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(57) Abstract

A recipient-dosage delivery system comprises spheroidal particles of a bio-affecting agent for delivery to a recipient. The particles are highly flowable and are packaged in a vessel which stores them and provides for metered dosage. The particles may be produced under liquiflash conditions and exhibit sufficient flowability so as to allow administration of the metered dose to the recipient under the force of gravity without a mechanized device.

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RECIPIENT-DOSAGE DELIVERY SYSTEM

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

BACKGROUND OF THE INVENTION

This invention relates to a delivery system for administering bio-affecting agents, ie., drugs or medicaments, to recipients.

It is common to deliver medicaments by conventional formats, such as tablets and capsules. However, these formats may pose problems, e.g., the non-medicament components of some may be incompatible with the medicaments. Further, the use of these formats generally precludes oral absorption of the medicament, the tablet or capsule having to be broken down by the recipient's body before the medicament can be absorbed. The required breakdown of the medicament may delay its absorption for significant periods of time. Also, certain active ingredients are incompatible with digestive fluids. Finally, certain individuals, such as the elderly, have difficulty swallowing tablets and/or capsules.

In attempts to overcome these problems, the art has used powdered or multiparticulate products for oral dosing. Such products have been packaged in single dose packages. Depending upon the characteristics of the medicament, e.g., stability and the type of packaging used, storage, transportability and cost could pose problems.

While some of these powders were delivered using mechanized devices, others were not. Nonetheless, prior art powders typically suffered from physical limitations, such as caking, dusting, or adherence to the boundaries of packages. These limitations, as well as the limited flowability of these powders made the consistent and accurate delivery of metered dosages by the recipient impractical and/or impossible.

There is a need in the art for a delivery system that allows direct delivery of a metered dosage of solid particulate bio-affecting agent by a recipient from a package or vessel without the use of tablets or capsules.

SUMMARY OF THE INVENTION

The present invention relates to a recipient-dosage contact delivery system, including particles, such as shearlite particles, of a bio-affecting agent for delivery to a

recipient. The particles are packaged in a metered doses and are sufficiently flowable to be administered under the force of gravity, when tipped at a suitable angle. The system typically includes a bifunctional vessel for sterile storage and transportation of the particles and for subsequent delivery of the particles to the recipient.

The invention further relates to a method of delivering a metered dose of a bio-affecting agent directly to a recipient without use of a conventional delivery format, such as tableting. The method includes the step of sealingly packaging a metered dose of spherical or spheroidal particles of a bio-affecting agent in a bifunctional storage and delivery vessel. The method includes the further step of accessing and thereafter administering the packaged particles at an angle of repose effective to induce flow of the particles from the container to a receiving cavity of the recipient.

The present invention preferably relates to a delivery system including shearlite particles produced by a liquiflash process. The particles are provided in a metered dose and are sufficiently flowable to be administered under the force of gravity. The system further provides for packaging in a vessel for storage and subsequent delivery of the particles.

One 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. The spheroidal particles may then be coated with medicament or other coatings, including taste masking agents.

Another preferred embodiment is a discrete shearlite particle comprising a medicament which has a solid spherical or shperooidal body having substantially no discontinuity therein. Consequently, the body can contain or be a substrate for 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.

Preferably, the spherical or shperoidal body or bodies are shearlite microspheres as defined herein. As a result of the present invention, drugs or combinations of drugs can be combined with excipients and prepared on a commercial scale to provide spherical or spheroidal particles having a high degree of size

consistency. This capability provides a major advantage in the art of preparing sustained released delivery systems.

The products of the present invention can be true amalgams of different drugs or active components or combinations of amalgams and mixtures of drug and non-drug ingredients, including ingredients previously believed incompatible, interreactive or unstable, e.g., vitamin B-12 and certain minerals.

Other aspects and 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.

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. The preferred embodiments of certain aspects of the invention 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;

Figure 6 depicts a spoon-shaped recipient-dosage delivery system;

Figure 6A is a sectional view of the delivery system of Figure 6;

Figure 7 depicts a multiple-vessel arrangement of recipient-dosage delivery system;

Figure 8 shows another embodiment of the recipient-dosage delivery system;

Figure 8A is an elevational view of the embodiment of Figure 8 showing the breakaway lid in an open position;

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 depicts a view of a multiple-vessel arrangement of the recipient-dosage delivery system of Figure 8;

Figure 18 depicts an alternative multi-vessel arrangement;

Figure 19 depicts a multiple dosage recipient-dosage delivery system;

Figure 20 depicts an alternative vessel for the recipient-dosage delivery system of the present invention;

Figure 20A depicts the vessel of Figure 20 with a breakaway lid thereon;

Figure 21 depicts a cup-shaped vessel for use with the present delivery system;

Figure 21A is a sectional view of the vessel of Figure 21;

Figure 22 depicts an elongate tubular-shaped vessel for use with the present delivery system;

Figure 22A depicts the vessel of Figure 22 with the breakaway lid in the open position.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes a method of making discrete particles of material by harnessing nature's mass forming capability, as well as products and methods in which flowable spherical or spheroidal particles are employed to deliver drugs via recipient dosing. The inventors herein have harnessed nature's tendency to provide optimum mass for minimum surface area by instantaneous transformation from solid to liquiform to solid. While the shearlite paticles described herein are prefered spherical particles for use in the invention, any similar particles may be used. The method of the present invention is preferably implemented by subjecting a feedstock capable of being transformed to liquiform in the absence of a dissolving medium to liquiflash 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.

It is known to those skilled in the art of material processing, and, especially to artisans familiar with the technology of the owner of this 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 Nos. 5,236,734; U.S. 5,238,696; U.S. 5,370,881 and U.S. 5,518,730, the contents of all of which are hereby 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.

"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 is meant less than seconds, in most cases on the order of fractions of a second, most preferably milli-seconds. Thus, certainly the transformation from solid to liquid to solid takes place in a time period of less than five seconds, preferably less than one second, and most preferably less than 0.1 seconds.

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 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 discretization of liquiform feedstock.

The discretized particles separated from the mass of flowing feedstock are cooled. In a preferred form of the present invention the discretized particles are monodispersed. "Monodispersed" as used herein refers to the production of a plurality of uniform spherical particulates, e.g., shearlites. As explained hereinabove methods for barrier processing of feedstock known in the art generally results 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.

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 can be 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.

Moreover, the feedstock contemplated for use herein must be capable of undergoing the required transformation without substantial and preferably no significant deterioration of the material present therein.

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. 5,427,811 and U.S. 5,458,823, both of which are 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 liquefy it

instantaneously.

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 microspheres. 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 the 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 L 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 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 discrete 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 be introduced into a formulation as highly uniform spheroids, or can be coated with 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 the 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, was employed 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 microspheres of acetaminophen.

It is also contemplated that spheroidal particles useful in the present invention may be produced using conventional particle manufacturing techniques, including milling, as long as such spheroidal particles conform to the properties as herein disclosed.

FEEDSTOCK

The feedstock which is contemplated for use herein includes organic materials, such as 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, eg., taste-altering substances. Quite surprisingly, it has been found saccharides and drugs can be processed without deterioration.

Generally, metals, silicates, inorganic carbonates and high molecular weight proteinaceous materials are not suitable feedstocks.

If two or more drug components included in the feedstock have similar melting points, the product will usually be a true amalgam of the drug components. If one or more of the active ingredients has a higher melting point than one or more of the other components, the higher melting drug will disperse substantially consistently throughout the liquiform when the lower melting point ingredients are processed. Finally, one of the components, such as the low melting point ingredient, can be a non-active ingredient. For example, sucrose can be used in combination with active ingredients to form a spherical particulate product having an active ingredient substantially evenly distributed throughout. One particularly useful combination of active agents includes agents used as cough and cold treatment.

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-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, 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, antithromobotic 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-uricemic drugs and mixtures thereof. Other active ingredients contemplated for use in the present invention are H_2-antagonists.

