A METHOD OF PREPARING A DOSAGE UNIT BY DIRECT TABLETING AND PRODUCT THEREFROM

The present invention is a process and apparatus for making a dosage unit by direct tableting of shearlite particles. The present invention also includes the dosage unit itself. Shearlite particles, which are prepared by subjecting a feedstock material to liquiflash processing, can be directly fed from a shearlite device to a tableting apparatus without the necessity of any intermediate steps of additional ingredients to facilitate flowability or tablet formation.
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A METHOD OF PREPARING A DOSAGE UNIT BY DIRECT TABLETING AND PRODUCT THEREFROM

This application is a continuation-in-part application of pending U.S. application Serial No. 08/330,412 filed October 28, 1994.

BACKGROUND OF THE INVENTION

This invention relates to the preparation of oral dosage units, i.e., compressed tablets, for delivering bio-affecting agents to recipients.

Compressed tablets are made by compressing a formulation containing a bio-affecting agent, i.e., a medicinal substance or drug, and other ingredients, such as excipients. There are currently three basic methods for making tablets: wet granulation, dry granulation and direct compression.

Wet granulation is expensive, involving many processing steps and costly equipment, as well as energy and space which should be environmentally controlled.

Dry granulation also has disadvantages. It requires specialized equipment; it does not permit uniform color distribution; it may retard the dissolution of difficultly soluble drugs; and dry processes tend to create dust, which can cause contamination.

Direct compression has drawbacks as well. They include: difficulty in obtaining sufficient flow and problems in bonding particles to form a strong tablet. Also, high dosage drugs generally have poor compressibility when directly compressed.

All three of these processes produce fines, which interfere with tableting operations. Also, a significant percentage of non-compressed particulate is lost because the fines are dispersed and cannot be recaptured.

There is a need in the art for a method of making tablets, which method does not have the disadvantages associated with prior art processes.
SUMMARY OF THE INVENTION

The present invention is a process and apparatus for making a dosage unit for delivering a bio-affecting agent and a product resulting from their use. The process includes directly tableting shearlite particles. The invention includes the dosage unit.

“Shearlite particles” are defined herein as discrete particles which are prepared by subjecting a solid organic-based feedstock to liquiflash and shearing conditions.

“Direct tableting” means, in general, the compression of shearlite particles, after their formation, without intermediate processing steps or additional ingredients.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the invention have been chosen for purposes of illustration and description, but are not intended in any way to restrict the scope of the present invention. Some preferred embodiments are shown in the accompanying drawings, wherein:

Figures 1A and 1B, are photomicrographs at 125x magnification of acetaminophen before and after processing in accordance with the present invention;

Figure 1C is a photomicrograph at 500x magnification of a cross-section of a sphere shown in Figure 1A;

Figures 2A, 2B, and 2C are schematic representations of the liquiflash process in accordance with the present invention;

Figures 3A, 3B, and 3C depict one shearlite device useful in the present invention;

Figures 4A, 4B, and 4C depict a second shearlite device which has been used in the present invention;

Figures 5A, 5B, and 5C depict a third shearlite device used in the process of the present invention;

Figures 6A and 6B depict another shearlite device used in the process of the present invention;

Figure 7 depicts an additional shearlite device used in the present invention;

Figure 8 depicts yet another shearlite device used in the present invention;
Figure 9 is a photomicrograph at 50x magnification of a sucrose product prepared in accordance with the present invention;

Figure 10 is a photomicrograph at 125x magnification of another embodiment of the present invention in which microspheres produced in accordance with Example II have been coated;

Figure 11 is a photomicrograph at 50x magnification of ibuprofen shearlite product prepared in accordance with the present invention;

Figures 12A and 12B are photomicrographs at 50x magnification of pseudoephedrine prepared in accordance with the present invention;

Figure 13 is a photomicrograph at 50x magnification which depicts a pseudoephedrine product prepared in accordance with the invention;

Figure 14 is a photomicrograph at 50x magnification of a dextromethorphan product prepared in accordance with the present invention;

Figure 15 is a photomicrograph taken at 50x magnification of amalgam of shearlite particles containing a cough and cold treatment formed in accordance with the present invention;

Figure 16 is a photomicrograph taken at 50x magnification of spheres formed from an amalgam of three (3) active ingredients (also a cough and cold treatment) in accordance with the present invention;

Figure 17 is a schematic of a prior art process;

Figure 18 is a schematic of the process of the present invention;

Figure 19A and 19B are schematic representations of a loaded precompression tablet mold comparing the inventive procedure and the prior art, respectively; and

Figures 20A and 20B are schematic representations of a loaded tablet mold during compression comparing the inventive procedure and the prior art, respectively.

**DETAILED DESCRIPTION OF THE INVENTION**

The processes and apparatuses of the invention are used to produce, as dosage units, compressed tablets. Preferably, the invention involves the direct tableting of shearlite particles and formulations containing shearlite particles.
In other words, the invention includes a method of making a compression tablet via direct tableting of a shearlite particles ("shearlites") or a mixture of shearlites with one or more other ingredients. The tablet possesses a rigid structure and a surface which has hardness, i.e., resists penetration and deformation. In the prior art, such tablets were produced by a complex arrangement of machinery required to carry out processing steps and/or to incorporate ingredients necessary to feed a tablet mold and form a tablet.

"Directly tableting" as used herein means to compress shearlite particles, subsequent to their formation, without any intermediate processing steps or additional ingredients, if so desired. Thus, "directly" is a term identifying the elimination of steps and/or ingredients normally considered essential in traditional tablet making procedures. With reference to wet granulation and dry granulation procedures, the present invention has eliminated many interim steps and ingredients used to obtain the proper size of particles and adequate flowability to enable transport to and through tableting apparatus. The present invention has also removed the requirement for many excipients (e.g., fillers, disintegrants and lubricants), previously considered necessary even in traditional direct compression methods. However, as previously described, excipients in the form of shearlite particles can be beneficially utilized in accordance with the present invention.

The present invention improves the art of tableting because it reduces the requirement for several processing steps and additional ingredients which facilitate flow through the apparatus. Moreover, the process is improved so that other drawbacks associated with the prior art, such as production of fines, are reduced or eliminated.

Tableting machines useful for preparing compression tablets usually include a die and a punch. Feeding mechanisms direct the granulation to the die cavity and punches compress the tablet once the granulation has been placed in the die cavity. The tablet press may be a single station (or single punch press) or, alternatively, a multistation (e.g., rotary) press.

In commonly-owned, copending U.S. Application Serial No.08/194,682, filed February 10, 1994, a material is fed to a tableting machine as a free-form agglomerate
in which selected ingredients, such as a medicinal substance, and a carrier material are fused together. The free-form agglomerate is distinguished from agglomerates formed from wet and dry granulations, but they are not shearlite particles.

The method of the present invention involves shearlite particles. "Shearlite particles" are prepared by subjecting a solid feedstock capable of being transformed to liquiform in the absence of a dissolving medium to liquiflash and shearing conditions to provide substantially unimpeded internal flow. The feedstock contemplated for use in the present invention is a feedstock which is capable of being transformed instantaneously from a solid to a liquid and back to a solid. The feedstock may be one ingredient or an amalgam of more than one ingredient.

It has become known to those skilled in the art of material processing, and, especially to artisans familiar with the technology of the owner of the present invention, that "flash flow" refers to conditions of temperature and force required to transform a solid feedstock to a new solid having a different morphology and/or chemical structure in the absence of a heat history. Flash flow can be implemented by "flash heat" processing. The term flash heat is understood to mean a process which includes subjecting the feedstock to combinations of temperature, thermal gradients, flow, flow rates and mechanical forces of the type produced in the machines referred to herein. The term "flash flow" is described in the co-owned U.S. Patents 5,236,734; 5,238,696; 5,370,881 and 5,518,730, the all of which are incorporated herein by reference.

Flash flow processing known to the art to date contemplates transformation of feedstock material substantially immediately upon reaching a flow condition whereby the material can move at a subparticle level. Liquiflash processing, however, contemplates the reduction of the feedstock material under conditions of heat and pressure to a condition wherein any resistance to liquid flow, e.g., viscosity which impedes the propensity to form liquid droplets, is eliminated. On a macro scale, this condition appears to provide a liquid or liquiform, which terms are used interchangeably herein.

With liquiflash processing, once the feedstock is reduced to a condition wherein substantially all resistance to liquid flow is removed, shear force is imparted to
the flowing feedstock in an amount sufficient to separate individual or discrete particles from the mass. The particles produced by this separation process, referred to herein as discretization, have a size and shape influenced only by the natural mass separation of the flowing feedstock in the presence of the impinging shear force. The particles thus formed are referred to as shearlite particles or particulates. If the impinging force is such that the separation created is that of a continuous stream, discretization has not occurred.

"Liquiflash conditions" as used herein means those conditions which provide transformation of a solid to a liquid state and then to the solid state (e.g., solid-liquid-solid) instantaneously. By "instantaneously" we mean less than seconds, in most cases, fractions of a second, most preferably milli-seconds. Thus, the transformation from solid to liquid to solid takes place in less than five seconds, preferably less than one second, and most preferably less than 0.1 second.

During this rapid transition, shear forces can act on the material to discretize the feedstock. Thus, liquiflash conditions involve the combination of temperature and force which induce an organic-based feedstock to flow and re-solidify into a changed shape as it is being discretized by the action of shear force. Preferably, the size and shape are highly consistent among the discretized particles. It is preferred that the shape be spheroidal and size distribution be limited, with only minor variations.

The highly consistent spheroidal shape and the narrow range of size distribution causes the shearlite particles to flow evenly and easily. The discrete shearlite particles produced are preferably microspheres, which as used herein preferably means sizes not greater than about 500 μm, more preferably not greater than about 400 μm, and most preferably not greater than about 300 μm. In a preferred method, the liquiflash conditions are provided by a spinning head having a heated peripheral barrier with exit openings provided therethrough for passage of feedstock flowing under centrifugal force. The shear force referred to above is imparted to flowing feedstock by resistance of air pressure against the liquiform feedstock as it exits the spinning head.

