Description

This invention relates to a sustained release form of ibuprofen, and is more particularly concerned with an ibuprofen-containing matrix formed from granulations of ibuprofen mixed with inactive powdered excipients plus ethylcellulose using an aqueous-alcoholic solution of Povidone U.S.P. (polyvinylpyrrolidone — PVP) as the granulating fluid, which granulations are dried, milled, blended with additional inactive powdered excipients, and then compressed into a tablet, and to the process of making the ibuprofen-containing matrix in a manner so that the rate of release of ibuprofen can be easily varied or controlled.

Ibuprofen is a very well-known anti-inflammatory and analgesic drug. In the United States, it is available in dosage forms of 400 mg, 600 mg, and 800 mg tablets by prescription, and as 200 mg tablets for non-prescription over-the-counter sales. For treatment with ibuprofen over a long period of time, e.g., over 12 hours, the patient now must typically take one 200 mg tablet or caplet, another four hours later, and a third four hours after that. In doing so, the levels of the ibuprofen in blood plasma will reach peak levels shortly after the ibuprofen tablets are taken, and then the plasma levels will decrease fairly rapidly. It would obviously be better to reduce the number of peaks and valleys so as to have a more uniform rate of release of ibuprofen into the blood plasma leading to more uniform or constant concentrations of ibuprofen in the plasma. A way to do this has now been found in a more convenient manner, using the present invention, whereby a single 600 mg tablet or caplet can be formulated which has a sustained rate of release resulting in much more even plasma levels over twelve (12) hours, as contrasted to three (3) 200 mg tablets or caplets. In addition, the quantity (amount) of the matrix can be adjusted up or down to produce tablets for sustained release that have more than or less than 600 mg of ibuprofen. For example, a tablet containing 800 mg of ibuprofen can be manufactured from the same composition by simply increasing the size and weight of the final tablet by a multiple of 4/3- The present invention can be utilized to obtain any desired sustained release ibuprofen tablets of different dosages, e.g. an 800 mg sustained release tablet which results in higher blood plasma levels over twelve (12) hours, than with the 600 mg tablets, desired longer or shorter time periods e.g. eight (8) hours are possible. From a practical standpoint twelve (12) hours might be the most desired interval. The matrix of the present invention can be utilized to make ibuprofen sustained release pharmaceutical preparations in compressed tablet form. The matrix materials used are compressed into a shaped tablet form. The term "tablet" as used herein includes tablets of any shape, and includes caplets, which are tablets having a capsule shape.

Both ethylcellulose and polyvinylpyrrolidone have been used in pharmaceutical compositions, such as tablets, including sustained release compositions. Ethyl cellulose is often used as a coating for particles or in combination with another polymer. Ethyl cellulose and PVP have even been used together, e.g., in German Offenlegungsschrift DE 3331262A1, published March 1, 1984, dealing with a food supplement which contains in addition to various amino acids and other ingredients both PVP and ethyl cellulose. The PVP and ethylcellulose are there used in different amounts with different other materials to make a completely different type of final product than in the instant invention.

Controlled release formulations of ibuprofen are known. Dunn et al. U.S. Patent No. 4,308,251 (Example 38) discloses ibuprofen controlled-release tablets containing in carefully controlled amounts, both an erosion-promoter agent, specifically, corn starch, and a release-controlling agent, specifically, cellulose acetate phthalate. The process disclosed is to intimately mix the ibuprofen with the corn starch, and to add to this a solution of ethanol + methylene chloride containing cellulose acetate phthalate to form granules, which are dried, blended with colloidal silicon dioxide, and compressed into tablets. The Dunn et al. patent suggests at column 5 that (1) while the preferred release controlling agent is cellulose acetate phthalate, various other suitable agents may be used, including ethyl cellulose, and (2) while the preferred erosion-promoting agent is corn starch, various other suitable agents may be used including various vegetable starches, cellulose derivatives and cross-linked polyvinylpyrrolidone. The instant invention utilizes some of these suggested alternative ingredients in a different manner, (in the instant invention the ethyl cellulose is mixed with ibuprofen as a dry powder while the polyvinylpyrrolidone [which is a non-crosslinked PVP, and is a completely different material with different properties than the Dunn, et al. material] is dissolved in alcohol, which is the opposite of what Dunn et al. teaches) and in different proportions to make a different type of controlled-release tablet than Dunn et al.

US-A-3773921 discloses a sustained release therapeutic composition comprising a mixture of (1) a therapeutically active sulfa drug (2) dibasic calcium phosphate, (3) a binder and (4) a lubricant.

The ibuprofen sustained release matrix pharmaceutical tablets of the present invention are made by adding granulating fluid to a dry powder blend of active drug and inactive excipients to form wet granulations, which are then dried and finely divided, e.g., by being milled into powder form and then blended with additional inactive powdered excipients and compressed into tablets. They can be easily manufactured using conventional tabletting equipment.

