REC'D
RTMPLS COPY
THIS SHEET HAS BEEN REPLACED

PROCESS FOR THE PREPARATION OF MICROGRANULES SUITABLE FOR SUSPENSION AFTER COATING IN PHARMACEUTICAL LIQUID COMPOSITIONS

FIELD OF THE INVENTION

This invention involves a granulation process to obtain microgranules for use in pharmaceutical compositions. Said microgranules have a limited size distribution and morphological characteristics that ensure both uniform coating and easy suspension after coating, even in low-density aqueous vehicles.

BACKGROUND OF THE INVENTION

The technology to produce granulates from powder mixtures has long been known in pharmaceutics. For purposes of administration, these granulates are usually converted into tablets, enclosed in capsules or in sachets.

It has also been long known that granules or tablets can be coated with films, which can serve to delay the release of the active ingredient they contain, disguise an unpleasant taste, and/or improve the stability of the composition.

A major limitation of the use of such coated granulates in liquid formulations is that it has been difficult to obtain particles of an appropriate size to enable them to be easily suspended and kept in suspension in the fluid vehicle.

Particles of a size larger than about 500 µm tend to settle rapidly, resulting in a non-homogeneous distribution of the product within the vehicle. It is instead essential that the suspension remain homogeneous, after a slight stirring, for the time required to

This Sheet Has Been Replaced

guarantee a consistent administration. It is also preferable to avoid the unpleasant sensation that one may have when ingesting a suspension containing a coarse solid particulate (sand effect).

These requirements may generally be fulfilled by reducing the size of the microgranules to be suspended so that they do not exceed 500 µm. However, the commonly known technologies described below can not be readily applied to obtain final granules of this size range.

One of the most commonly used technologies involves depositing the active ingredient on inert spherical-shaped particles called "cores", which are available on the market in different sizes but which are unlikely to result in microgranules of a diameter smaller than 500 µm.

After sequential deposition on an inert core of the active ingredient, the binder and the subsequent polymer coatings, the final granule size is unlikely to be smaller than 800-1000 µm. Even using 250 µm (60 mesh) saccharose crystals as inert cores, the quantity of material to be deposited is such that final particles of sizes smaller than 500-800 µm are difficult, if not impossible, to obtain. The final granulate forms resulting from this process are therefore totally unsuitable for inclusion in liquid dosage.

The known coating techniques for crystals or granulates which are generally meant to disguise the taste of the active ingredient, to control release, or to give stability to the product, can in theory be applied to particles smaller than 500 µm. Generally, however, they require specific processes such as microencapsulation by

coacervation or interface polymerization.

Specific disadvanages of these methods are: the huge quantity of solvents used, the inherent cost of solvent recovery and the more complex production technology.

Although film-coating can be used to coat crystalline particles of a size smaller than 300 µm, an important requirement is that the particles be as much as possible identical one to the other in size and shape.

During the filming process, very small particles tend to adhere to one another, forming agglomerates that would adversely affect the consistency and reproducibility of the active ingredient release profile.

Furthermore, the problems caused by agglomeration tend to become worse as treated product volumes increase. In addition, it is difficult to ensure consistent coating characteristics, as the very dispersed particle-size distribution and the non-homogeneous particle shapes cause very variable surface areas. This leads to a correspondingly variable quantity of deposited coating per unit surface area, leading ultimately to a non-homogeneous release of the active ingredient.

The crystalline form and the density of the material being processed are important factors in the coating of crystals. Needle-shaped crystals can be coated with extreme difficulty, using special precautions; inevitably, resulting coating is distributed in a non-homogeneous way on the core surface and is thinner at the crystal edges. Cuboidal crystals are easier to coat, but also present

problems related to the presence of edges. In addition, it is necessary for the density of the crystals to be such that the above-mentioned agglomeration and adhesion problems can be avoided.

Since crystal shape and density are characteristic of the crystalline form itself, it is evident that such properties cannot be readily modulated to suit the requirements of the filming process.

The choice of the equipment also has a significant influence on the microgranulate preparation and characteristics. The equipment generally used includes: fluid-bed granulators, conventional mixers, spheroidal-shaping extruders and fast mixers.

In a fluid-bed apparatus the powder is kept in suspension by an appropriate air flow, while the granulation fluid is simultaneously sprayed. The resulting product has an even shape, but is very porous and has a low density. The granulate is therefore unsuitable for subsequent coating, as it is inclined to break with a change in surface area and does not exhibit a uniform film/surface unit ratio. Furthermore, the material to be subjected to a fluid-bed coating process must be made up of particles of sufficient density to avoid the agglomeration phenomenon described. Otherwise, the particles tend to occupy the upper section of the apparatus, are not subject to the normal movement inside the apparatus, and thus do not receive an appropriate gradual coating.

A conventional mixer-granulator consists of a vessel, which may be of varying shape, equipped with an agitator that keeps the powder

moving while the granulation fluid is being added. The motion is slow and the resulting granulate, even though suitable for making conventional dosage forms such as tablets or capsules, does not exhibit the density, shape and particle-size distribution suitable for subsequent coating.

Unlike conventional mixer-granulators, extruder-spheronizers can produce spherical particles of homogeneous sizes and even shapes and surfaces. The limitation that prevents their application to microgranulates suitable for liquid suspensions is the average product size, which is rarely smaller than 1-2 mm and in any case never smaller than 500 μm.

