Description

The present invention relates to a water-dispersible tablet formulation containing acyclovir (UK patent no. 1523865). A divisional application relating to a water-dispersible tablet formulation containing lamotrigine is co-pending (EP Appln No 95105628.2)

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 general 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 (™) 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. Primogel (™), Explotab (™)), cross-linked povidone (e.g. Kollidon CL(™)), and a cross-linked sodium carboxymethylcellulose (e.g. Starch, and Ac-Di-Sol(™)) in an acyclovir tablet, but found that they did not provide a satisfactory commercial water-dispersible tablet. 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 penetration of water during dispersion, but in all cases the disintegration time was high.

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. UK patent no. 1523865, which is incorporated herein by reference teaches how to make acyclovir and the infections or medical conditions which can be treated by it.

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 alone such as sodium starch glycollate, cross-linked povidone and cross-linked sodium carboxymethylcellulose.

According to a first aspect of the invention there is provided a water dispersible tablet comprising 50 to 95% w/w acyclovir or a pharmaceutically acceptable salt thereof and 0.25 to 40% w/w of a pharmaceutically acceptable swellable clay which is present within the granules of the tablet, 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 710 µm in accordance with the test for dispersible tablets defined in the British Pharmacopoea 1988, volume II, page 895.

Swellable clays such as Veegum(™) 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.

The present invention further provides a process for the preparation of a water-dispersible tablet having 200mg to 800mg of acyclovir comprising 50 to 95% w/w acyclovir or a pharmaceutically acceptable salt thereof, and 0.25 to 40% w/w of a pharmaceutically acceptable swellable clay, said process comprising bringing acyclovir into association with said swellable clay to form granules, and then compressing 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 710 µm 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 acyclovir, and the 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, and flavouring 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 710 µm 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 710 µm sieve).

After the dispersion has passed through the 710 µm 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.

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 swallowing 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.

The references herein to tablets according to the invention include both film-coated and non-film-coated tablets.

The particle size distribution of the dispersion particularly 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)

It will be appreciated that reference to acyclovir 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), corrensiten (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 polygorskite 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 (™).

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.

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 O.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. 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 defined hereinbefore, 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 40% w/w, preferably 0.5 to 40% 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 1 to 10% 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 acyclovir, depending on the desired dosage and the total weight of the tablet.

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.

In general the tablets according to the invention contain acyclovir in the following percentage proportions: 20 to 90% w/w, preferably 45 to 85% w/w.

When acyclovir is present in an amount of at least 60% w/w in tablets according to the invention, we have surprisingly 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 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 be incorporated into a tablet according to the invention are: microcrystalline cellulose (e.g. Avicel (™)) 0 to 30% w/w, preferably 5 to 10% w/w, Sodium carboxymethyl cellulose (e.g. Nymcel (™)) 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 (™)) 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 (™), Primojel (™)) 0 to 10% w/w, preferably 0.5 to 5% w/w, modified corn starch (e.g. starch 1500 (™)) 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 other active compounds is supportive of the view that if lowhydroxypropylcellulose (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).
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 acyclovir 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 acyclovir 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°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 tablet 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.

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

a) A granulate comprising acyclovir for a water-dispersible tablet as defined hereinbefore wherein the swellable clay is a pharmaceutically acceptable magnesium aluminium silicate compound;

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

c) A water-dispersible pharmaceutical tablet formulation comprising acyclovir as defined hereinbefore wherein the swellable clay is a pharmaceutically acceptable magnesium aluminium silicate compound;

d) A process for the preparation of a water-dispersible tablet as defined hereinbefore, said process comprising admixing acyclovir with a magnesium aluminium silicate compound as the swellable clay 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 which conform with the B.P. test given hereinbefore. 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	2	3	4
Intra-granular:	mg/tablet	mg/tablet	mg/tablet	mg/tablet
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)	$\overline{1248}$.0	$\overline{1048}$.0	$\overline{1163}$.2	$\overline{1191}$.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	6	7	8	9
	mg/tablet	mg/tablet	mg/tablet	mg/tablet	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	11	12
	mg/tablet	mg/tablet	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	14	15
Component (mg/tablet)	mg/tablet	mg/tablet	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	79.65	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	0.99	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

Method of Preparation

The tablets described in Examples 1-31 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% v/v 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.

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°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°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°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, 250µ, 150µm, 106µm and 53µm were used. The WMD was calculated from the cumulative percentage undersize size distribution using a computer programme.

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 (μm)	Tablet shape/ maximum diameter
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'	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

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9 (coated)	1053	1062.4	6.99	16.1	negligible	1'05"	4.06	138	Caplet

** All dispersions passed through a 710 µm 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 (μm)	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 μm 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 (μm)	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 µm 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".

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

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, SE

1. A water dispersible tablet comprising 50 to 95% w/w acyclovir or a pharmaceutically acceptable salt thereof, 0.25 to 40% of a pharmaceutically acceptable swellable clay which is present within the granules of the tablet 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 tablet as claimed in any of the preceding claims wherein the swellable clay is a smectite or attapulgite.

3. A tablet as claimed in claim 2 wherein the smectite is selected from the montmorillonoid group.

4. A tablet as claimed in claim 3 wherein the montmorillonoid is selected from the group consisting of montmorillonite, sauconite, vermiculite, bentonite, hectorite, and aluminium magnesium silicate.

5. A tablet as claimed in claim 4 wherein the montmorillonoid is magnesium aluminium silicate or bentonite.

6. A tablet as claimed in claim 5 wherein the magnesium aluminium silicate is Veegum F.

7. A tablet as claimed in any one of the preceding claims wherein the swellable clay is present within the granules of the tablet in an amount of 1 to 40% w/w.