The ambient atmosphere can be undisturbed except by the motion of the spinning head. Alternatively, the ambient atmosphere about the spinning head can be a
positive counter or concurrent flow adjacent the outside surface of the processing barrier. This permits greater control of separation of the liquiform feedstock.

The discrete particles separated from the mass of flowing feedstock are cooled. In a preferred form of the present invention the discrete particles are monodispersed.

"Monodispersed" refers to the production of a plurality of uniform spherical particulates, e.g., shearlites.

It has been found that liquiflash conditions and the subsequent shear force imparted thereto in the method of the present invention can be provided by "barrier processing" which is closely akin to flash heat processing as described herein. The flash heat process is a process wherein feedstock can be introduced to a "cotton candy" fabricating type machine. The spinning machine used to achieve a flash heat process can be a cotton candy type machine such as the ECONO FLOSS Model 3017 manufactured by GOLD METAL PRODUCTS COMPANY of Cincinnati, Ohio. Machines useful in the process of the present invention can be found in U.S. Patent 5,458,823, incorporated herein by reference.

However, in order to implement the liquiflash process as required in the present invention, the flash heat apparatus and process have been modified. In particular, modifications have been made to deliver sufficient energy to the point of transformation of the feedstock, e.g., the barrier of the spinning head, to liquify it instantaneously.

As explained above, known methods for barrier processing generally result in a product having a wide variety of sizes and shapes. This is due to many factors, all of which contribute to a basic lack of control over the formation of particulates.

In the present invention, however, natural mass forming forces available in minute material masses, e.g., entropy, et al., provide a predictable uniform size. Thus, monodispersed means that at least about 40% by weight, preferably at least about 60% by weight and most preferably at least about 80% of the product herein have a largest diameter which is within 60% of the mean particle diameter. Particle diameter is the dimension which is the greatest straight line dimension in the largest plane taken through a three dimensional particulate. Generally, when the particulate is spheroidal in shape, the particulate diameter is the diameter of the spheroid. In a preferred
embodiment, monodispersability means that at least 40% of the particulates are within
50% of the mean particulate diameter, and, in a most preferred embodiment, within
40% of the mean particulate diameter.

In a preferred embodiment of the present invention, the feedstock material
includes a medicament so that the resulting product can be used in a delivery system
for a dosage unit.

Another preferred embodiment is a sucrose product having a highly consistent
small size and spheroidal shape. The size range is from 5 μm to 100 μm, and is
preferably from 10 μm to 50 μm -- ideally 15μ - 30μ, centered around 25 μm.

In one preferred embodiment the shearlite discrete particles consist of a
medicament which has a solid spherical body having substantially no discontinuity
therein. Consequently, the spherical body can be a substantially pure drug or active
ingredient which is at least 80% of the theoretical density of the drug at standard
temperature and pressure, and is preferably at least 90%, and most preferably not less
than 95% theoretical density.

The feedstocks contemplated for use herein must be capable of undergoing the
required transformations without substantial and preferably no significant deterioration
of the material present therein.

Considerations for successfully carrying out the objects of the present invention
reside in the appropriate combination of the following features:

I. spinner head;

II. liquiflash conditions of temperature and centrifugal force;

III. the character and size of the barrier; and

IV. the character of the ambient conditions adjacent the spinner head.

Spinner heads may be adapted to produce shearlite particles. In general, some
of the spinner heads presently available can be modified to provide sufficient energy to
the feedstock so that in the presence of appropriate centrifugal force the feedstock
transforms to liquiform and is processed substantially instantaneously. Gas (air)
resistance discretizes the feedstock. Elements identified hereinabove can be adjusted
to optimize discretization for a particular feedstock.
In order to deliver sufficient energy to achieve liquiflash conditions, the inventors herein have devised configurations of equipment in which the heat delivered to the barrier is increased. This requirement has been achieved in apparatus disclosed in commonly owned U.S. 5,458,823, which has been incorporated herein by reference. For example, the number of individual heaters at the periphery of the spinning head can be increased. Another way of increasing the thermal energy delivered to the feedstock is by providing a tortuous path which retards movement of feedstock through the barrier on the periphery of the spinning head. Those skilled in the art will appreciate that the combination of increasing the delivery of heat and retarding flow of feedstock can be combined by various design features to obtain optimum results in the process and, consequently, the product. As indicated above, it is intended to cover all such variations of control over the delivery of heat and the rate of passage of the feedstock through the barrier as a means of providing liquiflash conditions.

It is preferred that the surface of the spinner head which contacts the feedstock be coated with a low free surface energy substance. For example, a Teflon® based coating will reduce friction between the feedstock and the surface of the spinner head as the feedstock travels towards the processing boundary and is forced thereagainst.

Referring to Figures 2A, 2B and 2C, the unique phenomenon of liquiflash is schematically depicted. Centrifugal force created in the spinning head flings the feedstock F to the barrier found at the periphery of the spinning head. Heating elements H provided at the periphery reduce the feedstock to a liquiform condition wherein internal flow becomes unimpeded.

In this liquiform condition, centrifugal force moves the feedstock through the openings O between heating elements H provided in the peripheral barrier so that the liquid is exposed to shear force provided by the ambient atmosphere found immediately outside the head. It is believed that the flowing feedstock creeps as a layer l along the surface of the exterior of the head until a sufficient volume is built up in the Laminar flow whereby a tiny mass m of liquiform feedstock begins to form a generally deformed drop, e.g., a teardrop shape, T, which is met by the atmosphere surrounding the spinning head. The shear force imparted on the teardrop T being formed by the flowing feedstock separates a droplet D as a discrete particle by natural
mass separation. Natural mass separation at this point is the combination of weight, internal cohesive intra- and intermolecular forces present in the liquiform feedstock and adhesive forces between the liquiform feedstock and the exterior surface of the spinning head. Inasmuch as there is a continuous flow of feedstock, the teardrops are continuously formed and separated as discrete shearlite particles D. As a consequence of this unique process the discrete particles formed thereby have been found to be highly uniform microspheres, i.e., pearl like spheres having a size of not greater than 500 µm, and in most cases having a magnitude of between 25 and 300 µm.

Moreover, the particles produced as a result of this process have been found to have a high degree of purity. Thus, drugs which are processed in the absence of any additives whatsoever have been found to experience a change in morphology which makes them ideal for predictable drug delivery systems. The drug product can also be augmented by processing with additional ingredients which are active or inactive, e.g., delivery ingredients, taste masking ingredients, taste modifiers, dissolution retardants, dissolution expedients, etc.

It is also contemplated that the force required to separate the discrete shearlite particles can be varied by modifying the atmosphere surrounding the spinning head. For example, the apparatus can be operated in a chamber having multiples of atmospheric pressure, or virtually no pressure.

The conditions of liquiflash, i.e. principally temperature and centrifugal force, must be carefully controlled so that on melting to a degree that permits centrifugal force to move the liquiform material to and through the exit orifices, can be accomplished. To obtain this with pure compounds the operator can be guided by its known melting point. With mixtures of materials test melting points can be obtained as a rough guide before starting a run. With little experimentation, heater resistance power can be slowly supplied to a spinner head containing the material to be converted into shearlite microspheres and simultaneously increase rate of spinning of the head can be increased until liquiflash conditions are met. The appearance of microspheres of the desired size range verifies that the optimum liquiflash conditions have been met for this particular material. For instance in Example II, set forth below, acetaminophen powder m.p. 169-170.5°C, has been processed in the described apparatus and the heat
was progressively increased toward the melting point of the powder while the spinner head increased to about 3600 rpm. Upon melting, and when spheres in the size range of up to 420 μ appeared, this constituted the optimum liquiflash conditions for this size range shearlites of acetaminophen.

**TABLETING**

In prior art tableting processes, the particles are prepared by different methods. A wet granulation method has been shown in Figure 17 in comparison to the inventive process shown in Figure 18. In wet granulation procedures, individual powder particles are coated and then formed into agglomerates which are called granules. Fusion of the ingredients in prior art procedures depends in large part on compression of the ingredients. In the present invention, amalgamation of the ingredients occurs during shearlites formation entirely prior to compression.

Referring to Figure 18, it can be clearly seen that the inventive process eliminates many steps and/or ingredients required to prepare the feedstock for tableting by the prior art wet granulation method. Moreover, the present invention is also an improvement over traditional direct compression tableting procedures. Direct compression has been known in the art to define a process by which tablets are compressed directly from powder blends of the active ingredient and excipients, such as fillers, disintegrants, and lubricants, which will flow uniformly into a die cavity for tableting by compression. However, traditional direct compression still requires: 1) milling of drugs and excipients; 2) mixing of the ingredients; and 3) tablet compression. See *Pharmaceutical Dosage Forms*, edited by Lieberman et al., vol. 2, pages 112 and 147-161 (1980). The present invention significantly improves the traditional direct compression method by reducing the separate steps of milling and mixing and eliminating the need for excipients to provide adequate flow properties.

Referring to Figure 18 the process and apparatus of the present invention are schematically depicted. The process include liquiflash processing wherein the active (and/or inactive) ingredients are combined and shearlites particles are formed. These particles are readily flowable and can be transported automatically to and through tablet making machinery without the necessity of excipient(s), and without need for a
coating to facilitate flow. Moreover, the shearlite particles can be tableted without the
requirement of excipient(s) and/or coatings. Thus, the process of the present invention
is simply (1) the forming of shearlite particles followed by (2) direct tableting. "Direct
tableting" as used herein means without requirement of excipients and/or coatings, and
without required additional process steps and/or flow agents, if so desired. Thus, these
other ingredients, and/or steps (such as coatings) may be utilized--not out of necessity,
but to engineer or "fine tune" the desired product.

As previously described, it has been advantageously found that excipients in the
form of the shearlite particles overcome the disadvantages normally associated with the
use of such excipients in a non-shearlite condition. The transformation of an excipient
feedstock material to the form of shearlite particles provides the excipient with a shape
and size that is compatible with the active shearlite particles. This in turn enables the
tableting formulation to maintain a flowability that facilitates direct tableting of the
formulation.

