplet
20	1057.6	1052.4	6.71	9.1	2.45	0'20"	0'23"	1.81	90	Caplet
21	1048.8	1052.4	7.24	11.5	0.85	2'18"	2'59"	1.15	341	Caplet
22	1743.9	1828.56	10.40	11.6	2.19	0'29"	0'31"	1.84	83	Caplet
23	1054.2	1052.4	6.90	11.5	0.09	0'43"	0'51"	1.84	157	Caplet

** All dispersions passed through a 710 m sieve (BP uniformity of dispersion test).

Example Number	Actual Average Tablet Weight (mg)	Target Tablet Weight (mg)	Average Thickness (mm)	Average Breaking Strength (Kp)	Friability (%)	Disintegration time ** First Tablet	Disintegration time ** Last Tablet	Granule Properties Loss on Drying (% LOD)	Granule Properties Weight median diameter WMD (m)	Tablet shape/ maximum diameter
24	1059.1	1052.4	6.90	11.4	0.02	0'55"	1'00"	0.68	142	Caplet
25	1052.6	1052.4	6.70	11.9	0.09	1'30"	1'42"	1.59	118	Caplet
26a)#	130.6	131.55	2.80	4.2	0.56	0'25"	0'28"	1.34	296	7.4mm Round
26b)#	526.0	526.2	4.81	12.84	0.79	0'26"	0'30"	1.34	296	11.0mm Round
26c)#	1216.5	1215.0	8.20	11.10	0.83	0'45"	0'51"	1.34	296	Caplet
27	125.7	124.4	3.68	3.68	0.71	0'33"	0'39"	1.21	334	7.4mm Round
28	124.7	124.1	2.78	3.55	0.65	0'44"	0'47"	1.90	332	7.4mm Round
29	982.9	989.95	5.46	10.8	0.34	6'27"	7'26"	1.43	315	Caplet
30	1041.2	1052.1	-	11.8	-	1'30"	1'55"	1.62	227	Caplet
31	1038.6	1044.1	-	16.6	1.59	1'50"	2'10"	1.96	150	Caplet

* Approximate dimensions of caplet were: 19.3mm long, 9.0mm wide, 7.0mm thick.

** Disintegration times measured in accordance with BP test for dispersible tablets. All dispersions passed through a 710 m sieve (BP uniformity of dispersion test).

Same granule formulation, but different compression weights giving approximately: a=100mg, b=400mg and c=925mg of acyclovir per tablet.

*** Examples 13, 14 and 15 disintegrated in 0'30" to 1'30".

Lamotrigine Granule and Tablet Evaluation Results

Example Number	Actual Average Tablet Weight (mg)	Target Tablet Weight (mg)	Average Thickness (mm)	Average Breaking Strength (Kp)	Friability (%)	Disintegration time ** First Tablet	Disintegration time ** Last Tablet	Granule Properties Loss on Drying (% LOD)	Granule Properties Weight median diameter WMD (m)	Tablet shape/ maximum dia-meter
32	251.0	250.0	-	4.8	1.32	-	0'24"	2.28	74	8.6 round
33a)##	62.06	62.55	2.30	1.5	0.9	-	0'09"	1.90	98	5.6 round
33b)	630.0	625.5	5.40	9.6	0.71	-	0'33"	1.90	98	11.8 round
34	61.95	62.70	2.27	1.3	1.3	-	0'06"	1.96	102	5.6 round
35	150.2	150.5	3.32	4.5	1.01	0'23"	0'26"	3.9	168	7.4 round
36	245.7	245.0	-	4.9	1.44	-	0'20"	3.0	-	8.6 round
38	237.5	242.2	3.79	5.2	1.42	0'30"	0'36"	3.1	182	8.6 round
40a)+	62.4	62.8	-	1.5	1.10	-	0'19"	1.4	-	5.6 round
40b)+	248.7	251.24	-	4.5	1.45	-	0'44"	1.4	-	8.6 round

+ Tablets containing lamotrigine a) 25mg and b) 100mg made by varying the tablet compression weight.

Tablets containing a) 5mg and b) 50mg lamotrigine made by varying the tablet compression weight.