8. A tablet as claimed in claim 7 wherein the swellable clay is present in an amount of 1 to 10% w/w.

9. A tablet as claimed in claim 8 wherein the swellable clay is present in an amount of 5 to 10% w/w.

10. A tablet as claimed in any one of the preceding claims wherein acyclovir or a salt thereof is present in at least 60% w/w.

11. A tablet as claimed in any one of the preceding claims wherein acyclovir or a salt thereof is present in an amount of 200 to 800mg.

12. A tablet as claimed in any one of the preceding claims which further comprises a disintegrating agent.

13. A tablet as claimed in claim 12 wherein the disintegrating agent is sodium starch glycollate.

14. A tablet as claimed in any one of the preceding claims which further comprises a binder.

15. A tablet as claimed in claim 14 wherein the binder is povidone K30.

16. A tablet as claimed in any one of the preceding claims which further comprises a filler.

17. A tablet as claimed in claim 16 wherein the filler is microcrystalline cellulose.

18. A tablet as claimed in any one of the preceding claims which is further film coated and wherein the dispersion time can be up to 5 minutes.

19. A tablet as claimed in any one of the preceding claims which is capable of dispersing in water within a period of 2 minutes.

* C L M S *

Particle size: (as equivalent spherical volume)

<710µm-100%
<300µm - 98.7%
<200µm - 86.7%
<130µm - 50% (median particle size).

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, SE

1. A water dispersible tablet comprising 50 to 95% w/w acyclovir or a pharmaceutically acceptable salt thereof, 0.25 to 40% of a pharmaceutically acceptable swellable clay which is present within the granules of the tablet 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 tablet as claimed in any of the preceding claims wherein the swellable clay is a smectite or attapulgite.

3. A tablet as claimed in claim 2 wherein the smectite is selected from the montmorillonoid group.

4. A tablet as claimed in claim 3 wherein the montmorillonoid is selected from the group consisting of montmorillonite, sauconite, vermiculite, bentonite, hectorite, and aluminium magnesium silicate.

5. A tablet as claimed in claim 4 wherein the montmorillonoid is magnesium aluminium silicate or bentonite.

6. A tablet as claimed in claim 5 wherein the magnesium aluminium silicate is Veegum F.

7. A tablet as claimed in any one of the preceding claims wherein the swellable clay is present within the granules of the tablet in an amount of 1 to 40% w/w.

8. A tablet as claimed in claim 7 wherein the swellable clay is present in an amount of 1 to 10% w/w.

9. A tablet as claimed in claim 8 wherein the swellable clay is present in an amount of 5 to 10% w/w.

10. A tablet as claimed in any one of the preceding claims wherein acyclovir or a salt thereof is present in at least 60% w/w.

11. A tablet as claimed in any one of the preceding claims wherein acyclovir or a salt thereof is present in an amount of 200 to 800mg.

12. A tablet as claimed in any one of the preceding claims which further comprises a disintegrating agent.

13. A tablet as claimed in claim 12 wherein the disintegrating agent is sodium starch glycollate.

14. A tablet as claimed in any one of the preceding claims which further comprises a binder.

15. A tablet as claimed in claim 14 wherein the binder is povidone K30.

16. A tablet as claimed in any one of the preceding claims which further comprises a filler.

17. A tablet as claimed in claim 16 wherein the filler is microcrystalline cellulose.

18. A tablet as claimed in any one of the preceding claims which is further film coated and wherein the dispersion time can be up to 5 minutes.

19. A tablet as claimed in any one of the preceding claims which is capable of dispersing in water within a period of 2 minutes.

* C L M S *

20. A tablet as claimed in any one of the preceding claims wherein the dispersion contains particles having a particle size distribution of 100% less than 710µm, and more than 50% less than 300µm.

21. A tablet as claimed in claim 19 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.

22. A tablet as claimed in any one of the preceding claims wherein the tablet comprises 200 to 800mg of acyclovir or a salt thereof and has a formulation of acyclovir 70 to 90% w/w, povidone or pregelled starch 0.25 to 5% w/w, magnesium aluminium silicate or bentonite 0.5 to 30% w/w, microcrystalline cellulose or lowhydroxypropylcellulose-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.

23. A tablet as claimed in claim 20 wherein the formulation is acyclovir 75 to 85% w/w, povidone or pregelled starch 0.5 to 2% w/w, magnesium aluminium silicate or bentonite 0.5 to 10% w/w, microcrystalline cellulose or lowhydroxypropylcellulose-LH11 5 to 15% w/w, sodium starch glycollate 0 to 5% w/w, magnesium stearate 0.25 to 1.0% 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.

24. A tablet as claimed in any one of the preceding claims wherein the active compound is acyclovir.

25. A tablet as claimed in claim 1 wherein the acyclovir or a salt thereof is present in 750 to 850mg, the total tablet weight is 1000mg to 1200mg, and the amount of swellable clay present is 40 to 120mg.

26. A tablet as claimed in claim 1 which consists of 800mg acyclovir, 89mg Avicel PH101, 53mg magnesium aluminium silicate, 42mg sodium starch glycollate, 11mg povidone, and 9.4mg magnesium stearate.

27. A process for the preparation of a water-dispersible tablet comprising 50 to 95% w/w acyclovir or a salt thereof and 0.25 to 40% w/w of a pharmaceutically acceptable swellable clay, said process comprising bringing acyclovir into association with said swellable clay to form granules, and then compressing 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 test for dispersible tablets defined in the British Pharmacopoeia, 1988, volume II, page 895.

28. A process as claimed in claim 27 comprising the steps of:

a) admixing in dry, finely-divided form acyclovir or a salt thereof, and the swellable clay optionally with the addition of one or more other pharmaceutical carriers or excipients;

b) addition of a quantity of a granulation fluid 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, and flavouring 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.