Consequently, the mechanical system of the present invention is characterized
by a unique combination of apparatus characterized by the absence of devices such as
mixers, milling, machines, etc., which are generally included in tablet-making systems.
Referring again to Figure 18, the apparatus of the present invention is schematically
depicted as a shearlite device (such as those disclosed herein) and a
tablet-making machine which are simply connected for transfer of shearlite particles
from the shearlite device to the tablet-making machine. Transfer of shearlite particles
can be easily accomplished by uninterrupted transport over a conveyor which connects
the shearlite device and the tablet-making machine in Figure 18. The apparatus of the
present invention is defined herein mean "in the absence of required additional
apparatus and/or components." Other apparatus or devices, such as a coating device,
may be included to obtain desired result, but these additional devices are not required.

The advantage of the tableting procedure of the present invention are shown
schematically in Figures 19A, 19B, 20A and 20B. Figures 19A and 20A depict
respectively, a filled mold cavity (precompression) and the results of compressing the
feedstock in accordance with the present invention. Figures 19B and 20B depict,
respectively, the prior art process of filled mold cavity (precompression) and the results of compressing prior art feedstock.

In particular, in Figure 19A, shearlite particles are shown after they have been fed into a compression die. In Figure 19B pre-compression components of a tablet which have not been subjected to shearlite processing are depicted in a die. There are basically three components represented by +s, ∆s, and o's. Consequently, the ingredients are not part of flowable shearlite particles.

In Figure 19A, each of the components are part of the shearlite particles as, for example, an amalgam, while in Figure 19B the components are subject to separation as a result of the feeding mechanisms which direct the particles into the die cavity. The components are not amalgamate and can agglomerate in "clumps of components" as displayed in Figure 20B.

Figure 20A shows shearlite particles fused together with all components remaining in amalgam even under compression. Deformation resulting from the force of compression does not force the ingredients out of mixture or cause "clumping." The homogeneity of the mixture is not disturbed as a result of compression.

Figure 20B shows the compression stroke of the prior art process forcing the components into clumps. This phenomenon reduces the homogeneity. Consequently, particles will be together in a non-homogeneous mixture.

**SHEARLITE FEEDSTOCK**

Feedstock which is contemplated for use herein includes saccharides especially sugars such as sucrose, sugar alcohols such as mannitol, mixtures thereof, and medicaments which can include active agents alone or in combination with other active agents or other ingredients. Quite surprisingly, it has been found saccharides and drugs can be processed without deterioration.

Medicaments which can be used in the present invention are varied. A non-limiting list of active agents which can be included in medicaments herein is as follows: antitussives, antihistamines, decongestants, alkaloids, mineral supplements, laxatives, vitamins, antacids, ion exchange resins, anti-cholesterolemic, anti-lipid agents, antiarrhythmics, antipyretics, analgesics, appetite suppressants, expectorants, anti-
anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psycho-tropics, antimanics, stimulants, gastrointestinal agents, sedatives, antidiarrheal preparations, anti-anginal drugs, vasodialators, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, antitumor drugs, anticoagulants, antithrombotic drugs, hypnotics, anti-emetics, anti- nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants, mucolytics, anti-uricemia drugs and mixtures thereof. Other active ingredients contemplated for use in the present invention are H₂-antagonists.

Anti-inflammatory substances include non-steroidal anti-inflammatory agents selected from salicylates, acetic acids, propionic acids, fenamates, oxicams, tenidap and the like. A particularly preferred non-steroidal anti-inflammatory agent is ibuprofen which is a propionic acid anti-inflammatory agent. Other propionic acid anti-inflammatory agents includes flurbiprofen, naproxen, and ketoprofen.

Calcium carbonate (CaCO₃), alone or in combination with magnesium hydroxide and/or aluminum hydroxide, can be included with other feedstock used as a carrier. Thus, such antacid ingredients can be used in combination with H₂-antagonists, ibuprofen, ketoprofen, etc., which are capable of undergoing liquiflash processing.

Active antacid ingredients include, but are not limited to, the following:
aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-odibasic or mono-dibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.
Analgesics include aspirin, acetaminophen, and acetaminophen plus caffeine.

Other preferred drugs or other preferred active ingredients for use in the present invention include anti-diarrheals such as Imodium AD®, antihistamines, antitussives, decongestants, vitamins, and breath fresheners. Also contemplated for use herein are anxiolytics such as Xanax®, antipsychotics such as Clozaril® and Haldol®, non-steroidal anti-inflammatory (NSAID's) such as Voltaren® and Lodine®; antihistamines such as Seldane®, Hismanal®, Relafen®, and Tavist®; antiemetics such as Kytril® and Cesamet®; bronchodilators such as Bentolin®, Proventil®; antidepressants such as Prozac®, Zoloft®, and Paxil®; antiglobulins such as Imigran®, ACE-inhibitors such as Vasotec®, Capoten® and Zestril®, anti-Alzheimer agents, such as Nicergoline®, and Ca²⁺-antagonists such as Procardia®, Adalat®, and Calan®.

The popular H₂-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Alternatively, dosage units of the present invention can be formed from the shearlite particles of medicament mentioned above and an excipient material in a non-shearlite condition, e.g., a floss or powder.

Another aspect of the present invention is a new particulate resulting from providing a shearlite particulate substrate in combination of at least one coating. The substrate can either be a non-active ingredient such as a saccharide based material, preferably a sugar such as sucrose, or the substrate can be an active agent, or a combination of active agents. Thus, in one manifestation of this aspect of the invention the substrate can be sugar shearlite particles such as those produced in Example I herebelow. Drugs can then be coated thereover either alone or in combination with other types of coating materials. Further coatings can be added as desired.

Alternatively, the shearlite particles themselves can be an active ingredient or a combination of active ingredients such as those discussed above with respect to the formation of amalgams. As a result of the narrow size range and the unique and reproducible shape of the particle, coating material can be deposited highly efficiently
as very thin even coatings. Consequently, the desired effects such as time-release, flavor enhancement or alteration, can be achieved economically and efficiently.

In one specific embodiment of the present invention, the shearlite particles can be designed to deliver an active ingredient and an antidote. For example, a shearlite particle can be prepared from an active ingredient, an antidote, a non-active ingredient, or a combination of such ingredients. If the particle is an antidote, it can be coated with an active ingredient. If the particle is made from a non-active ingredient, it can be coated with an antidote and subsequently again coated with an active ingredient. In either case a controlled-release coating can be provided thereover and/or interspersed between coatings. Furthermore, another coating such as a muco-adhesive can be deposited to ensure that the active ingredient is delivered to the desired part of the body.

A further preferred embodiment of the present invention includes providing combinations of active ingredients which are designed as a cough and cold treatment. Thus, for example, two or more actives can be included in the feedstock to form an amalgam which can then be directly tableted to form a tablet or coated and then tableted.

In an additional embodiment, two or more combinations of ingredients that prior to the present invention were generally believed to be unstable, interactive or otherwise incompatible may be combined in the feedstock to produce shearlite particles or may be produced separately as shearlite products and coatings and subsequently combined.

"Controlled-release" is used herein to describe a method and composition for making an active ingredient available to the biological system of a host. Controlled-release includes the use of instantaneous release, delayed release, and sustained release. "Instantaneous release" is self-explanatory in that it refers to immediate release to the biosystem of the host. "Delayed release" means the active ingredient is not made available to the host until some time delay after administration. (Dosages are usually administered by oral ingestion in the context of the present invention, although other forms of administration are not precluded from the scope of the present invention). "Sustained Release" generally refers to release of active ingredient whereby the level of
active ingredient available to the host is maintained at some level over a period of time. The method of effecting each type of release can be varied.

The patent and scientific literature is replete with various sustained release (SR) methods and formulations. For common methods of obtaining SR systems, see Sustained and Controlled Release Drug Delivery Systems, Robinson, Joseph R., Ed., PP 138-171, 1978, Marcel Dekker, Inc. New York, NY. Sustained release can be effected by use of coatings, but the present invention also contemplates SR by incorporating the necessary ingredients in the shearlite particles themselves. Coatings which do not detract from the direct tableting aspect of the invention can also be used.

Conventional SR formulations are generally designed to release their actives over an extended period of time, usually 8-24 hours. Conventional SR formulations use waxes or hydrophilic gums to prolong the release of the active ingredients. Conventional waxes and waxy materials used in pharmaceutical formulations are carnauba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, partially hydrogenated vegetable oils, cerasin, paraffin, myristyl alcohol, stearyl alcohol, cetyl alcohol and stearic acid. They are generally used in amounts of about 10 to about 50% by weight of the total formulation.

Hydrophilic gums have also been known to be reasonably effective as SR carriers for both high-dose and low-dose drugs. Typical hydrophilic gums used as SR carrier materials are acacia, gelatin, tragacanth, veegum, xanthin gum, carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC). Generally these materials are present in amounts of about 10 to 50% by weight of the final formulation.

Starch USP (potato or corn) can be used as a component in controlled-release formulation. It generally functions in conventional applications as a diluent or as a disintegrant in oral dosage forms. Starch paste is also often used as a binder in these products. Various modified starches, such as carboxymethyl starch currently marketed under the trade name Explotab or Primojel are used as disintegrating agents. The literature discloses that native and modified starches are useful in promoting rapid release of drugs from solid oral dosage forms.
In all controlled release technologies it is desirable to be able to incorporate the active ingredient in its controlled-release pattern in a single dosage unit without deteriorating the active ingredient. Moreover, the dosage unit should be able to deliver the system without interfering with its release pattern.

Polymers are also quite useful in the present invention. Solution coatings and dispersion coatings can be used to coat the shearlite particles. Plasticizers are also normally included in both organic solvent systems and aqueous systems. Some polymers useful for coating include, but are not limited to, the following: methylcellulose (Methocel® A made by Dow Chemical), hydroxypropylmethylcellulose (Methocel® E provided by Dow Chemical or Pharmacoat® provided by Shin Etsu), ethyl cellulose, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate (provided by Eastman Kodak), carboxymethyl ethyl cellulose (Duodcel®/Freund), hydroxypropyl methylcellulose phthalate, polymethacrylic acid-methacrylic acid copolymer (Type A 1:1 Eudragit® L100; Type B 1:2 Eudragit® S100; and Type C 1:1 Eudragit® L100-55, aqueous dispersion 30% solids, Eudragit® L30D), poly(meth)acrylic ester: poly(ethyl acrylate, methyl methacrylate 2:1), Eudragit® NE30D aqueous dispersion 30% solids, polyaminomethacrylate Eudragit® E100, poly(trimethylammonioethyl methacrylate chloride)-ammoniomethacrylate copolymer, Eudragit® RL30D and Eudragit® RS30D.