A high-shear mixer-granulator is made up of a vessel in which the mixture to be granulated is introduced that is equipped with a mixer and a mill that rotate with a normal mixer motion. Since the mixer and the mill have variable and adjustable speeds, they ensure densification and preparation of the granulate in shorter times as compared to conventional granulates.

It has now been found that, using high-shears mixer-granulators and operating within specific critical ranges of the parameters that control the granulation process, it is possible to obtain a microgranulate of a size smaller than 500 μm possessing critical chemical-physical characteristics, which make them particularly suitable for coating and for suspension in low density fluids.

More particularly, the Applicant has unexpectedly found the critical rages of size distribution, density, surface and shape of the particles produced that makes them particularly suitable for coating

and for suspension in low density fluids.

SUMMARY OF THE INVENTION

Object of the invention is a process for the preparation of microgranules containing at least one active ingredient mixed with pharmaceutically acceptable excipients, suitable for suspension after coating in pharmaceutical liquid compositions.

Operating with high-shear mixer-granulators within clearly established crucial parameter ranges, this process permits to obtain microgranules having a particle size distribution, a density, a surface and a shape which make them particularly suitable for uniform coating such as controlled-release coatings and a subsequent suspension in pharmaceutical liquid compositions.

The present microgranules can be easily coated with common coating methods, such as film-coating, giving rise to coated particles with a size smaller than 500 μm.

DETAILED DESCRIPTION OF THE INVENTION

The microgranulate preparation process can be summarized as follows:

- mixing the active ingredient with pharmaceutically acceptable excipients, the active ingredient and the excipients being generally in the form of powders, inside a high-shear mixer-granulator equipped with a mixer and a mill,
- wetting the mixture with a binding fluid at a set flow rate, note, preferably by atomizing so as to ensure a more homogeneous dispersion of the granulation fluid while the product is subject to the combined actions of the mixer and the mill.

- kneading for a fixed time after wetting, by the combined mixer and mill actions,
- drying to a residual humidity of 1-10%, preferably 5-8%, and
- sieving for selection of the required particle size.

Important process parameters that affect the finished product characteristics include: quantity of granulation fluid, fluid addition rate, kneading time, atomizing pressure, and mixer and mill rotating speeds during wetting and kneading.

Specific combinations and acceptable and preferred ranges of these parameters as described below are also objects of this invention and result in a product that has the required size and the most suitable characteristics for a subsequent coating process.

Table 1 shows the maximum range for each parameter within which it is possible to obtain the required product (column I) and the preferred range which produces an optimum quality product (column II):

TABLE 1

Process parameters	I	II
Fluid (g/Kg of product)	80 - 180	100 - 150
Spray rate (g/min)	10 - 40	20 - 30
Kneading time (min)	5 - 15	8 - 12
Spray pressure (bars)	1.5 - 2.5	2
Mixer speed (rpm)	50 - 600	175 - 350
Mill speed (rpm)	1500 - 4000	2000 - 4000

The active ingredients suitable for formulation into microgranules include any solid pharmaceutical substance suitable for oral administration. Nonlimiting examples include:

- analgesics: such as acetaminophen, phenacetin, sodium salicilate;
- antitussive: such as dextromethorphan, pholcodine, isoaminile, codeine phosphate, moguisteine;
- bronchodilators: such as diprophylline, albuterol, procaterol;
- antipsychotics: such as droperidol, haloperidol, oxypertine, perycyazine, chlorpromazine;
- selective 2 agonists: such as salbutamol, orciprenaline sulphate, pirbuterol, terbutaline, ephedrine, tolbuterol;
- calcium channel blockers: such as nifedipine, nicardipine, diltiazem, verapamil, lercanidipine;
- antiparkinson drugs: such as benzhexol, biperiden, norphenadrine, procyclidine, pergolide;
- NSAIDs: such as aspirin, ketoprofen, indomethacin, ibuprofen,

diclofenac sodium, piroxicam, naproxen, ketorolac;

- antihistaminics: such as brompheniranine, cholrpheniramine, cyproheptadine, pheniramine, mebhydrolin, trimeprazine, triprolidine, acrivastine, terfenadine, clemastine, dimethindene;

- nausea and vomiting treatment drugs: such as prochlorperazine, domperidone, cyclizine, ondansetron, triethyl perazine;

- antidiarrhoeal drugs: such as loperamide, sulphasalazine;

- anxiolytics: such as chlordiazepoxide, oxazepam, medazepam, alprazolam, clonazepam, lorazepam;

- oral antidiabetic drugs: such as gliquidone, glicazide;

- opioid analgesics: such as dextromoramide, morphine, dihydrocodeine, methadone, dipipanone, phenozacine;

- motility stimulants: such as cisapride;

- diuretics: such as bumetanide, bendrofluazide, hydrochlorotiazide, meftuside, merthylclothiazide, xipamide, furosemide, ethacrynic acid;

- nitrates: such as isosorbide dinitrate;

- β-blockers: such as propanolol;

- antispasmodics: such as hyoscine butylbromide, poldine methylsulphate, dicyclomine, pipenzolate, propanthelin, flavoxate, terflavoxate;

- peripheral vasodilators: such as cinnarizine, thymoxamine;

- lipid lowering drugs: such as fenofibrate;

- antidepressants: such as protriptyline, iprindole, trazodone, clomipramine, fluexetine, citalopram, amitryptiline;

- anti-diarrhoeal drugs: such as sulphasalazine;
- laxatives: such as bisacodyl, danthron;
- 4-quinolones: such as nalidixic acid;
- vitamins: such as pyridoxine;
- antiasthmatic drugs: such as teophylline, aminophylline;
- antiepilectic drugs: such as valproate, carbamazepine, phenytoin;

and their pharmaceutically acceptable salts.