Calcium carbonate ($CaCO_3$), 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 H_2-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 antidiarrheals such as Imodium AD ®, antihistamines, antitussives, decongestants, vitamins such as vitamin B-12, minerals and breath fresheners. Also contemplated for use herein are anxiolytics such Xanax ®; antipsychotics such as Clozaril ® and Haldol ®; non-steroidal anti-inflammatories (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 a Prozac ®, Zoloft ®, and Paxil ®; antimigraines such as Imigran ®, ACE-inhibitors such as Vasotec ®, Capoten ® and Zestril ®; anti-Alzheimer agents, such as Nicergoline ®; and Ca(II)-antagonists such as Procardia ®, Adalat ®, and Calan ®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

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

hereinbelow. 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 either an antidote or a non-active ingredient. 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 coated as desired for taste alteration and/or controlled-release. Alternatively, the cough and cold active ingredients can be provided in one or more of the substrate and the layers deposited thereover.

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

The product of the present invention can also be used as a substrate on which a substance can be deposited to remove toxins from a bio-system. Since the present product is an excellent delivery vehicle for a bio-system, a substance which removes,

for example, toxins, can be deposited thereon. The deposited substance can be an adsorbent or absorbent which acts mechanical, chemically, or biologically to extract an unwanted agent from the bio-system, e.g., the human body. Such substance can be psyllium, epichlorhydrin, or a biological conjugate, etc.

"Controlled-release" is used herein to describe a method and composition for making an active ingredient available to the biological system of a recipient. 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 recipient. "Delayed release" means the active ingredient is not made available to the recipient 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 recipient 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. SR can be effected by use of coatings which include gels, waxes, fats, emulsifiers, combination of fats and emulsifiers, polymers, starch, etc.

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, ceresin, paraffin, myristyl alcohol, stearyl alcohol, cetylalcohol 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), hydroxypropl 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 quite useful as coatings 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), hydroxypropyl-methylcellulose (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), carboxymethylethyl 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)acryl 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 sebaccate.

Aqueous polymeric dispersions useful for coating 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 for aqueous coatings 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 phlatate (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 (spermaceti) 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 beaf 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 coatings 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-glyceryl 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; the '810 reference is hereby incorporated by reference.

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.

Another manifestation of the present invention is the combination of a low melting coating such as a fat or wax with an active ingredient which has been transformed to spheroidal particles. The active particles can be extruded and subjected to flash shear processing, or spray coated using traditional spray congealing.

In yet another example of the unique advantage provided by the present invention, an antidote material can be transformed to spheroidal particles and then coated by 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. Thus, 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 butylhydroxy hydroquinone (TBHQ), parabans, 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.

Other applications include the ability to load non-drug materials on to or into spherical particles such as laundry enzymes into saccharides, or to combine different drugs or different families of drugs into a single spherical particle, including those combinations that previously were believed to be incompatible, interreactive or

otherwise unstable. Inasmuch as the particles are predictably highly uniform, simple mixing ensures drug uniformity as well as delivery uniformity.

Particulate products can be produced on a commercial scale for several applications such as industrial and food uses. Sugar microspheres can be manufactured and used as a support for coating with, for example, polyvinyl alcohol (Elvanol™). Sugar or starch microspheres can be used as support or substrates for stabilizing enzymes and to prevent dusting, e.g., elimination of dust resulting handling of enzyme-containing material.

Examples of other industrial chemicals which can benefit from less dusting and better flow property afforded by the present invention include, but are not limited to phenol, styrene, butylated hydroxy anisole (BHA), tert butylhydroxy hydroquinone (TBHQ), parabans, hydroquinone, insecticides, herbicides, combinations of insecticides and herbicides, antifungals. There are many other such chemical substances which present damages from explosion and/or personal contact. The present invention includes processing all such substances under liquiflash conditions and/or coating as an aspect of the invention.

DELIVERY SYSTEM

According to the present invention, a substance, e.g., a bio-affecting agent, is processed to produce spherical or spheroidal particles which may thereafter be packaged for subsequent delivery to a recipient, i.e., a patient requiring administration of the bio-affecting agent. Of course, it is contemplated that other substances in addition to bio-affecting agents may be utilized in or subjected to liquiflash conditions to produce shearlite or other spherical or spheroidal particles which can thereafter be packaged in suitable containers. These other substances include sucrose, flavor enhancers and various industrial chemicals and the like. In one particularly preferred embodiment, a bio-affecting agent is delivered with and/or carried by shearlite particles of sucrose and/or various flavor enhancers.

As described hereinabove, there are many applications, particularly in the medical field, where the ability to accurately deliver a metered dose of a

multiparticulate substance directly to a recipient in the absence of a conventional delivery format is highly desirable. However, the very fact that a substance is reduced to a multiparticulate form has in the past necessitated the need for use of a mechanized delivery device, e.g., a low velocity spray apparatus, because multiparticulates suffer from various physical limitations such as adherence to boundaries, caking and dusting. Thus, it becomes impractical and/or impossible to consistently and accurately deliver a metered dosage of a multiparticulate substance in the absence of a mechanized delivery system. As also discussed above, the use of mechanized delivery devices has certain disadvantages associated therewith including: i) the need to carry the device, ii) size and cost of the device, iii) sterility of the device, iv) accuracy and consistency of delivery of the device, and v) other various inherent limitations.

It has been discovered herein that particles produced by subjecting a bio-affecting agent to liquiflash conditions or other spherulizing treatment provide the basis for a novel recipient-dosage delivery system. This delivery system, which entails contact of a metered dose of spheroidal particles of a bio-affecting agent and a recipient, e.g., an oral cavity of a host, is produced by the packaging of such spheroidal particles in a suitable vessel. This vessel is preferably bifunctional in nature inasmuch as the vessel provides for 1) sterile storage and ready transportation of the packaged particles, and 2) serves to deliver the particle to the recipient (i.e., the particles are delivered directly from the vessel to the recipient without use of a mechanized device or instrument).

As mentioned, a metered dose of particles is packaged in the vessel. Thereafter, the vessel is opened and the spheroidal particles are administered to the recipient, e.g., to the oral cavity of the host. (The term "administer" as used herein is defined as meaning that greater than 95%, preferably greater than 98%, and more preferably substantially 100%, of the particles are transferred from the vessel to the recipient, this transfer occurring under the force of gravity). In one particular application, the recipient opens the vessel and self-administers the contents thereof, such as shearlite particles of a bio-affecting agent, by positioning the vessel adjacent to his or her mouth and holding the vessel at an angle of repose whereby the shearlite particles flow from the vessel into the oral cavity of the recipient, whereupon such

particles are immediately dissolved and absorbed by the body of the recipient.

The particles comprising a bio-affecting agent are preferably packaged in a bifunctional vessel. These vessels, as further described hereinbelow, may be produced from various well known manufacturing processes such as injection molding, blow molding and die forming, thus providing a suitable container for sterile storage of the shearlite particles. In this regard, the vessels are readily transportable by the recipient, and are discarded after use. The vessels may be formed from various materials including high density polyethylene, polypropylene, polystyrene, acetyl butyl styrene, propyl acetate and polyethylene terephthalate. In one embodiment, the vessel is preferably formed from a material which is electrically compatible with the shearlite particles inasmuch as contact between the vessel and the shearlite particles does not tend to create and/or retain a static electric charge. Alternatively, the vessel and/or shearlite particles, either before or after packaging of the particles, may be subjected to a static discharge operation.

The vessel is preferably shaped to facilitate delivery of the particles directly from the vessel to the recipient, e.g., the vessel may include a spout and/or lip which directs and thus facilitates the flow of the particles from the vessel. The vessel is preferably sealed closed with a removable closure whereupon removal of the closure by the recipient allows access to the packaged particles for delivery thereof. For example, peel-away backings or covers formed of aluminum foil laminated with polyethylene or mylar film may be adhered around the rim of the vessel following filling of the vessel. Alternatively, various break-away lids or caps can be used to close the vessel. Of course, it is contemplated that other suitable closures may be utilized herein.

In one particularly preferred embodiment, a plurality of vessels are detachably secured to one another thus providing a multi-vessel transportable package of recipient-dosage delivery systems. Such multi-vessel arrangements facilitate the packaging of the product at the manufacturing level, facilitate dispensing of the medicaments, and also facilitate subsequent handling and transportation of the vessels. For example, a multi-vessel arrangement of seven vessels would allow a physician to readily prescribe a week's supply of a particular medicament (assuming the

medicament is administered one time per day). In addition, the multi-vessel arrangement allows the recipient to readily transport the medicament.