The tablets of the present invention have many advantageous features. They are bioerodible when swal-

lowed, leaving no insoluble tablet shaped device to be excreted or removed from the body. The ibuprofen sustained release matrix uses ethyl cellulose (ethylcellulose NF) and povidone (povidone USP) (Plasdone®® K29/32) as the matrix binding agents for obtaining the sustained release effect. This combination of two well-known relatively inexpensive, pharmaceutically acceptable polymers, in the relative proportions here used and in the manner here used is believed to be a major novel feature of the present invention. In the most preferred embodiments of the invention, the amount of ethylcellulose used is on the general order of two percent or less of the amount of ibuprofen, while the amount of povidone is on the general order of four percent or less of the amount of ibuprofen used. This means that the ibuprofen sustained release matrix of the present invention is capable of producing dosage forms having very high drug/matrix binding agent ratios. This results in reducing the size or number of tablets needed, making the product less expensive and more desirable to the consumer.

An advantage of the process of this invention is that the rate of matrix erosion when the tablet is swallowed can be modified so that the degree and/or length of the sustained release effect of the matrix can be easily modified by simply altering the levels of the other excipients, aside from the ethylcellulose and the povidone (PVP). Thus, the rate of release of ibuprofen from the tablet for absorption into the bloodstream can be modified to match the desired blood plasma concentration versus time profile.

The ibuprofen sustained release matrix of the present invention can be used alone as a tablet (or caplet which is a tablet shaped like a capsule), or as part of a multi-layered tablet. Sometimes it is desirable to have a multi-layered tablet with an immediate or quick-release layer to begin raising the blood levels of ibuprofen relatively quickly until the sustained release portion of the tablet can begin to take over the effect. Thus, one can use the present invention to have two or more layers, each with a significantly different release rate of the same component or different components where a combination of drugs is desired.

In our currently preferred embodiments, the ibuprofen-sustained release matrix tablets of the present invention contain approximately 1.4 percent ethylcellulose and approximately 2.8 percent PVP, with the balance consisting of various pharmaceutically acceptable, common excipients. The tablets of the present invention have a very high drug-to-excipients ratio on the order of at least 80 percent ibuprofen to 20 percent excipients by weight. This results in a drug to total matrix weight ratio of approximately 1 : 1.2.

In addition to the ethylcellulose and PVP polymers discussed above which are matrix binding agents, the commonly used excipients which are granulated with the ibuprofen include a wicking agent (to wick fluids into the matrix) such as microcrystalline cellulose and an "erosion promoter" such as Pregelatinized Starch. Additional excipients which are added to the granulated and dried ingredients include a wicking agent such as microcrystalline cellulose, an erosion promoter such as pregelatinized starch, a lubricant such as magnesium stearate and a glidant, such as colloidal silicon dioxide. The lubricant optionally may be omitted, but is a currently preferred ingredient.

For each of the ingredients used in the sustained release matrix of the present invention, aside from the ibuprofen, the ethylcellulose and the Povidone (PVP), there exists less preferred alternative or equivalent materials which could be used in its place. The following Table I lists : each of the various preferred ingredients, the purpose of the ingredient, the preferred weight of such preferred ingredient, the usable weight range of the preferred ingredient, other less preferred alternatives or equivalents which can be substituted for the preferred ingredient, the preferred weight of such alternative ingredient and the usable weight range of such alternative ingredient for a sustained release layer containing 440 mg of ibuprofen. [For tablets (caplets) of a higher or lower level of ibuprofen, the amounts of ingredients and their ranges would be proportionately increased or decreased.]

The ingredients are listed in table I under part I active & excipients, part II granulating agent, part III excipients, since they are used in this manner in the process by which the tablets of the present invention are made.

The preferred process which is utilized to form the most preferred ibuprofen-sustained release matrix of the present invention is to mix together the dry powdered active drug, ibuprofen, the dry powdered matrix binding polymer, ethyl cellulose, and the dry powdered excipients, microcrystalline cellulose and pregelatinized starch in a mixer/granulator. A granulating agent (fluid or solution) is formed by mixing alcohol (ethanol) and water to obtain a 1 : 1 mixture, into which Povidone is dissolved to obtain a 12.25 percent (weight-by-weight) solution. The resultant granulating agent is sprayed onto the above admixed powders while they are being mixed in the mixer/granulator so as to form a wet granulation. The wet granulation thus obtained is dried and milled. At this point a small amount of dry powdered excipients such as pregelatinized starch, microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide are added and mixed with the milled granulations, after which they are compressed thereby forming the sustained release matrix.

