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GRANULATION PROCESS

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This invention relates to a method of granulation suitable for the preparation of tablets.

The initial step in the preparation of tablets involves the conversion of the ingredients from a finely powdered to a granulated form. A conventional method of granulation, referred to as the moist granulating process, consists of the addition to the powder mixture of moistening liquids, such as alcohol, water or acetone with a binder dissolved therein, causing the fine particles to adhere and to remain adherent after drying. Binder solutions which are commonly used include sucrose syrups, gelatin solutions, mucilage of acacia, mucilage of tragacanth, etc. The use of this method is objectionable in many cases because of the initial destructive effect of the solvent or the subsequent instability of the substances to be compressed. The process is likewise unsuitable for mixtures which are incompatible in the presence of moisture.

An alternative method of granulation is that of precompression or slugging. The mixed ingredients, in finely powdered form, are compressed into rather large discs or slugs which are then broken and passed through a sieve of the proper size. Unsatisfactory results are obtained if the ingredients either possess poor compression qualities, or are of a hygroscopic nature.

An object of this invention is to provide a new and improved process for the granulation of substances which are either hydroscopic or can be slugged only with difficulty.

Another object of this invention is to provide a new and improved granulation process for the preparation of tablets of improved stability. A further object of this invention is to provide a granulation process for the production of medicinal tablets that will retain their therapeutic potencies for relatively long periods of time.

A still further object of this invention is to provide a new and improved granulation process for the preparation of catalysts in tablet form suitable for industrial purposes.

Other objects and advantages will be readily apparent from the following disclosure.

It has been discovered that the granulation of finely divided material may be effected by the use of a mixture consisting of an anhydrous halogenated non-polar solvent, together with a binder that is soluble in this solvent and also soluble in water. The mixture to be tableted is mixed with a solution of the water soluble binding agent dissolved in the non-polar solvent, the amount of binder used ranging from 1–6% of the composite weight of the mixture. Sufficient non-polar solvent is used to dissolve the binder therein and to convert the mixture to a damp non-fluid mass. The moistened mass is forced through a sieve, dried and sieved again. The size of the mesh used depends upon the size of the tablet to be made.

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A small amount of a dry, finely powdered lubricant is added to the granulated material to facilitate the subsequent compression of the material into tablets.

Solvents such as ethylene dichloride and chloroform have been found to be effective, while solid polyethylene glycols have been found to be suitable as binders. A typical binder is "Carbowax-6000," a trade name for a mixture of non-volatile, solid polyethylene glycols which are soluble in both water and organic liquids, and which have an average molecular weight of about 6000 to 7500. These substances resemble natural waxes in appearance and texture but are soluble in a much wider range of solvents. In addition, "Carbowax-6000" is an excellent lubricant for the subsequent compression of the granules into tablets.

Inert substances such as sucrose, lactose, starch, etc. are commonly added when the mixtures to be tableted are insufficient to give a tablet of practical size; otherwise their use is unnecessary. A lubricant such as stearic acid, or preferably a salt of this acid, such as magnesium stearate, is well distributed in finely divided form over the granulation prior to compression. The use of a lubricant insures uniform feeding into the dies preventing (*a*) malformations of the tablets caused by granules adhering to the dies and punches after the compression operation, and (*b*) sticking of the punches.

A unique feature in this process, of particular and singular importance in the production of granulated, tableted and extruded catalysts to be used in the chemical and petroleum industries, is the fact that the final products contain a very low percentage of organic material, as compared to the products made with conventional binders such as sucrose, gelatin, acacia, tragacanth, etc. Likewise, another feature is the maintenance of anhydrous conditions throughout the process.

The method of this invention has been advantageously applied to the preparation of various medicinal tablets including tablets of thiamine hydrochloride (Vitamin B_1), tablets of "Urecholine," tablets of 1-isoamidone, tablets of aspirin, phenacetin and caffeine, etc. Heretofore, these tablets could not be conveniently prepared by the conventional moist granulating process.

In addition, by using this special granulating process, it has been possible to prepare tablets of therapeutic compositions such as ascorbic acid tablets, penicillin tablets, etc. which are completely soluble in water, thereby facilitating the oral administration of these substances to adults and infants as aqueous solutions or in combination with soluble nutrients.

Likewise, the difficulties associated with the production of stable effervescent granules and

tablets have been obviated by the use of my method. The resulting products are completely and rapidly soluble possessing none of the hygroscopic properties usually associated with these types of products.

Granulated, tableted and extruded catalysts, including the catalyst commonly used in the synthesis of methyl alcohol, said catalyst containing 50 mole percent each of chromic oxide and zinc oxide, have also been prepared by this improved process.