In another particularly preferred embodiment, at least two adjacent vessels may be arranged so as to allow simultaneous removal of their respective closures for simultaneous delivery of the metered doses contained in such vessels. For example, it may be practical to separately package two different medicaments which are to be simultaneously administered by the recipient. In non-medical applications, it may be desirable to separately package and thereafter simultaneously deliver two industrial chemical or two active ingredient, e.g., a laundry enzyme and a laundry bleach.

As mentioned, the shearlite particles produced under liquiflash conditions and others useful herein exhibit enhanced flowability. More particularly, these shearlite particles are capable of undergoing restricted flow under the force of gravity. Thus, the shearlite particles not only will flow from a generally open-sided vessel, but will flow through a restricted passage, e.g., a funnel-shaped apparatus. This unexpected ability to undergo restricted flow is significant in that it allows the shearlite particles to be packaged in a vessel having an elongated neck or otherwise restricted flow passage leading therefrom which facilitates transfer of the particles from the vessel to the recipient. As described hereinabove, multiparticulate substances which have not been subjected to suitable conditions, such as liquiflash conditions, do not exhibit restricted flow capability, and thus are not suitable for packaging in a restricted flow vessel, or any other vessel for that matter, because the non-processed multiparticulates adhere to the walls of the container, cake, dust and/or generally provide inadequate transfer of the packaged medicament from the vessel to the recipient. The restricted flow capabilities of the shearlite particles of the present invention are also significant in that restricted flow passages are found in various commercial machinery. That is, the ability of the shearlite particles to undergo restricted flow ensures that such particles may be readily transferred through and/or along the machinery.

Referring to Figs. 6 and 6A, shearlite particles of a bio-affecting agent, e.g., a medicament, may be administered to a recipient via a spoon-shaped vessel 100. Vessel 100 includes a particle-storing bowl 102 sized to receive and hold a metered dose of shearlite particles 104 of a desirable bio-affecting agent and a handle 106 configured to

allow manipulation of the vessel by the recipient. The vessel further includes a peel-away backing 108 which is sealingly secured to a rim 110 surrounding bowl 102 following the filling of the bowl with the metered dose of shearlite particles. Backing 108 preferably includes at least one corner tab 112 which allows the recipient to easily peel-away the backing and access the packaged particles.

In one preferred embodiment, as shown in Fig. 7, a second vessel, i.e., vessel 100', is fabricated together with vessel 100, thus providing a plurality of interconnected recipient-dose delivery systems, i.e., a multi-vessel transportable package 114. (Of course, it is contemplated herein that any number of vessels may be fabricated together in integral fashion.) Vessel 100' includes a second particle-storing bowl, i.e., bowl 102', affixed to a handle 106'. Handles 106 and 106' are attached along a score line 116 which allows one of the bowls to be readily separated from the multi-vessel arrangement and thereafter discarded once the metered dose of shearlite particles packaged therein has been delivered to the recipient. The multi-vessel transportable package facilitates dispensing and subsequent transportation of the recipient-dosage delivery systems by the recipient. Multi-vessel transportable package 114, which includes two recipient-dosage delivery systems, is particularly suitable for patients who are required to administer two daily dosage of a medicament. An individual self-administers one metered dose of medicament (the first daily administration), breaks off the empty bowl along score line 116, and retains the remaining sealed bowl of medicament for the subsequent second daily administration.

To administer the metered dosage of medicament contained in bowl 102 of vessel 100, the individuals grasps tab 112 of backing 108 and peels away the backing from rim 110, thereby exposing the previously-packaged particles. The individual then empties the contents of the bowl into his or her mouth. Because of the enhanced flowability exhibited by the shearlite particles of the present invention, the particles readily flow from the bowl into the individual's mouth when the vessel is tipped at a suitable angle of repose, typically less than 45°. Moreover, this flow is accomplished without adhering of the particles to the walls of the bowl, caking and/or dusting of the particles and, further, results in the complete emptying of the bowl, that is, substantially 100% of the particles are transferred from the bowl to the recipient.

An additional storage and delivery vessel, i.e., vessel 118, is shown in Figs 8 and 8A. Vessel 118 includes a flask-shaped particle-storing body 120 having an elongated neck 122 connected thereto. After body 120 is filled with a metered dosage of shearlite particles, the vessel is sealed closed with a backing 124 (shown in Fig. 8A) secured around a rim 126 surrounding the flask-shaped body. The vessel is preferably scored along score line 128, thus allowing a user to readily "break off" the lid and thereby access the packaged particles.

Flask-shaped vessel 118 is particularly suitable for multi-vessel packaging, as shown in Fig. 17. That is, a plurality of interconnected vessels which allow ready separation may be simultaneously fabricated. More particularly, a multi-vessel transportable package 130 includes a plurality of vessels 118 which are detachably secured to one another along score lines 132. As mentioned, the use of multi-vessel packaging facilitates the dispensing and subsequent handling of the delivery systems. For example, the delivery systems may be fabricated in transportable packages of any convenient size, e.g., 7 delivery systems (a one week supply).

An alternative multi-vessel transportable package, i.e., package 134, is shown in Fig. 18. In the disclosed arrangement, the user removes a vessel 136 from the package 134, thus leaving the remaining sealed vessel for subsequent use. Inasmuch as the vessel includes a break-away lid 138 attached to a centrally-disposed tab 140 along score lines 142, the removing of the vessel from the pack results in its opening . The user is then ready, upon removal of the vessel, to deliver the vessels contents.

In one particularly preferred embodiment, as shown in Fig. 19, a multi-dosage delivery system 144 is provided (as compared to the single dosage delivery systems discussed above). The multi-dosage delivery system includes a plurality of vessels arranged to allow for simultaneous opening of multiple vessels and subsequent simultaneous delivery thereof. As shown, multi-dosage delivery system 144 includes two particle-storing bodies 146. Each of bodies 146 includes an elongated neck 148 connected thereto. In turn, each neck is sealed closed with a break-away lid 150. The lids are secured to a common tab 152, which upon application of pressure thereto simultaneously breaks off both of the lids, thus allowing the user to simultaneously access and thereafter deliver the shearlite particles packaged in each of the vessels.

Applications which may require simultaneous delivery of a plurality of metered dosages include among others various asthma medicaments.

Referring to Figs. 20 and 20A, the shearlite particles may be packaged in a discrete vessel, i.e., vessel 154. Vessel 154 includes a particle-storing body 156 having an elongated restricted flow neck 158 connected thereto. The vessel may be sealed with a peel-away cover 160, although alternative closures such as twist-off caps may also be used. One particularly preferred embodiment (shown in Fig. 23A) includes a break-away lid 162 adopted to break off of neck 158 along score line 164 upon application of pressure thereto. Lid 162 preferably includes a finger-engaging tab 164 to facilitate breakage of the lid from the neck. Once vessel 154 has been opened, the recipient thereafter self-administers the particles by tipping the vessel and allowing them to flow through the neck and into his or her mouth.

In addition, the shearlite particles of the present invention may be packaged in any number of additional manners, including but not limited to a cup-shaped vessel 166 as shown in Figs. 21 and 21A and an elongate tubular-shaped vessel 168 as shown in Figs. 22 and 22A.

BARRIER PROCESSING APPARATUS

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. 5,427,811, the content of which is incorporated herein by reference.

Referring to the spinning head shown in Figure 3A, a heating element(s) is 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 12. 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. 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 U.S. 5,445,769. 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. 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, as shown in Figure 5C, 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.

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.

EXAMPLES

EXAMPLE I

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 9 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 125 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 500 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 Pharmo, 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 125 magnification. A very uniform coated product has been shown which can be easily used in feeding the coated active ingredient to machinery for tabletting 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 50. As can be seen from Figure 11, the spheres have a highly consistent particle size ranging from about 50-200 microns in diameter.