The materials (other than the pharmaceutical itself) that can be used in making the base granulate are any of those commonly used in pharmaceutics and should be chosen on the basis of compatibility with the active ingredient. For instance, the excipient or excipients used can be chosen from those commonly used in a wet mixture, that is:

- lubricants such as: talc or magnesium stearate;
- binders such as: polyvinylpyrrolidone, polyvinylpyrrolidone /vinyl acetate copolymer or cellulose derivatives such as for instance methyl cellulose, carboxymethyl cellulose and the like;
- fillers such as: dibasic calcium phosphate, lactose, microcrystalline cellulose, starch, sugar, glucose or high molecular weight hydrogenated vegetable oils.

The choice of the excipients to be used in combination with a given active ingredient should take into account the physico-chemical properties of the active ingredient; this is particularly important when the active ingredient comprises more than 60% of the total weight of the granulate.

As a nonlimiting example, with a highly soluble active ingredient it

is necessary to use excipients that are insoluble, swell or have hydrophobic characteristics. This limits the diffusion of the active ingredient from the microgranular core, and obviates the need to apply excessive film quantities in order to control release. In this case, the choice of the excipients may be confined to calcium phosphate, hydrogenated vegetable oil, starch and cellulose derivatives.

On the other hand, with poorly soluble active ingredient it is important to aid dissolution and avoid a situation in which the granulate core itself interferes with the function of the coating to modulate release. To this end, highly soluble excipients such as sucrose can be useful.

The choice of the binder (e.g., polyvinylpyrrolidone, polyvinylpyrrolidone / vinylacetate or any mixtures thereof) depends on the required friability of the finished granule. If the friability is too high, the granules may break during coating, causing a change in the surface area values and a consequent change in the ratio between applied film and surface unit.

The mixing fluid can be water or organic solvents such as, for instance, ethyl alcohol or other commonly used solvents, or mixtures of water and solvents.

To determine that a suitable granulate has been obtained, the following characteristics of the granulated product are monitored:

Particle Size Distribution

Particle size distribution is determined by sieving (Advances in

Pharmaceutical Sciences; Vol. 2, page 95-174, 1967; Acad. Press Ed. - New York). The granulate is placed over a set of sieves with meshes of decreasing size placed one over the other and subjected to vibration for the time necessary to obtain a constant result for the distribution values. For example, in most of cases, 5 to 10 minutes are sufficient. At the end of the procedure, the quantity of granules left in each sieve is determined by weight.

By plotting the logarithm of the average mesh against the percent frequency of the oversize cumulative weight, a line is obtained that represents the particle size distribution. From this plot, using standard statistical techniques, it is possible to obtain the value of:

1) The Mean Geometric Diameter (d_g), which is the diameter corresponding to 50% of the sieved particles; and

2) The Geometric Standard Deviation (δ_g) which is the measure of how much the granule size deviates from d_g and is the ratio between the diameter corresponding to 15.87% of the particles and d_g.

Acceptable values are obtained when more than 85% of the granules have a size between 90 and 300 μm. The preferred range is 125-300 μm.

Density

The following density measures were evaluated for granulate characterization (Advances in Pharmaceutical Sciences; Vol. 2, pages 181-220, 1967; Acad. Press Ed. - New York):

1) Aerated Density is the ratio between the powder mass and

the volume of the bed poured into a graduated container.

2) Packed Density is the ratio between the powder mass and the volume filled by the powder bed after a standard number of vibrations and followed by settling.

3) Apparent Density is the ratio between the powder mass and volume filled by the powder mass excluding superficial porosities. This value is determined by calculating the difference between the volume filled by a solvent in an empty graduated vessel and the volume of solvent displaced by the sample introduced into the same vessel. The ratio between the sample mass and the difference between the volumes is the apparent density value. This parameter is relevant to a determination of surface area. See, infra.

Carr Index (Compressibility Percentage)

This index is an indirect measure of the granulate flowability. It is determined by the ratio:

packed density - aerated density / packed density * 100

(Pharmaceutical Preformulation; pages 209-214, 1988; Ellis Horwood Ed. - Chichester, England). The relationship between the Carr Index and flowability is given in Table 2. The flowability grading follows selection criteria that are stricter than those normally adopted for granulate evaluation, precisely in consideration of the particular requirements of the product obtained by the invention.

TABLE 2

Compressibility %	Flowability
5-10	Good
11-15	Adequate
16-21	Inadequate

Angle of repose

Together with microscopic observation, the angle of repose provides information on the product shape. The powder is dropped from a standard funnel onto a surface, forming a cone, and the base angle of the cone is measured. The smaller the cone base angle, the more even the shape of the particle (Pharmaceutical Preformulation; pages 209-214, 1988; Eliis Horwood Ed. - Chichester, England)

The relationship between angle of repose and flowability is given in Table 3.