Granule and Tablet Evaluation Results for Other Actives

Example Number	Actual Average Tablet Weight (mg)	Target Tablet Weight (mg)	Average Breaking Strength (Kp)	Fria-bility (%)	Disintegration time ** First Tablet	Disintegration time ** Last Tablet	Granule Properties: Loss on Drying (% LOD)	Granule Properties: Weight median diameter WMD (m)	Tablet shape size
41	-	333.3	9.5	0.31	0'28"	0'32"	1.40	112	9.4mm round
42	536.7	535.5	9.0	0.87	0'45"	0'50"	1.00	246	11.0mm round
43	993.6	1001.1	17.0	1.26	0'50"	1'05"	1.87	167	14.0mm round
44	706.7	707.0	16.5	0.80	0'45"	0'50"	1.90	83	12.6mm round
45	63.3	62.6	2.6	0.79	0'05"	0'07"	2.06	-	5.6mm round

** All dispersions passed through a 710 m sieve (BP uniformity of dispersion test).

A particle size analysis was carried out on the dispersion of a tablet of Example 9 in accordance with the following method.

The particle size distribution was determined using a Malvern 2600 particle analyser as follows. The instrument was set to analyse particles in liquid with magnetic stirrer fitted. A 300mm focal length lens was used.

1. Disperse tablet in 100ml of de-ionised water.
2. Agitate solution for approximately 2 hours.
3. Filter or centrifuge solution to obtain liquor which should be saturated with all ingredients present in the tablet.
4. Disperse second tablet in 50ml of saturated liquor allowing 3 minutes to fully disperse. Agitate vigorously and remove a sample of the dispersion within 5 minutes adding sufficient quantity to the Malvern PIL cell containing the liquor to obtain an observation value of 0.15-0.30. Analyse sample.

The particle size distribution was as follows:

Particle size: (as equivalent spherical volume)
<710μm - 100%
<300μm - 98.7%
<200μm - 86.7%
<130μm - 50% (median particle size).

CLAIMS

1) A water-dispersible tablet comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an anti-viral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol, an anti-convulsant 1,2,4 triazine derivative and trimethoprim (optionally in combination with sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay to provide a tablet which is capable of dispersing in water within a period of 3 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710μm in accordance with the test for dispersible tablets defined in the British Pharmacopoeia, 1988, Volume II, page 895.

2) A water-dispersible film-coated tablet comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an antiviral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol, anti-convulsant 1,2,4-triazine derivative and trimethoprim (optionally in combination with sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay to provide a film-coated tablet which is capable of dispersing in water within a period of 5 minutes to provide a dispersion which is capable of passing through a sieve screen having a mesh aperture of 710μm in accordance with the test for dispersible tablets defined in the British Pharmacopoeia, 1988, Volume II, page 895.

3) A tablet as claimed in claim 1 or 2 which is capable of dispersing in water within a period of 2 minutes.

4) A tablet as claimed in any one of claims 1 to 3 wherein the dispersion contains particles having a particle size distribution of 100% less than 710μm, and more than 50% less than 310μm.

5) A tablet as claimed in claim 4 wherein the dispersion contains particles having a particle size distribution of 100% less than 710μm, more than 70% less than 310μm, and more than 50% less than 200μm.

6) A tablet as claimed in any of the preceding claims wherein the active compound is selected from the group consisting of acyclovir, lamotrigine, diazepam, paracetamol, 1-(β-D-arabinofuranosyl)-5-propy-1-ynyl-uracil, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone, allopurinol, 3'-azido-3'-deoxythymidine), 5-prop-1-ynyl-1-(5-trimethylacetyl-β-D-arabinofuranosyl)uracil, 2-(2-amino-1,6-dihydro-6-oxo-9H(purin-9-yl)methoxy)-ethyl-valinate, 2',3'- dideoxy-5-ethynyl-3'-fluorouridine, 5-chloro-1-(2,3-dideoxy-3-fluoro-β-erythropentofuranosyl)uracil, penciclovir, famciclovir, E-5-(2-bromovinyl)-1-β-arabinofuranosyluracil, dextromethorphan, pseudophedrine, acrivastine, triprolidine, guaiphenesine, dihydrocodeine, codeine phosphate and ascorbic acid.

7) A tablet as claimed in any oe the preceding claims wherein the swellable clay comprises a smectite or attapulgite.

8) A tablet as claimed in claim 7 wherein the smectite is selected from the montmorillonite group.