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, 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 shearlite particles produced in accordance with Example IV were classified according to sieve size. The portion passing through the No. 80 mesh was used to feed a tabletting press. The tabletting 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 Figures 9A. As can be seen in this figure, the product was a very uniform spherical bead. The actual content of pseudoephedrine in the product shown in Figure 12A 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 50 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 50 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% dextro-methorphan, 25% pseudoephedrine, and 62.5% Myverol. The active ingredients 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

Chloropheniramine-Diphenhydramine-Pseudoephredine Amalgam

In this example, the active ingredients were combined to provide another cough and cold treatment medicament. In particular, chloropheniramine 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 ϕ = h/r or ϕ = Arctan h/r.

The results 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 test have been set forth hereinbelow in the angle of repose table.

Table 1

Material	Flow Rate	Angle of Repose
Processed APAP	less then 1 second	19.53°
100% Non-Processed APAP	No Flow	NA
Processed Ibuprofen	1 second	22.93°
Unprocessed Ibuprofen	No Flow	NA
100% Ibuprofen Drug Unprocessed	No Flow	NA

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.

The highly flowable particles described herein are packaged in vessels that are shaped to facilitate dispensing of the particles directly into the recipient's mouth when the vessels are tipped at suitable angles of repose. Typically, the vessels will be cup-, spoon- or flask- shaped. They may have spouts or other features to aid in dispensing

the particles. In addition, the vessels may be part of an optionally connected multi-vessel system, with packaging designed to facilitate any or all of the following: handling; transportation; prescription by a physician and self-administration by the recipient.

The combination of the particles enhanced flowability and their packaging in metered dosages in a plurality of vessels makes possible, for example, a transportable one week supply of the medicament. In addition, multi-vessel packages can be such that a user can remove one vessel from the package, leaving the remaining sealed vessel(s) for subsequent use. Alternatively, the vessels can be arranged so that the user can simultaneously administer a plurality of metered dosages.

Various features can be used in the multifunctional vessels and packaging systems contemplated herein. Vessels may be sealed with removable closures to permit access to the packaged particles therein. Useful features include: break-away lids, scoring, twist-off caps, peel-away covers, finger-engaging tabs and the like. The accompanying figures depict several features which, along with others, may be used in the delivery systems of the invention.

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 recipient-dosage delivery system consisting essentially of:

I) flowable, highly uniform spheroidal particles comprising at least one bio-affecting agent; and

ii) a vessel in which said particles are packaged, which vessel is adapted to store and deliver at least one metered dose of the spheres in response to the force of gravity.

2. The system of claim 1 wherein the particles flow from the walls of the vessel at an angle of repose of less than about 45°.

3. The system according to Claim 1 wherein said vessel is shaped to facilitate transfer of said particles directly from the vessel to a recipient without the use of a mechanized delivery device.

4. The system of claim 2 wherein the vessel and the particles are electrically compatible so that contact between them does not tend to create or retain a static electric charge.

5. The system of claim 4 wherein at least of the vessel and the particles is subjected to a static discharge operation before or after packaging.

6. The system according to Claim 1 wherein said vessel is detachably secured to at least one second vessel thus providing a multi-vessel transportable package of said recipient-dosage contact delivery systems.

7. The system according to Claim 6 wherein said first and second vessels are sealed closed with removable closures, and wherein said vessels are arranged to allow simultaneous removable of said closures for simultaneous delivery of said metered dosages.

8. The system according to Claim 1 wherein said particles are capable of undergoing restricted flow under the force of gravity; and wherein said vessel includes a restricted flow passage which is traversed by said particles during delivery thereof.

9. The system according to Claim 1 wherein said vessel comprises a bowl affixed to a finger-engaging handle, said bowl defining a surrounding rim.

10. The system according to Claim 9 wherein said bowl is sealingly closed with a peel-away backing during storage and transportation of said vessel, said peel-away backing being secured around said rim of said bowl.

11. The system according to Claim 10 further comprising a second vessel having a second bowl and a second finger engaging handle, and wherein said second handle is attached to the first handle so that said bowls are positioned opposite one another.

12. The system according to Claim 1 wherein said vessel comprises a flask-shaped body having an elongated neck fluidly connected thereto which allows flow of said particles from said body to said recipient.

13. The system according to Claim 12 wherein said neck is formed with a breakaway lid, and wherein said lid is secured to a finger-engaging tab which upon application of pressure thereto allows said recipient to readily remove said lid from said neck.

14. The system according to Claim 13 wherein said vessel is detachably secured to a second similarly configured vessel such that said elongated necks are arranged parallel to one another.

15. The system according to Claim 14 wherein said vessel is detachably secured to a second similarly configured vessel such that said elongated necks are arranged along a common axis, and wherein each said lid is secured to a common centrally-disposed finger engaging tab.

16. The system according to Claim 1 wherein said vessel comprises an open sided container defined by a circumferentially-extending rim, said container being sealingly closed with a peel-away cover during storage and transportation of said vessel, said peel-away cover being secured around said rim of said container.

17. The system according to Claim 1 wherein said vessel comprises an elongate tubular particle-storing body having a removable cap releasably secured to one end thereof.

18. The system according to Claim 1 wherein said particles are produced by a process comprising 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, and

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

19. The system according to Claim 18 wherein said bio-affecting agent is 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, 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, antithromobotic 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, H_2-antagonists, anti-uricemic drugs and mixtures thereof.

20. The system according to Claim 1 further comprising a flavor enhancer delivered together with said shearlite particles.

21. The system according to Claim 20 wherein said flavor enhancer is coated on said particles.

22. The system according to Claim 1 further comprising at least a first and a second vessel, wherein said first vessel is detachably secured to at least said second vessel thus providing a multi-vessel transportable package of said recipient-dosage delivery systems; and wherein said at least first and second vessels are sealed closed with removable closures, and wherein said vessels are arranged to allow simultaneous removable of said closures for simultaneous delivery of said metered doses.

23. The system of Claim 1 wherein the spheroidal particles are produced using a spheronization process.

24. The system of Claim 23 wherein the spheronization process includes a milling step.

25. A method of delivering a metered dose of a bio-affecting agent directly to a recipient comprising:

i) sealingly packaging a metered dose of spheroidal particles comprising a

bio-affecting agent in a storage and delivery vessel;

ii) accessing and thereafter administering said packaged particles at an angle of repose effective to induce flow of said particles from said container to a receiving cavity of said recipient.

26. The method according to Claim 20 wherein said angle of repose is less than about 45°.

27. The method according to Claim 26 wherein said particles are produced by a process comprising the steps of:

a) subjecting a solid, organic 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, and

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

28. The method according to Claim 27 wherein said bio-affecting agent is 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, 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, antithromobotic 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, H_2-antagonists, anti-uricemic drugs and mixtures thereof.