29. A process as claimed in claim 28 wherein a binder is also added with the acyclovir or a salt thereof and swellable clay.

30. A process as claimed in claims 27 to 29 wherein a disintegrating agent is also added with the acyclovir or a salt thereof and swellable clay.

31. A process as claimed in any one of claims 27 to 30 wherein a filler is also added with acyclovir or salt thereof, the swellable clay, and other excipients.

32. A process as claimed in any one of claims 27 to 30 wherein a high shear mixer granulator is used to mix the acyclovir, swellable clay and other excipients.

* C L M S *

33. A process as claimed in any one of claims 27 to 31 wherein the tablet is then further film coated.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a water-dispersible tablet comprising 50 to 95% w/w acyclovir or a pharmaceutically acceptable salt thereof and 0.25 to 40% w/w of a pharmaceutically acceptable swellable clay, said process comprising bringing acyclovir into association with said swellable clay to form granules, and then compressing 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 test for dispersible tablets defined in the British Pharmacopoeia, 1988, volume II, page 895.

2. A process as claimed in claim 1 comprising the steps of:

   a) admixing in dry, finely-divided form acyclovir or a pharmaceutically acceptable salt thereof, and the swellable clay optionally with the addition of one or more other pharmaceutical carriers or excipients;

   b) addition of a quantity of a granulation fluid 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, and flavouring 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.

3. A process as claimed in any of the preceding claims wherein the swellable clay is a smectite or attapulgite.

4. A process as claimed in claim 3 wherein the smectite is selected from the montmorillonoid group.

5. A process as claimed in claim 4 wherein the montmorillonoid is selected from the group consisting of sauconite, vermiculite, bentonite, hectorite and aluminium magnesium silicate.

6. A process as claimed in claim 5 wherein the montmorillonoid is magnesium aluminium silicate or bentonite.

7. A process as claimed in claim 6 wherein the magnesium aluminium silicate is Veegum F.

8. A process as claimed in any one of the preceding claims wherein the swellable clay is present in an amount of 1 to 40% w/w.

9. A process as claimed in claim 8 wherein the swellable clay is present in an amount of 1 to 10% w/w.

10. A process as claimed in claim 9 wherein the swellable clay is present in an amount of 5 to 10% w/w

11. A process as claimed in any one of the preceding claims wherein a disintegrating agent is added with the acyclovir or salts thereof and swellable clay.

12. A process as claimed in claim 11 wherein the disintegrating agent is sodium starch glycollate.

13. A process as claimed in any one of the preceding claims wherein a binder is added with the acyclovir or salts thereof and swellable clay.

14. A process as claimed in any one of the preceding claims wherein the binder is povidone K30.

15. A process as claimed in any one of the preceding claims wherein a filler is added with the acyclovir or salts thereof and swellable clay.

16. A process as claimed in claim 15 wherein the filler is microcrystalline cellulose.

17. A process as claimed in any of the preceding claims wherein a high shear mixer granulator is used to mix the acyclovir or salts thereof, swellable clay and other excipients.

18. A process as claimed in any one of the preceding claims wherein the tablet is further film coated.

19. A process as claimed in any one of the preceding claims wherein the dispersion contains particles having a particle size distribution of 100% less than 710µm, and more than 50% less than 300µm.

20. A process as claimed in claim 19 wherein the tablet 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.

21. A process as claimed in claims 1 or 2 for preparing a tablet having 200mg to 800mg acyclovir, the process comprising:

a) admixing 70 to 90% w/w acyclovir, 0.5 to 30% magnesium aluminium silicate or bentonite, 5 to 25% w/w microcrystalline cellulose or low hydroxypropyl cellulose-LH11, 0 to 8% w/w sodium starch glycollate;

b) addition of a quantity of granulation fluid comprising 0.25 to 5% w/w povidone or pregelled starch and granulation of the resulting mixture to form granules;

c) drying the granules and blending the granules with 0.25 to 2% magnesium stearate;

d) compressing the granules to form a tablet; and

e) optionally film-coating the tablet with 0.1 to 2% w/w opadry and 0.1 to 0.5 w/w polyethylene glycol 8000.

22. A process as claimed in claim 20 wherein the components are acyclovir 75 to 85% w/w, povidone or pregelled starch 0.5 to 2% w/w, magnesium aluminium silicate or bentonite 0.5 to 10% w/w, microcrystalline cellulose, or low hydroxypropyl cellulose-LH11 5 to 15% w/w, sodium starch glycollate 0 to 5% w/w, magnesium stearate 0.25 to 1.0% 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.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, SE

1. Wasserdispergierbare Tablette, umfassend 50 bis 95 % G/G Acyclovir oder ein pharmazeutisch annehmbares Salz davon, 0,25 bis 40 % G/G eines pharmazeutisch annehmbaren quellfähigen Tons, der innerhalb der Granulatkörner der Tablette vorliegt, um eine Tablette zur Verfügung zu stellen, die in der Lage ist, in Wasser innerhalb eines Zeitraums von 3 Minuten zu dispergieren, wodurch eine Dispersion zur Verfügung gestellt wird, die in der Lage ist, durch ein Sieb mit einer Maschenweite von 710 µm in Übereinstimmung mit dem in der British Pharmacopoeia 1988, Band II, Seite 895, definierten Test durchzutreten.

2. Tablette nach einem der vorhergehenden Ansprüche, worin der quellfähige Ton ein Smektit oder Attapulgit ist.

3. Tablette nach Anspruch 2, worin der Smektit ausgewählt ist aus der Montmorillonit-Gruppe.

4. Tablette nach Anspruch 3, worin das Montmorillonit ausgewählt ist aus der Gruppe bestehend aus Montmorillonit, Sauconit, Vermiculit, Bentonit Hectorit und Aluminiummagnesiumsilicat.

