METHOD OF PREPARING PARTICLES FOR AGGLOMERATION

FIELD OF THE INVENTION

The present invention relates broadly to the formation of agglomerates, to particulate solid carriers, and/or binders, and/or pharmaceutically active materials for use in the formation of agglomerates, and to methods of forming same and agglomerates so produced. More specifically, the present invention relates to the field of pharmaceutical dosage form design and, in particular, the production of unique solid carriers and/or pharmaceutically active materials and agglomerated dosage forms for administration of pharmaceutically active materials to patients.

INTRODUCTION TO THE INVENTION

There are several known methods of treating diseases and conditions of the upper and lower airway passages and the lungs. These conditions include, for example, asthma and rhinitis. One such technique involves administering certain pharmacologically active agents or drugs such as, for example, mometasone furoate, topically to the airway passages or lungs in an immediately useable form. Mometasone furoate is a topically effective, steroidal anti-inflammatory.

Oral inhalation therapy is one method of delivering such topically active drugs. This form of drug delivery involves the oral administration of a dry powdered drug directly to the afflicted area in a form which is readily available for immediate benefit.

However, inhalation therapy is a particularly demanding dosing system and it involves its own set of unique design and performance problems. Among those problems is a concern over the accuracy and repeatability of dosing. One must try to ensure that the same amount of drug is administered each and every time. Moreover, unlike pills, capsules and creams, oral inhalation therapy must concern itself with not only the dosage form itself, but also a drug delivery device

and the interaction between them. One has only to consider over-the-counter nasal sprays to understand this problem. When one squeezes a conventional spray bottle, it is difficult to apply the same amount of force each and every time. With even a slight difference in force, differences in the amount of drug administered can result. Even with somewhat more consistent pump style spray applicators, variations in dosing can occur. While such variation is usually not a problem when administering OTC nasal sprays, variation should be minimized where possible when administering potent prescription medications for such serious conditions as asthma. The dangers of over-medicating or under-medicating and the consequences of such unwanted deviation can be profound. The problem becomes even more complex when the size of the doses are as small as they often are in oral inhalation therapy.

To help mitigate these problems, companies such as Schering Corporation have developed complex and highly accurate inhaler systems for administering powdered medications such as those described in PCT International Publication WO 94/14492, the text of which is hereby incorporated by reference. Such inhaler systems were designed to meter out an exact dose of a powdered medication using a dosing hole of a specific size. The hole is completely filled with drug prior to administration and the entire contents of the dosing hole are then delivered to the patient through a nozzle. The dosing hole is then filled again for the next dose. These devices have been specifically designed to remove, as much as possible, human error and mechanically induced variability in dosing.

While such devices represent a significant advance in oral inhalation therapy, there are still some circumstances in which problems may remain. These problems often center on the properties of the pharmacologically active agent and their interaction with the inhaler. For example, certain drugs are not "free-flowing" and that may make it difficult to move the drug from storage in a reservoir, to measurement in a dosing hole, to delivery from the inhaler. Other drugs may suffer from electrostatic charge problems or may exhibit an unacceptable degree of cohesive force. Such drugs may be "sticky," even when in powdered form. These drugs may clog the inhaler/applicator, affecting its ability to properly meter the intended amount of medication. Such powders may also adhere to the nozzle of the applicator, thus reducing the amount of medication actually delivered. This is often

referred to as "hang up." Drugs may also be "fluffy" which makes handling and loading sufficient drug into a dosing hole a real challenge. To make matters even worse, these and other physical properties of various pharmacologically active agents may vary within a single batch of material. This can defeat attempts to compensate.

Related problems may also result based upon the small size of the particles which are generally used in inhalation therapy. Inhalation therapy commonly involves drug particles which are on the order of 10 microns or below. This ensures adequate penetration of the medicament into the lungs of the patient as well as good topical coverage. In order to provide adequate dispensing of such medicines, tight control must be maintained on the size of the particles of the drug. However, powders of this size can be extremely difficult to work with, particularly when small dosages are required. Such powders are typically not free-flowing and are usually light, dusty or fluffy in character, creating problems during handling, processing, and storing. In addition, it can be difficult to repeatedly and accurately load such materials into the dosing hole of an inhaler. Thus not only the properties of the drug, but also the required size of the therapeutic particulate, can combine to cause considerable problems in terms of handling and dosing.