TABLE I

SUSTAINED RELEASE IBUPROFEN

Preferred ingredient	Purpose	Wt./Tablet (mg)	(mg) Wt. Range	Alt./or Equiv.	Wt./Tablet (mg)	(mg) Wt. Range
Part I - Active & Excipients						
Ibuprofen USP	Active drug	440.0	-	-	-	-
Ethylcellulose NF (Ethocel® N-10)	Matrix binding agent	7.3	3-12			
Microcrystalline cellulose NF (Avicel*) pH 101, 102, 103, 105	Wicking agent	22	10-35	Powdered cellulose (Solka Floc®)	22	10-35
Pregelatinized starch NF (corn, wheat or potato source)	Erosion promoter	14	5-25	Starch NF (corn, wheat or potato) or rice starch	14	5-25
Part II - Granulating Agent						
Povidone USP Plasdone®/K 29/32	Matrix binding agent	14.7	5-30			
Alcohol	Solvent	[1:1 alcohol-		Dehydrated alcohol USP, Methyl alcohol USP,		

Purified water USP	Solvent	water 8.5.]		Isopropyl alcohol USP			
[alcohol can be used either alone, or with water in a ratio of up to about 1 part alcohol to 2 parts water]							
Part III - Excipient							
Pregelatinized starch NF (corn, wheat, or potato source)	Erosion promoter	8	3-20	Starch NF (corn, wheat or potato) or rice starch	8	3-20	
				Sodium starch glycolate NF (Explotab®)	4	1-15	
				Croscar-mellose sodium NF (Ac Di Sol®)	4	1-15	
				Crospovidone NF (Povidone XL®)	4	1-15	
Microcrystalline cellulose NF	Wicking agent	7.3	3-20	Powdered cellulose (Solka Floc®)	7.3	3-20	
Magnesium stearate NF	Lubricant	5	0-10	Stearic acid NF	5	0-10	
Colloidal Silicon dioxide NF (Cab-O-Sil®)	Glidant	5	2-10	Fumed silicon dioxide (Syloid®)	5	2-10	

The sustained release matrix of the present invention is pH independent. Hydration of the matrix by fluids in the gastrointestinal tract bioerodes the matrix allowing ibuprofen to be exposed through the bioerosion. The rate of erosion and hence the rate of dissolution controls the absorption ibuprofen and the resultant plasma concentration v. time profiles. Merely changing the amount of any of the ingredients which are used for the purpose of erosion promotion will result in change in the rate of erosion of the final tablet.

If desired, a pharmaceutically acceptable coloring agent may be added to one or more of the layers of the tablet. One way of doing this is to add a dry powdered lake to part III of the sustained release Ibuprofen.

If desired, the compressed tablet may be coated with a pharmaceutically acceptable polymer, gelatin, or sugar coating.

While various listed ingredients in the specification and claims have the suffix "U.S.P." (United States Pharmacopia) or "NF" (National Formulary), this is intended only to better identify the ingredient, or its purity, and not to limit the invention in any way to the use of ingredients so marked, since identical materials are available under other designations e.g. in foreign countries.

The following examples are illustrative of the most preferred embodiments of the present invention. Any of the alternative or equivalent ingredients shown in table I could be substituted if desired.

EXAMPLES

Example I — Ibuprofen Sustained Release Bi-Layer Tablet

This example illustrates a bi-layer tablet in which there is both an immediate release layer and a sustained release layer. The immediate release layer is analogous in composition and manufacturing procedure to currently available over-the-counter ibuprofen non-sustained release tablets, except the amount of ibuprofen in this layer of this example is 160 mg instead of 200 mg. It is the sustained release layer, which utilizes the matrix of the present invention.

The bi-layer tablet uses the following ingredients :

Ingredient	mg/Tablet
A. Immediate Release Layer	
Part I Active and Excipients	
ibuprofen USP	160.0 mg
microcrystalline cellulose NF (Avicel® PH 101)	32.0 mg
starch NF	32.0 mg
pregelatinized starch NF (Starch® 1500)	16.0 mg
sodium starch glycolate NF	6.4 mg
Part II Granulating Agent	
hydroxypropyl methylcellulose 2910 USP (Methocel® E-5)	1.6 mg
purified water USP	q.s.
Part III Excipients	
sodium starch glycolate NF (Explotab®)	1.6 mg
coloidal silicon dioxide NF	0.8 mg
Total	250.4 mg

Ingredient			mg/Tablet
B. Sustained Release Layer			
Part I Active & Excipients			
ibuprofen USP			440.0 mg
ethylcellulose NF (Ethocel® N-10)			7.3 mg
microcrystalline cellulose NF (Avicel® PH 101)			22.0 mg
pregelatinized starch NF (Starch® 1500)			14.0 mg
Part II Granulating Agent			
povidone USP			14.7 mg
alcohol USP	)	1:1 mixture	q.s.
purified water USP	)		
Part III Running Powder			
pregelatinized starch NF (Starch® 1500 LM)			8.0 mg
microcrystalline cellulose NF (Avicel® PH 101)			7.3 mg
magnesium stearate NF			5.0 mg
colloidal silicon dioxide NF (Cab-O-Sil®)			5.0 mg
		Total	523.3 mg
		Total tablet weight	773.7 mg

The above ingredients are utilized to make a bi-layer tablet to the following working directions :

WORKING DIRECTIONS

A. Immediate Release Layer

1. Weigh the components of part I and preblend them in a high shear mixer (Fielder : impeller speed of approximately 118 RPM for 3 minutes).
2. Prepare the granulating agent (part II) by dissolving the hydroxypropyl methylcellulose 2910 USP into the purified water USP (a ratio of 3.2 grams of hydroxypropyl methylcellulose to 200 grams water).
3. Deliver the granulating agent to the powders of part I, in the high shear mixer. Granulate the mixture for

20 minutes (Fielder : impeller speed of approximately 118 RPM).