TABLE 3

Angle (degrees)	Flowability
< 25	Excellent
25 - 30	Good
30 - 40	Acceptable
> 40	Poor

Parametric Filming-Suitability Characteristics

The average values and the preferred values within which a microgranulate may be defined as suitable for a subsequent coating process are described in Table 4:

TABLE 4

Characteristics	Average	Preferred
Mean geom. diameter (d_g)(µm)	120 - 200	130 - 170
Standard deviation (δ_g)	1.4 - 2.0	1.5 - 1.8
Aerated density (g/ml)	0.4 - 0.7	0.50 - 0.66
Packed density (g/ml)	0.5 - 0.9	0.55 - 0.80
Apparent density (g/ml)	1.2 - 1.5	1.30 - 1.45
Carr index (%)	5 - 15	6 - 12
Angle of repose (°)	20 - 40	26 - 30

The observations of shape and surface made by electron microscopy and stereomicroscopy are also taken into account. A spheroidal shape and a smooth surface free of roughness are directly correlated to granule flowability and are quantified with the above Carr Index and Angle of repose values.

Surface Area (mm^2/g)

If the particles are spherical, the surface area can be calculated according to the formula: $SA = 6 / AD * d_{vs}$.

where AD = apparent density and d_{vs} = geometric diameter volume surface.

d_{vs} is obtained from the values of d_g and δ_g using the formula: $\log d_{vs} = \log d_g - 1.151 \log^2 \delta_g$.

The apparent density is used to calculate SA, since this measure more than any allows for surface porosities, a factor of major interest when considering the actual surface to be coated [Drug Development and Industrial Pharmacy, 14 (4), 573 (1988)].

The coating quantity to be applied per surface unit can be calculated from the SA value. The total surface area to be coated is obtained by multiplying the SA value for the total granulate weight in grams. This allows to maintain constant the amount of coating and the obtained release profile from a preparation to a subsequent one.

There is an inverse proportional relationship between the film amount and the active ingredient dissolution rate. The dissolution rate, however, should be determined case by case, since, for each single active ingredient, it depends on the particular granulate and the type of coating used.

Testing of Suitability for Coating

The suitability of a granule preparation for coating is assessed by sequential deposition on the granules of equal quantities of two different coatings, followed by testing the controlled-release properties of the active ingredients.

According to the present invention, the microgranules to be coated have spheroidal shapes and even surfaces, suitable for coating, comprising a mean geometric diameter of 120-200 μm with a standard deviation of 1.4-2.0; an aerated density of 0.4-0.7 g/ml; a packed density of 0.5-0.9 g/ml; an apparent density of 1.2-1.5 g/ml; a Carr

Index of 5-15% and a angle of repose of 20-40°.

Preferred microgranules are those having the Carr Index, or the angle or repose, or both of them, within the preferred ranges according to Table 4 (Carr Index of 6-12%, an Angle of Repose of 26-30°), and in addition, at least two of the following parameters are within the ranges provided in (a, b, c) below:

(a) mean geometric diameter of 130-170 µm with a standard deviation of 1.5-1.8;

(b) aerated density of 0.50-0.66 g/ml; and

(c) packed density of 0.55-0.80 g/ml or apparent density of 1.30-1.45 g/ml.

Among the preferred microgranules, further preferred are those having both the Carr Index and the angle of repose within the preferred ranges.

The first coating, laid directly on the granule and made up of ethyl cellulose mixed with plasticizers as appropriate, is suitable for controlling the release of the active ingredient and has mostly lipophilic characteristics. The second coating, laid on the first coating and made up of cellulose acetate phthalate mixed with plasticizers, has the function of aiding contact with the dissolution vehicle and has hydrophilic characteristics.

The uncoated microgranules have essentially no controlled release properties. For the purpose of controlling release of the active ingredient, the deposition of the first coating containing ethyl cellulose is fundamental. The quantity of this coating applied to the different granulates should therefore take into account the

intrinsic solubility of the active ingredient. Assuming the granule core sizes being equal, the more soluble the active ingredient, the thicker the coating required for controlling release.

Table 5 compares the quantity of the first coating that needs to be applied to granules having identical shape, size and surface characteristics but containing active ingredients with different characteristics, in order to obtain comparable release profiles.

TABLE 5

	Diprophylline	Acetaminophen	Ibuprofen
Solubility in Water w/v	33%	1.5%	< 0.1%
Quantity 1st Coating w/w	10 - 11%	4 - 5%	2-3%

w/v = product weight/solvent volume

w/w = coating weight/granule weight

The present invention is described further in specific working examples that are intended to describe the invention without limiting its scope.

EXAMPLE 1: Preparation of a Base Granulate Containing an Active Ingredient Very Soluble in Water at Ambient Temperature

Composition	%
Diprophylline	50
Dicalcium Phosphate / Maize starch	5/35
Polyvinylpyrrolidone Vinyl Acetate	10

In a Diosna P25 high-shear mixer-granulator (Dierk & Sohne - Osnabruck - Germany), four 5-Kg preparations (A, B, C, A*) of the above composition were prepared according to the following procedure: mix the powders in a high-shear mixer-granulator, then wet the mixture by atomizing an aqueous solution at steady flow and pressure while the product is subjected to the combined actions of the mixer and mill, until a homogeneous mixture is obtained. Knead for a fixed time, at the end of wetting, still with the combined mixer and mill actions. At the end of kneading the product was dried so as to reach a residual humidity of 5-7%.