It should be noted that the process of this invention can be used for the preparation of tablets generally, and is not in any way restricted or confined to tablets used for medicinal or therapeutic purposes solely.

The following examples illustrate the methods of carrying out the present invention, but it is to be understood that these examples are given by way of illustration and not of limitation.

Example 1

Tablets of thiamine hydrochloride containing the following ingredients were prepared as follows:

	Per Tablet	Per 750 Tablets
Thiamine hydrochloride—g	0.0500	37.50
Lactose—g	0.1250	93.75
"Carbowax-6000"—g	0.0040	3.00
Ethylene dichloride—cc		(75.00)
Corn starch—g	0.0200	15.00
Magnesium stearate—g	0.0010	0.75
	0.2000	150.00

The thiamine hydrochloride and lactose were triturated in a mortar and then sifted through a #40 sieve. The "Carbowax-6000" was dissolved in the ethylene dichloride and this solution was added to the thiamine-lactose mixture with trituration. After thorough incorporation, the damp mass was pressed through a #10 sieve and the resulting granules were dried at 40° C. for 0.5 hour. The granules were then pressed through a #16 sieve.

The corn starch and magnesium stearate were triturated in a mortor and sifted through a #60 sieve onto the granulation. After thorough mixing, the granulation was compressed into 0.200 g. tablets.

In this and in the subsequent examples, the granules were compressed into tablets of a Stokes "F" single punch tablet machine, punches of various sizes being used to prepare tablets of different weights.

Example 2

Tablets of "Urecholine" containing the following ingredients were prepared as follows:

	Per Tablet	Per 1000 Tablets
"Urecholine"—g	0.0050	5.0
Lactose—g	0.0610	61.0
"Carbowax-6000"—g	0.0015	1.5
Ethylene dichloride—cc		(35)
Corn starch—g	0.0071	7.1
Magnesium stearate—g	0.0004	0.4
	0.0750	75.0

The "Urecholine" and lactrose were thoroughly triturated in a mortar and then moistened with the ethylene dichloride solution of "Carbowax-6000." The mass was pressed through a #10 sieve and dried for 0.5 hour at 40° C. The dried granules were then pressed through a #16 sieve. The corn starch and magnesium stearate were triturated together and sifted through a #60 sieve onto the granulation. After thorough mixing, the granulation was compressed into tablets of 0.075 g.

Example 3

Tablets of 1-isoamidone containing the following ingredients were prepared as follows:

	Per Tablet	Per 1000 Tablets
1-Isoamidone hydrochloride monohydrate—g	0.0050	5.0
Lactose—g	0.1400	140.0
Sucrose—g	0.0300	30.0
"Carbowax-6000"—g	0.0040	4.0
Ethylene dichloride—cc		(35)
Corn starch—g	0.0200	20.0
Magnesium stearate—g	0.0010	1.0
	0.2000	200.0

The 1-isoamidone hydrochloride monohydrate, lactose and sucrose were thoroughly triturated in a mortar and moistened with a solution of the "Carbowax-6000" in ethylene dichloride. The mass was pressed through a #12 sieve, and the product was dried at 40° C. for 0.5 hour. The dried granules were then pressed through a #16 sieve and the excess fines were removed with a #60 sieve. The corn starch and magnesium stearate were triturated and sifted onto the granulation with a #60 sieve. After thorough mixing, the granulation was compressed into 0.200 g. tablets.

Example 4

Tablets of aspirin, phenacetin and caffeine containing the following ingredients were prepared as follows:

	Per Tablet	Per 1000 Tablets
Aspirin—g	0.1950	195
Phenacetin—g	0.1300	130
Caffeine—g	0.0330	33
"Carbowax-6000"—g	0.0040	4
Carbon tetrachloride—cc		(60)
Corn starch—g	0.0130	13
Talc—g	0.0230	23
Magnesium stearate—g	0.0020	2
	0.4000	400

All ingredients were dried at 50° C. for 24 hours. The aspirin was granulated by mixing with it a solution of 2 g. of "Carbowax-6000" in 30 cc. of carbon tetrachloride and pressing the moist mass through a #10 sieve. The phenacetin and caffeine were thoroughly mixed and granulated in the same manner with a solution of 2 g. of "Carbowax-6000" in 30 cc. of carbon tetrachloride. After drying the two lots of granules for 1 hour at 40° C., they were pressed separately through a #14 sieve. The corn starch, talc and magnesium stearate were triurated together in a mortar and divided in half. One half was sifted through a #60 sieve onto the aspirin granulation, and the second half onto the phenacetin-caffeine granulation. The two separate granulated masses were then thoroughly mixed and compressed into 0.400 g. tablets.