29. The method of 25 wherein the spheroidal particles are produced using a spheronization process.

30. The method of claim 29 wherein the spheronization process includes a milling step.

FIG-1A

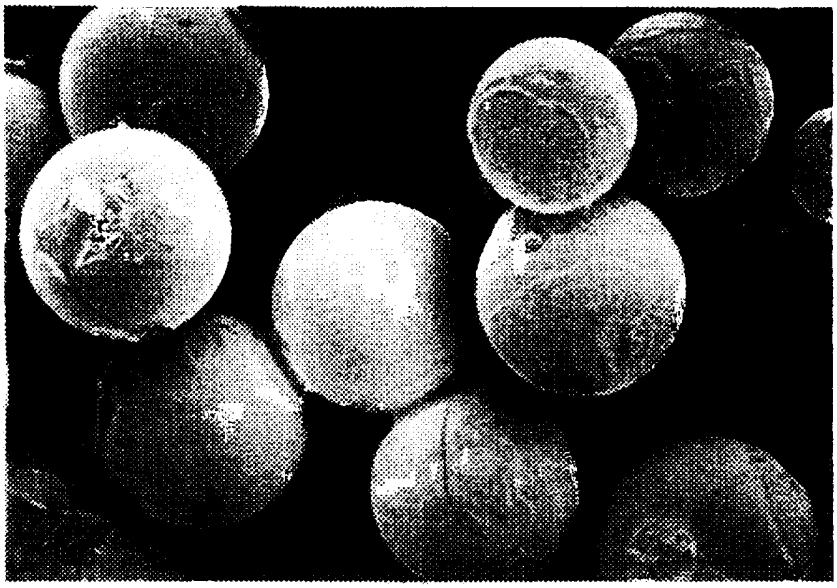


FIG-1B

FIG-1C

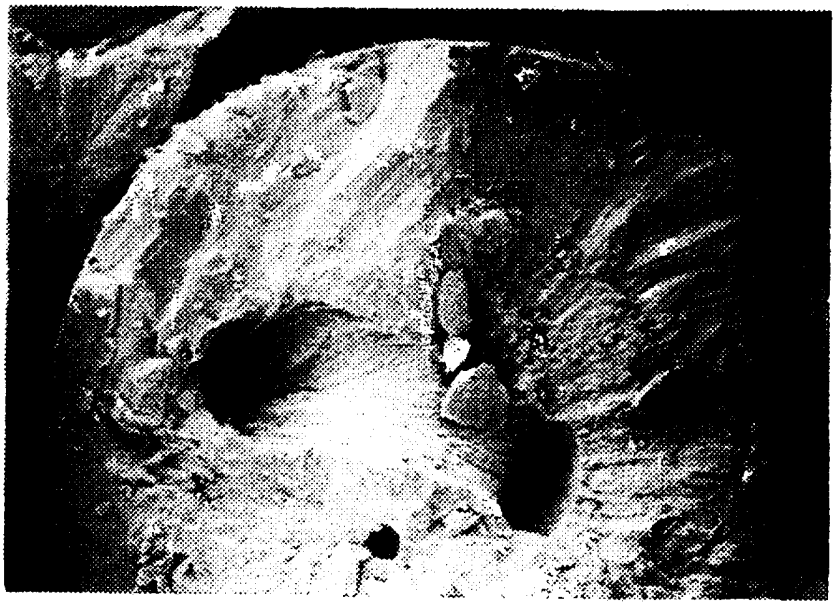