4. Remove the completed wet granulation from the high shear mixer and load into the product bowl of a fluid bed apparatus (e.g. Aeromatic or Glatt). With an inlet air temperature of approximately 60°C, dry the granulation to a moisture level of 0.5 to 1.1% as determined by loss on drying (e.g. Computrac). The wet granulation can also be dried on trays in drying ovens.
5. Sieve the dried granulation (e.g. Glatt Quick Sieve : Stator No. 3, Screen No. 1.5 mm, 1000 RPM). Other machines such as a Fitzpatrick Communition Mill can be used.
6. Blend the sieved and dried granulation with the powders of part III using a suitable mixer such as a twin-shell, ribbon or planetary mixer.

B. Sustained Release Layer

1. Weigh the components of part I and preblend them in a high shear mixer (Fielder : impeller speed of approximately 250 RPM for 1 minute).
2. Prepare the granulating agent (part II) by dissolving the povidone USP in a 1 : 1 mixture of alcohol USP and purified water USP (a ratio of 12.25 grams of povidone to 100 grams of alcohol/water).
3. Spray the granulating agent at a rate of 600ml/min. onto part I in the high shear mixer. Granulate the mixture for one minute after the addition of part II (Fielder : impeller speed of approximately 250 RPM).
4. Remove the completed wet granulation from the high shear mixer and load it into the product bowl of a fluid bed apparatus (e.g. Aeromatic or Glatt). With an inlet air temperature of approximately 60°C, dry the granulation to a moisture level of 0.3 to 0.8% as determined by loss on drying (e.g. Computrac). The wet granulation can also be dried on trays in drying ovens.
5. Sieve the dried granulation (Fitzpatrick Communition Mill, Model D6 : medium speed, knives forward, 0.093 screen). Other machines such as Glatt Quick Sieve can also be used.
6. Blend the sieved and dried granulation with the powerds of part III using a suitable mixer such as a twin-shell, ribbon or planetary mixer.

C. Compression of Tablets or Caplets

1. Load the granulation of the immediate release layer into one hopper and the granulation of the sustained release layer into the second hopper a bilayer tableting machine (e.g. Stokes Versapress). Compress tablets using 0.749 × 0.281 × 0.060 extra deep concave capsule shaped tooling. (Tablet tooling of other shapes such as oval or round can also be used). The sustained release layer has a target weight of 523.3 mg and the immediate release layer has a target weight of 250.4 mg. Ideal tablet hardness immediately after compression is 11 to 12 Kp.

The tablets of Example I were tested in twelve adult human male subjects and compared to non-sustained release (immediate release only) tablets in a corss-over design. A single tablet of Example I, which contained 600 mg of ibuprofen, was dosed at time = 0 hour. The non-sustained tablets, each containing 200 mg ibuprofen, were dosed at time = 0 hours, 4 hours and 8 hours. Subjects were fasted 8 hours prior to administration of the first dose. Blood samples were taken from each subject, in each dosing regimen at 0, 1, 1.5, 2, 3, 4, 5, 5.5, 6, 8, 9, 9.5, 10, 12, 16 and 24 hours. Plasma was separated from the blood and the concentration of ibuprofen in each sample was determined. The results are shown numerically in Tables 2a, and 2b and graphically in the drawing. The results show that one bi-layer tablet of Example 1 reduces the number of peaks and valleys of the plasma concentration versus time profile and provides equivalent area under the curve (AUC) when compared to three non-sustained release tablets, each containing 200 mg ibuprofen.

TABLE 2a

Sustained Release Ibuprofen 600 mg (Example 1) Average Plasma Concentration Levels of Ibuprofen (mcg/ml) in twelve subjects. Average AUC equaled 174 µg/h.

	TIME (Hours) Post Dosing														
0	1.0	1.5	2.0	3.0	4.0	5.0	5.5	6.0	8.0	9.0	9.5	10	12	16	24
Average (µg/ml)															
0	12.3	12.6	13.7	11.5	9.7	9.2	9.6	9.9	11.6	11.4	11.4	11.7	8.8	4.0	1.5

TABLE 2b

Non-sustained Release Ibuprofen 200 mg Tablets ; Average Plasma Concentration Level of Ibuprofen (µg/ml) for dosing at 0, 4 and 8 hours in twelve subjects. Average AUC equaled 180 µg/h.

	TIME (Hours) Post Dosing														
0	1.0	1.5	2.0	3.0	4.0	5.0	5.5	6.0	8.0	9.0	9.5	10	12	16	24
Average (µg/ml)															
0	19.1	15.4	12.5	8.5	6.0	13.0	14.9	14.7	9.9	11.8	14.9	14.6	9.9	3.1	0.3

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Example II — Ibuprofen Sustained Release Bi-layer Tablet containing a Total of 800 mg Ibuprofen

This example illustrates a bi-layer tablet which is analogous to the tablet described in Example I, except all amounts of ingredients per tablet and final weight of the tablet are 4/3 times the amounts and final weight of Example I. The working directions for the immediate release layer and the sustained release layer are analogous to the working directions described in Example I. Tablets can be compressed using capsule, oval, round or other appropriately shaped tooling. The sustained release layer has a target weight of 697.8 mg and the immediate release layer has a target weight of 333.8 mg.