One method of improving the ability to administer fine powdered medicaments is by the inclusion of dry excipients such as, for example, powdered lactose. However, it has been determined that when particularly small doses of medication are required, such as under about 100-500 μg of drug, the inclusion of conventional excipients may not adequately compensate for the problems associated with the use of fine drug particles. In addition, dry excipients as commonly used generally have particle sizes which are significantly larger than the particle size of the drug. Unfortunately, the use of such large particles can have a significant impact on the amount of drug delivered from dose to dose. Moreover, the intended benefits of the use of such excipients begins to diminish as the size of the dose decreases. Therefore, particle retention within the metering device or the inhalation nozzle and other handling issues can become a serious problem.

Alternatively, drug products can be processed to form agglomerates or pellets which are generally more free-flowing and bulky. One method of agglomerating drugs is described in PCT International Publication WO 95/09616.

As described therein, agglomerates of finely divided powder medicaments, such as micronized powders having a particle size smaller than 10 μm, can be produced which require no binders. However, they can be formed with excipients. These agglomerates can then be administered through an inhaler for powdered medications.

The ability to create particles without an added binder is significant to inhalation therapy and can pose a great advantage over other techniques which use water or other traditional binders in agglomerate formation. Agglomerates of pure drug can provide great advantages when formulating and handling powders. It has been found, however, that at doses of about 100-500 μg of a drug such as mometasone furoate and below, agglomerates of pure drug can suffer from hang up and dosing variability can be a genuine concern. Even in dosing systems designed to provide relatively larger doses of pharmacologically active agent, such as over 500 μg, the resulting agglomerates of pure drug can still suffer from integrity problems. These agglomerates are still relatively soft and can be crushed during metering thereby providing variability in dosing. The material can also be broken fairly readily by, for example, dropping an inhaler from a height of about four feet. This would prematurely result in the formation of smaller particles which are more difficult to handle. In fact, it is the handling difficulties of the fine drug particles that originally necessitated agglomeration.

If binder-containing agglomerates are to be used, such agglomerates can be made by the methods described in, for example, U.S. Patent 4,161,516 and Great Britain Patent 1,520,247 which disclose the use of certain binding materials, including water, for the production of agglomerates for oral inhalation. According to the processes described therein, prior to agglomeration, the moisture content of certain "self agglomerating" or hygroscopic micronized drugs are elevated. After the micronized powder has been elevated to the desired water content level, it is agglomerated. Non-hygroscopic materials must be bound with more traditional binders as described therein. Similarly, PCT International Publication WO 95/05805 discloses a process for forming agglomerates where a mixture of homogeneous micronized materials is treated with water vapor to eliminate any convertible amorphous content which may destabilize at a later point. After treatment with water vapor, the now crystalline material is agglomerated. However, this application warns

that if the vapor exposure is conducted after agglomeration, the product is "useless in an inhalation device."

The effect of moisture on the tableting characteristics of anhydrous lactose is discussed in Sebhatu, Elamin and Ahlneck, "Effect of Moisture Sorption on Tableting Characteristics and Spray Dried (15% Amorphous) Lactose," *Pharmaceutics Research*, Vol. 11, No. 9, pp. 1233-1238 (1994). The article does not, however, discuss the formation of agglomerates, or the production of agglomerates which can yield an acceptable "fine particle fraction," also known as a "respirable fraction" when administered as part of oral inhalation therapy.

One particularly important approach to agglomerate formation was disclosed in PCT International Publication WO 98/41193. The invention described therein included a process of producing agglomerates. The process included the steps of providing particles of at least one first material, generally a pharmacologically active agent, and providing particles of at least one solid binder or solid carrier. At least one of these two particles, the drug or the solid binder, included convertible amorphous content. The convertible amorphous content of the binder and/or the drug should be capable of being converted to a crystalline form upon exposure to a pre-selected stimulus which includes, among other things, humidity.

The particles of binder or carrier and drug are then agglomerated while maintaining the convertible amorphous content. After agglomeration is complete, the convertible amorphous content within the agglomerates is exposed to the pre-selected stimulus and is converted to a crystalline form.

