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<p>(54) Title: PHARMACEUTICAL FORMULATIONS</p>		
<p>(57) Abstract</p> <p>A stable pharmaceutical composition suitable for oral administration comprising a suspension of particulate cimetidine in an aqueous phase, and a suspending agent, wherein substantially all of the cimetidine present is of the polymorphic B form, and optionally any other pharmaceutical excipients.</p>		

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PHARMACEUTICAL FORMULATIONS

This invention relates to new pharmaceutical compositions and methods for their preparation, and in particular it relates to suspensions comprising cimetidine.

Cimetidine is a histamine H₂-antagonist which has been used for a number of years in the treatment of duodenal and benign gastric ulceration, recurrent and stomal ulceration, oesophageal reflux disease and other conditions where reduction of gastric acid by cimetidine has been shown to be beneficial, for example persistent dyspeptic symptoms with or without ulceration. It is widely recognised that there are considerable technical difficulties in producing stable and acceptable pharmaceutical compositions of cimetidine, particularly liquid solution and suspension compositions. Firstly, there is the difficulty of polymorphism which gives rise to problems of polymorphic transitions and crystal growth. It is generally recognised that cimetidine can exist in at least 5 different polymorphic forms and that these polymorphic forms differ in crystal habit and crystallisation properties, thermodynamic stability, and solubility and rate of dissolution in water. It is generally recognised that the polymorphic form A has been used almost exclusively in compositions, B. Hegedüs and S. Görög, J. Pharmaceutical & Biomedical Analysis, Vol. 3, No. 4, pp.303-313, 1985. Secondly, there is the problem that cimetidine has a very bitter taste and palatability of oral compositions is a major consideration.

It is clear that there has been a need for compositions of cimetidine which are liquid based and are palatable. Cimetidine is absorbed almost exclusively in the small intestine and liquid-based compositions offer

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the possibility that they could be absorbed more quickly and more efficiently than tablet compositions, particularly tablet compositions which have been coated to minimise unpleasant tastes. However, with solutions of cimetidine, the unpleasant bitter taste is a particular problem. Suspensions of cimetidine could in principle offer the advantage of being more palatable but until recently no stable suspension compositions of cimetidine have been described or sold. Some companies have tried to meet the apparent need for such a product by selling cimetidine powder or granules in sachets which can be extemporaneously mixed with water to produce suspension compositions.

EPA O 138 540-A describes suspensions containing cimetidine and the preferred examples are buffered solutions of high viscosity. Because of the high viscosity, such suspensions are not easily poured from a bottle and consequently are usually formulated in sachets.

Aqueous suspensions of cimetidine polymorph A are thermodynamically unstable and it is found that when many such suspensions are prepared having relatively low viscosity, they are likely, when subjected to fluctuating temperatures, to undergo polymorphic transition into the polymorphic B form. This polymorphic transition, forms polymorph B in situ as very long needle-like crystals, which makes the suspensions lumpy and non-homogeneous thereby introducing dosage inaccuracy and giving rise to an unpleasant mouth feel.

It is an object of this invention to provide a suspension of cimetidine which is stable and, in particular, is of relatively low viscosity such that it can be easily poured from a bottle and easily administered

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using a spoon or like device so that various dosages can be exactly and accurately measured. It is also an object of this invention to form a stable composition to which other ingredients such as antacids or alginates can be added.

We have now found that by preparing suspensions from cimetidine polymorph B, the problem of polymorphic transition and the growth in situ of long needle-like crystals can be avoided.

According to the invention, there is provided a stable pharmaceutical composition suitable for oral administration comprising a suspension of particulate cimetidine in an aqueous phase having a pH of at least 7, and a suspending agent, wherein substantially all of the cimetidine present is of the polymorphic B form, and optionally any other pharmaceutical excipients.

Preferably at least 90% and particularly preferably at least 95% of the cimetidine is in the polymorphic B form. It is preferred that substantially no polymorph A is present.

By stable is meant a suspension which is capable of remaining in a pharmaceutically acceptable condition for a prolonged period, for example at least six months, preferably at least a year and most preferably for more than three years. Thus there should not be significant crystal growth, and any sediment formed should be capable of being re-suspended with only mild agitation, i.e. the sediment should not take the form of a "cake" or lumps which cannot readily be re-suspended. Preferably no sediment should form at all.