Ingredient	mg/Tablet
A. Immediate Release Layer	
Part I Active and Excipients	
ibuprofen USP	23.3
microcrystalline cellulose NF (Avicel® PH 101)	42.7
starch NF	42.7
pregelatinized starch NF (Starch® 1500)	21.3
sodium starch glycolate NF (Explotab®)	8.5
Part II Granulating Agent	
hydroxypropyl methylcellulose 2910 USP	2.1
purified water USP	
Part III Excipients	
sodium starch glycolate NF (Explotab®)	2.1
colloidal silicon dioxide NF	1.1

B. Sustained Release Layer

Part I Active and Excipients		
ibuprofen USP		586.7
ethylcellulose NF (Ethocel® N-10)		9.7
microcrystalline cellulose NF (Avicel® PH 101)		29.3
pregelatinized starch NF (Starch® 1500)		18.7
Part II Granulating Agent		
povidone USP (Plasdone® K 29/32)		19.6
alcohol USP (ethanol) purified water USP	1:1 mixture	q.s.
Part III Excipients		
pregelatinized starch NF (Starch® 1500)		10.7
microcrystalline cellulose NF (Avicel® PH 101)		9.7
magnesium stearate NF		6.7
colloidal silicon dioxide NF (Cab-O-Sil®)		6.7
	Total	697.8
	Total Tablet Weight	1031.6

Example III — Ibuprofen Sustained Release Tablet containing 600 mg of Ibuprofen in Matrix Form

This example illustrates a mono-layer (all matrix) tablet in which there is only a sustained release layer. The working directions are analogous to the working directions for the sustained release layer described in Example I except that the amounts of all ingredients are proportionally increased such that the final tablet contains 600 mg ibuprofen. Tablets can be compressed using capsule, oval, round or other appropriately shaped tooling. The final target weight of the compressed tablet is 713.6 mg.

Ingredient	Mg/tablet
Part I Active and Excipients	
ibuprofen USP	600
ethylcellulose NF (Ethocel® N-10)0	10
microcrystalline cellulose NF (Avicel® PH 101)	30
pregelatinized starch NF (Starch® 1500)	19.1
Part II Granulating Agent	
povidone USP (Plasdone® K 29/32)	20
ethanol USP	
purified water USP	
Part III Excipients	
pregelatinized starch NF (Starch® 1500)	10.9
microcrystalline cellulose NF (Avicel® PH 101) 1:1 mixture	10
magnesium stearate NF	6.8
colloidal silicon dioxide NF (Cab-O-Sil®)	6.8
Total Tablet Weight	713.6

Example IV — Ibuprofen Sustained Releaae Tablet containing 800 mg of Ibuprofen in Matrix Form

This example illustrates a mono-layer (all matrix) tablet in which there is only a sustained release layer. The working which there is only a sustained release layer. The working directions are analogous to the working directions for the sustained release layer described in Example I except that the amounts of all ingredients are proportionally increased such that the final tablet contains 800 mg ibuprofen. Tablets can be compressed using capsule, oval, round or other appropriately shaped tooling. The total tablet weight of the compressed tablet is 951.5 mg.

Ingredient		mg/tablet
Part I Active and Excipients		
ibuprofen USP		800
ethylcellulose NF (Ethocel® N-10)		13.3
microcrystalline cellulose NF (Avicel® PH 101)		40
pregelatinized starch NF (Starch® 1500)		25.5
Part II Granulating Agent		
povidone USP (Plasdone® K 29/32)		26.7
alcohol USP)	1:1 mixture	q.s.
purified water USP)		
Part III Excipients		
pregelatinized starch NF (Starch® 1500)		14.5
microcrystalline cellulose NF (Avicel® PH 101)		13.3
magnesium stearate NF		9.1
colloidal silicon dioxide NF (Cab-O-Sil®)		9.1
	Total tablet weight	951.5

Claims

1. The process of preparing an ibuprofen-sustained release shaped and compressed tablet characterized by a long-lasting slow and relatively regular incremental release of the ibuprofen upon administration comprising the following steps :

A) forming a granulating agent by dissolving 5-30 parts by weight povidone in alcohol or an alcohol-water mixture ;

B) blending together the following ingredients in dry powder form ;

* C L M S *

Ingredient			mg/tablet
Part I Active and Excipients			
ibuprofen USP			800
ethylcellulose NF (Ethocel® N-10)			13.3
microcrystalline cellulose NF (Avicel® PH 101)			40
pregelatinized starch NF (Starch® 1500)			25.5
Part II Granulating Agent			
povidone USP			26.7
alcohol USP	)	1:1 mixture	q.s.
purified water USP	)		
Part III Excipients			
pregelatinized starch NF (Starch® 1500)			14.5
microcrystalline cellulose NF (Avicel® PH 101)			13.3
magnesium stearate NF			9.1
colloidal silicon dioxide NF (Cab-O-Sil®)			9.1
		Total tablet weight	951.5