Not surprisingly it is very important to the performance of the agglomerates and to the ability to deliver an acceptable fine particle fraction of free particles of the pharmaceutically active materials that the properties of the agglomerate carrier or binder be tightly controlled. It is also important to control the properties of the drug particles. Desirably one would be able to provide not only particles of a specified size, but also a very tight particle size distribution. Ideally, one could coordinately provide a desirable amount of convertible amorphous content. The amorphous content can be critical to the strength, bulk density and/or hardness of the resulting agglomerate. If too little amorphous content is present, then the agglomerates will be insufficiently robust to withstand packaging, shipment

and use. If too much amorphous content is provided, then there is a risk that the agglomerate will be too strong and/or hard and that an unacceptable fine particle fraction will be delivered from a powder inhaler. Similarly, the size of the particles and the particle size distribution are critical to accurately formulating the agglomerates to provide an acceptable fine particle fraction and to provide accurate dose delivery uniformity due to consistency of the resulting bulk density. Unfortunately, no processes are known for reproducibly producing particles of drugs and/or solid carriers with accurately controlled particle size distribution and amorphous content. It is to this improvement that the present invention is directed.

SUMMARY OF THE INVENTION

The present invention is directed to a method of producing a particulate substance which is particularly suitable for use in producing agglomerates containing a pharmaceutically active material and preferably a solid binder or solid carrier. The particulate produced by the process is also contemplated. The method includes the steps of micronizing a particulate material from an original particle size to an intermediate particle size in a manner which imparts an increase in the amount of amorphous content of the particulate. Some or all of that imparted amorphous content is convertible amorphous content. The particle size distribution is reduced by this micronizing step. Thereafter, the micronized particulate is "cured" by exposure to a pre-determined stimulus such as, for example, exposure to controlled relative humidity at a specified temperature. This curing process is conducted for a time sufficient to reduce at least a portion, and in many instances preferably all, of the amorphous content of the particulate which is convertible when exposed to that particular stimulus. Thereafter, the cured particulate is micronized again wherein the particulate is reduced further in size from the intermediate particulate size to a final particulate size. A desired level of convertible amorphous content is also created by the subsequent micronizing step.

The particulate can be any pharmaceutically acceptable material including a pharmaceutically active material (i.e., a drug) or a non-therapeutically active material such as a solid carrier, solid binder or other pharmaceutical excipient. Indeed, particulate can be composed of both at the same time.

Stated another way, the method of producing a particulate in accordance with the present invention includes the steps of micronizing a particulate material having a first particle size distribution, from that first particle size distribution to intermediate particles having a second particle size distribution. The second particle size distribution is different than the first particle size distribution as the particulate has been made smaller, on average. Micronization is accomplished in a manner which imparts an increase in the amorphous content of the intermediate particulate relative to the starting particulate before the preceding micronization step. The intermediate particulate is then cured to reduce its amorphous content. Finally, the cured intermediate particulate is re-micronized to a third particle size distribution, which is different than the first or second particle size distribution because the particles are again made smaller on average. The re-micronized particulate also have an amount of amorphous content which is greater than that of the cured intermediate particulate. Thus, in a first micronizing step, an amount of amorphous content is imparted to the particles. Curing will reduce an amount of amorphous content which is convertible when exposed to the stimulus. This also reduces the total amorphous content. Thereafter, upon re-micronizing, the particles contain additional amorphous content, preferably convertible amorphous content.

Preferably, the final particle size of particulate solid carrier produced in accordance with this process is at least about 60% by volume less than or equal to 5 µm and its pre-determined convertible amorphous content (as determined by specific heat of crystallization, using techniques described *infra*) is between about 1 and about 20 Joules/gram ("J/g" or "J/gram"). More preferably, the final particle size of the particulate solid carrier is at least about 70% by volume less than or equal to 5 µm and a pre-determined convertible amorphous content is between about 2 and about 16 Joules/gram. Most preferably, the final particle size of the particulate solid carrier is at least about 80% by volume less than or equal to 5 µm and the pre-determined amorphous content is between about 3.8 and about 7 Joules/gram.

Preferably, the final particle size of particulate pharmaceutically active material produced in accordance with these methods is at least about 60% by volume less than or equal to 5 microns and a pre-determined convertible amorphous content is between about 1 and about 20 Joules/gram. More preferably, the final particle size of the particulate pharmaceutically active material is at least about 80%

by volume less than or equal to 5 microns and a pre-determined convertible amorphous content is between about 2 and about 16 Joules/gram. Most preferably, the final particle size of the particulate pharmaceutically active material is at least about 90% by volume less than or equal to 5 microns.