FIG-2A

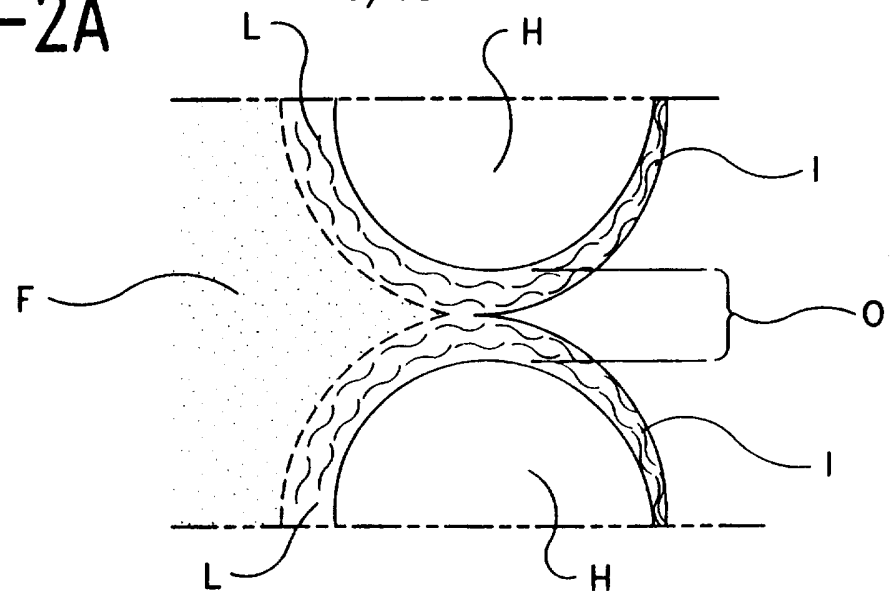


FIG-2B

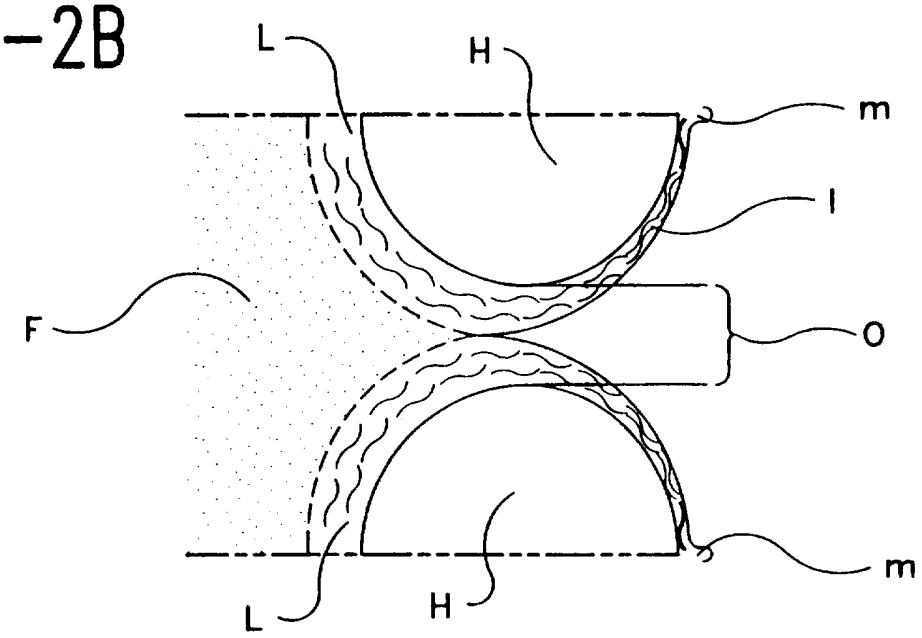


FIG-2C

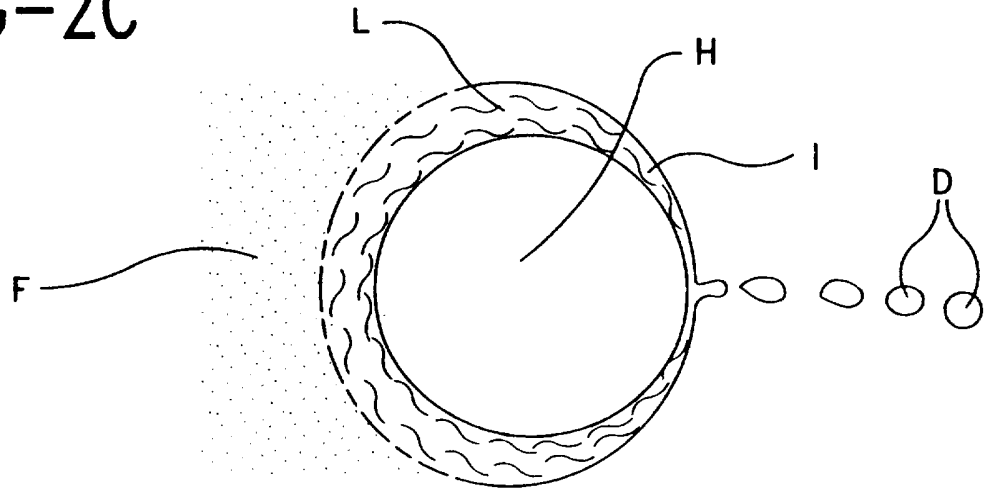


FIG-3A

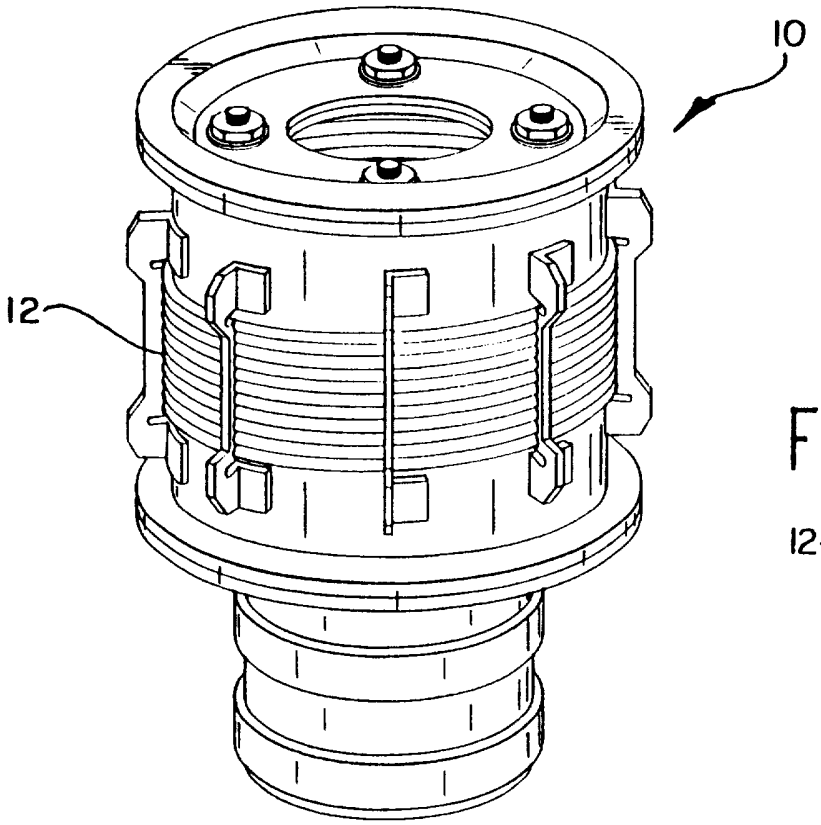


FIG-3C

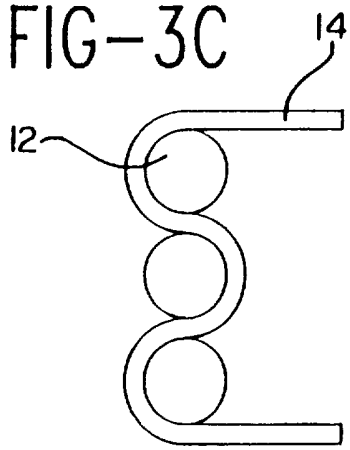


FIG-3B