Claims

1. The process of preparing an ibuprofen-sustained release shaped and compressed tablet characterized by a long-lasting slow and relatively regular incremental release of the ibuprofen upon administration comprising the following steps :

A) forming a granulating agent by dissolving 5-30 parts by weight povidone in alcohol or an alcohol-water mixture ;

B) blending together the following ingredients in dry powder form ;

* C L M S *

Ingredient	Parts by Weight
ibuprofen	440
ethylcellulose	3-12
wicking agent	10-35
erosion promoter	5-25

C) adding the granulating agent from step A to the blended powders from step B, and mixing in a high shear granulator to form a wet granulation ;
D) drying the wet granulation of step C ;
E) milling the dried granulation from step D ;
F) thoroughly blending the milled dried granulation from step E with the following ingredients in dry powder form ;

Ingredient	Parts by Weight
erosion promoter	1-20
wicking agent	3-20
lubricant	0-10
glidant	2-10

G) compressing the final granulation from step F into a tablet or tablet layer.

2. The process of claim 1 wherein :
in step A the alcohol used in alcohol USP or dehydrated alcohol USP or methyl alcohol USP or isopropyl alcohol USP ;
in step B the wicking agent used in microcrystalline cellulose or powdered cellulose and the erosion promoter used is pregelatinized starch or starch NF or rice starch ;
in step F the erosion promoter used is 3-20 parts by weight of either pregelatinized starch or starch NF or rice starch or is 1-15 Parts by weight of sodium starch glycolate or croscarmellose sodium or crospovidone; the lubricant used in magnesium stearate or stearic acid, and, the glidant used is colloidal silicon dioxide or fumed silicon dioxide.

3. The process of claim 2 wherein :
in step A the alcohol is alcohol USP ;
in step B the wicking agent used is microcrystalline cellulose, the erosion promoter used is pregelatinized starch ; in step F the erosion promoter used is pregelatinized starch ; in step F the erosion promoter used is pregelatinized starch ; the lubricant used is magnesium stereate ; and the glidant used is colloidal silicon dioxide.

4. The process of claim 3 wherein the specific ingredients and amounts used are :

* C L M S *

Step A	Ingredient	Parts by Weight
A	alcohol-water (1:1)	q.s.
	povidone	14.7
B	ibuprofen	440.0
	ethylcellulose	7.3
	microcrystalline cellulose	22
	pregelatinized starch	14
F	pregelatinized starch	8
	microcrystalline cellulose	7.3
	magnesium stearate	5
	colloidal silicon dioxide	5

5. The process of claim 4 wherein the parts by weight shown refer to milligrams per tablet.

6. A shaped and compressed sustained release therapeutic composition comprising ibuprofen as the therapeutically-active medicament and granulating agent and excipients combined into a matrix, characterized by a long-lasting slow and relatively regular incremental release of the ibuprofen medicament upon administration, wherein the granulating agent and excipients includes a combination of two polymers, ethylcellulose and povidone, and wherein the total amount of granulating agent and excipients is less than 20 percent of the weight of said shaped and compressed composition.

7. A shaped and compressed ibuprofen sustained release tablet obtainable by wet granulating the active & excipients ingredients of part I with the granulating agent of part II, drying and milling the resultant granulations, and then blending with the excipients of part III and compressing into a tablet, wherein the ingredients of parts I, II and III comprise the following :

* C L M S *

	Ingredient	Parts by Weight Range Tablet
Part I	Active & Excipients	
	ibuprofen	440
	ethyl cellulose	3-12
	microcrystalline cellulose	10-35
	pregelatinized starch	5-25
Part II	Granulating Agent	
	povidone	5-30
	alcohol or alcohol-water	
Part III	Excipients	
	pregelatinized starch	3-20
	microcrystalline cellulose	2-10
	magnesium stearate	2-10
	colloidal silicon dioxide	2-10

8. The tablet of claim 7 wherein the parts by weight refer to milligrams per tablet, and wherein the ingredients are present either in the weights indicated or in such weights multiplied by an appropriate fraction.

Patentansprüche

1. Verfahren zur Herstellung einer geformten und komprimierten Ibuprofen-Tablette mit verzögerter Freisetzung, gekennzeichnet durch eine lang andauernde, langsame und relativ regelmäßig zunehmende Freisetzung des Ibuprofens nach der Verabreichung, mit folgenden Stufen :

A) Herstellen eines Granuliermittels durch Auflösen von 5 bis 30 Gewichtsteilen Povidon in Alkohol oder einem Alkohol-Wasser-Gemisch ;

B) Vermischen der folgenden Bestandteile in trockener Pulverform :

Bestandteile	Gewichtsteile
Ibuprofen	440
Ethylcellulose	3-12
Dochtmittel	10-35
Erosionspromotor	5-25

C) Zugeben des Granuliermittels aus Stufe A) zu den vermischten Pulvern aus Stufe B) und Vermischen in einem Granulator mit hoher Scherung zur Herstellung eines nassen Granulats ;

D) Trocknen des nassen Granulats aus Stufe C) ;

E) Mahlen des getrockneten Granulats aus Stufe D) ;

F) Eingehendes Vermischen des gemahlenen getrockneten Granulats aus Stufe E) mit den folgenden Bestandteilen in trockener Pulverform :

Bestandteile	Gewichtsteile
Erosionspromotor	1-20
Dochtmittel	3-20
Schmiermittel	0-10
Gleitmittel	2-10

G) Komprimieren des Endgranulats aus Stufe F) zu einer Tablette oder einer Tablettenschicht.