In the four preparations some of the process parameters shown in Table 1 were changed, whereas others were kept constant (Diagram 1). The preparation with an asterisk (*) was purpose- fully made outside the parameter ranges considered essential to obtain a granulate suitable for coating.

DIAGRAM 1

Parameter	A	B	C	A*
Water (g/Kg of product)	60	120	100	200
Spray Rate (g/min)	45	25	20	45
Kneading time (min)	3	8	10	20
Spray pressure (bars)	2 (steady)			
Mixer speed wetting/kneading (rpm)	175 (steady)			
Mill speed wetting/kneading (rpm)	2,000 (steady)			

EXAMPLE 2: Preparation of a Base Granulate Containing an Active Ingredient of Average Solubility in Water at Ambient Temperature

Composition	%
Acetaminophen	80.0
Dibasic calcium phosphate dihydrate	10.0
Talc	2.5
Polyvinylpyrrolidone vinyl acetate	7.5

In a Diosna P25 high-shear mixer-granulator, four 3-Kg preparations (D, E, F, D*) of the above composition were prepared according to the procedure described in Example 1.

In the four preparations some of the process parameters shown in Table 1 were changed, whereas others were kept constant (Diagram 2). The preparation with an asterisk (*) was purposefully made outside

the parameter ranges considered essential to obtain a granulate suitable for coating.

DIAGRAM 2

Parameter	D	E	F	D*
Water (g/Kg of Product)	75	120	140	200
Spray rate (g/min)	45	30	25	45
Kneading time (min)	20	15	10	20
Spray pressure (bars)	2 (steady)			
Mixer speed wetting (rpm)	175 (steady)			
Mixer speed kneading (rpm)	350 (steady)			
Mill speed wetting/kneading (rpm)	4,000 (steady)			

EXAMPLE 3: Preparation of a Base Granulate Containing an Active Ingredient Insoluble in Water at Ambient Temperature

Composition	%
Ibuprofen	80
Lactose	10
Polyvinylpyrrolidone	10

In a Diosna P25 high-shear mixer-granulator, four 4-Kg preparations (G, H, I, G*) of the above composition were prepared according to the procedure described in Example 1.

In the four preparations some of the process parameters shown in

Table 1 were changed, whereas others were kept constant (Diagram 3). The preparation with an asterisk (*) was purposefully outside the parameter ranges considered essential to obtain a granulate suitable for coating.

DIAGRAM 3

Parameter	G	H	I	G*
Water (g/Kg of product)	80	150	130	200
Spray rate (g/min)	45	20	25	45
Kneading time (min)	20	15	10	20
Spray pressure (bars)	2 (steady)			
Mixer speed wetting (rpm)	175 (steady)			
Mixer speed kneading (rpm)	350 (steady)			
Mill speed wetting/kneading (rpm)	2,000 (steady)			

EXAMPLE 4: Physical Tests on a Base Granulate

9 Different preparations (A to I) were tested by determining the following parameters:

D.Ae.: Aerated density; D.Pa.: Packed density; D.Ap.: Apparent density; d_g: Mean geometric diameter; δ_g: Geometric standard deviation; R.A.: Angle of repose; C.I.: Carr index; FL.:Flowability ((I) = inadequate, (A) = adequate, (G) = good).

Preparations (A, B, C), containing a very soluble product, were prepared as described in Example 1, preparations (D, E, F), containing a product of medium solubility, and (G, H, I),

containing an insoluble product, were prepared as described in Examples 2 and 3 respectively.

The results are described in Table 6:

TABLE 6

	D.Ae. (g/ml)	D.Pa. (g/ml)	D.Ap. (g/ml)	dg (μm)	δg	R.A.	C.I. %	FL
A	0.571	0.735	1.410	110.2	1.61	42°12'	22	(I)
B	0.542	0.625	1.450	156.7	1.62	29°23'	13	(A)
C	0.584	0.648	1.380	138.0	1.58	28°34'	10	(G)
D	0.598	0.724	1.427	102.5	1.57	38°35'	17	(I)
E	0.596	0.684	1.429	138.7	1.50	29°24'	13	(A)
F	0.628	0.695	1.429	132.0	1.55	27°46'	10	(G)
G	0.513	0.625	1.200	183.0	1.44	38°46'	17	(I)
H	0.513	0.576	1.220	179.2	1.44	35°23'	11	(A)
I	0.536	0.580	1.280	177.7	1.42	30°34'	8	(G)

Also granulates A, D and G present some characteristics which are outside the averages values shown in Table 4. In particular, the Carr Index and the Angle of Repose are indicative of a rather uneven surface. Granulates B, C, E, F, H, I have all the paramenters within the average values of Table 4 and at least two parameters (compulsory including the Carr Index or the Angle of Repose) within the preferred values of Table 4.

Tables 6 does not show the values relative to the asterisk preparations, because the material, which was obtained operating

THIS SHEET HAS BEEN
REPLACED

outside the operating range established by the invention, was always of a rough construction, with 85-90% of the particle size distribution over 350 µm and with a mean diameter of 550 µm. Furthermore, a granule break-up was found in all the asterisk preparations, with a considerable loss of workable material.