5. Tablette nach Anspruch 4, worin das Montmorillonit aus Magnesiumaluminiumsilicat oder Bentonit ist.

6. Tablette nach Anspruch 5, worin das Magnesiumaluminiumsilicat Veegum F ist.

7. Tablette nach einem der vorhergehenden Ansprüche, worin der quellfähige Ton in den Granulatkörnern der Tablette in einer Menge von 1 bis 40 % G/G vorliegt.

8. Tablette nach Anspruch 7, worin der quellfähige Ton in einer Menge von 1 bis 10 % G/G vorliegt.

9. Tablette nach Anspruch 9, worin der quellfähige Ton in einer Menge von 5 bis 10 % G/G vorliegt.

10. Tablette nach einem der vorhergehenden Ansprüche, worin das Acyclovir oder ein Salz davon mindestens 60 % G/G beträgt.

11. Tablette nach einem der vorhergehenden Ansprüche, worin das Acyclovir oder ein Salz davon in einer Menge von 200 bis 800 mg vorliegt.

12. Tablette nach einem der vorhergehenden Ansprüche, die zusätzlich ein Sprengmittel enthält.

13. Tablette nach Anspruch 12, worin das Sprengmittel Natriumstärkeglycolat ist.

14. Tablette nach einem der vorhergehenden Ansprüche, das zusätzlich ein Bindemittel enthält.

15. Tablette nach Anspruch 14, worin das Bindemittel Povidon K30 ist.

16. Tablette nach einem der vorhergehenden Ansprüche, das zusätzlich einen Füllstoff enthält.

17. Tablette nach Anspruch 16, worin der Füllstoff mikrokristalline Cellulose ist.

18. Tablette nach einem der vorhergehenden Ansprüche, die ferner filmbeschichtet ist, und worin die Dispersionszeit bis zu 5 Minuten sein kann.

19. Tablette nach einem der vorhergehenden Ansprüche, die in der Lage ist, sich in Wasser innerhalb eines Zeitraums von 2 Minuten zu dispergieren.

20. Tablette nach einem der vorhergehenden Ansprüche, worin die Dispersion Teilchen mit einer Teilchengrössenverteilung von 100 % kleiner als 710 µm und mehr als 50 % kleiner als 300 µm enthält.

21. Tablette nach Anspruch 19, worin die Dispersion Teilchen mit einer Teilchengrössenverteilung von 100 % kleiner als 710 µm, mehr als 70 % kleiner als 310 µm und mehr als 50 % kleiner als 200 µm enthält.

22. Tablette nach einem der vorhergehenden Ansprücheworin die Tablette 200 bis 800 mg Acyclovir umfasst und eine Formulierung wie folgt hat: Acyclovir 70 bis 90 % G/G, Povidon oder vorgelierte Stärke 0,25 bis 5 % G/G, Veegum F oder Bentonit 0,5 bis 30 % G/G, mikrokristalline Cellulose oder Niedrighydroxypropylcellulose-LH11 5 bis 25 % G/G, Natriumstärkeglycolat 0 bis 8 % G/G, Magnesiumstearat 0,25 bis 2 % G/G und wahlweise Filmüberzugsverbundstoffe aus Opadry 0,1 bis 2 % G/G, Polyethylenglycol 8000 0,1 bis 0,5 % G/G.

23. Tablette gemäss Anspruch 20, dadurch **gekennzeichnet,** dass die Formulierung ist: Acyclovir 75 bis 85 % G/G, Povidon oder vorgelierte Stärke 0,5 bis 2 % G/G, Veegum F oder Bentonit 0,5 bis 10 % G/G, mikrokristalline Cellulose oder Niedrighydroxypropylcellulose-LH11 5 bis 15 % G/G, Natriumstärkeglycolat 0 bis 5 % G/G, Magnesiumstearat 0,25 bis 2,0 % G/G und wahlweise Filmüberzugsverbundstoffe aus Opadry 0,25 bis 1,0 % G/G und Polyethylenglycol 8000 0,1 bis 0,2 % G/G.

24. Tablette gemäss einem der vorhergehenden Ansprüche worin die aktive Verbindung Acyclovir ist.

25. Tablette nach Anspruch 1, worin das Acyclovir oder ein Salz davon in einer Menge von im wesentlichen 750 bis 850 mg vorliegt, das Gesamt-Tablettengewicht im wesentlichen 1000 bis 1200 mg ist, und die Menge an quellfähigem Ton im wesentlichen 40 bis 120 mg ist.

26. Tablette nach Anspruch 1, die aus im wesentlichen 800 mg Acyclovir, im wesentlichen 89 mg Avicel PH101, im wesentlichen 53 mg Magnesiumaluminiumsilicat, im wesentlichen 42 mg Natriumstärkeglycolat, im wesentlichen 11 mg Povidon und im wesentlichen 9,4 mg Magnesiumstearat besteht.

27. Verfahren zur Herstellung einer wasserdispergierbaren Tablette, umfassend 50 bis 95 % G/G Acyclovir oder ein Salz davon und 0,25 bis 40 % G/G eines pharmazeutisch annehmbaren Tons, wobei das Verfahren das in Kontakt bringen des Acyclovirs mit dem quellfähigen Ton unter Bildung von Granulatkörpern umfasst, und Pressen der Granulatkörper unter Bildung einer Tablette die in der Lage ist, in Wasser innerhalb eines Zeitraums von 3 Minuten zu dispergieren, wodurch eine Dispersion zu Verfügung gestellt wird, die in der Lage ist, durch ein Sieb mit einer Maschenweite von 710 µm in Übereinstimmung mit dem in der British Pharmacopoeia 1988, Band II, Seite 895, definierten Test für dispergierbare Tabletten durchzutreten.