Plasticizers used in the above solvent plasticizers which may be used in the present invention are as follows: diethyl phthalate, dibutyl phthalate, triethyl citrate, glycerol triacetate, and dibutyl sebacate.

Aqueous polymeric dispersions useful in the present invention include

Eudragit® L30D and RS/RL30D, and NE30D, Aquacoat brand ethyl cellulose, Surelease brand ethyl cellulose, EC brand N-10F ethyl cellulose, Aquateric brand cellulose acetate phthalate, Coateric brand Poly(vinyl acetate phthalate), and Aqoat brand hydroxypropyl methylcellulose acetate succinate. Most of these dispersions are latex, pseudolatex powder or micronized powder mediums.
Plasticizers which can be used include, but are not limited to, the following: propylene glycol, polyethylene glycol (PEG 400), triacetin, polysorbate 80, triethyl citrate, diethyl d-tartrate.

For example, enteric release agents and/or coating broadly include porous cellulose acetate phthalate (provided by Eastman Kodak) in combination with beeswax for blocking its pores. Other combinations include shellac and ethyl cellulose mixtures, and shellac, methyl alcohol and castor oil mixtures. Also an ethylene-vinyl acetate copolymer can be used, such as duPont ELVAX® 40.

Other enteric substances used in or with the present invention are polyacrylate substances bearing many carboxyl groups in their molecules as part of a shearlite amalgam or as a coating. Examples are methacrylic acids-ethyl acrylate copolymers [manufactured by Rhom-Pharma Co. (West Germany) Eudragit® L300D], methacrylic acid-methyl methacrylate copolymer (Eudragit® L or Eudragit®S), hydroxy propyl methyl cellulose phthalate (manufactured by Shin-Etsu Chemical Co., HP-50, HP-55, HP-55S), hydroxypropyl methyl cellulose acetate phthalate (manufactured by Shin-Etsu Chemical Co., AS-LG, AS-LF, AS-MG, AS-MF, AS-HG, AS-HF), carboxymethyl ethyl cellulose [manufactured by Fruent Industry Co. (Japan)], cellulose acetate phthalate, and vinyl methyl ether malic anhydride copolymer [manufactured by GAP Co. (US), AN-139, AN-169].

Preferably, Eudragit® L, Eudragit® S and HP 55 are employed, because they have high contents of carboxyl groups with high safety.

In general, processes known in the art for preparing coated particles can be used. For example, process for preparing particles as disclosed in U.S. Patent No. 4,971,805 are contemplated for use with the shearlite particles. These processes are incorporated herein by reference and the disclosure set forth in the '805 patent is specifically incorporated herein by reference. See also U.S. Patent No. 4,948,622 to Kokubo, et al. which is incorporated herein by reference.

In the Kokubo, et al. '622 patent, the granules, beads and tablets were coated with a dispersion of cellulose ether and then subjected to wax treatment with heating to form a masking layer of wax. It is also contemplated to use waxes as a coating material in the present invention. As previously mentioned waxes include carnauba,
beeswax, vegetable waxes, animal waxes (sperraceti) and synthetic wax such as carbowax, e.g., polyether. Also contemplated for use herein includes hydrocarbon waxes such as paraffins and petrolatums. Higher alcohols such as cetyl alcohol and stearyl alcohol, higher fatty acids such as stearic acids, esters of higher fatty acids, fatty acids esters of glycerins such as beef tallow, lard, hardened soybean oil and hardened castor oil and polyethylene glycols such as PEG-6000 and PEG-20,000 as well as various commercial products sold under the trade names of Lubri Wax - 100 prectrol, which is a mixture of mono-, di- and tripalmitates of glycerin, and the like. These wax materials can be used either singly or as a mixture of two kinds or more according to the need.

The present invention also contemplates the use of fats in the products produced by the present invention. Fats include esters of higher fatty acids, e.g., glycerides of C_{10-24} fatty acids, alcohols, salts, ethers or mixtures thereof. They are classed among the lipids. It is also contemplated that emulsifiers to be included in conjunction with the fats. Emulsifiers include salts of ethanolamines with fatty acids and sulfated fats and oils. Preferred fats include compositions which have mono-, di-or tri-glycerol esters of long chain of fatty acids. These include but are not limited to stearates, palmitates, laurates, linoleates, oleates, and residues or mixtures thereof having melting points greater than 50°C. U.S. Patent No. 5,213,810 is directed to compositions including these materials and the '810 reference is hereby incorporated.

The coating process can be effected by spray coating with multiple fats or waxes onto the shearlite particles.

Such coatings can typically be used for taste-masking and controlled-release. As a result of the high uniformity and narrow size distribution, shearlite particles permit the use of substantially less coating materials to produce the intended effect. Thus, with a single complete but thin coat, a high degree of taste-masking and efficient controlled-release can be effected.

In order to illucidate this benefit, an example has been included hereinbelow (Example XII) wherein ibuprofen feedstock is coated and compared to ibuprofen shearlite particles which are coated. The two coated ibuprofen materials were compared for taste. The coated ibuprofen which was not converted to shearlite
particles was unacceptable, whereas the processed ibuprofen (subsequently coated) was found to be highly acceptable. Microscopic examination of the unprocessed ibuprofen revealed agglomerated needles of ibuprofen which had varying thicknesses of coating. To the contrary, the shearlite ibuprofen particles displayed a uniform thickness of coating which is ideal for taste-masking and controlled-release.

The present invention contemplates a combination of a low melting fat or wax with an active ingredient which has been transformed to shearlite particles. The material is processed and fed to direct tableting. The fat or wax can also be used as a coating.

In yet another example of the unique advantage provided by the present invention, an antidote material can be transformed to shearlite particles in conjunction with an active ingredient. Both the antidote and the active ingredient may or may not include controlled-release agents to enhance dissolution or to retard dissolution. Any combination of active in antidote can be formulated depending on the need of the practitioner. The active agent can be the shearlite particle while the antidote can be the coating. Additional coatings can be included in a multiple coated product to provide active and antidote. Any combination of these agents suitable for the desired purpose are contemplated as covered by the present invention.

Furthermore, liquiflash processing and products from industrial chemicals which benefit from reduction in dusting and better flow properties are contemplated as part of the present invention. Such industrial chemicals include, but are not limited to, the following: phenol, styrene, butylated hydroxy anisole (BHA), tert-butylhydroxyhydroquinone (TBHQ), parabens, hydroquinone, insecticides, herbicides, combinations of insecticides and herbicides, anti-fungals and other agents which suffer from dusting which may cause explosion or may endanger personnel by contact therewith.

As described herein and as illustrated in the following examples, the shearlite particles produced in accordance with the present invention exhibit unexpectedly high flowability. That is, the shearlite particles produced under liquiflash conditions flow easily and evenly under the force of gravity. The term "flow" as used herein is defined to mean that greater than 95%, preferably greater than 98%, and more preferably substantially 100%, of the shearlite particles will flow away from a previously-
confining boundary (e.g., a wall of a vessel) without any significant adherence of the particles to the boundary. The particles will also flow away from the boundary without any significant caking or dusting of the particles. More to the point, the particles will flow away from such boundary at a low angle of repose. (The angle of repose defines the angle required to induce flow of the particles from a level "at rest" position.) The particles of the present invention exhibit an angle of repose of less than about 45°, and more preferably less than about 30°.

As will be apparent to those skilled in the art, the ability to convert a non-flowable material into a flowable material improves certain existing applications and processes, and also creates entirely new applications. Thus, any substance capable of being subjected to liquiflash conditions may be processed to provide shearlite particles exhibiting enhanced flowability, without the negative properties commonly associated with multiparticulates such as adherence to boundaries, caking and/or dusting. Moreover, it is contemplated that substances which may not themselves be subjected to liquiflash conditions can be carried by shearlite particles of a compatible material.

**SHEARLITE DEVICE**

Referring to Figures 3A, 3B, and 3C, a first spinning head has been shown which can be used in the liquiflash process. The assembled head 10 is depicted in Figure 3A. This head is of the type which is disclosed in U.S. Serial No. 07/954,257 filed September 30, 1992 and its continuation in part application bearing U.S. Serial No. 08/192,133 filed February 4, 1994 (both of which are incorporated herein by reference).

Referring to the spinning head shown in Figure 3A, a heating element(s) are depicted as continuous cable 12 which is helically wound thereabout. The cable heating element can consist of several cables or even just one cable which is continuously wound around the periphery of the head 10. The embodiments disclosed in the two (2) applications referred to above have certain characteristics, such as slits, etc., for flash flow processing.

In the present invention, however, the small openings in the head are achieved by lacing a shim 14 between the coils of the heater 10. Figure 3C is a diagrammatic
sketch of this embodiment. The shim material 14 is preferably a very thin strip of food grade metal such as stainless steel. The thickness of the shim can be from .001 to .006 inch in thickness. Preferably, the thickness of the shim is about 0.002 inch. The shim can be about 0.100 inches wide. The lacing can be provided at several locations around the perimeter of the head. Furthermore, teflon coating insulators can be provided in conjunction with the heating cable in order to reduce the friction of the surface of the heating elements.

Yet another embodiment of apparatus which can be used in the present invention is shown in Figures 4A, 4B, and 4C. The apparatus of the type used herein has been disclosed in U.S. Patent 5,445,769, which is incorporated herein by reference.

Referring to Figures 4A-C, a spinning head silhouette 16 is shown having spaced apart protruding ribs 17 in which tiny openings have been drilled. Preferably the openings are on the order of 0.020 inches in diameter. Referring to Figure 4B, a cut-away section of the head of Figure 4A is shown with the holes 18 in the raised ribs 17. A heating element 19 can then be wound around the outside surface of the head 16 in order to provide heat sufficient to melt the feedstock on the interior surface of the spinning head.