EXAMPLE 5: Granulate Coating

In order to test the granulate suitability for filming, the granulates prepared as described in Example 1 were coated, using a Wurster Glatt GPCG3 apparatus, with two successive coatings having the following compositions:

	Composition	%
First coating	Ethyl cellulose	3.0
	Diethyl phthalate	1.0
	Polyethylene glycol 400	0.1
	Chloroform	74.0
	Ethanol	21.9
Second coating	Cellulose acetate phthalat	4.6
	Diethyl phthalate	1.1
	Acetone	70.7
	Isopropanol	23.6

The central partition in the apparatus is set at a height of 8 mm and fitted with a spray nozzle with a 1.2 mm diameter.

The incoming air temperature is set at 45°C and the air flow is set at 50 m^3/hour. The apparatus is switched on when the outgoing air

This Sheet Has Been Replaced

temperature reaches 30°C, the product is then fed and the coating solution is sprayed at a 2 bar pressure and a 20-24 g/min flow rate. At the end the product is allowed to dry in a fluid motion at 45 °C for 5 minutes.

Two coatings are sufficient to test the granulate suitability for filming. Obviously, if necessary, a further series of different coatings may be superimposed on the first two.

EXAMPLE 6: Evaluation of Dissolution Profiles

The dissolution profiles of the granulates coated as described in Example 5 were tested according to the method provided in USP XXII, apparatus 2 (paddle), under the following operating conditions: temperature = 37°C; rotating speed = 50 rpm; dissolution medium 0.1 N HCL for the first hour, then phosphate buffer pH = 7.5 from the 2nd to the 8th hour.

Table 7 shows the release profiles of the coated granulates prepared as described in the preceding examples.

TABLE 7

Hour	% Active Ingredient Released								
	Diprophylline			Acetaminophen			Ibuprofen		
	A	B	C	D	E	F	G	H	I
1	39.6	5.8	4.0	35.4	20.3	21.9	49.0	36.0	14.3
2	66.8	43.7	22.3	67.3	43.6	40.9	68.0	40.2	23.2
4	89.6	73.2	38.7	83.9	64.9	58.5	82.2	50.3	36.2
8	98.0	88.2	59.8	97.6	85.5	74.3	97.4	62.5	54.6

As a granulate acceptance criterion, with respect to suitability for

filming, release of the active ingredient should not exceed a limit of 50% within the first two hours of performance of the dissolution test, but at least 33% should be released within 4 hours.

The release profiles of granulates A, D and G confirmed they are not suitable for filming, as predicted from the relevant Carr Index and Angle of repose values (Table 6). The granulate surface roughness leads to excessive product release during the first two hours of dissolution.

Granulates B, E and H showed adequate flowability, granulates B and E having the Angle of Repose value within the preferred limits (Tables 2, 3, 4, 6) and granulate H having the Carr Index within the preferred limits. Less than 50% of the active ingredient contained in the granules is released in the first two hours.

Granulates C, F and I, which showed Angle of Repose and Carr Index values both within the optimum values, permit a better modulation of the coating quantity based on the required release profile. This is because, thanks to their optimum surface characteristics, permit a more uniform coating.

EXAMPLE 7: Superficial Morphological Characteristics of the Granulate

Figures 1-4 display the surface characteristics of four different microgranulate preparations:

Fig. 1: Microgranules with uneven shapes and surfaces, corresponding to preparation A in Example 1.

(Image taken with a 33 x stereomicroscope.)

THIS SHEET HAS BEEN REPLACED

Fig. 2: Microgranules with even shapes and surfaces, corresponding to preparation C in Example 1.

(Image taken with a 33 x stereomicroscope.)

Fig. 3: Microgranules with spheroidal shapes and uneven surfaces, corresponding to preparation G in Example 3.

(Image taken with a 100 x electron microscope.)

Fig. 4: Microgranules with spheroidal shapes and even surfaces, corresponding to preparation F in Example 2.

(Image taken with a 101 x electron microscope.)

The images in Figures 1-4 completely agree with the considerations reported in Example 4.

This Sheet Has Been Replaced



CLAIMS

1. A process for the preparation of microgranules containing at least one active ingredient mixed with pharmaceutically acceptable excipients, suitable for suspension after coating in pharmaceutical liquid compositions, said microgranules having spheroidal shapes and even surfaces and comprising a mean geometric diameter of 120-200 μm with a standard deviation of 1.4-2.0; an aerated density of 0.4-0.7 g/ml; a packed density of 0.5-0.9 g/ml; an apparent density of 1.2-1.5 g/ml; a Carr Index of 5-15% and an angle of repose of 20-40°, said process being characterized in that it is carried out in a high-shear mixer-granulator equipped with a mixer and a mill, by mixing the active ingredient with appropriate excipients, wetting the mixture with 80 - 180 g binding fluid per kg mixture, said solvent being applied at a spray rate of 10 - 40 / min, and a spray pressure of 1.5 - 2.5 bar, followed by kneading of the mixture with solvent for 5 - 15 minutes using a mixer speed of 50 - 600 rpm and a mill speed of 1500 - 4000 rpm.

2. A process according to Claim 1, wherein the quantity of said binding fluid used for granulation, ranges from 100 to 150 grams, per kilogram of mixture processed.

3. A process according to Claim 1, wherein said spray rate at which said binding fluid is added to said mixture ranges from 20 to 30 g per minute.

4. A process according to Claim 1, wherein said spray pressure at which said binding fluid is sprayed onto said mixture is 2 bars.

* C L M S *

5. A process according to Claim 1, wherein the kneading time used for granulation ranges from 8 to 12 minutes.

6. A process according to Claim 1, wherein the mixer rotating speed is 175 - 350 rpm and the mill rotating speed is 2000-4000 rpm.