28. Verfahren gemäss Anspruch 27, umfassend die folgenden Schritte:

(a) Mischen in trockener, feinverteilter Form des Acyclovirs oder eines Salzes mit einer wirksamen Menge eines pharmazeutisch annehmbaren quellfähigen Tons, wahlweise unter Zugabe eines oder mehrerer anderer pharmazeutischer Träger oder Arzneimittelträger;

(b) Zugabe einer Menge einer pharmazeutisch annehmbaren Flüssigkeit, die ausreicht, um die trockene Mischung zu befeuchten;

(c) Granulierung der resultierenden feuchten Mischung unter Bildung von Granulatkörnern;

(d) Trocknen der Körner und wahlweise Mischen der Körner mit anderen wahlweisen Trägern oder Arzneimittelträgern, wie Schmiermitteln, Gleitmitteln, Geschmacksstoffen und Tablettensprengmitteln; und

(e) Pressen der Granulatkörner unter Bildung einer Tablette, die in der Lage ist, in Wasser innerhalb eines Zeitraums von 3 Minuten zu dispergieren, so dass eine Dispersion zur Verfügung gestellt wird, die durch ein Sieb mit einer Maschenweite von 710 µm in Übereinstimmung mit dem oben definierten British Pharmacopoeia-Test für dispergierbare Tabletten durchtreten wird.

29. Verfahren nach Anspruch 28, worin ein Binder zusammen mit dem Acyclovir oder einem Salz davon und dem quellfähigen Ton zugegeben wird.

30. Verfahren nach Ansprüchen 27 bis 29, worin ein Sprengmittel auch mit dem Acyclovir oder einem Salz davon und dem quellfähigen Ton zugegeben wird.

31. Verfahren nach einem der Ansprüche 27 bis 30, worin ein Füllstoff zusammen mit dem Acyclovir oder einem Salz davon und dem quellfähigen Ton und anderen Exzipienten zugegeben wird.

32. Verfahren nach einem der Ansprüche 27 bis 30, worin ein Granulatormixer mit hoher Schwerkraft zur Mischung des Acyclovirs, des quellfähigen Tons und der anderen Exzipienten verwendet wird.

33. Verfahren nach einem der Ansprüche 27 bis 31, worin die Tablette dann filmbeschichtet wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer wasserdispergierbaren Tablette, umfassend 50 bis 95 % G/G Acyclovir oder ein pharmazeutisch annehmbares Salz davon, 0,25 bis 40 % G/G eines pharmazeutisch annehmbaren quellfähigen Tons, der innerhalb der Granulatkörner der Tablette vorliegt, um eine Tablette zur Verfügung zu stellen, die in der Lage ist, in Wasser innerhalb eines Zeitraums von 3 Minuten zu dispergieren, wodurch eine Dispersion zur Verfügung gestellt wird, die in der Lage ist, durch ein Sieb mit einer Maschenweite von 710 µm in Übereinstimmung mit dem in der British Pharmacopoeia 1988, Band II, Seite 895, definierten Test durchzutreten.

2. Verfahren gemäss Anspruch 1, umfassend die folgenden Schritte:

(a) Mischen in trockener, feinverteilter Form des Acyclovirs oder eines Salzes mit einer wirksamen Menge eines pharmazeutisch annehmbaren quellfähigen Tons, wahlweise unter Zugabe eines oder mehrerer anderer pharmazeutischer Träger oder Arzneimittelträger;

(b) Zugabe einer Menge einer pharmazeutisch annehmbaren Flüssigkeit, die ausreicht, um die trockene Mischung zu befeuchten;

(c) Granulierung der resultierenden feuchten Mischung unter Bildung von Granulatkörnern;

(d) Trocknen der Körner und wahlweise Mischen der Körner mit anderen wahlweisen Trägern oder Arzneimittelträgern, wie Schmiermitteln, Gleitmitteln, Geschmacksstoffen und Tablettensprengmitteln; und

(e) Pressen der Granulatkörner unter Bildung einer Tablette, die in der Lage ist, in Wasser innerhalb eines Zeitraums von 3 Minuten zu dispergieren, so dass eine Dispersion zur Verfügung gestellt wird, die durch ein

Sieb mit einer Maschenweite von 710 µm in Übereinstimmung mit dem oben definierten British Pharmacopoeia-Test für dispergierbare Tabletten durchtreten wird.

3. Verfahren nach einem der vorhergehenden Ansprüche, worin der quellfähige Ton ein Smektit oder Attapulgit ist.

4. Verfahren nach Anspruch 3, worin der Smektit ausgewählt ist aus der Montmorillonit-Gruppe.

5. Verfahren nach Anspruch 4, worin das Montmorillonit ausgewählt ist aus der Gruppe bestehend aus Montmorillonit, Sauconit, Vermiculit, Bentonit Hectorit und Aluminiummagnesiumsilicat.

6. Verfahren nach Anspruch 5, worin das Montmorillonit aus Magnesiumaluminiumsilicat oder Bentonit ist.

7. Verfahren nach Anspruch 6, worin das Magnesiumaluminiumsilicat Veegum F ist.

8. Verfahren nach einem der vorhergehenden Ansprüche, worin der quellfähige Ton in einer Menge von 1 bis 40 % G/G vorliegt.

9. Verfahren nach Anspruch 8, worin der quellfähige Ton in einer Menge von 1 bis 10 % G/G vorliegt.

10. Verfahren nach Anspruch 9, worin der quellfähige Ton in einer Menge von 5 bis 10 % G/G vorliegt.

11. Verfahren nach einem der vorhergehenden Ansprüche, worin ein Sprengmittel zusammen mit dem Acyclovir oder einem Salz davon und quellfähigem Ton zugegeben wird.