The spacing and configuration of the holes can be adjusted by those skilled in the art to achieve the results which are desired. A discussion of this has been fully set forth in the above-identified pending U.S. application. Other variations of this embodiment including size of holes, spacing between the holes, and shape of the openings through the head can be varied depending upon the application. It has also been found that the openings in the configuration shown in Figures 4A-C are ideally provided by drilling with a laser beam.

Yet another apparatus used in the present process is shown in Figures 5A, 5B, and 5C. The apparatus shown in these figures is of the type disclosed in commonly owned U.S. Patent 5,458,823. In Figure 5A, a spinning head 20 is shown with upright closely spaced heating elements 22. In a preferred embodiment, electrical current can be provided to each element. In this way, a high degree of control can be maintained over the heat supplied to the processing barrier. Furthermore, the elements can be
spaced as closely together as possible in order to provide a restricted passageway for passage of liquiform material.

In another preferred embodiment as shown in Figure 5B, a continuous screen can be interwoven between the heating elements in order to affect the size of openings through the barrier and also to provide a barrier with relief which enhances drop formation. It has been found that screens with 60 mesh and 30 mesh can be used. The actual opening size, e.g., mesh, can be selected by the artisan.

In yet another embodiment, each heating element 22 can be individually provided with a shim 24 which further reduce the size between the heating elements. As a result of using the shims, opening sizes on the order of 0.005-0.007 inch can be reduced to openings on the order of 0.002 inch.

In each of the embodiments, the head has a diameter of about 3 inches. The apparatus in the present invention has currently been run at a rotational velocity in the area from around 3,000-5,000 rpm. The actual speed can vary from as low as 500 rpm to as great as 100,000 rpm. It is contemplated that many commercial embodiments will be run in the area of 35,000-40,000 rpm. Once again, the size of the head and the rotational speed of the head will depend on the desired results, and other factors such as the size and nature of the feedstock, and the ambient atmosphere adjacent to the spinning head.

Referring to Figures 6A and 6B, a further modification of spinner head 10, particular useful with pharmaceutical product, as described above, is shown. Spinner head 10 is modified in a manner similar to the embodiment set forth above wherein a number of tubular heating elements 30 have been provided. However, in order to narrow the opening through which feedstock materials expelled, this embodiment employs individual modular blocks 32 which fit over heating elements 30.

Each modular block 32 includes a metallic heat conductive body having a central cylindrical passage 34 therethrough which is constructed and arranged to accommodate individual tubular heating elements 30. Each modular block 30 also has a generally trapezoidal cross-section having a smaller wall 36 which faces inwardly toward the feedstock chamber and an opposite wider outer wall 38. In a preferred form, the outer wall 38 may include angular surface 39, which provides for longer
opposed side walls 40 and 42 without increasing the mass of modular blocks 30. The
modular blocks 30 can be slipped over tubular heating elements 30. As shown in
Figure 6B, walls 40 and 42 form radially directed slots between adjacent modular
blocks 32 through which feedstock material may be processed and expelled in a
manner similar to that explained above with respect to the previous embodiments. The
radially directed slots can be adjusted to alter the size of the passage through which the
feedstock material is expelled.

As shown in Figure 6B, blocks 32 can be rotated about tubular heating element
30 (see arrows B) to cant or twist the blocks, thereby changing the spacing and/or
direction of the slots. The rotation of blocks 32 can be accomplished individually or
may be rotated in unison with an appropriate mechanism (not shown). With such a
mechanism, modular blocks 32 may move in a manner similar to an iris diaphragm of a
camera to increase or decrease the size of the passage defined by the slots.

A further construction of block 50 is shown in Figure 7, where transverse slots
are formed. Modular block 50 can include a body formed to have a series of vertically
spaced horizontally extending fins 52. Modular block 50 can be constructed so that
one set of fins 52a interleave with an adjacent set of fins 52b of an adjacent modular
block 50. In this manner a series of vertically spaced transverse slots 54 are formed
through which feedstock material may be processed.

Referring now to Figure 8, still further embodiment of the spinner head of the
present invention is shown. Spinner head 55 of the present invention includes a
generally circumferential array 55a of horizontally disposed tubular heating elements
56. A set of vertically spaced horizontally extending heating elements 56 can be
positioned between an adjacent pair of vertically extending support elements 57. Each
of support elements 57 can be positioned and spaced in circumferential fashion about
base 55b. Appropriately, configured retaining openings 55c are provided to
accommodate support elements 57.

Horizontally disposed tubular heating elements 56 can be of similar
construction to tubular elements previously described hereinabove. All or selected
ones of tubular heating elements 56 may be individually powered in accordance with
the present invention. It is also contemplated that vertical support elements 57 in
additional to supporting horizontally extending tubular heating elements 56 may also provide a common power bus to energize the individual tubular heating elements. Vertical support elements 57 include appropriate openings spaced therealong which accommodate the ends of tubular heating elements 56 therein in an interference fit such that the securement between the tubular heating elements 56 and the vertical support elements 57 is achieved under both ambient and running temperatures. The space is between adjacent horizontally disposed tubular heating elements 56 can be adjusted to vary the openings through which feedstock material is processed.

It is further contemplated that tubular heating elements of uniform size and configuration or of differing size and configuration may be employed within the same spinner head. An arrangement of the same or different size tubular heating elements allows the spinner head to be statically and/or diametrically balanced. As described above with respect to the spinner head having vertically disposed tubular heating elements, horizontally positioned tubular heating elements 56 of the present embodiment can be canted are skewed with respect to support elements 57.

Furthermore, even though Figure 8 shows one circumferential arrangement of array 55a, other arrangements are also within the contemplation of the present invention. Further, plural concentric sets of arrays of horizontally disposed tubular heating elements are within the contemplation of the present invention.

The embodiment shown in Figure 8 also has particular utility with respect to pharmaceutical products since the individual tubular heating elements 56 supported between a common bus such as vertical support element 57 can be easily removed for cleaning as necessary in the processing of pharmaceutical products.

Those skilled in the art will appreciate that other factors will directly affect the size and shape of the apparatus, and is intended to include all variations that come within the spirit of the invention as defined in the appended claims.

**DIRECT TABLETING**

Some details of the tableting process are discussed under “Tableting” above.
Generally, shearlite particles, optionally including other materials other than shearlite particles, are tableted immediately after their production using conventional tableting devices and processes. Die and punch devices are generally suitable.

In a preferred process, shearlites containing active agent(s) are screened and mixed with one or more excipients. The mixture is then fed to a die and tableting device. Using compaction forces of 0.5 tons to 5 tons pressure, tablets are made.

In practicing the invention, the mixture to be tableted flows freely in the apparatus and is easily directed to the die. Also, the tablets do not display capping or cracking in the apparatus. In most cases, stacking is minimal, so that extraction from the tableting apparatus is facilitated.

In a preferred process, shearlite particles of sucrose are mixed with shearlite particles containing a drug and one or more excipients and made into tablets using the following steps:

(a) drug-containing shearlites are mixed with at one binder;

(b) sucrose shearlites are added, in several increments or in one addition, and mixed;

(c) additional excipients are then added to the mixture of step (b) and mixed; and

(d) the mixture of step (c) is fed directly into a die and punch type device.

Another aspect of the present invention is an apparatus for making dosage unit which includes a shearlite particle making device ("shearlite device") connected for direct feed of shearlite particles to a tablet-making machine. The shearlite device is one such as that described in the parent application, and tablet-making machine similar to those known in the art can be used in the present invention. Direct feed from the shearlite device to the tablet-making machine can be a particulate conveyor (e.g., conduit, tray, track, etc.) which is used to transfer shearlite particles and is used herein to identify the lack of required assisting mechanisms.

As a result of the present invention, substances which are known to require multiple preparation steps and/or additional ingredients to prepare a tablet, can now be tableted without such steps and/or ingredients.
For example, ascorbic acid, which was previously considered tabletable only after preparation with additional steps and ingredients, can now be directly tableted in the sense of the present invention.

Another advantage of the present invention is that excipients can be provided having a particle size and shape thoroughly compatible with the active-containing shearlite particles. This condition, in turn, provides complete physical homogeneity and enhances machine handling of the tableting formulation. More specifically, it has been found that the excellent flowability of the tableting formulation to the tableting apparatus is maintained while utilizing non-active shearlite particles as an excipient.

Other and further advantages of the present invention will be realized by those skilled in the art in view of the disclosure set forth herein, and it is intended to include all such advantages as part of the present invention, and to be included within the scope of the claims appended hereto.

**EXAMPLES**

**EXAMPLE 1**

**Sucrose Spheres**

In the first example, the apparatus disclosed in figure 5A was used in the liquiflash process for transforming sucrose. The opening between adjacent heating elements in the apparatus shown in Figure 5A was 0.20 inches. The head was spun at 3600 rpm as it was heated to 180°C.

As the temperature reached its peak, sucrose was subjected to liquiflash conditions and exited the spinning head as a result of centrifugal force. Solid spheres (i.e., shearlite particles) were formed which ranged in size from about 100-200 μm in diameter. The very unique and uniform size distribution is clearly shown in the photomicrograph herein at Figure 9. The magnification of Figure is 50.

In this particular case, the size of the rock candy prevented passage through the barrier and provided delay at the barrier sufficient to cause sucrose to transform to liquiform and be instantaneously processed to the highly uniform microspheres depicted in Figure 9. These spheres are substantially solid throughout, and can be used in a variety of ways, such as a substrate for depositing of material thereon.
It should be noted that microspheres having a diameter of from about 5-50 μm and preferably around 25 μm are excellent for use in conjunction with chocolate. Very small and highly uniform microspheres enable the practitioner to provide a highly acceptable low fat chocolate product. Thus, the processing of sucrose, such as in the form of rock sugar, could be used quite effectively to provide an ingredient for the preparation of a chocolate product.