35

It is in general preferred that the pH of the suspension is within the range 7-9.5, preferably 7.4-8.4, and particularly 7.8-8.2. It will be appreciated that the suspensions can be either buffered or unbuffered.

5

It is preferred that the suspensions of the present invention have a viscosity of less than 1,500 mPa.s but greater than 200 mPa.s, for example within the range 1,200 mPa.s to 500 mPa.s. The skilled man will be aware that the viscosity values obtained for a given system depend on the temperature, the shear rate and the shear history. The above figures refer to freshly shaken and poured suspensions at approximately 25°C subjected to a shear rate of 0.7 sec.⁻¹.

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An advantage of suspensions having a viscosity within the range 200 mPa.s to 1,500 mPa.s is that they are readily pourable. This is in contrast to suspensions prepared from cimetidine polymorph A which frequently are required to be of a high viscosity in order to remain stable, i.e. to minimise polymorphic interconversion, the viscosity being such that they are not readily pourable. By readily pourable is meant that they are capable of being easily poured from a suitable container such as a bottle. It will be readily appreciated that where the composition is a reversible gel, it may be necessary to shake the container before pouring in order to disrupt the gel structure.

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When the suspension contains alginate, the thickening effect of the alginate means that the viscosity of the suspension is generally higher than the range 200-1,500 mPa.s quoted above and typically is in the range 2,500-5,000 mPa.s for example approximately 3,500 mPa.s.

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Examples of suspending agents include xanthan gum, hydroxypropylmethylcellulose, methylcellulose, carageenan, sodium carboxymethyl cellulose, and sodium carboxymethyl cellulose/microcrystalline cellulose mixtures, particularly sodium carboxymethyl cellulose/microcrystalline cellulose mixtures. Preferred suspending agents are thixotropic suspending agents such as xanthan gum, carageenan and sodium carboxymethyl cellulose/microcrystalline cellulose mixtures and particularly preferred suspending agents are Avicel RC591, Avicel RC581 and Avicel CL611. Avicel is a trademark of FMC Corporation, and RC591, RC581 and CL611 are mixtures of microcrystalline cellulose and sodium carboxymethyl cellulose. The amount of suspending agent present will vary according to the particular suspending agent used and the presence or absence of other ingredients which have an ability to act as a suspending agent or which contribute significantly to the viscosity of the composition. In general, however, the amount of suspending agent will lie in the range 0.1-1.5% w/w of the total weight of the composition. When the suspending agent is xanthan gum, it will usually be present in an amount corresponding to 0.1-0.5% w/w of the total weight whereas when Avicel is used, the amount typically will lie in the range 0.6-1.5% w/w, particularly approximately 1.2% w/w. When carageenan is used, typically this will constitute 0.5-1% w/w of the composition. Compositions containing alginate, which has a significant thickening effect, will, in general, contain lower concentrations of suspending agent in order to avoid the problem of the viscosity being so great that the composition cannot be poured.

The suspension can contain ingredients which improve its taste, for example sweeteners, bitter-taste maskers such as sodium chloride and taste-masking flavours such

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as contramarum, flavour enhancers such as monosodium glutamate, and flavouring agents.

5 Examples of sweeteners include bulk sweeteners such as sucrose, hydrogenated glucose syrup, the sugar alcohols sorbitol and xylitol, and sweetening agents such as sodium cyclamate, sodium saccharin, aspartame and ammonium glycyrrhizinate.

10 A bulk sweetener will usually be present in an amount corresponding to about 15-70% w/w of the total weight of the suspension, the amount depending in part upon whether other ingredients, e.g. alginate, are present which have a thickening effect on the composition.
15 For example, when sorbitol is used as the sole bulk sweetener and no thickener (e.g. alginate) is present, typically the dry weight of sorbitol present is in the range 35-55% w/w of the total weight of the suspension, for example at a concentration of approximately 45% w/w.

20 When hydrogenated glucose syrup (solids content approximately 74%) is used as the sole bulk sweetener, typically it is present as 55-70% w/w of the suspension, for example at a concentration of approximately 65% w/w
25 (equivalent to 49% solids). It will be appreciated that combinations of bulk sweeteners can be used, for example combinations of sorbitol and hydrogenated glucose syrup, or sucrose and sorbitol.