Example 5

Tablets of Ascorbic Acid containing the following ingredients were prepared as follows:

	Per Tablet	Per 100 Tablets
Ascorbic acid—g—	0.6400	64.0
Citric acid—g—	.0640	6.4
Dextrose anhydrous—g—	.1860	18.6
Starch, corn—g—	.0400	4.0
"Carbowax-6000"—g—	.0200	2.0
Ethylene dichloride—cc—		(25)
Starch, corn—g—	.0500	5.0
	1.0000	100.0

The ascorbic acid, citric acid, anhydrous dextrose and 4.0 g. of the corn starch were triturated thoroughly in a mortar. The "Carbowax-6000" was dissolved in the ethylene dichloride, and this solution was added to the mixed powders with trituration. After thorough incorporation, the damp mass was pressed through a #10 sieve, and the resulting granules were dried at 40° C. for 0.5 hour. These granules were then broken down to proper size by first repressing through a #10 sieve and then through a #14 sieve. 5.0 g. of corn starch was sifted onto the dried granules (#60 sieve) and the lubricated granule mixture was tumbled for 0.5 hour to effect mixing. The granules were then compressed into tablets weighing 1.00 g. each.

These tablets, stored in screw-capped glass jars at room temperature for 12 months, showed no loss in ascorbic acid content.

Example 6

Tablets of penicillin containing the following ingredients were prepared as follows:

	Per Tablet	Per 100 Tablets
Penicillin calcium (450 units/mg.)—g—	0.0460	4.60
Sodium citrate-powdered (#60 sieve) and dried at 110° C. for 24 hrs—g—	0.3940	39.40
"Carbowax-6000"—g—	0.0100	1.00
Ethylene dichloride—cc—		(10)
Corn starch—g—	0.0500	5.00
	0.5000	50.00

The penicillin calcium was weighed out under low humidity conditions (less than 20% relative humidity) to protect the penicillin remaining in the container. The following operations were carried out at a relative humidity of 31% and at a temperature of 26° C. The penicillin calcium and sodium citrate were triturated in a mortar. The "Carbowax-6000" was dissolved in the ethylene dichloride and this solution was added to the mixed powders with trituration. After thorough mixing, the damp mass was pressed through a #10 sieve, and the resulting granules were dried at 40° C. for 0.5 hour. These granules were then broken down to proper size by first repressing them through a #10 sieve and then through a #14 sieve. The corn starch was sifted onto the dried granules with a #60 sieve and a lubricant granule mixture was tumbled for 0.5 hour to effect thorough mixing. The granules were then compressed into tablets weighing 0.500 g. each.

These tablets, stored in screw-capped glass jars at room temperature for 12 months, retained full therapeutic penicillin potency.

Example 7

Effervescent tablets containing the following ingredients were prepared as follows:

	Per Tablet	Per 175 Tablets
Citric acid, dried at 55° C. for 48 hrs—g—	0.1084	19.0
Tartaric acid, dried at 55° C. for 48 hrs—g—	0.1595	28.0
Sodium bicarbonate, dried at 55° C. for 48 hrs—g—	0.3019	53.0
"Carbowax-6000"—g—	0.0302	5.3
Ethylene dichloride—cc—		(53)
	0.6000	105.3

The following operations were carried out at a relative humidity of 28% and at a temperature of 25° C. The citric acid and tartaric acid were triturated with a mortar and pestle to a fine powder. 0.8 g. "Carbowax-6000" was dissolved in sufficient ethylene dichloride to make 8 cc. of a solution, which was added to the damp acids with trituration. After thorough mixing, the damp mass was pressed through a #10 sieve and the resulting granules were dried at 40° C. for 0.5 hour. These granules were then broken down to proper size by first repressing them through a #10 sieve and then through a #14 sieve.

The sodium bicarbonate was granulated with a solution of 4.5 g. of "Carbowax-6000" in sufficient ethylene dichloride to make 45 cc. of solution. This solution was added to the sodium bicarbonate in a mortar and after thoroughly incorporating the solution, the damp mass was granulated in a manner identical to that described in the preceding paragraph.

The acid granules and the sodium bicarbonate granules were combined and thoroughly mixed by tumbling for 0.5 hour. The mixed granules were compressed without additional lubrication into tablets of 0.60 g.

These tablets were stored in screw-capped jars at room temperature for 12 months. At the end of this period of time, there has been no change in physical appearance or decrease in effervescence on addition to water, nor had there been any release of carbon dioxide in the glass jar.