12. Verfahren nach Anspruch 11, worin das Sprengmittel Natriumstärkeglycolat ist.

13. Verfahren nach einem der vorhergehenden Ansprüche, worin ein Bindemittel zusammen mit dem Acyclovir oder einem Salz davon und quellfähigem Ton zugegeben wird.

14. Verfahren nach einem der vorhergehenden Ansprüche, worin das Bindemittel Povidon K30 ist.

15. Verfahren nach einem der vorhergehenden Ansprüche, worin ein Füllstoff zusammen mit dem Acyclovir oder einem Salz davon und quellfähigem Ton zugegeben wird.

16. Verfahren nach Anspruch 15, worin der Füllstoff mikrokristalline Cellulose ist.

17. Verfahren nach einem der vorhergehenden Ansprüche, worin ein Granulatormixer mit hoher Schwerkraft zur Mischung des Acyclovirs, des quellfähigen Tons und der anderen Exzipienten verwendet wird.

18. Verfahren nach einem der vorhergehenden Ansprüche, worin die Tablette dann filmbeschichtet wird.

19. Verfahren nach einem der vorhergehenden Ansprüche, worin die Dispersion Teilchen mit einer Teilchengrössenverteilung von 100 % kleiner als 710 µm und mehr als 50 % kleiner als 300 µm enthält.

20. Verfahren nach Anspruch 19, worin die Dispersion Teilchen mit einer Teilchengrössenverteilung von 100 % kleiner als 710 µm, mehr als 70 % kleiner als 310 µm und mehr als 50 % kleiner als 200 µm enthält.

21. Verfahren nach Anspruch 1 oder 2 zur Herstellung einer Tablette, enthaltend 200 bis 800 mg Acyclovir, umfassend:

(a) Mischen von 70 bis 90 % G/G Acyclovir, 0,5 bis 30 % G/G Magnesiumaluminiumsilcat oder Bentonit, 5 bis 25 % G/G mikrokristalline Cellulose oder Niedrighydroxypropylcellulose-LH11, 0 bis 8 % G/G Natriumstärkeglycolat;

(b) Zugabe einer Menge an Granulationsflüssigkeit, enthaltend 0,25 bis 5 % G/G Povidon oder vorgelierte Stärke, und Granulieren der erhaltenen Mischung zur Bildung von Granulatkörnern;

(c) Trocknen der Granulatkörner und Mischen der Granulatkörner mit 0,25 bis 2 % Magnesiumstearat;

(d) Pressen der Granulatkörner zur Bildung von Tabletten; und

(e) wahlweise Filmbeschichten der Tabletten mit 0,1 bis 2 % G/G Opadry und 0,1 bis 0,5 % G/G Polyethylenglykol 8000.

22. Verfahren nach Anspruch 20, worin die Komponenten sind: Acyclovir 75 bis 85 % G/G, Povidon oder vorgelierte Stärke 0,5 bis 2 % G/G, Magnesiumaluminiumsilicat oder Bentonit 0,5 bis 10 % G/G, mikrokristalline Cellulose oder Niedrighydroxypropylcellulose-LH11 5 bis 15 % G/G, Natriumstärkeglycolat 0 bis 5 % G/G, Magnesiumstearat 0,25 bis 2,0 % G/G und wahlweise Filmüberzugsverbundstoffe aus Opadry 0,25 bis 1,0 % G/G und Polyethylenglycol 8000 0,1 bis 0,2 % G/G.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT LI, LU, MC, NL, SE

1. Comprimé dispersible dans l'eau comprenant 50 à 95 % poids/poids d'acyclovir ou d'un sel pharmaceutiquement acceptable de celui-ci, 0,25 à 40 % d'une argile gonflable pharmaceutiquement acceptable qui est présente dans les granules du comprimé pour fournir un comprimé qui est capable de se disperser dans l'eau en une période de 3 minutes pour fournir une dispersion qui est capable de traverser un tamis à ouverture de mailles de 710 µm conformément au test pour comprimés dispersibles défini dans la Pharmacopée Britannique 1988, volume II, page 895.

2. Comprimé tel que revendiqué dans la revendication précédente dans lequel l'argile gonflable est une smectite ou une attapulgite.

3. Comprimé tel que revendiqué à la revendication 2, dans lequel la smectite est choisie dans le groupe des montmorillonoïdes.

4. Comprimé tel que revendiqué à la revendication 3, dans lequel la montmorillonoïde est choisie parmi le groupe constitué de montmorillonite, sauconite, vermiculite, bentonite, hectorite, et silicate de magnésium et d'aluminium.

5. Comprimé tel que revendiqué à la revendication 4, dans lequel la montmorillonoïde est un silicate de magnésium et d'aluminium ou la bentonite.

6. Comprimé tel que revendiqué à la revendication 5, dans lequel le silicate d'aluminium et de magnésium est le Veegum F.

7. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel l'argile gonflable est présente à l'intérieur des granules du comprimé en une quantité de 1 à 40 % poids/poids.

8. Comprimé tel que revendiqué à la revendication 7, dans lequel l'argile gonflable est présente en une quantité de 1 à 10 % poids/poids.

9. Comprimé tel que revendiqué à la revendication 9, dans lequel l'argile gonflable est présente en une quantité de 5 à 10 % poids/poids.

10. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel l'acyclovir ou un sel de celui-ci est présent à au moins 60 % poids/poids.

11. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel l'acyclovir ou un sel de celui-ci est présent en une quantité de 200 à 800 mg.

12. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes qui comprend en outre un agent de désintégration.

13. Comprimé tel que revendiqué à la revendication 12, dans lequel l'agent de désintégration est le glycolate d'amidon sodique.

14. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes qui comprend en outre un liant.

15. Comprimé tel que revendiqué à la revendication 14 dans lequel le riant est la Povidone K30.

16. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes qui comprend en outre une charge.