30 Other excipients which can be used include humectants such as propylene glycol and glycerol and colourants such as titanium dioxide.

35 Typically the total quantity of humectant present is in the range 0-10% w/w. Thus, for example, propylene glycol and glycerol can each be present in an amount approximating to 4% w/w.

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It is preferred that the suspensions contain preservatives to prevent microbial contamination. Examples of preservatives are the alkylparabens, particularly propylparaben and butylparaben. Parabens
5 tend to be unstable at high pH values and hence most suitably are employed when the pH is below 8.2.

Preferably the suspension contains from 1.0 to 4.5% w/w cimetidine.
10

In one preferred embodiment of the invention there is provided a composition containing 1.5-3.5% w/w of cimetidine, 35-45% w/w of water, 35-55% of sorbitol, 0-10% w/w of a humectant which is propylene glycol
15 and/or glycerol, 0.6-1.5% w/w of a mixture of sodium carboxymethyl cellulose and microcrystalline cellulose and optionally other pharmaceutical excipients.

The compositions of this invention can optionally contain an antacid. An antacid is a pharmaceutically acceptable basic material of sufficient neutralising capacity to neutralise stomach acid. Examples of antacids are aluminium hydroxide, magnesium hydroxide, magnesium carbonate, calcium carbonate and co-dried gels
20 for example aluminium hydroxide-magnesium carbonate co-dried gel. Preferably the amount of antacid is such that a unit dose contains 10-30 milliequivalents.
25

In a further embodiment of the invention, there is provided a suspension of cimetidine polymorph B
30 additionally containing alginate.

The purpose of the alginate is to form a raft of mucilage which floats on the contents of the stomach thereby preventing gastro-oesophageal reflux (GORD) or
35 reducing its symptoms. Usually a carbonate salt such as

potassium bicarbonate or sodium bicarbonate is added.
Reaction of the carbonate with the acidic gastric juices
generates carbon dioxide which aerates the alginate raft,
reducing its density and thereby enabling it more easily
5 to float on the stomach contents.

When bicarbonate salts are present, the suspensions
are maintained at a pH of 7.5 or more in order to prevent
premature decomposition and evolution of carbon dioxide.
10 Typically the pH is maintained in the range 7.8-8.4, for
example by using a buffering agent such as a phosphate
buffer.

In order to avoid too great an increase in the
15 viscosity of the suspension, a low viscosity grade of
alginate is used. Low viscosity grades of alginate
suitable for use in the compositions of the present
invention will generally have a viscosity of 4-10 mPa.s
in 1% aqueous solution at 20°C. Alginates are polymers
20 composed of mannuronic and guluronic acid monomer
units. The ratio of mannuronic to guluronic acids
determines the raft-forming properties of the alginate
and, in general, alginates having a high
guluronic:mannuronic ratio (e.g. 70% guluronic acid) form
25 the strongest rafts. Alginates containing such high
levels of guluronic acid are preferably used in the
compositions of the present invention, and one such
alginate is Protanal LFR 5/60.

30 The concentration of alginate will be chosen so as
to optimise the raft-forming ability of the suspension
whilst not adversely affecting the pourability of the
suspension by increasing the viscosity too much.

35 In practice, the concentration of alginate (w/w)
typically is less than 10% relative to the total weight

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of the suspension. Preferably the alginate is present at a concentration of approximately 5%.

5 The alginate is usually present as an alkali metal salt such as sodium alginate.

A problem which has been encountered in the preparation of cimetidine/alginate suspensions is that the cimetidine can be oxidised to its sulphoxide.
10 Cimetidine sulphoxide is a known metabolite of cimetidine and whereas its presence in the suspension does not give rise to problems of toxicity, the sulphoxide is essentially inactive as an H₂-antagonist and thus the oxidation of cimetidine may lead to a reduction in
15 efficacy of the composition.

The mechanism of sulphoxide formation is not known. The addition of standard antioxidants such as propyl gallate and sodium sulphite does not inhibit the
20 formation of the sulphoxide. Moreover certain chelating agents such as polyphosphates and trisodium citrate have been added but have also been found to be ineffective in preventing oxidation. However, it has now surprisingly been found that sulphoxide formation can be significantly
25 inhibited by the addition of ethylenediaminetetraacetic acid (EDTA) and salts thereof.