9) A tablet as claimed in claim 8 wherein the montmorillonite is Veegum F or bentonite.

10) A tablet as claimed in any of the preceding claims wherein the swellable clay is present within the granules of the tablet in an amount of 0.25% to 60% w/w.

11) A tablet as claimed in claim 10 wherein the swellable clay is present within the granules of the tablet in an amount of 0.25% to 40% w/w.

12) A tablet as claimed in claim 11 wherein the swellable clay is present within the granules of the tablet in an amount of 1 to about 10% w/w.

13) A tablet as claimed in any of the preceding claims containing the active ingredient in an amount of 5 to 90% w/w.

14) A tablet as claimed in any of the preceding claims which has a general formulation of active compound 5 to 90% w/w, swellable clay 0.25 to 60% w/w, binder 0 to 25% w/w, disintegrating agent 0 to 20% w/w, water-soluble filler 0 to 95% w/w, water-insoluble filler 0 to 95% w/w, wetting agent 0 to 5% w/w, lubricant 0.1 to 5% w/w, colours, flavours, sweeteners 0 to 10% w/w.

15) A tablet as claimed in any one of the preceding claim wherein the active compound is acyclovir.

16) A tablet as claimed in claim 15 wherein acyclovir is present in an amount of 50 to 95% w/w and the swellable clay is present within the granules of the tablet in an amount of 0.5 to 40% w/w.

17) A tablet as claimed in claim 16 wherein the tablet comprises 200 to 800mg of acyclovir and has a formulation of acyclovir 70 to 90% w/w, povidone or pregelled starch 0.25 to 5% w/w, Veegum F or bentonite 0.5 to 30% w/w, microcrystalline cellulose or LHPC-LH11 5 to 25% w/w, sodium starch glycollate 0 to 8% w/w, magnesium stearate 0.25 to 2% w/w, and optional film-coating composites of opadry 0.1 to 2% w/w, polyethylene glycol 8000 0.1 to 0.5% w/w.

18) A tablet as claimed in claim 17 wherein the formulation is acyclovir 75 to 85% w/w, povidone or pregelled starch 0.5 to 2% w/w, Veegum F or bentonite 0.5 to 10% w/w, microcrystalline cellulose, or LHPC-LH11 5 to 15% w/w, sodium starch glycollate 0 to 5% w/w, magnesium stearate 0.25 to 2.0% w/w, and optional film-coating composites of opadry 0.25 to 1.0% w/w, and polyethylene glycol 8000 0.1 to 0.2% w/w.

19) A tablet as claimed in any of claims 1 to 14 wherein the active compound is lamotrigine.

20) A tablet as claimed in claim 19 wherein lamotrigine is present in an amount of 2 to 90% w/w and the swellable clay is present within the granules of the tablet in amount of 0.25 to 40% w/w.

21) A tablet as claimed in claim 20 wherein the tablet comprises 25 to 200mg of lamotrigine and has a formulation of lamotrigine 30 to 50% w/w, calcium carbonate 26 to 46% w/w, LHPC-LH11 or microcrystalline cellulose 5 to 30% w/w, Veegum F or bentonite 0.25 to 30% w/w, povidone or pregelled starch 1.0 to 8.0% w/w, sodium starch glycollate 0 to 8% w/w, magnesium stearate 0.25 to 2% w/w, and optional film-coating composites of opadry 0.1 to 2% w/w, and polyethylene glycol 8000 0.1 to 0.5 w/w.

22) A tablet as claimed in claim 21 wherein the formulation is lamotrigine 35 to 45% w/w, calcium carbonate 31 to 41% w/w, LHPC-LH11 or microcrystalline cellulose 5 to 15% w/w, Veegum F or bentonite 0.25 to 10% w/w, povidone or pregelled starch 2 to 5% w/w, sodium starch glycollate 0 to 5% w/w, magnesium stearate 0.25 to 1% w/w, and optional film-coating composites of opadry 0.25 to 1% w/w, polyethylene glycol 8000 0.1 to 0.2% w/w.