EXAMPLE II

Acetaminophen Spheres

In this example, acetaminophen was processed using the apparatus showed in Figure 5B wherein the screen was a 60 mesh screen positioned in serpentine fashion between adjacent heating elements. Acetaminophen powder (melting point 169-170.5°C) was fed to a spinning head run at about 3600 rpm. While the feedstock was subjected to centrifugal force, the temperature was raised until the acetaminophen powder was reduced to liquiform. The force generated by the spinning head expelled acetaminophen out of the spinner head, and impelled it through the 60 mesh screen. The product was permitted to free fall below the head a distance of from about 6 to 8 feet.

During this transition, fine spheres all of which were less than about 420 μm, were formed. 4.33 kilograms of this material was passed through a 40 mesh screen and 1.39 kilogram of the product was retained.

The feedstock, and product resulting from this experiment have been shown herein in Figures 1A, 1B, and 1C. In Figure 1B, a photomicrograph of the feedstock is shown at 125x magnification. After processing, the resulting product was collected and a photomicrograph taken which is shown in Figure 1A. As can be seen, a highly consistent and very uniform spherical product was produced. Comparing the product shown in Figure 1A to the feedstock at Figure 1B, the skilled artisan can readily ascertain the enhanced predictability and processability which is provided as a result of the present invention. Figure 1C is a photomicrograph at 500x magnification taken of a cross section of a sphere shown in Figure 1A. As can be seen, the sphere is substantially solid throughout having virtually no openings or voids therein. Once
again, this product enables the artisan to provide a highly efficient drug product which can be used readily in delivery systems.

**EXAMPLE III**

**Coated Acetaminophen Spheres**

Acetaminophen spheres prepared in Example II, were then coated with a formula consisting of 2.5% Eudragit® E100, 7.5% ethocel in a solvent having acetone and methanol in 8 to 1 ratio. Eudragit® is a polymer of methacrylic acid and methyl methacrylate available from Rohm Pharma, Wetterstadt, Germany.

The finished product provided 568 grams of finely coated acetaminophen beads. The coated product of the present example has been shown herein in Figure 10 at 125x magnification. A very uniform coated product has been shown which can be easily used in feeding the coated active ingredient to machinery for tableting and for the purpose of filling capsules.

Thin, uniform coatings such as that provided herein results in much less coating material required to obtain better resulting taste masking and controlled release. As a result of the monodispersed characteristic of the present product, there is less loss of product as a result of oversize material.

Coating in general is tremendously enhanced by providing a uniformly dispersed microsphere of the present invention. For example, in fluidized-bed type coating, the equilibrium condition established in the fluidized bed has a tendency to retain particles having a similar size for consistent and efficient coating. Thus, large and small particles outside the range of the uniform particle size leave the bed during coating. In that case, the active ingredient must be recycled and reprocessed to obtain the active ingredient for coating. In the present invention, non-uniform sizes are virtually eliminated.

**EXAMPLE IV**

**Ibuprofen Spheres**

Using the same apparatus as shown in Figure 5B, with a 60 mesh screen, ibuprofen was processed in accordance with the present invention.
An ibuprofen powder feedstock was fed to the spinning head and the head was rotated at about 4800 rpm while the heating elements were raised to a temperature which produced the liquiflash conditions. The feedstock also consisted of 15% Compritol 888 ATO and 5% Gelucire 50/13. (Compritol 888 ATO is a glycerol behenate NF made available by Gattefosse S.A., a French company. Gelucire is surfactant also available from Gattefosse S.A.).

The spinning head forced the material through the screen and the product was permitted to free fall a distance of from 6-8 feet below the spinning head. The product collected is shown in the photomicrograph of Figure 11 which has a magnification of 50x. As can be seen from Figure 11, the spheres have a highly consistent particle size ranging from about 50-200 microns in diameter.

The product was also subjected to dissolution testing to determine the time required for dissolution of the active ingredient. The monograph is provided by the U.S. Pharmacopoeial Convention, Inc. in the U.S. Pharmacopoeial National Formulary Monograph For Ibuprofen Dissolution Study, U.S. 23 NF 18, page 786 (1995). At a composition level of 80% ibuprofen, it can be seen that the time for dissolution of most of the ibuprofen occurred at about 15 minutes and virtually total dissolution occurred at around 20-25 minutes. These results show high predictability for delivery to a bio-system by use of microspheres produced in accordance with the present invention.

EXAMPLE V

Ascorbic Acid Spheres

In this Example, ascorbic acid was processed by the liquiflash process using the apparatus described in Figure 5C. As a result of the short brass veins having a thickness of about 0.006 inches surrounding each of the heating elements, gaps of 0.002 inches were provided. Moreover, the head was positioned 10 feet from the collecting surface to permit an unobstructed formation and solidification of shearlite particles in accordance with the present invention.

Ascorbic acid powder was fed into the spinner revolving at about 1800 rpm while the head was heated to a point at which the powder was changed to liquiform for
purposes of liquiflash processing. Fine beads were expelled from the spinning head. Bead formation began after about 15 seconds and the product formation was completed in about 15-20 seconds actual spinning time.

The bead size production was as follows: 0.10% retained on No. 10 mesh; 5 0.62% on No. 20 mesh; 21.10% on No. 40 mesh; 40.35% on No. 60 mesh; 23.10% on No. 80 mesh; and 14.70% passed through No. 80 mesh. Thus, it can be seen that a high degree of predictability of shearlites were produced from ascorbic acid using the process of the present invention.

EXAMPLE VI

Ascorbic Acid Tablet Production Without A Binder

The ascorbic acids shearlites particles produced in accordance with Example V were classified according sieve size. The portion passing through the No. 80 mesh was used to feed a tableting press. The tableting press used was a Specac Model 15.011 tablet press.

Quite interestingly, the ascorbic acid product was able to be fed efficiently into the tablet press using a very small angle of repose. By angle of repose, it is meant the angle required to induce flow of the tablet feedstock into the tablet press. A low angle of repose is highly desirable for purpose of efficient processing.

Tablets were produced under 42 tons per square inch of pressure. The resulting tablets displayed excellent cohesiveness and have a shiny surface which exhibited no sticking during removal from the die. Moreover, the superior tablet product prepared as a result of the present invention did not require a binder or any other additive to ensure cohesiveness of the tablet.

EXAMPLE VII

Pseudoephedrine Beads

Two experiments were run to determine the processability of pseudoephedrine as a feedstock material. The apparatus used in these examples is that depicted and described in Figures 4A, 4B, and 4C.
A feedstock consisting of 95% pseudoephedrine (Kroll 331151) and 5% polyethylene glycol (PEG 1450) was prepared by melting the polyethylene glycol and adding thereto the pseudoephedrine and blending and then permitting the mixtures to solidify. The solidified mixture was then powdered in a grinding apparatus.

The spinning head was spun at 3300 rpm and the feedstock material was introduced until the material was reduced to liquiflash condition. The product resulting therefrom was very uniform in shape and the majority of the spheres were around 160 microns.

The results of this first experiment are shown in the photomicrograph of Figure 12A. The product was a very uniform spherical bead which demonstrated immediate dissolution of the active ingredient. The actual content of pseudoephedrine in the product shown in Figure 12A and 12B was 95%.

A second portion of this example was performed using the same ingredients as reported in the first experiment and the outcome was also similar.

The product, which has been shown here in Figure 12B has a very uniform spherical shape having a size of between 160 and 180 µm. The actual content of active ingredient was 96.06%.

**EXAMPLE VIII**

**Pseudoephedrine And Glycerol Monostearate**

In this example, 30% pseudoephedrine and 70% glycerol monostearate (Myverol 18-06) was blended and introduced to the apparatus shown in Figure 4A, 4B, and 4C. The head was spun at 3300 rpm and the temperature raised until the feedstock became liquiform.

The product formed as a result of the liquiflash processing was a uniform spherical product ideally suited for inclusion in a delivery system. The product is shown in Figure 13, which is a photomicrograph taken at 50x magnification.
EXAMPLE IX

Dextromethorphan and Glycerol Monostearate

In this example, the active, dextromethorphan, was mixed with glycerol monostearate (Myverol 18-06). Dextromethorphan HBr (30%) was mixed with 70% Myverol 18-06 brand glycerol monostearate blended and then introduced to a spinning head as described above.

The spinning head was run at 3300 rpm and the temperature raised until the feedstock was processed as a liquiform. Spheres appeared as two major size groups, one at the 40 to 80 micron range and another group at the 160-200 micron range. These two groups were very uniform in shape and many spheres showed small crystalline particles encapsulated within them. The product was very clean and have been shown in the photomicrograph at 50x magnification in Figure 14.

EXAMPLE X

Dextromethorphan-Pseudoephedrine Amalgam

In this example, a cough and cold treatment was produced by preparing an amalgam from pseudoephedrine and dextromethorphan. Shearlite particles were made from the two active ingredients. Dextromethorphan HBr and pseudoephedrine HCl were mixed with Myverol 18-06 in amounts which provided 12.5% dextromethorphan, 25% pseudoephedrine, and 62.5% Myverol. The active agents were mixed and then added to Myverol after which they were blended. The blend was then subjected to liquiflash processing at 3300 rpm in an apparatus shown in Figures 4A-C.

The product was a shearlite particle very uniform in shape and size. Two size groups were produced, one between 20 and 80 microns and another between 120 and 220 microns. A photomicrograph of the product is shown in Figure 15.

The product was an excellent amalgam which can be used as a cough and cold medicinal treatment.
EXAMPLE XI
Chlorpheniramine-Diphenhydramine-Pseudoephredine Amalgam

In this example, the active ingredients were combined to provide another cough and cold treatment medicament. In particular, chlorpheniramine maleate was combined at a rate of 2.8% with 17.5% diphenhydramine HCl and 21% pseudoephredine HCl in combination with 58.7% Myverol 18-06. The active ingredients were blended and then mixed with Myverol and again blended.

The resulting mixture was liquiflash processed in an apparatus such as that shown in Figures 4A-C at 3300 rpm. Photomicrographs of the products produced in accordance with this example are shown in Figure 16.

Excellent shearlite particles were produced with the combination of the three drugs. Two major size ranges were produced, one at 40-80 microns and another at 160-220 microns.

This example shows that true amalgams can be formed of different active ingredients to provide medicinal treatments to suit the medical practitioner. Furthermore, coatings can be provided as desired in accordance with the present invention. Thus, controlled-release and taste masking can be effected by coating the shearlite particles.