Preferably, when the pharmaceutically acceptable material useful for the formation of an agglomerate treated by these processes is a non-therapeutically active, non-pharmaceutically active material, the pharmaceutically acceptable material can be a common additive or excipient such as lactose (including both hydrous and anhydrous lactose), and the like. However, since the same process can be performed on the pharmaceutically active material as well, the pharmaceutically active material can be agglomerated with either a traditional solid carrier or a solid carrier which has also been produced in accordance with the methods of the present invention. The pharmaceutically active material produced using these methods will have both controlled particle size distribution and controlled amorphous content and can also be used to form agglomerates without an additional solid carrier and/or with another pharmaceutically active agent, one treated by this method or otherwise.

The present invention also relates to an agglomerate produced by agglomerating a pharmaceutically active substance and/or solid carrier particles at least one of which has been produced in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, the term "pharmaceutically acceptable material" can include either pharmaceutically active materials or non-pharmaceutically active materials. Pharmaceutically active materials are drugs, vitamins, minerals, herbs, dietary supplements and the like, which produce a therapeutic benefit when administered to a patient in need thereof. Non-pharmaceutically active materials can include, *inter alia*, solid carriers, solid binders and other traditional, pharmaceutically acceptable excipients which generally do not exhibit a therapeutic benefit to a patient when administered as part of a dosage form. An "agglomerate," in accordance with the present invention, generally means an amalgamation of smaller particles to form larger particles. These smaller

particles can be held together by traditional binders or by crystallizing the convertible amorphous content imparted to a particle by the processes of the present invention.

"Amorphous content" as used herein, refers to a portion of at least the surface of a particle of a pharmaceutically acceptable material which is non-crystalline. "Convertible amorphous content" refers to that portion of the amorphous content of a pharmaceutically acceptable material which, upon exposure to a predetermined stimulus, can be converted from an amorphous form to a crystalline form. The amount of convertible amorphous content desired may depend on a number of factors relating to the specifics of the agglomerates contemplated and the degree and manner of processing. The amount of convertible amorphous content is also related to the stimulus used. A particulate produced in accordance with the present invention may have a greater amount of convertible amorphous content relative to one stimulus than relative to another. Therefore, the desired convertible amorphous content can dictate the degree of processing and/or the stimulus used. A drug might have too much convertible amorphous content if a first stimulus is used, but the desired level of convertible amorphous content if some other stimulus is used.

Convertible amorphous content can be measured by known methods, such as X-ray powder diffraction, differential scanning calorimetry, solution calorimetry and others. These can more preferably include isothermal microcalorimetry, such as by the use of a Thermometrics 2277 Thermal Activity Monitor (Thermometrics AB, Sweden) where convertible amorphous content can be quantified in terms of Joules/gram by measuring the specific heat of crystallization of that particulate. Using techniques offered by the manufacturer, a known quantity of material having amorphous content is exposed to an environment of about 38% relative humidity ("RH"), generated by a saturated solution of sodium iodide, at 25°C and the heat evolved is plotted against time.

The heat of crystallization thus measured is the total heat evolved by an amount of a particulate, having convertible amorphous content, during the entire crystallization process. This total heat evolved can include not only that heat evolved during the transition from amorphous form to crystalline form, but also, where applicable, the heat evolved during moisture absorption before the transition.

Thus, the convertible amorphous content of a particulate corresponds to the heat of crystallization of the particulate when exposed to a specific stimulus, measured in Joules/gram. The higher the relative heat of crystallization, the higher the degree of convertible amorphous content. For anhydrous lactose, about 45 Joules/gram roughly equals 100% amorphous content. A measured heat of 3.2-6 Joules/gram roughly equates to between about 7 and about 13% amorphous content.

The "stimulus," as used herein, is preferably humidity. However, other stimuli can include, without limitation, temperature, solvent vapor and the like. When humidity is used, the relative humidity and length of exposure should be coordinated to provide a desired degree of conversion of the convertible amorphous content.

Agglomerates produced in accordance with the present invention can be made from a plurality of particles of at least one pharmaceutically acceptable material prepared in accordance with the present invention, with or without other particulates or excipients. Where, for example, the pharmaceutically acceptable material treated in accordance with the present invention is a pharmaceutically active material or drug, it is not necessary that any of the other materials used in agglomerate formation contain convertible amorphous content. However, there may be an advantage to using one or more different types of particles, all of which have been produced in accordance with the present invention and therefore all have a controlled particle size distribution and convertible amorphous content.

It is also possible in accordance with the present invention to produce an agglomerate of a pharmaceutically active material produced in accordance with the present invention with no other binder or excipient. In addition, where a first pharmaceutically active material is treated in accordance with the present invention to provide a specified particle size distribution and a convertible amorphous content, it can be agglomerated with a second drug, one which has not been treated in accordance with the present invention. The first drug can, in essence, function as a solid binder/carrier.