In a preferred aspect of this invention, therefore, there is provided a pharmaceutical suspension as ;
30 hereinbefore defined comprising cimetidine polymorph B and, additionally, alginate and EDTA or a salt thereof. Typically the EDTA is present in an amount from approximately 0.05% (w/w) to approximately 0.25% (w/w) of the total weight of the suspension; particularly
35 approximately 0.1% (w/w). The EDTA is usually added as a salt, particularly the disodium salt.

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In the compositions of the present invention, typically the particle size of the cimetidine is such that in the final suspension 80% by weight of the particles are less than 200μ in size but are greater than approximately 5μ in size. The sizes referred to are the apparent diameters as measured by a Malvern 3600E Laser Particle Sizer (supplied by Malvern Instruments Limited, Spring Lane, Worcester, U.K.).

The compositions of the present invention can be prepared by mixing the cimetidine polymorph B with the suspending agent, and any other ingredients to be included, to form a suspension.

The cimetidine polymorph B can be prepared by forming a solution of cimetidine acetate in aqueous isopropanol (10% isopropanol), clarifying by filtration and basifying with aqueous ammonia (10% excess) as described in Appendix A. The mixture is then stirred to allow the polymorph B to crystallise completely, then the product is isolated by filtration, washed well with water and dried to constant weight.

The invention is illustrated but in no way limited by the following examples. In the examples, all references to cimetidine refer to the B polymorph unless otherwise stated.

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Example 1Cimetidine Suspension (200 mg in 10 ml)

	INGREDIENTS	QTY (g)	UNIT DOSE mg/10ml
5	Cimetidine Base (B Polymorph)	120.0	200
	Avicel RC591	90.0	150
10	Water	1500.0	2500
	Propylene Glycol	300.0	500
	Glycerol	300.0	500
	Butylparaben	6.0	10
	Propylparaben	3.0	5
15	Sodium Saccharin	2.4	4
	Vanilla (Firmenich 54.286C)	3.0	5
	Cream (FDO FC 900772)	6.0	10
	Titanium Dioxide 50% in Glycerol	24.0	40
	Sorbitol 70% in water*	4940.0	8234

20

*Sorbitol 3460 g, Water 1480 g.

PROCESS

25 The Avicel is dispersed in demineralised water using a low shear propeller mixer and the resulting dispersion is passed through a Premier colloid mill (Premier Colloid Mills Ltd., Walton-on Thames, Surrey, U.K.) on high speed at 25 μ gap. The Avicel high shear dispersion is mixed

30 with 3.6 kg of the sorbitol 70% solution and to the mixture is added the glycerol followed by a solution of the parabens in propylene glycol. The flavourings and the titanium dioxide paste are then added with stirring to give a homogenous mixture. Cimetidine is then added

35 followed by the remainder of the sorbitol to give a total volume of 6 litres. The batch is then passed through a

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colloid mill on low speed set to the smallest possible gap (approx 25 μ) such that the milling process does not cause the temperature of the milled material to exceed 35°C. The pH of the resulting suspension is approximately 7.8.

Example 2

Cimetidine Suspension (200 mg in 5 ml)

This has a similar composition to that described in Example 1 except that the quantity of cimetidine is doubled.

Example 3

Cimetidine Suspension in Hydrogenated Glucose Syrup

This has a composition analogous to that described in Example 2 except that instead of sorbitol 70%, an equivalent volume of hydrogenated glucose syrup (74% solids) is used as the vehicle.

Example 4

Determination of the viscosities of the formulations of Examples 1 to 3, 6 and 8

The viscosities of the compositions of Examples 1 to 3, 6 and 8 were determined using a Rheomat 30 Rheometer supplied by Contraves of Switzerland. The measurements were conducted at 27°C and the results are shown in Table 2.

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Table 2

Shear Rate (sec. ⁻¹)	Apparent Viscosity (η_a) (mPa.s)			
	Examples 1 and 2	Example 3	Example 6	Example 8
0.7	700	1000	3400	1000
7	400	800	1000	500
70	200	300	500	200
700	100	200	300	100

15

Example 5Comparative Stabilities of Suspensions containing
Polymorph A and Suspensions containing Polymorph B

i) Compositions as described in Example 1 were subjected to isothermal storage for one year at temperatures of 4°, 22°, 30° and 40°C. Microscopic examination after this time indicated that no crystal growth had occurred.