17. Comprimé tel que revendiqué à la revendication 16, dans lequel la charge est une cellulose microcristalline.

18. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes qui est en outre revêtu d'un film et pour lequel le temps de dispersion peut aller jusqu'à 5 minutes.

19. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes qui est capable de se disperser dans l'eau en une période de 2 minutes.

20. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel la dispersion contient des particules ayant une distribution de taille où 100 % des particules ont moins de 710 µm, et plus de 50 % moins de 300 µm.

21. Comprimé tel que revendiqué à la revendication 19, dans lequel la dispersion contient des particules ayant une distribution de taille où 100 % des particules ont moins de 710 µm, plus de 70 % moins de 310 µm, et plus de 50 % moins de 200 µm.

22. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel le comprimé comprend 200 à 800 mg d'acyclovir ou d'un sel de celui-ci et a une formulation d'acyclovir de 70 à 90 % poids/poids, Povidone ou amidon prégélifié 0,25 à 5 % poids/poids, silicate d'aluminium et de magnésium ou bentonite 0,5 à 30 % poids/poids, cellulose microcristalline ou hydroxypropylcellulose LH11 5 à 25 % poids/poids, glycolate d'amidon sodique 0 à 8 % poids/poids, stéarate de magnésium 0,25 à 2 % poids/poids, et éventuellement des constituants d'un revêtement de type film d'Opadry 0,1 à 2 % poids/poids, polyéthylèneglycol 8000 0,1 à 0,5 % poids/poids.

23. Comprimé tel que revendiqué à la revendication 20, dans lequel la formulation est acyclovir 75 à 85 % poids/poids, Povidone ou amidon prégélifié 0,5 à 2 % poids/poids, silicate d'aluminium et de magnésium ou bentonite 0,5 à 10 % poids/poids, cellulose microcristine ou hydroxypropylcellulose LH11 5 à 15 % poids/poids, glycolate d'amidon sodique 0 à 5 % poids/poids, stéarate de magnésium 0,25 à 1,0 % poids/poids, et éventuellement des constituants d'un revêtement de type film d'Opadry 0,25 à 1,0 % poids/poids, et polyéthylèneglycol 8000 0,1 à 0,2 % poids/poids.

24. Comprimé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel le composé actif est l'acyclovir.

25. Comprimé tel que revendiqué à la revendication 1, dans lequel l'acyclovir ou un sel de celui-ci est présent sensiblement à raison de 750 à 850 mg, le poids total du comprimé est sensiblement 1000 mg à 1200 mg, et la quantité d'argile gonflable présente est sensiblement 40 à 120 mg.

26. Comprimé tel que revendiqué à la revendication 1 qui consiste en sensiblement 800 mg d'acyclovir, sensiblement 89 mg d'Avicel PH101, sensiblement 53 mg de silicate d'aluminium et de magnésium, sensiblement 42 mg de glycolate d'amidon sodique, sensiblement 11 mg de Povidone, et sensiblement 9,4 mg de stéarate de magnésium.

27. Procédé pour la préparation d'un comprimé dispersible dans l'eau comprenant 50 à 95 % poids/poids d'acyclovir ou d'un sel de celui-ci et 0,25 à 40 % poids/poids d'une argile gonflable pharmaceutiquement acceptable, ledit procédé comprenant les étapes consistant à mettre l'acyclovir en association avec ladite argile gonflable pour former des granules, puis à comprimer les granules pour former un comprimé qui est capable de se disperser dans l'eau en une période de 3 minutes pour fournir une dispersion qui est capable de traverser un tamis à ouverture de mailles de 710 µm conformément au test pour comprimés dispersibles défini dans la Pharmacopée Britannique, 1988, volume II, page 895.

28. Procédé tel que revendiqué à la revendication 27 comprenant les étapes consistant à :

a) mélanger sous forme sèche, finement divisée, l'acyclovir ou un sel de celui-ci, et l'argile gonflable éventuellement avec l'addition d'un ou plusieurs autres véhicules ou excipients pharmaceutiques;

b) ajouter une quantité d'un fluide de granulation suffisante pour hydrater le mélange sec;

c) effectuer la granulation du mélange humide résultant pour former des granules;

d) sécher les granules et eventuellement mélanger les granules avec d'autres véhicules ou excipients éventuels tels que des lubrifiants, des agents de glissement et des agents aromatisants; et

e) comprimer les granules pour former un comprimé qui est capable de se disperser dans l'eau en une période de 3 minutes pour fournir une dispersion qui traversera un tamis à ouverture de mailles de 710 µm conformément au test pour comprimés dispersibles de la Pharmacopée Britannique défini ci-dessus.

29. Procédé tel que revendiqué à la revendication 28, dans lequel on ajoute également un liant à l'acyclovir ou à un sel de celui-ci et à l'argile gonflable.

30. Procédé tel que revendiqué aux revendications 27 à 29, dans lequel on ajoute également un agent de désintégration à l'acyclovir ou à un sel de celui-ci et à l'argile gonflable.

31. Procédé tel que revendiqué dans l'une quelconque des revendications 27 à 30, dans lequel on ajoute également une charge à l'acyclovir ou à un sel de celui-ci, à l'argile gonflable, et autres excipients.

32. Procédé tel que revendiqué dans l'une quelconque des revendications 27 à 30, dans lequel on utilise un mélangeur-granulateur à fort cisaillement pour mélanger l'acyclovir, l'argile gonflable et les autres excipients.