Agglomerates can be used in a formation of a tablet, capsule or other traditional dosage form or they can be administered directly, such as in oral inhalation therapy. Agglomerates can be produced in any known manner, but preferably, they are produced by the techniques described in PCT International

Publication WO 98/41193, the text of which is hereby incorporated by reference. This process is generally described in the foregoing introductory section.

A "solid carrier" in accordance with the present invention is an excipient with which a drug or pharmaceutically active material can be agglomerated. The solid carrier may act as a solid binder where, for example, one seeks to capitalize on the convertible amorphous content imparted to the solid carrier and its subsequent conversion to crystalline form as a means of binding the agglomerate particles. If a traditional binding system is used, or if the drug will provide the total convertible amorphous content, the more generic term, "solid carrier," is more appropriate.

Particles of solid carrier in accordance with the present invention, preferably will be produced such that they have a pre-determined convertible amorphous content ranging from between about 1 to about 20 Joules/gram and a particle size distribution of at least 60% by volume less than or equal to 5 μm. More preferably, the particles of solid carrier will have a pre-determined convertible amorphous content ranging from between about 2 to about 16 Joules/gram and a particle size distribution of at least 70% by volume less than or equal to 5 μm. Most preferably, the particles of solid carrier will have a pre-determined convertible amorphous content ranging from between about 3.8 to about 7 Joules/gram and a particle size distribution of at least 80% by volume less than or equal to 5 μm.

These same ranges of convertible amorphous content and particle size distribution can also apply to particles of a pharmaceutically active material. However, preferably the particle size distribution for pharmaceutically active materials is finer than for solid carriers. Preferably, particles of pharmaceutically active materials produces in accordance with the present invention will have an particle size distribution of about 80% by volume less than or equal to 5 μm. More preferably, the drug component will have an particle size distribution of at least 90% by volume less than or equal to 5 μm.

Note that when particles having a specified convertible amorphous content and particle size distribution are mixed with other particles having a different convertible amorphous content and particle size distribution, the convertible amorphous content and particle size distribution for the system will change proportionally. Particle size and particle size distribution can be determined by any

of the many techniques known and used in industry. These can include the use of a Sympatec HELOS Laser Diffraction Particle Size Analyzer with a RODOS Dry Powder Disperser, using standard techniques provided by the manufacturer. This device is available from Sympatec, Inc. of Princeton, New Jersey USA.

When an agglomerate is formed from pharmaceutically acceptable particulate material including both a drug and a solid carrier which have been treated in accordance with the present invention, it is not a requirement that both particulates fall within the ranges of particle size distribution and convertible amorphous content discussed above. However, it may be desirable that both meet the described standards.

The pharmaceutically acceptable material in accordance with the present invention can include solid carriers/solid binders such as, without limitation, non-therapeutically active materials including polyhydroxy aldehydes, polyhydroxy ketones, and amino acids. Preferred polyhydroxy aldehydes and polyhydroxy ketones are hydrated and anhydrous saccharides including, without limitation, lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, mannitol, melezitose, starch, xylitol, mannitol, myoinositol, their derivatives, and the like. Lactose is preferred.

Pharmaceutically active materials contemplated for use in accordance with the present invention include, for example, drugs, vitamins, herbs, natural products, dietary supplements and the like. Particularly preferred pharmaceutically active materials in accordance with the present invention include, without limitation, corticosteroids such as mometasone furoate, beclomethasone dipropionate, budesonide, fluticasone, dexamethasone, flunisolide, triamcinolone, (22R)-6α, 9α-difluoro-11β, 21-dihydroxy-16α, 17α-propylmethylenedioxy-4-pregnen-3,20-dione, tipredane and the like. β-agonists (including β_1 and β_2-agonists) including, without limitation, salbutamol (albuterol), terbutaline, salmeterol and bitolterol may also be used. Formoterol (also called "eformoterol"), e.g. as the fumarate or tartrate, a highly selective long-lasting β_2-adrenergic agonist having bronchospasmolytic effect, is useful. Another β-agonist which can be used in accordance with the present invention is (2(1H)-Quinolinone,8-hydroxy-5-[1-hydroxy-2-[[2-(4-(methoxyphenyl)-1-methylethyl]amino] ethyl]-mono-hydrochloride, also identified by Chemical Abstract Number CAS-137888-11-0, disclosed in U.S. Patent No. 4,579,854, the text of which