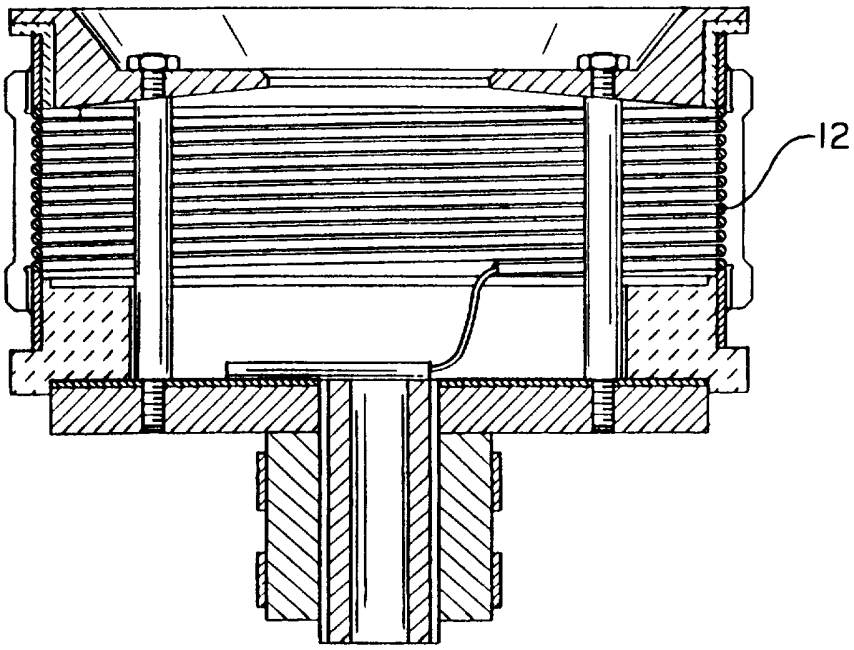


FIG-4A

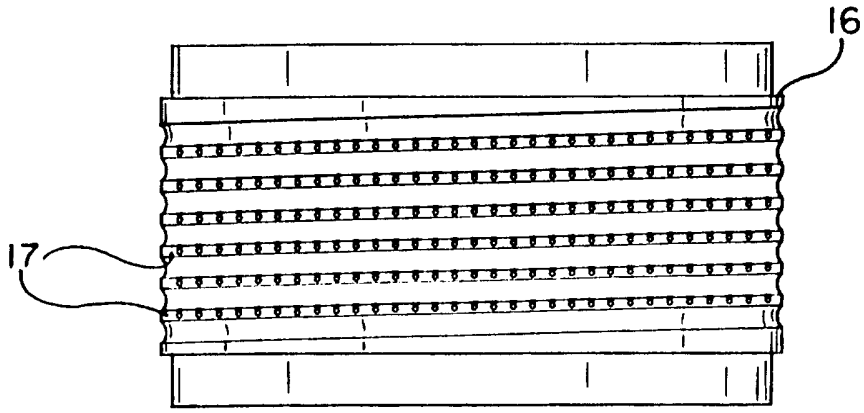


FIG-4B

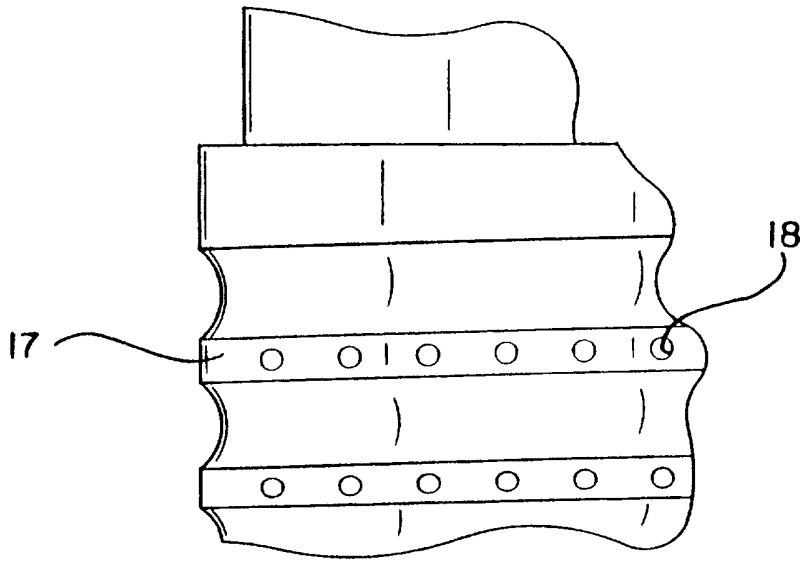


FIG-4C

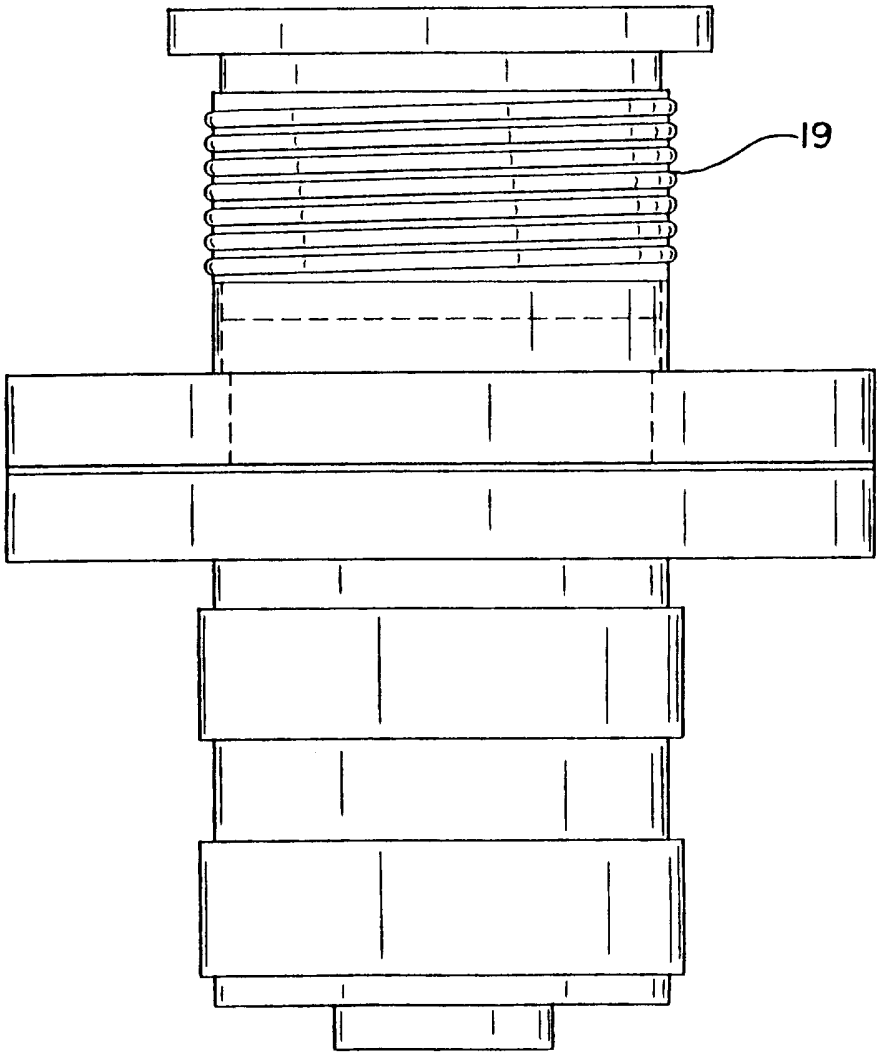


FIG-5A

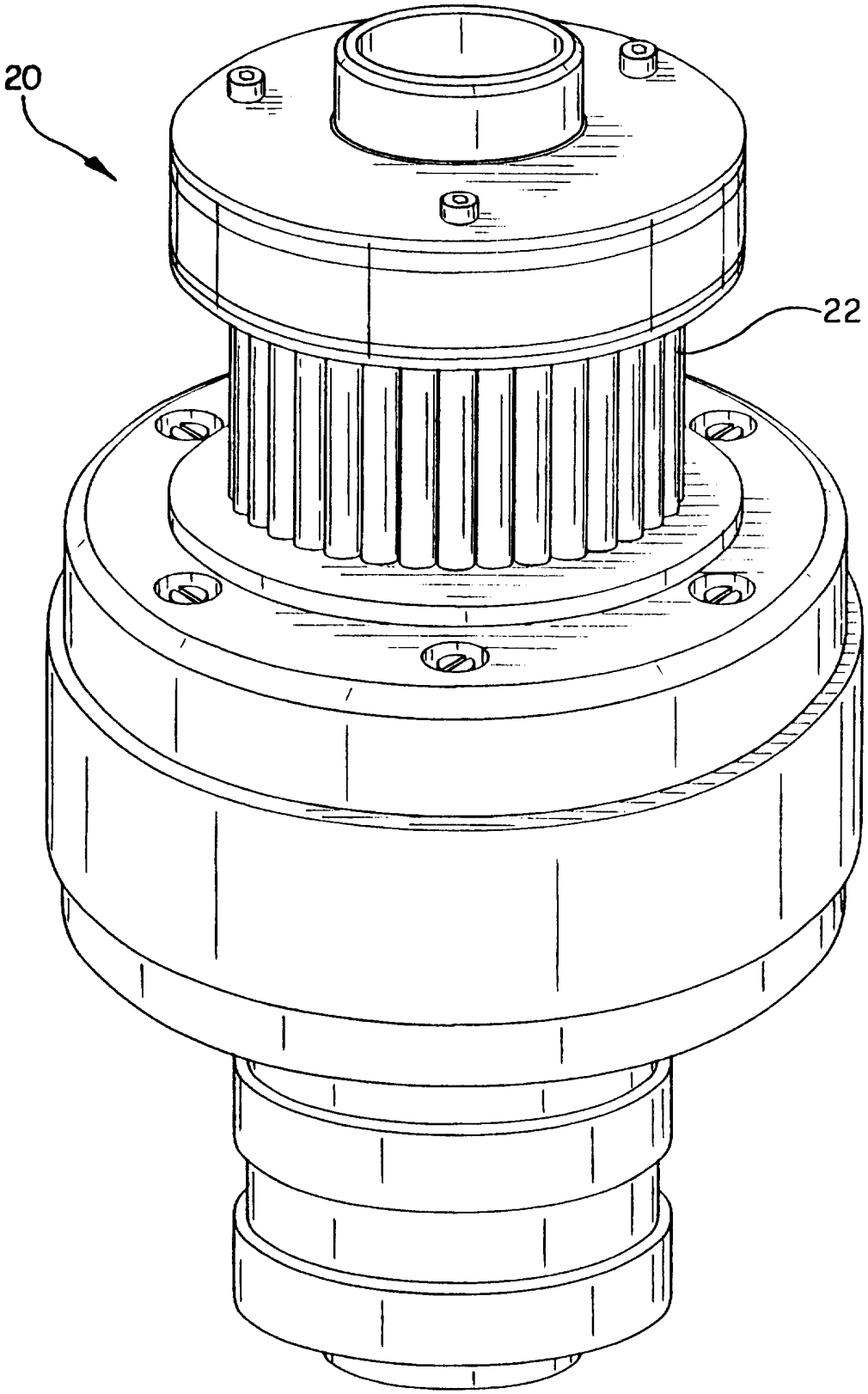


FIG-5B

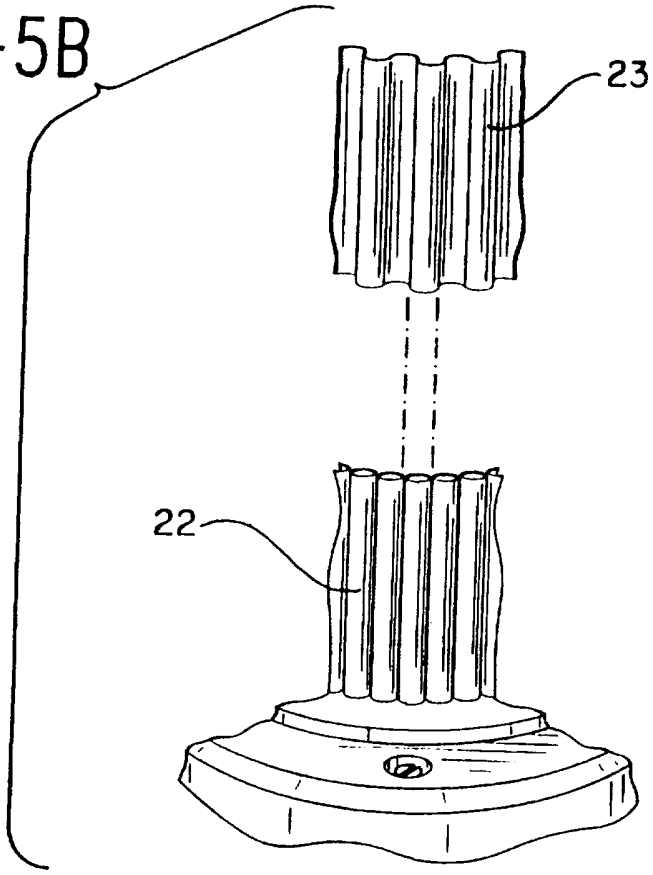