2. Verfahren nach Anspruch 1, in dem
in Stufe A) der verwendete Alkohol Alkohol USP (USA-Pharmakopoe) oder wasserfreier Alkohol USP oder Methylalkohol USP oder Isopropylalkiohol USP ist;
in Stufe B) das verwendete Dochtmittel mikrokristalline Cellulose oder Cellulose-Pulver ist und der verwendete Erosionspromotor vorgelatinisierte Stärke oder Stärke NF (National Pharmakopoe) oder Reisstärke ist;
in Stufe F) der verwendete Erosionspromotor 3 bis 20 Gewichtsteile von entweder vorgelatinisierter Stärke oder Stärke NF oder Reisstärke oder 1 bis 15 Gewichtsteile Natrium-Stärkeglykolat oder Natrium-Croscarmellose oder Crospovidon ist, das verwendete Schmiermittel Magnesiumstearat oder Stearinsäure ist und das verwendete Gleitmittel Siliciumdioxid oder kolloidales pyrogenes (fumed) Siliciumdioxid ist.

3. Verfahren nach Anspruch 2, in dem
in Stufe A) der verwendete Alkohol Alkohol USP ist;
in Stufe B) das verwendete Dochtmittel mikrokristalline Cellulose ist, der verwendete Erosionspromotor vorgelatinisierte Stärke ist;
in Stufe F) der verwendete Erosionspromotor vorgelatinisierte Stärke ist;
in Stufe F) der verwendete Erosionspromotor vorgelatinisierte Stärke ist, das verwendete Schmiermittel Magnesiumstearat und das verwendete Gleitmittel kolloidales Siliciumdioxid ist.

4. Verfahren nach Anspruch 3, in dem die verwendeten spezifischen Bestandteile und Mengen folgende sind:

Stufe	Bestandteile	Gewichtsteile
A	Alkohol-Wasser (1:1)	ausreichend
	Povidon	14.7
B	Ibuprofen	440.0
	Ethylcellulose	7.3
	mikrokristalline Cellulose	22
	vorgelatinisierte Stärke	14
F	vorgelatinisierte Stärke	8
	mikrokristalline Cellulose	7.3
	Magnesiumstearat	5
	kolloidales Siliciumdioxid	5

5. Verfahren nach Anspruch 4, in dem sich die angegebenen Gewichtsteile auf mg je Tablette beziehen.

6. Geformte und komprimierte therapeutische Zusammensetzung mit verzögerter Freisetzung, die Ibuprofen als therapeutisches wirksames Medikament, ein Granuliermittel und Hilfsstoffe enthält, die zu einer Matrix kombiniert sind, gekennzeichnet durch eine lang andauernde, langsame und relativ regelmäßig zunehmende Freisetzung des Ibuprofen-Medikaments nach der Verabreichung, wobei das Granuliermittel und die Hilfsstoffe eine Kombination von zwei Polymeren, Ethylcellulose und Povidon einschließen und die Gesamtmenge an Granuliermittel und Hilfsstoffen geringer als 20 % des Gewichts der geformten und komprimierten Zusammensetzung ist.

7. Geformte und komprimierte Ibuprofen-Tablette mit verzögerter Freisetzung, erhältlich durch nasses Gra-

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nulieren des Wirkstoffs und der Hilfsstoff-Bestandteile des Teils I mit dem Granuliermittel des Teils II, Trocknen und Mahlen der entstandenen Granulate und dann Vermischen mit den Hilfsstoffen des Teils III und Komprimieren zu einer Tablette, wobei die Bestandteile der Teile I, II und III wie folgt sind :

	Bestandteile	Gewichtsteilbereich je Tablette
Teil I:	Wirkstoff & Hilfsstoffe	
	Ibuprofen	440
	Ethylcellulose	3 - 12
	mikrokristalline Cellulose	10 - 35
	vorgelatinisierte Stärke	5 - 25
Teil II:	Granuliermittel	
	Povidon	5 - 30
	Alkohol oder Alkohol-Wasser	
Teil III:	Hilfsstoffe	
	vorgelatinisierte Stärke	3 - 20
	mikrokristalline Cellulose	2 - 10
	Magnesiumstearat	2 - 10
	kolloidales Siliciumdioxid	2 - 10

8. Tablette nach Anspruch 7, in der sich die Gewichtsteile auf mg je Tablette beziehen und in der die Hilfsstoffe entweder in den angegebenen Gewichtsmengen oder in diesen mit einer entsprechenden Bruchzahl multiplizierten Gewichtsmengen vorhanden sind.