7. Microgranules containing at least one active ingredient mixed with pharmaceutically acceptable excipients suitable for suspension after coating in pharmaceutical liquid compositions, having spheroidal shapes and even surfaces and comprising a mean geometric diameter of 120-200 μm with a standard deviation of 1.4-2.0; an aerated density of 0.4-0.7 g/ml; a packed density of 0.5-0.9 g/ml; an apparent density of 1.2-1.5 g/ml; a Carr Index of 5-15% and an angle of repose of 20-40°, said microgranules being obtainable with a process as claimed in any claim from 1 to 6.

8. Microgranules according to claim 7, having at least one characteristic selected from the group consisting of a Carr Index equal to 6-12% and an angle of repose equal to 26°-30°C, and having in addition at least two of the following parameters within the ranges provided in a), b) c) below:

(a) mean geometric diameter of 130-170 μm with a standard deviation of 1.5-1.8;

(b) aerated density of 0.50-0.66 g/ml; and

(c) packed density of 0.55-0.80 g/ml or apparent density of 1.30-1.45 g/ml.

* C L M S *

PROCESS FOR THE PREPARATION OF MICROGRANULES SUITABLE FOR SUSPENSION AFTER COATING IN PHARMACEUTICAL LIQUID COMPOSITIONS

ABSTRACT

Object of the invention is a process for the preparation of microgranules to be used after coating in liquid pharmaceutical compositions, particularly in controlled-release compositions.

Operating with high-shear mixer-granulators within clearly established crucial parameter ranges, this process permits to obtain microgranules having a particle size distribution, a density, a surface and a shape which make them particularly suitable for coating and to be subsequently suspended in fluids.