23) A tablet as claimed in claim 20 wherein the tablet comprises 5mg to 50mg of lamotrigine and has a formulation of lamotrigine 3 to 13% w/w, lactose or calcium carbonate 50 to 60% w/w, microcrystalline or LHPC-LH11 20 to 35% w/w, sodium starch glycollate 0 to 8% w/w, Veegum F or bentonite 0.25 to 30% w/w, povidone K30 or pregelled starch 1.0 to 8.0 w/w, sodium docusate 0 to 0.5% w/w, sodium saccharine 0 to 3% w/w, magnesium stearate 0.25 to 2% w/w, and optional film-coating composites of opadry 0.1 to 2.0 w/w, and polyethylene glycol 8000 0.1 to 0.5% w/w.

24) A tablet as claimed in claim 23 wherein the formulation is lamotrigine 5 to 11% w/w, lactose or calcium carbonate 53 to 59% w/w, microcrystalline or LHPC-LH11 24 to 30% w/w, sodium starch glycollate 0 to 5% w/w, Veegum F or bentonite 0.25 to 10% w/w, povidone K30 or pregelled starch 2 to 5% w/w, sodium docusate 0.5 to 0.15% w/w, sodium saccharine 0.5 to 2% w/w, magnesium stearate 0.25 to 1% w/w, and optional film-coating composites of opadry 0.25 to 1% w/w, and polyethylene glycol 8000 0.1 to 2% w/w.

25) A process for the preparation of a water-dispersible tablet comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an anti-viral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol, anti-convulsant 1,2,4 triazine derivative and trimethoprim (optionally in combination with sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay which comprises bringing the said active compound into association with the said swellable clay to provide a water-dispersible tablet which is capable of dispersing in water within a period of 3 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710μm in accordance with the test for dispersible tablets defined in the British Pharmacopoeia, 1988, Volume II, page 895.

26) A process as claimed in claim 25 comprising the steps of

a) admixing in dry, finely-divided form the active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an anti-viral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol, anti-convulsant 1,2,4 triazine derivative, and trimethoprim (optionally in combination with sulphamethoxazole) with an effective amount of a pharmaceutically acceptable swellable clay, optionally with the addition of one or more other pharmaceutical carriers or excipients;

b) addition of a quantity of a pharmaceutically acceptable liquid sufficient to moisten the dry mixture;

c) granulation of the resulting moist mixture to form granules;

d) drying the granules and optionally blending the granules with other optional carriers or excipients such as lubricants, glidants, flavouring agents and disintegrating agents; and

e) compression of the granules to form a tablet which is capable of dispersing in water within a period of 3 minutes to provide a dispersion which will pass through a sieve screen with a mesh aperture of 710μm in accordance with the above-defined British Pharmacopoeia test for dispersible tablets.

27) Granules for a water-dispersible tablet according to any one of claims 1 to 24 comprising a therapeutically active compound selected from the group consisting of an analgesic propionic acid derivative, a tranquillising benzodiazepine, an anti-viral nucleoside derivative, an anti-protozoal napthoquinone, allopurinol, oxopurinol and an anti-convulsant 1,2,4 triazine derivative, and trimethorpim (optionally in combination with

sulphamethoxazole), together with an effective amount of a pharmaceutically acceptable swellable clay.

28) Use of granules as claimed in claim 27 in the preparation of a water-dispersible tablet according to any one of claims 1 to 24.

29) Use of a pharmaceutically acceptable swellable clay as a dispersing agent in the preparation of a water-dispersible tablet according to any one of claims 1 to 24.

30) A pharmaceutically acceptable swellable clay for use as a dispersing agent for water-dispersible tablets.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00163

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/20 A 61 K 33/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0350701 (FARMA RESA) 17 January 1990, see the claims; page 3, lines 41-50 ---	1,7,10, 25,27-30
X	Database WPI, accession no. 67-04040H [00], Derwent Publications Ltd, (London, GB), & JP,A,3024078 (NISSAN CHEM. IND. LTD), see the whole abstract ---	1,3,10, 25
A	EP,A,0391851 (CIBA-GEIGY) 10 October 1990, see the claims 1,9,15,18,20,30,36 ---	1,3-4, 10,25, 27
A	DE,A,2016622 (BAYER) 21 October 1971, see the claims 1-2,7-8; page 41, line 25; page 42, lines 18-20; page 44, example -----	1,9-10, 25

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20-03-1992	29. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200163 SA 55749

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/04/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0350701	17-01-90	JP-A-	2059515	28-02-90
EP-A- 0391851	10-10-90	AU-A-	5304290	11-10-90
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DE-A- 2016622	21-10-71	None		