EXAMPLE XII
Taste Comparison of Coated Unprocessed Ibuprofen
and Coated Processed Ibuprofen

Raw ibuprofen feedstock was coated with Ethocel™ brand ethylcellulose:PVP blend at 90:10 ratio. The coating were deposited at a rate of 10% coating.

Furthermore, ibuprofen shearlite particles prepared as set forth in Example IV were also coated at a rate of 10% coating with Ethocel™ brand coating.

Products resulting from both coating procedures were then subjected to a taste panel to determine whether or not effective taste masking had been accomplished. In a comparison between the two products, it was found that the raw ibuprofen was not effectively taste masked, while the processed ibuprofen had a high degree of taste masking.
Moreover, upon microscopic inspection, it was seen that the coating on unprocessed ibuprofen was uneven, whereas the processed ibuprofen was evenly coated with a thin coating of the Ethocel™ brand coating.

Therefore, it can be seen that active agents converted to shearlite particles by being subjected to liquiflash conditions provide a excellent substrate for applying coating which masks the unappealing taste of the active agent.

**EXAMPLE XIII**

**Demonstration of Enhanced Flowability**

Experiments were also conducted to demonstrate the enhanced flowability resulting from subjecting a feedstock material to liquiflash processing.

In one method, a flow rate test was conducted by using a funnel having a set diameter of 20 millimeters at the outlet thereof. A measured weight of raw feedstock, i.e., 30 grams, was poured into the funnel while blocking the outlet side. The flow was then timed upon unblocking the outlet. The active ingredients used in the test were acetaminophin and ibuprofen.

Shearlite particles of both ingredients were prepared using the apparatus shown in Figure 4A-C. The ibuprofen was processed using 80% ibuprofen, 15% Compritol 888 ATO and 5% Gelucire. Acetaminophin was processed without the addition of other ingredients.

The unprocessed ibuprofen and acetaminophin did not flow from the exit opening of the funnel even after administering tapping on the side of the funnel.

Both the ibuprofen and the acetaminophine which had been processed under liquiflash conditions, however, exit the opening of the funnel. The ibuprofen formula required one tap on the top of the funnel and the entire 30 grams emptied in only one second. The processed acetaminophin required no tapping on the funnel and passed through the exit opening of the funnel in less than one second.

Thus, the present invention can be seen to be highly effective in improving the flow characteristic of active ingredients.
EXAMPLE XIV

Further Demonstration of Improved Flow Characteristic

In this example raw active agent and shearlite particles were tested to compare improvement of the angle of repose. Thus, the ability of the raw material to flow was directly compared to the flowability of the shearlite particle resulting from the present invention.

The method used to measure the angle of repose is a fixed cone method. Reference: "Multi-Particle Oral Drug Delivery," Isaac Ghebre-Sellassie, Vol. 65, Marcel Dekker, Inc., New York. In this method, powder is dropped through a funnel at a controlled distance from a dish which has vertical sides. The powder is poured until it just touches the tip of the funnel. The radius of the powder circle in the dish and the height to the tip of the funnel are measured. The comparison test were run by clamping a funnel 14 millimeters above the bottom of the glass petri dish. The angle of repose is then calculated using the following equation $\tan \phi = h/r$ or $\phi = \arctan h/r$.

The results of the test indicated that only the shearlite particles of acetaminophine and ibuprofen flowed through the funnel and therefore possess a measurable angle of repose. The angle of repose is also very low, i.e., less than 45°.

The results of the flow test have been set forth hereinbelow in the angle of repose table, Table 1.

<table>
<thead>
<tr>
<th>Material</th>
<th>Flow Rate</th>
<th>Angle of Repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processed APAP</td>
<td>less then 1 second</td>
<td>19.53°</td>
</tr>
<tr>
<td>100% Non-Processed APAP</td>
<td>No Flow</td>
<td>NA</td>
</tr>
<tr>
<td>Processed Ibuprofen</td>
<td>1 second</td>
<td>22.93°</td>
</tr>
<tr>
<td>Unprocessed Ibuprofen</td>
<td>No Flow</td>
<td>NA</td>
</tr>
<tr>
<td>100% Ibuprofen Drug Unprocessed</td>
<td>No Flow</td>
<td>NA</td>
</tr>
</tbody>
</table>
It can be seen that the process of the present invention provides an active ingredient with significantly enhanced flow characteristic. Basically, it converts non-flowable material to flowable material and improves flowability where there is little or no flow capability.

EXAMPLE XV

Sucrose/Mannitol Spheres

Following the procedure of Example I, a 50-50 weight percent (wt. %) mixture of granulated sucrose and mannitol were subjected to liquiflash conditions utilizing a spinning head at 3600 rpm at approximately 195°C. The resulting product was 100% distribution of solid spheres. These solid spheres, as in Example I, ranged in size from about 100 to about 200 μm in diameter. These spheres are substantially solid throughout, and can be used in the variety of ways, such as an excipient in the production of dosage units. More importantly, the use of a 50-50 wt. % mixture of sucrose and mannitol facilitated 100% distribution of spheres. Thus, the utilization of a 50-50 wt. % mixture of sucrose and mannitol facilitated a more efficient production of the shearlite particles of the present invention.

EXAMPLE XVI

Direct Tableting Example

Acetaminophen shearlite particles, i.e., microspheres, prepared in accordance with Example II were used to determine whether or not direct tableting of acetaminophen microspheres could be accomplished. The present example set forth the results of an attempt to deliver the acetaminophen microspheres directly to a tableting machine and compressing under pressures of from 0.5 to 5 tons of force. In order to prepare the microspheres for tableting, 500 grams of 100% acetaminophen microspheres were passed through a 40 mesh screen and combined with approximately 26.5 grams of sodium starch glycolate sold under the trademark EXPLOTAB® by Edward Mendell Co.
The microsphere material was fed directly to a single press twelve (12) millimeter die and punch tableting apparatus. Compaction forces of from 0.5 tons to 5 tons were used, i.e., 0.5 ton, 1 ton, 2 tons, 3 tons, 4 tons and 5 tons of pressure.

The tablets made in accordance with the present example displayed no capping or cracking and were rated as "non-sticky" to the tableting apparatus. Moreover, the tablet mixture was free flowing and easily directed to the twelve (12) millimeter die.

Each of the tablets were then immersed in an aqueous environment and permitted to dissolve. As expected, tablets compressed at 0.5 tons dissolved somewhat faster, while the tablets prepared under increasingly greater compaction pressure disintegrated more slowly.

It is also important to note that in the present example, the microspheres used for tableting readily flowed into the die cavity and are considered suitable for feeding into automated tableting machines. Thus, the experiment reported herein in Example XV demonstrates the ability to subject microspheres to direct tableting without requirement of additional interim steps usually required to effect tableting in tableting machines.

**SHEARLITE EXCIPIENT EXAMPLES**

In accordance with the present invention various active-containing tableting formulations were prepared using excipient shearlite particles and active-containing shearlite particles. A summary of the range of ingredients to be used is shown in Table 2.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Range</th>
<th>Preferred Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient Shearlite Particles</td>
<td>0 - 99 wt.%</td>
<td>49.25 - 85 wt.%</td>
</tr>
<tr>
<td>Active-Containing Shearlite Particles</td>
<td>1 - 100 wt.%</td>
<td>15 - 50 wt.%</td>
</tr>
<tr>
<td>Flavoring Agents (Including Sweeteners)</td>
<td>0 - 20 wt.%</td>
<td>0.5 - 15 wt.%</td>
</tr>
<tr>
<td>Other Ingredients (E.g., Humectants, Flow Agents, Binding Agents, Etc)</td>
<td>0 - 15 wt.%</td>
<td>0.25 - 6 wt.%</td>
</tr>
</tbody>
</table>
EXAMPLE XVII

Ibuprofen Tablets Utilizing Amorphous Sucrose Spheres

Ibuprofen tablets were prepared utilizing the amorphous sucrose spheres (shearlite particles) prepared in accordance with Example I, and Ibuprofen shearlite particles. The Ibuprofen shearlite particles were formed from a composition containing 88 wt. % ibuprofen, 10 wt. % Compritol 888, 2 wt. % Gelucire 50/13 core with a 12 wt. % coating of Eudragit® NE 30D, HPMCP, microtalc, and adipic acid, to produce a composition having 77.4 wt. % total active ingredient.

The tableting formulation was prepared in the following manner. First, approximately 34.44 wt. % of ibuprofen shearlite particles was measured, to which 2.0 wt. % glycerin (a binding agent) was added thereto. This mixture was agitated by hand for approximately 30 seconds. The mixture was then placed in a turbulent mixer and agitated for approximately three minutes. Thereafter, 61.56 wt. % sucrose shearlite particles was measured and added to the ibuprofen particles in 1/3 increments. The mixture was agitated in the turbulent mixer after each addition. After the addition of the last increment, 0.5 wt. % lemon flavoring agent, 0.5 wt. % whipped cream flavoring agent, 0.5 wt. % aspartame and 0.5 wt. % citric acid were added to form a 100 wt. % mixture. The resulting mixture was then reagitated for approximately two minutes in the mixer.

The tableting formulation was then fed directly into a single press 18 millimeter die and punch tableting apparatus. Tablets were formed utilizing 60 pounds per square inch (psi) at a 0.2 second compression duration. The resulting product of the compression were tablets that were too thin. This procedure was then repeated utilizing a 15 millimeter die and punch tableting apparatus. The resulting tablets exhibited satisfactory cohesion.

To ascertain if tablet hardness could be improved by an increase in compression force, the above procedure was repeated utilizing increased compression forces. A first run was conducted utilizing a compression force of 80 psi with a 15 millimeter die and punch tableting apparatus for a compression duration of 0.2 seconds. The resulting tablets exhibited an improved hardness in comparison to the tablets produced with a compression force of 60 psi. The compression duration was subsequently
increased to 0.6 seconds to ascertain if an improvement in hardness could be achieved. The increased duration of compression did not effect the tablet hardness. The compression force was increased to 100 psi with a compression duration of 0.2 seconds. As a result of this increased compression force, a greater effort was required to remove the tablets from the tableting apparatus. Thus, a compression force of 80 psi at a compression duration of 0.2 seconds provided the best results in tablet formation.