Revendications

1. Procédé de préparation d'un comprimé formé et compressé d'ibuprofène retard, caractérisé par une libération lente et prolongée, progressive et relativement régulière, de l'ibuprofène lors de l'administration, comprenant les étapes suivantes :

A) former un agent de granulation en dissolvant 5-30 parties en poids de povidone dans un alcool ou un mélange d'alcool et d'eau ;

B) mélanger ensemble les ingrédients suivants, sous forme pulvérulente sèche :

Ingrédient	Parties en poids
Ibuprofène	440
Ethylcellulose	3-12
Agent à effet de mèche	10-35
Promoteur d'érosion	5-25

C) ajouter l'agent de granulation de l'étape A aux poudres mélangées de l'étape B et mélanger dans un granulateur à fort cisaillement pour former une granulation humide ;

D) sécher la granulation humide de l'étape C ;

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E) broyer la granulation séchée de l'étape D ;
F) mélanger intimement la granulation séchée et broyée de l'étape E avec les ingrédients suivants sous forme pulvérulente sèche ;

Ingrédient	Parties en poids
Promoteur d'érosion	1-20
Agent à effet de mèche	3-20
Lubrifiant	0-10
Agent de glissement	2-10

G) compresser la granulation finale de l'étape F en un comprimé ou une couche de comprimé.

2. Procédé selon la revendication 1, dans lequel :
dans l'étape A, l'alcool utilisé est un alcool USP ou un alcool déshydraté USP ou l'alcool méthylique USP ou l'alcool isopropylique USP ;
dans l'étape B, l'agent à effet de mèche utilisé est de la cellulose microcristalline ou de la cellulose pulvérulente et le promoteur d'érosion utilisé est de l'amidon prégélatinisé ou de l'amidon NF ou de l'amidon de riz ;
dans l'étape F, le promoteur d'érosion utilisé est 3-20 parties en poids d'amidon prégélatinisé ou d'amidon NF ou d'amidon de riz, ou est 1-15 parties en poids de glycolate d'amidon sodique ou de croscarmellose sodique ou de crospovidone ; le lubrifiant utilisé est le stéarate de magnésium ou l'acide stéarique ; et l'agent de glissement utilisé est le dioxyde de silicium colloïdal ou le dioxyde de silicium fumé.

3. Procédé selon la revendication 2, dans lequel :
dans l'étape A, l'alcool utilisé est un alcool USP ;
dans l'étape B, l'agent à effet de mèche utilisé est la cellulose microcristalline, le promoteur d'érosion utilisé est l'amidon prégélatinisé ; dans l'étape F, le promoteur d'érosion utilisé est l'amidon prégélatinisé, le lubrifiant utilisé est le stéarate de magnésium et l'agent de glissement utilisé est le dioxyde de silicium colloïdal.

4. Procédé selon la revendication 3, dans lequel les ingrédients et les quantités spécifiques utilisés sont :

Etape	Ingrédient	Parties en poids
A	Alcool-eau (1:1)	q.s.
	Povidone	14,7
B	Ibuprofène	440,0
	Ethylcellulose	7,3
	Cellulose microcristalline	22
	Amidon prégélatinisé	14
F	Amidon prégélatinisé	8
	Cellulose microcristalline	7,3
	Stéarate de magnésium	5
	Dioxyde de silicium colloïdal	5

5. Procédé selon la revendication 4, dans lequel les parties en poids indiquées sont exprimées en milligrammes par comprimé.

6. Composition thérapeutique retard formée et compressée comprenant de l'ibuprofène comme médicament thérapeutiquement actif et un agent de granulation et des excipients combinés en une matrice, caractérisée par une libération lente et prolongée, progressive et relativement régulière, du médicament ibuprofène lors de l'administration, dans laquelle l'agent de granulation et les excipients renferment une combinaison de deux polymères, l'éthylcellulose et la povidone, et dans laquelle la quantité totale d'agent de granulation et d'excipients est inférieure à 20% du poids de ladite composition formée et compressée.

7. Comprimé d'ibuprofène retard formé et compressé pouvant être obtenu par granulation humide de la substance active et des excipients de la partie I avec l'agent de granulation de la partie II, séchage et broyage

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des granulations résultantes, puis mélange avec les excipients de la partie III et compression en un comprimé, dans lequel les ingrédients des parties I, II et III comprennent les suivants :

	Ingrédients	Parties en poids par comprimé
Partie I	Substance active et excipients	
	Ibuprofène	440
	Ethylcellulose	3 - 12
	Cellulose microcristalline	10 - 35
	Amidon prégélatinisé	5 - 25
Partie II	Agent de granulation	
	Povidone	5 - 30
	Alcool ou alcool-eau	
Partie III	Excipients	
	Amidon prégélatinisé	3 - 20
	Cellulose microcristalline	2 - 10
	Stéarate de magnésium	2 - 10
	Dioxyde de silicium colloïdal	2 - 10

8. Comprimé selon la revendication 7, dans lequel les parties en poids sont exprimées en milligrammes par comprimé, et dans lequel les ingrédients sont présents dans les poids indiqués ou dans des poids multiples appropriés.

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