33. Procédé tel que revendiqué dans l'une quelconque des revendications 27 à 31, dans lequel le comprimé est ensuite revêtu d'un film.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un comprimé dispersible dans l'eau comprenant 50 à 95 % poids/poids d'acyclovir ou d'un sel pharmaceutiquement acceptable de celui-ci et 0,25 à 40 % poids/poids d'une argile gonflable pharmaceutiquement acceptable, ledit procédé comprenant les étapes consistant à mettre en association l'acyclovir avec ladite argile gonflable pour former des granules, puis à comprimer les granules pour former un comprimé qui est capable de se disperser dans l'eau en une période de 3 minutes, pour fournir une dispersion qui est capable de traverser un tamis à ouverture de mailles de 710 µm conformément au test pour comprimés dispersibles défini dans la Pharmacopée Britannique, 1988, volume II, page 895.

2. Procédé tel que revendiqué à la revendication 1 comprenant les étapes consistant à :

a) mélanger sous forme sèche, finement divisée, l'acyclovir ou un sel pharmaceutiquement acceptable de celui-ci, et l'argile gonflable éventuellement avec l'addition d'un ou plusieurs autres véhicules ou excipients pharmaceutiques;

b) ajouter une quantité d'un fluide de granulation suffisante pour hydrater le mélange sec;

c) effectuer la granulation du mélange humide résultant pour former des granules;

d) sécher les granules et éventuellement mélanger les granules avec d'autres véhicules ou excipients éventuels tels que des lubrifiants, des agents de glissement et des agents aromatisants; et

e) comprimer les granules pour former un comprimé qui est capable de se disperser dans l'eau en une période de 3 minutes pour fournir une dispersion qui traversera un tamis à ouverture de mailles de 710 µm conformément au test pour comprimés dispersibles de la Pharmacopée Britannique défini ci-dessus.

3. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel l'argile gonflable est une smectite ou une attapulgite.

4. Procédé tel que revendiqué à la revendication 3, dans lequel la smectite est choisie parmi le groupe des montmorillonoïdes.

5. Procédé tel que revendiqué à la revendication 4, dans lequel la montmorillonoïde est choisie parmi le groupe constitué de sauconite, vermiculite, bentonite, hectorite et silicate d'aluminium et de magnésium.

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6. Procédé tel que revendiqué à la revendication 5, dans lequel la montmorillonoïde est un silicate d'aluminium et de magnésium ou la bentonite.

7. Procédé tel que revendiqué à la revendication 6, dans lequel le silicate d'aluminium et de magnésium est le Veegum F.

8. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel l'argile gonflable est présente en une quantité de 1 à 40 % poids/poids.

9. Procédé tel que revendiqué à la revendication 8, dans lequel l'argile gonflable est présente en une quantité de 1 à 10 % poids/poids.

10. Procédé tel que revendiqué à la revendication 9, dans lequel l'argile gonflable est présente en une quantité de 5 à 10 % poids/poids.

11. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel on ajoute un agent de désintégration à l'acyclovir ou à des sels de celui-ci et à l'argile gonflable.

12. Procédé tel que revendiqué à la revendication 11, dans lequel l'agent de désintégration est le glycolate d'amidon sodique.

13. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel on ajoute un liant à l'acydovir ou à des sels de celui-ci et à l'argile gonflable.

14. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel le liant est la Povidone k30.

15. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel on ajoute une charge à l'acyclovir ou à des sels de celui-ci et à l'argile gonflable.

16. Procédé tel que revendiqué à la revendication 15, dans lequel la charge est une cellulose microcristalline.

17. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel on utilise un mélangeur-granulateur à fort cisaillement pour mélanger l'acyclovir ou des sels de celui-ci, l'argile gonflable et les autres excipients.

18. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel le comprimé est en outre revêtu d'un film.

19. Procédé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel la dispersion contient des particules ayant une distribution de taille où 100% des particules ont moins de 710 µm, et plus de 50 %moins de 300 µm.

20. Procédé tel que revendiqué à la revendication 19, dans lequel la dispersion du comprimé contient des particules ayant une distribution de taille où 100 % des particules ont moins de 710 µm, plus de 70 % moins de 300 µm, et plus de 50 % moins de 200 µm.

21. Procédé tel que revendiqué dans les revendications 1 ou 2 pour préparer un comprimé ayant 200 mg à 800 mg d'acyclovir, procédé qui comprend les étapes consistant à :

a) mélanger de l'acyclovir 70 à 90 % poids/poids, du silicate d'aluminium et de magnésium ou de la bentonite 0,5 à 30 %, de la cellulose microcristalline ou de l'hydroxypropylcellulose LH11 5 à 25 % poids/poids, du glycolate d'amidon sodique 0 à 8 % poids/poids;

b) ajouter une quantité de fluide de granulation comprenant 0,25 à 5 % poids/poids de Povidone ou d'amidon prégélifié et effectuer la granulation du mélange résultant pour former des granules;

c) sécher les granules et mélanger les granules avec du stéarate de magnésium 0,25 à 2 %;

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d) comprimer les granules pour former un comprimé ; et

e) éventuellement revêtir le comprimé d'un film avec de l'Opadry 0,1 à 2 % poids/poids et du polyéthylèneglycol 8000 0,1 à 0,5 % poids/poids.

22. Procédé tel que revendiqué à la revendication 20, dans lequel les composants sont l'acyclovir 75 à 85 % poids/poids, la Povidone ou l'amidon prégélifié 0,5 à 2 % poids/poids, le silicate d'aluminium et de magnésium ou la bentonite 0,5 à 10 % poids/poids, la cellulose microcristalline ou l'hydroxypropylcellulose LH11 5 à 15 % poids/poids, le glycolate d'amidon sodique 0 à 5 % poids/poids, le stéarate de magnésium 0,25 à 1,0 % poids/poids, et éventuellement des constituants d'un revêtement de type film d'Opadry 0,25 à 1,0 % poids/poids, et polyéthylèneglycol 8000 0,1 à 0,2 % poids/poids.