The composition of Example 1 was also subjected to 50 thermal cycles between 10 and 30°C. No crystal growth was detected following this test.

ii) Compositions identical to those described in Example 1, except that cimetidine polymorph A was used instead of cimetidine polymorph B, were also subjected to stability tests. The median particle size in the freshly prepared suspensions was approximately 40 μ .

35

After 5 months at room temperature filaments 750 μ in length were observed upon microscopic examination.

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At ten months filaments up to 2.5 mm were observed along with filamentous clusters up to 1 mm in length.

5 Upon storage at 30°C for 3 days, filaments up to 2.5 mm in length were observed and after storage at 40°C for 3 days a large filamentous aggregate of 4 mm overall length was detected.

10 After thermal cycling, 10-30°C, 9 cycles, numerous feather-like clusters up to 800 μ long and 200 μ wide were formed. One feather-like aggregate of 1.8 mm length was detected.

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Example 6100 Mg Cimetidine/Sodium Alginate Suspension

5	INGREDIENTS	UNIT DOSE QUANTITY (g/100 ml)
	Cimetidine Base	2.0
	Sodium Alginate (Protanal LFR 5/60)	5.0
10	Potassium Bicarbonate	3.18
	Propylene Glycol	5.0
	Glycerol	5.0
	Avicel CL-611 (Microcrystalline cellulose and sodium carboxymethylcellulose)	0.2
15	Sorbitol Solution BP (70% w/w)	22.0
	Hydrogenated Glucose Syrup (Lycasin 80/55)	4.0
	Butylparaben	0.1
	Propylparaben	0.05
	Ethylenediaminetetraacetic acid (disodium salt)	0.1
20	Sodium dihydrogen orthophosphate dihydrate	0.31
	Di-Sodium hydrogen orthophosphate dodecahydrate	0.475
25	Sodium Saccharin	0.2
	Passion Fruit Flavour	0.01
	Peppermint Flavour	0.02
	Titanium Dioxide in 50% Glycerol	0.8
	Demineralised Water	to 100 ml
30	<hr/>	

PROCESS

The hydroxybenzoates were dissolved in warm propylene glycol and to the resulting solution was added the glycerol. After the solution had cooled to room temperature, the cimetidine was added with stirring to give a smooth slurry.

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A sodium alginate mixture was prepared by dissolving the disodium edetate in demineralised water and then dispersing the sodium alginate in the solution using a high shear homogeniser.

5

The cimetidine slurry, sorbitol solution, hydrogenated glucose syrup and sodium alginate mixture were added to a dispersion of the Avicel in demineralised water and the resulting mixture was stirred until homogenous. The remaining ingredients were added, additional demineralised water being added as necessary to give the correct volume. Finally, the suspension was passed through a colloid mill set at low speed as described in Example 1.

15

Example 7

200mg/5ml Cimetidine/Magnesium hydroxide/
Aluminium hydroxide Suspension

	g/100ml	% (w/w)
20 Cimetidine	4	3.31
Magnesium hydroxide	4	3.31
Aluminium hydroxide (as Al ₂ O ₃)	2.4	1.98
Xanthan	0.3	0.25
25 Propylparaben	0.05	0.041
Butylparaben	0.10	0.083
Propylene glycol	5.0	4.13
Glycerol	2.0	1.65
Sorbitol (70%)	75	62.0
30 Water	to 100 ml.	

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Example 8100mg/5ml Cimetidine/Magnesium hydroxide/
Aluminium hydroxide Suspension

		g/100ml	% (w/w)
5	Cimetidine	2	1.65
	Magnesium hydroxide	4	3.31
	Aluminium hydroxide (as Al ₂ O ₃)	2.4	1.98
	Xanthan	0.3	0.25
10	Propylparaben	0.05	0.041
	Butylparaben	0.10	0.083
	Mint Flavouring	0.10	0.083
	Propylene Glycol	5.0	4.13
	Glycerol	2.0	1.65
15	Sucrose	35	28.9
	Sorbitol (70%)	25	20.7
	Water	to 100 ml.	