EXAMPLE XVIII

In an attempt to improve extraction of the tablets from the tableting apparatus, various concentrations of a flow agent, magnesium stearate, were added to the tableting formulation of Example XVII. In a first run, 0.5 wt. % of magnesium stearate was added to a sample of the tableting formulation of Example VIII. The tableting formulation was fed to a 15 millimeter die and punch apparatus operating at 100 psi. A compression duration of 0.2 seconds was utilized to form the tablets. This procedure was then repeated utilizing a sample of tableting formulation from Examples XVII with 1.0 wt. % of magnesium stearate. An improvement tablet extraction from the tableting apparatus was exhibited with both formulations.

EXAMPLE XIX

An ibuprofen tableting formulation in accordance with the tableting formulation of Example XVII was prepared with a decreased concentration of glycerin (i.e., binding agent). The tableting formulation contained 62.56 wt. % amorphous sucrose spheres, 34.44 wt. % ibuprofen, 1.0 wt. % glycerin, 0.5 wt. % lemon flavoring agent, 0.5 wt. % whipped cream flavoring agent, 0.5 wt. % Aspartame and 0.5 wt. % citric acid, to give a 100 wt. % formulation. The formulation was free flowing and was easily directed to the 15 millimeter die and punch. A compression force of 100 psi for a compression duration 0.2 seconds was utilized. As in Example XVII, the greater compression force required an increased effort to extract the tablets from the tableting apparatus. Otherwise, the resulting tablets were satisfactory.
EXAMPLE XX

An ibuprofen tableting formulation in accordance with of Example XIX was prepared having a further decreased glycerin concentration. The formulation contained 63.06 wt. % amorphous sucrose spheres, 34.44 wt. % ibuprofen, 0.5 wt. % glycerin, 0.5 wt. % lemon flavoring agent, 0.5 wt. % whipped cream flavoring agent, 0.5 wt. % aspartame, and 0.5 wt. % citric acid. Tablets were formed utilizing the procedure described in Example XIX. As in Example XIX, the resulting tablets required an increased effort to extract the tablets from the tableting apparatus. Otherwise, the resulting tablets were satisfactory.

EXAMPLE XXI

In an attempt to improve extraction of the tablets from the tableting apparatus 0.5 wt. % magnesium stearate as a flow agent was added to a sample of the ibuprofen composition of Example XIX. The formulation exhibited excellent flow properties and was easily directed to the 15 millimeter die. A compression force of 100 psi was utilized for a compression duration of 0.2 seconds. The formed tablets exhibited satisfactory cohesion and were easily extracted from the tableting apparatus.

EXAMPLE XXII

An ibuprofen tableting formulation was prepared with a sample of the composition of Example XIX with 1.0 wt. % magnesium stearate as a flow agent. The formulation was tableted singularly on a half inch FFBE punch. Although the tablets exhibited a high friability, they were easily extracted from the tableting apparatus.

Thus, while there have been described what are presently believed to be the preferred embodiments of the present invention, those skilled in the art will appreciate that other and further modifications can be made without departing from the true spirit of the invention, and it is intended to include all other such modifications and changes as come within the scope of the invention as set forth in the appended claims.
WHAT IS CLAIMED IS:

1. A process for making a dosage unit, which comprises the steps of:
   a) subjecting a solid, organic-based feedstock, capable of being
      transformed to a liquiform in the substantial absence of dissolving medium, to liquiflash
      conditions to provide substantially unimpeded internal flow of said feedstock;
     5  b) imparting shear force on said flowing feedstock resulting from step "a"
      in an amount sufficient to separate particles by natural mass separation of said flowing
      feedstock in the presence of said shear force impinging thereon while in said
      unimpeded-flow condition; and
     c) directly tableting said shearlite particles to form a dosage unit.

2. The process of Claim 1 wherein said discrete particles are microspheres.

3. The process of Claim 1 wherein said liquiflash conditions are provided
   by spinning said feedstock in a spinning head having a heated peripheral barrier with
   exit openings for passage of flowing feedstock therethrough in the presence of
   centrifugal force provided by said spinning head.

4. The process of Claim 1 wherein said shear force is imparted to said
   flowing feedstock by the resistance of ambient atmosphere against said flowing
   feedstock as it exits said spinning head.

5. The process of Claim 1 which further comprises cooling said separated
   particles.

6. The process of Claim wherein the shearlite particles comprise a bio-
   affecting agent.

7. The process of Claim 1 wherein said feedstock comprises one or more
   of a medicament, an excipient and mixtures thereof.
8. The process of Claim 1 wherein said directly tableting comprises transport of shearlite particles from a shearlite forming process to a tableting process.

9. The process of Claim 8 which further comprises coating said shearlite particles prior to said tableting procedure.

10. The process of Claim 1 wherein said shearlite particles comprise shearlite particles of a medicament and shearlite particles of an excipient.

11. The process of Claim 10 wherein said excipient shearlite particles are formed from a feedstock of a saccharide based material.

12. The process of Claim 1 wherein the shearlite particles of step c) comprise two or more types of shearlite particles, wherein:

   one or more types of particles contain active ingredients selected from the group consisting of: antitussives, antihistamines, decongestants, alkaloids, mineral supplements, laxatives, vitamins, antacids, ion exchange resins, anti-cholesterolemics, anti-lipid agents, antiarrhythmics, antipyretics, analgesics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, antimanics, stimulants, gastrointestinal agents, sedatives, anti diarrheal preparations, anti-anginal drugs, vasodilators, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, antitumor drugs, anticoagulants, antithrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants, mucolytics, anti-uricemia drugs, H₂-antagonists and mixtures thereof:
and the other types of particles contain excipients and other additives selected from the group consisting of: flavor enhancers, antidotes, controlled release agents, polymers, plasticizers, enteric coating agents, flow control agents, fillers, and mixtures thereof.

13. A dosage unit comprising:

directly tableted shearlite particles, wherein said shearlite particles are formed by the process including the steps of:

a) subjecting a solid organic-based feedstock, capable of being transformed to liquiflash in the substantial absence of dissolving medium, to liquiflash conditions to provide substantially unimpeded internal flow of said feedstock; and

b) imparting shear force on said flowing feedstock resulting from step "a" in an amount sufficient to separate particles by natural mass separation of said flowing feedstock in the presence of said shear force impinging thereon while in said unimpeded-flow condition.

14. The dosage unit of Claim 13 wherein said shearlite particles are microspheres.

15. The dosage unit of Claim 13 wherein said dosage unit has a substantially continuous compression body.

16. The dosage unit of Claim 13 wherein said shearlite particles are amalgams of more than one ingredient.

17. The dosage unit of Claim 13 wherein said liquiflash conditions are provided by spinning said feedstock in a spinning head having a heated peripheral barrier with exit openings for passage of flowing feedstock therethrough in the presence of centrifugal force provided by spinning said head.
18. The dosage unit of Claim 17 wherein said shear force is imparted to said flowing feedstock by the resistance of ambient atmosphere against said flowing feedstock as it exits said spinning head.

19. The dosage unit of Claim 13 wherein said separated particles are cooled upon exiting said spinning head.

20. The dosage unit of Claim 13 wherein said feedstock is a feedstock material selected from the group consisting of a medicament, an excipient and mixtures thereof.

21. The dosage unit of Claim 20 wherein said medicament is an amalgam of two or more active agents.

22. The dosage unit of Claim 21 wherein said amalgam comprises cough and cold treatment.

23. The dosage unit of Claim 22 wherein said amalgam comprises vitamins and minerals.

24. The dosage unit of Claim 13 wherein said shearlite particle comprises at least one active agent and has a solid spherical body with substantially no discontinuity therethrough.

25. The dosage unit of Claim 13 wherein said shearlite particles are coated.

26. The dosage unit of Claim 25 wherein said feedstock comprises a saccharide-based material.
27. The dosage unit of Claim 36 wherein said at least one coating is selected from the group consisting of a medicament, an antidote, a controlled-release substance, a taste-altering substance, and combinations thereof.

28. The dosage unit of Claim 27 wherein said at least one coating comprises at least one of fats, emulsifiers, and combinations thereof.

29. The dosage unit of Claim 25 wherein said feedstock comprises a medicament.

30. The dosage unit of Claim 25 wherein said at least one coating is selected from the group consisting of a medicament, an antidote, a controlled-release substance, a taste-altering substance, and combinations thereof.

31. The dosage unit of Claim 30 wherein said at least one coating comprises at least one of fats, emulsifiers, and combinations thereof.

32. The dosage unit of Claim 13 wherein said shearlite particles comprise shearlite particles of a medicament and shearlite particles of an excipient.

33. The dosage unit of Claim 32 wherein said excipient shearlite particles are formed from a feedstock of a saccharide based material.

34. The dosage unit of Claim 13 wherein said shearlite particles comprise shearlite particles of a medicament and an excipient in a non-shearlite condition.

35. The dosage unit of Claim 34 wherein said excipient in said non-shearlite condition is a excipient in the form of a floss.
36. Apparatus for manufacturing a dosage unit comprising:
   a shearlite device for forming shearlite particles;
   a tablet-making machinery for compression tableting; and
   a shearlite particle conveyor connected for directing flow of shearlite particle from said shearlite device to said tablet-making machine without need for additional devices or ingredients.
FIG-5B

FIG-5C

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FIG-13

FIG-14

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**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

| IPC 6 | A61K9/20 | A61K9/16 |

According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

**Minimum documentation searched (classification system followed by classification symbols)**

| IPC 6 | A61K |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>see page 3, line 14 - line 29 see page 13, line 55 - line 57 see page 14 - page 15; example IV</td>
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- **&** document member of the same patent family

1 **Date of the actual completion of the international search**

| 11 August 1997 |

2 **Date of mailing of the international search report**

| 27.08.97 |

**Name and mailing address of the ISA**

- **European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 spo nl, Fax (+31-70) 340-3016**

**Authorized officer**

- **Boulois, D**

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