FIG. 1

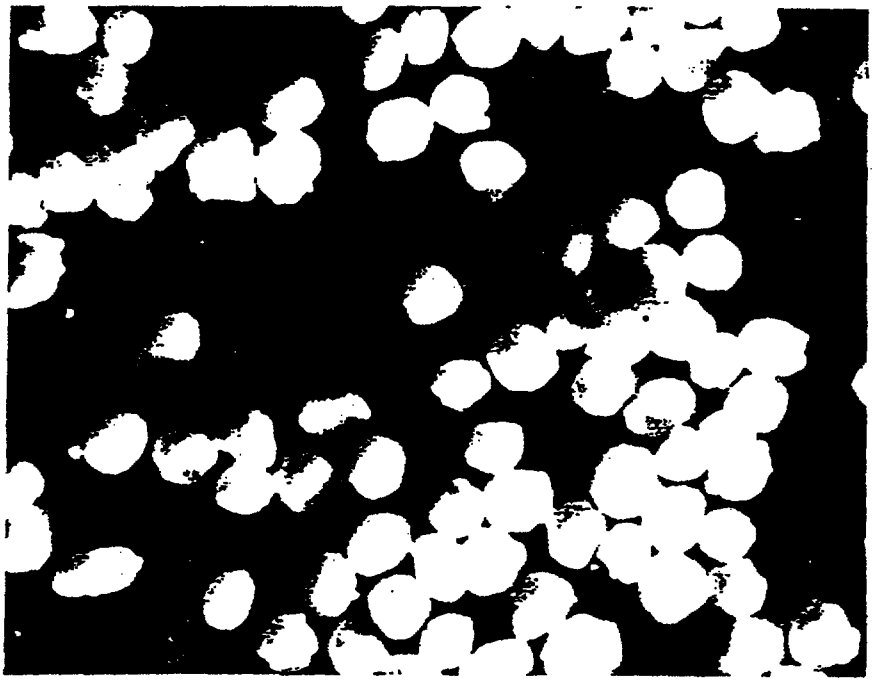


FIG. 2

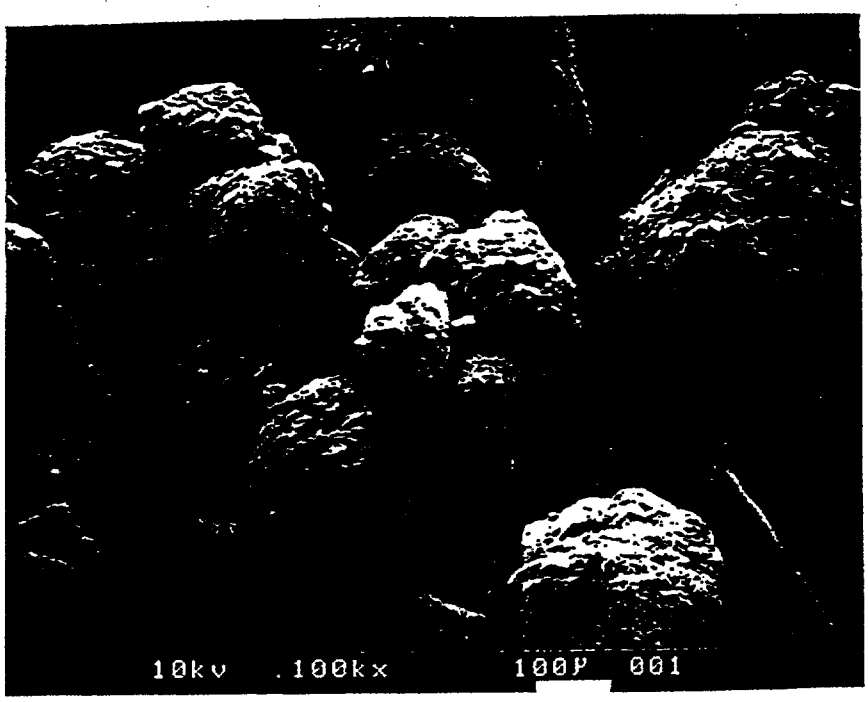


FIG. 3

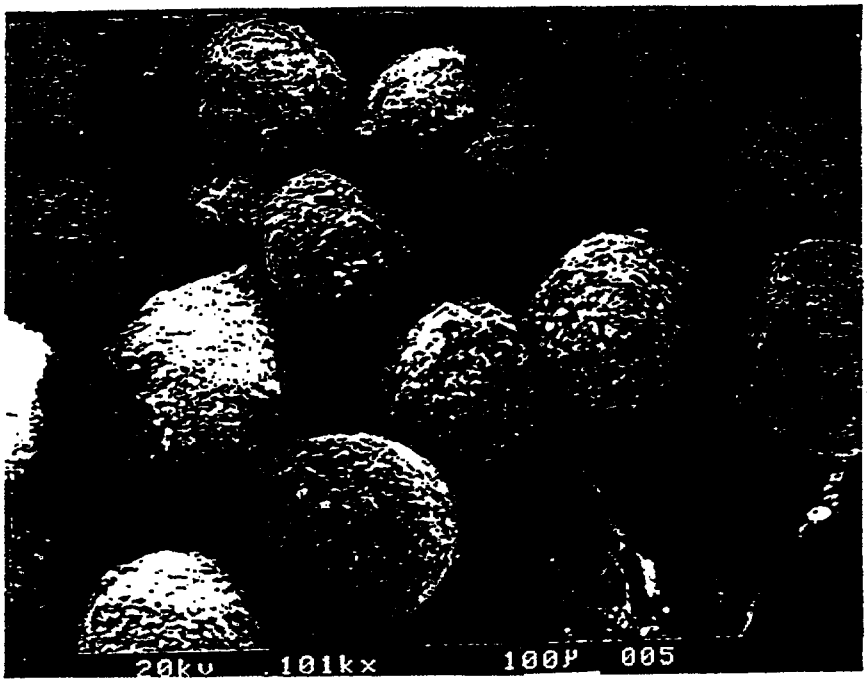


FIG. 4

REPLACEMENT SHEET
13 MAR 1997

PROCESS FOR THE PREPARATION OF MICROGRANULES SUITABLE FOR SUSPENSION AFTER COATING IN PHARMACEUTICAL LIQUID COMPOSITIONS

FIELD OF THE INVENTION

This invention involves a granulation process to obtain microgranules for use in pharmaceutical compositions. Said microgranules have a limited size distribution and morphological characteristics that ensure both uniform coating and easy suspension after coating, even in low-density aqueous vehicles.

BACKGROUND OF THE INVENTION

The technology to produce granulates from powder mixtures has long been known in pharmaceutics. For purposes of administration, these granulates are usually converted into tablets, enclosed in capsules or in sachets.

It has also been long known that granules or tablets can be coated with films, which can serve to delay the release of the active ingredient they contain, disguise an unpleasant taste, and/or improve the stability of the composition.

A major limitation of the use of such coated granulates in liquid formulations is that it has been difficult to obtain particles of an appropriate size to enable them to be easily suspended and kept in suspension in the fluid vehicle.

Particles of a size larger than about 500 μm tend to settle rapidly, resulting in a non-homogeneous distribution of the product within the vehicle. It is instead essential that the suspension remain homogeneous, after a slight stirring, for the time required to

REPLACEMENT SHEET
13 MAR 1997

outside the operating range established by the invention, was always of a rough construction, with 85-90% of the particle size distribution over 350 µm and with a mean diameter of 550 µm. Furthermore, a granule break-up was found in all the asterisk preparations, with a considerable loss of workable material.

EXAMPLE 5: Granulate Coating

In order to test the granulate suitability for filming, the granulates prepared as described in Example 1 were coated, using a Wurster Glatt GPCG3 apparatus, with two successive coatings having the following compositions:

	Composition	%
First coating	Ethyl cellulose	3.0
	Diethyl phthalate	1.0
	Polyethylene glycol 400	0.1
	Chloroform	74.0
	Ethanol	21.9
Second coating	Cellulose acetate phthalat	4.6
	Diethyl phthalate	1.1
	Acetone	70.7
	Isopropanol	23.6

The central partition in the apparatus is set at a height of 8 mm and fitted with a spray nozzle with a 1.2 mm diameter.

The incoming air temperature is set at 45°C and the air flow is set at 50 m^3/hour. The apparatus is switched on when the outgoing air

REPLACEMENT SHEET
13 MAR 1997

Fig. 2: Microgranules with even shapes and surfaces, corresponding to preparation C in Example 1.

(Image taken with a 33 x stereomicroscope.)

Fig. 3: Microgranules with spheroidal shapes and uneven surfaces, corresponding to preparation G in Example 3.

(Image taken with a 100 x electron microscope.)

Fig. 4: Microgranules with spheroidal shapes and even surfaces, corresponding to preparation F in Example 2.

(Image taken with a 101 x electron microscope.)

The images in Figures 1-4 completely agree with the considerations reported in Example 4.