Example 920 100mg/5ml Cimetidine/Calcium Carbonate Suspension

		g/100ml	% (w/w)
	Cimetidine	2	1.51
	Calcium carbonate	11.7	8.86
25	Avicel RC591	1.5	1.14
	Propyl paraben	0.05	0.038
	Butyl paraben	0.10	0.076
	Sodium saccharin	0.04	0.030
	Vanilla))Flavours	0.05	0.038
30	Cream)	0.10	0.076
	Titanium dioxide (50%)	0.4	0.30
	Propylene glycol	5.0	3.78
	Glycerol	5.0	3.78
35	Water	25	18.93
	Lycasin (hydrogenated glucose syrup)	to 100 ml 61.42	

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Example 10Cimetidine/Calcium carbonate/Magnesium
hydroxide Suspensions

		g/100ml	% (w/w)
5	Cimetidine	2	1.5
	Calcium Carbonate	10	7.52
	Magnesium hydroxide	1	0.75
	Avicel RC591	1.5	1.13
10	Propylparaben	0.05	0.038
	Butylparaben	0.10	0.075
	Sodium Saccharin	0.04	0.03
	Vanilla))Flavours	0.05	0.038
	Cream)	0.10	0.075
15	Titanium dioxide (50%)	0.4	0.30
	Propylene glycol	5.0	3.76
	Glycerol	5.0	3.76
	Water	25	18.79
	Lycasin (hydrogenated glucose syrup) to 100 ml		62.24

20

APPENDIX APreparation of Cimetidine Polymorph B

25 To a stirred suspension of 252 grams of cimetidine polymorph A in 2.0 litres of water and 250 ml of isopropanol was added a solution containing 60 grams of acetic acid in 125 ml water. The mixture was stirred and the resulting solution was clarified by filtration.

30 To the resulting clear solution was added with agitation a solution containing 68 ml of concentrated ammonia (27% w/w) in 125 ml of water. Following precipitation of the cimetidine base, the mixture was heated to

35 in-process checks* after this time indicated that the

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solid was completely form "B". The mixture was cooled, the product isolated by filtration, and washed well with water. The solid was dried at 60°C. to yield 240 grams (95%) of crystalline cimetidine "B" having a melting
5 point of 142.5-144°C.

* An appropriate process check is to obtain an infra-red spectrum of the product and calculate the ratio of the peak heights of the absorbance bands at 1004 and 993 cm^{-1} .
10 The concentration of polymorph C is then determined by reference to a calibration curve obtained by plotting the peak ratios for various standard mixtures of polymorph C and polymorph B.

15 The above-mentioned process for preparing cimetidine polymorph B is also disclosed and is claimed in a co-pending European Patent Application which derives priority from British Patent Application No. 8618846 filed on 1st August 1986. The term "polymorph B" as
20 used hereinabove includes a reference to crystalline cimetidine prepared according to the said process.

CLAIMS for the Designated States AUSTRALIA, DENMARK,
JAPAN and SOUTH KOREA:

- 5 1. A stable pharmaceutical composition suitable for oral administration comprising a suspension of particulate cimetidine in an aqueous phase having a pH of at least 7, a suspending agent and, optionally, additional pharmaceutical excipients, wherein substantially all of the cimetidine present is of the polymorphic B form.
- 10 2. A composition according to claim 1 wherein at least 95% of the cimetidine is in the polymorphic B form.
- 15 3. A composition according to either of claims 1 or 2 wherein the viscosity of the suspension, as measured at 25°C and at a shear rate of 0.7 sec⁻¹, is in the range 200 mPa.s to 1,500 mPa.s.
- 20 4. A composition according to claim 3 wherein the viscosity is 500 mPa.s to 1200 mPa.s.
- 25 5. A composition according to any one of claims 1 to 4 wherein the suspending agent is a mixture of sodium carboxymethylcellulose and microcrystalline cellulose, which mixture is present in an amount in the range 0.6-1.5% w/w of the total weight of the composition.
- 30 6. A composition according to any one of claims 1 to 5 wherein at least 80% of the cimetidine particles have an apparent diameter in the range 5 μ to 200 μ .
7. A composition according to any one of claims 1 to 6 which contains an antacid.

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8. A composition according to claim 1 containing
1.5-3.5% w/w of cimetidine, 35-45% w/w of water,
35-55% w/w of sorbitol, 0-10% w/w of a humectant which
is propylene glycol and/or glycerol, 0.6-1.5% w/w of a
5 mixture of sodium carboxymethyl cellulose and
microcrystalline cellulose and optionally other
pharmaceutical excipients.