Example 8

Catalyst tablets containing the following ingredients were prepared as follows:

	Per Tablet	Per 330 Tablets
Chromium trioxide—g—	0.3027	100.0
Zinc Oxide—g—	0.2460	81.4
"Carbowax-6000"—g—	0.0060	1.8
Ethylene dichloride—cc—		(30)
Talc—g—	0.0553	18.3
	0.6100	201.5

The following operations were carried out at 18% relative humidity and 23° C. temperature. The chromium trioxide and zinc oxide were triturated with a mortar and a pestle to a fine powder. 1.8 g. of "Carbowax-6000" was dissolved in 30 cc. of ethylene dichloride, and this solution was added to the oxides with trituration. After thorough mixing, the damp mass was pressed through a #10 sieve and the resulting granules were dried at 23° C. for 4 hours. These granules were then broken down to proper size by repressing them through a #16 sieve. 18.3 g. of talc was thoroughly mixed with these granules by tumbling, and the mixture was compressed into tablets weighing 0.6100 g. each.

Various changes and modifications may be made in carrying out the present invention without departing from the spirit and scope thereof. Insofar as these changes and modifications are within the scope of the appended claims, they are to be considered as part of this invention.

I claim:

1. The process of preparing granules of therapeutic materials comprising the steps of mixing an active therapeutic agent, together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the moist non-fluid mass thus obtained into discrete granules and removing said non-polar solvent from said granules.

2. The process of preparing granules of therapeutic materials comprising the steps of mixing an active therapeutic agent, together with a solid water-soluble polyethylene glycol dissolved in carbon tetrachloride, said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the non-fluid moist mass thus obtained into discrete granules and removing said carbon tetrachloride from said granules.

3. The process of preparing granules of therapeutic materials comprising the steps of mixing an active therapeutic agent, together with a solid water-soluble polyethylene glycol dissolved in ethylene dichloride, said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the damp non-fluid mass thus obtained into discrete granules and removing said ethylene dichloride from said granules.

4. The process of preparing granules of therapeutic materials comprising the steps of mixing an active therapeutic agent, together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent, said polyethylene glycol having a molecular weight of about 6000 to 7500 and being present in the amount of about 1–6% of the composite weight of the mixture, and the amount of said non-polar solvent being sufficient to convert said mixture to a damp non-fluid mass, forming said moist non-fluid mass thus obtained into discrete granules by extrusion through apertures of fixed size and removing said non-polar solvent from said granules.

5. The process of preparing therapeutic tablets comprising the steps of mixing an active therapeutic agent, together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent, said polyethylene glycol having a molecular weight of about 6000 to 7500 and being present in the amount of about 1–6% of the composite weight of the mixture, and the amount of said non-polar solvent being sufficient to convert said mixture to a damp non-fluid mass, forming said moist non-fluid mass thus obtained into discrete granules by extrusion through apertures of fixed size, removing said non-polar solvent from said granules and compressing said granules to form tablets.

6. The process of preparing thiamine hydrochloride tablets comprising the steps of mixing thiamine hydrochloride, together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent, said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the moist non-fluid mass thus obtained into discrete granules, removing said non-polar solvent from said granules, lubricating said granules and compressing said granules to form tablets.

7. The process of preparing stable water-soluble ascorbic acid tablets comprising the steps of mixing ascorbic acid together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent, said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the damp non-fluid mass thus obtained into discrete granules, removing said non-polar solvent from said granules, lubricating said granules and compressing said granules to form tablets.

8. The process of preparing an effervescent granule mixture which comprises mixing separately, the acid and basic constituents of said mixture, together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent, said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the damp non-fluid masses separately obtained into discrete granules by extrusion through apertures of fixed size, removing said non-polar solvent from said separate masses and mixing said dried acid and basic granules.

9. The process of preparing stable effervescent tablets comprising the steps of mixing separately, the acid and basic constituents of said mixture, together with a solid water-soluble polyethylene glycol dissolved in an anhydrous chlorinated non-polar solvent, said polyethylene glycol having a molecular weight of about 6000 to 7500, forming the damp non-fluid masses separately obtained into discrete granules, removing said non-polar solvent from said separate masses, mixing said dried acid and basic granules, and compressing said mixture of granules into tablets.

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REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,149,005	Bockmuhl	Feb. 29, 1939
2,195,596	Nitardy	Apr. 2, 1940

OTHER REFERENCES

McClelland, Chemical and Engineering News, vol. 23, Feb. 10, 1945, pages 247–50—251.