9. A composition according to any one of claims 1
10 to 6 which contains an alginate.

10. A composition according to claim 9 which
contains EDTA or a salt thereof in an amount from
approximately 0.05% w/w to approximately 0.1% w/w of the
15 total weight of the composition.

CLAIMS for the Designated State HUNGARY:

1. A process for preparing a stable pharmaceutical composition suitable for oral administration, said
5 composition comprising a suspension of particulate cimetidine in an aqueous phase having a pH of at least 7, a suspending agent and, optionally, additional pharmaceutical excipients, wherein substantially all of the cimetidine present is of the polymorphic B form, which
10 process comprises suspending the particulate cimetidine in the presence of the suspending agent and optionally additional pharmaceutical excipients in the aqueous phase.

2. A method of preparing a stable pharmaceutical
15 suspension of cimetidine which comprises milling cimetidine polymorph B to give particulate cimetidine in which 80% by weight of the cimetidine particles are less than 200 μ in size but are greater than approximately 5 μ in size, and suspending the cimetidine particles in
20 an aqueous phase having a pH of at least 7 with a suspending agent and optionally additional pharmaceutical excipients.

3. A process according to either of claims 1 or 2
25 in which at least 95% of the cimetidine is in the polymorph B form.

4. A process according to any one of claims 1 to 3
30 in which the suspending agent and/or optional additional pharmaceutical excipients are added in an amount such that the viscosity of the suspension, as measured at 25°C and at a shear rate of 0.7 sec⁻¹, is in the range 200 mPa.s to 1500 mPa.s.

35 5. A process according to claim 4 wherein the viscosity is 500 mPa.s to 1200 mPa.s.

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6. A process according to any one of claims 1 to 5
wherein the suspending agent is a mixture of sodium
carboxymethylcellulose and microcrystalline cellulose and
said suspending agent is added in an amount corresponding
5 to 0.6-1.5% w/w of the total weight of the composition.

7. A process according to any one of claims 1 to 6
wherein there is additionally added an antacid.

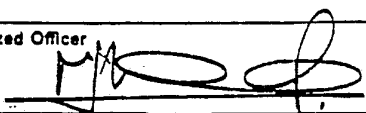
10 8. A process according to any one of claims 1 to 6
wherein there is additionally added an alginate.

9. A method of inhibiting formation of cimetidine
sulphoxide in a suspension prepared according to claim 8,
15 which method comprises incorporating into the suspension
EDTA or a salt thereof.

10. A method according to claim 9 wherein the EDTA
or salt thereof is incorporated into the suspension in an
20 amount from approximately 0.05% w/w to approximately 0.1%
w/w of the total weight of the composition.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 87/00539

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		
IPC ⁴ : A 61 K 31/415; A 61 K 9/10		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	A 61 K C 07 D	
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 ⁹	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP, A, 0138540 (SMITH KLINE DAUELSBERG) 24 April 1985 see page 2, lines 14-20; claims cited in the application --	1-10
Y	Chemical Abstracts, volume 96, no. 7, 7 February 1982, (Columbus, Ohio, US), see page 622, abstract 52307g, & JP, A, 81104868 (FUJIMOTO PHARMACEUTICAL CO., LTD) 20 August 1981 --	
A	FR, A, 2513636 (RICHTER GEDEON VEGYESZETI GYAR) 1 April 1983 see claims --	1
P,A	Chemical Abstracts, volume 106, no. 19, 11 May 1987, (Columbus, Ohio, US), H. Kokubo et al.: "Bioavailability and inhibitory effect for stress ulcer of cimetidine polymorphs in rats", see page 15, abstract 148940j, & Int. J. Pharm. 1987, 35(1-2), 181-3 -----	1
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
22nd October 1987		20 NOV 1987
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		M. VAN MOL 

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 87/00539 (SA 18127)

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 03/11/87

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- 0138540	24/04/85	WO-A- 8501656	25/04/85
		AU-A- 3503984	07/05/85
		JP-T- 61500223	06/02/86
		AU-B- 560608	09/04/87
FR-A- 2513636	01/04/83	BE-A- 894464	22/03/83
		DE-A- 3235459	14/04/83
		GB-A,B 2108117	11/05/83
		NL-A- 8203688	18/04/83
		US-A- 4537900	27/08/85

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82