FIG-5C

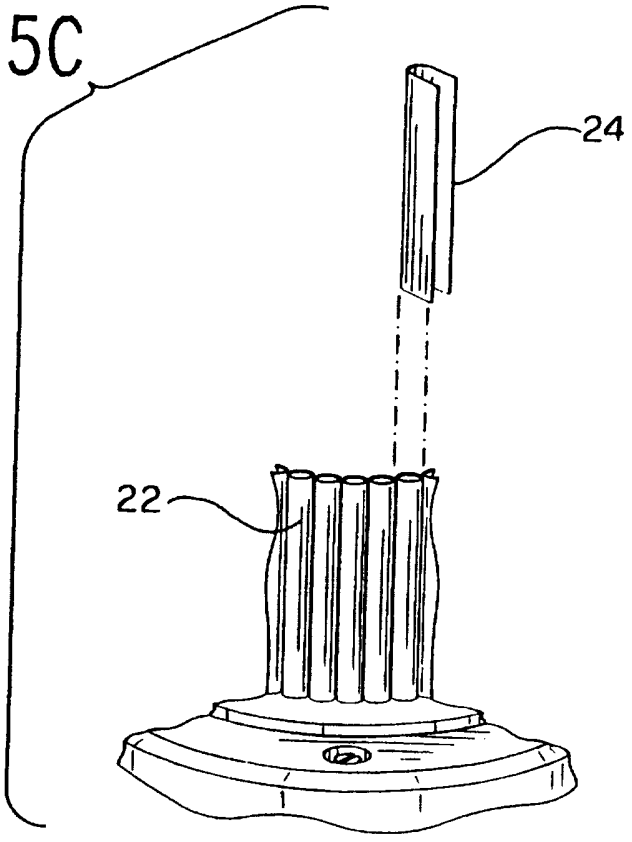


FIG-6

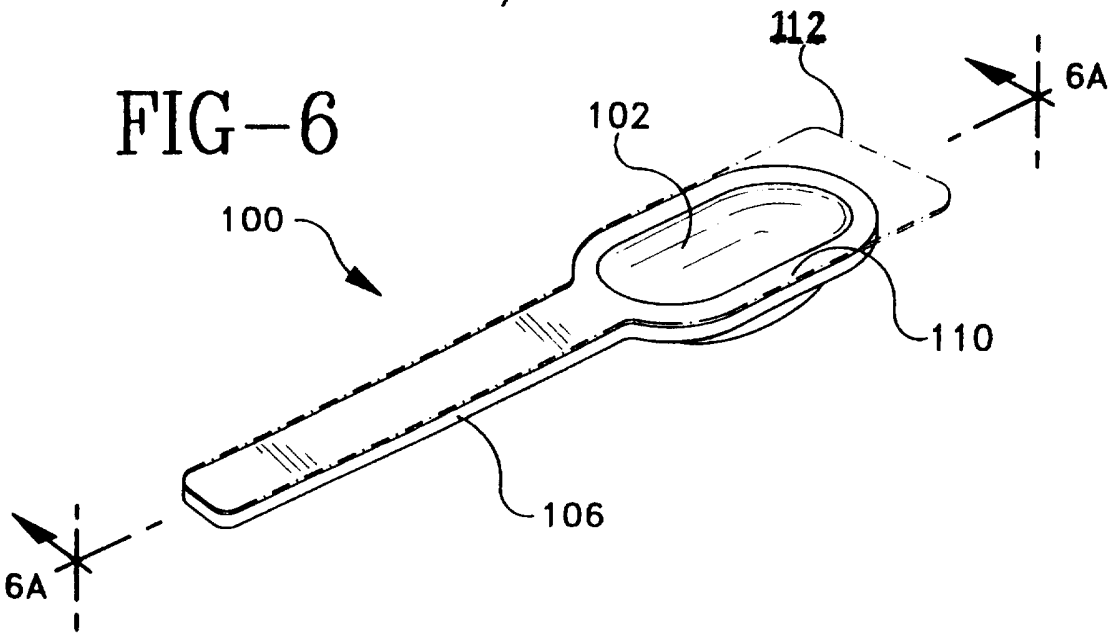


FIG-6A

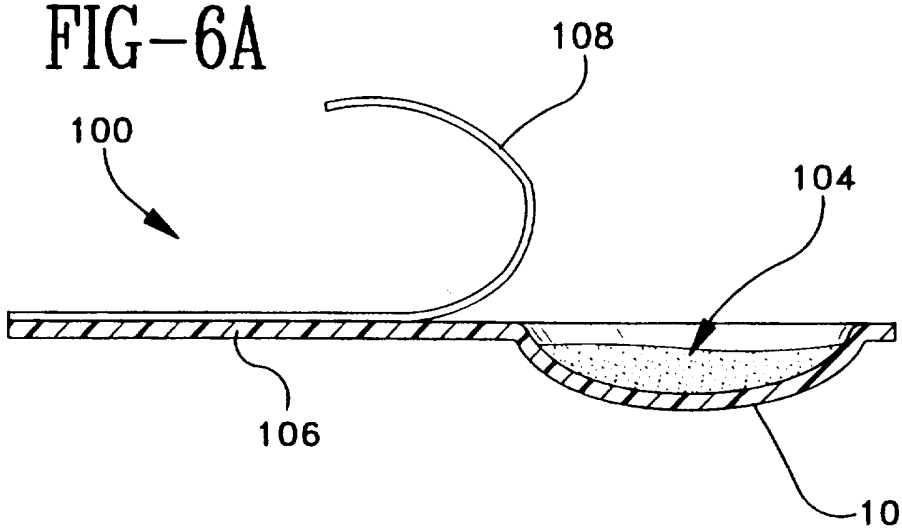


FIG-7

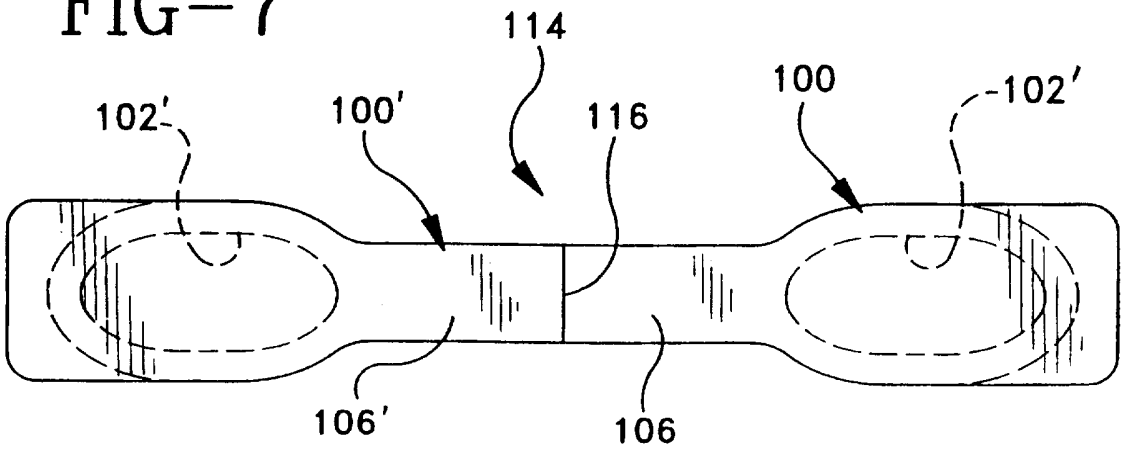


FIG-8

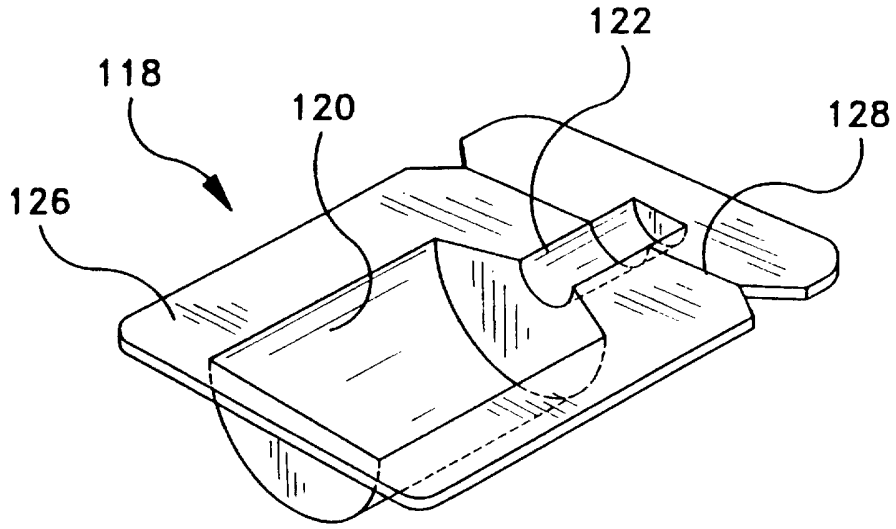


FIG-8A

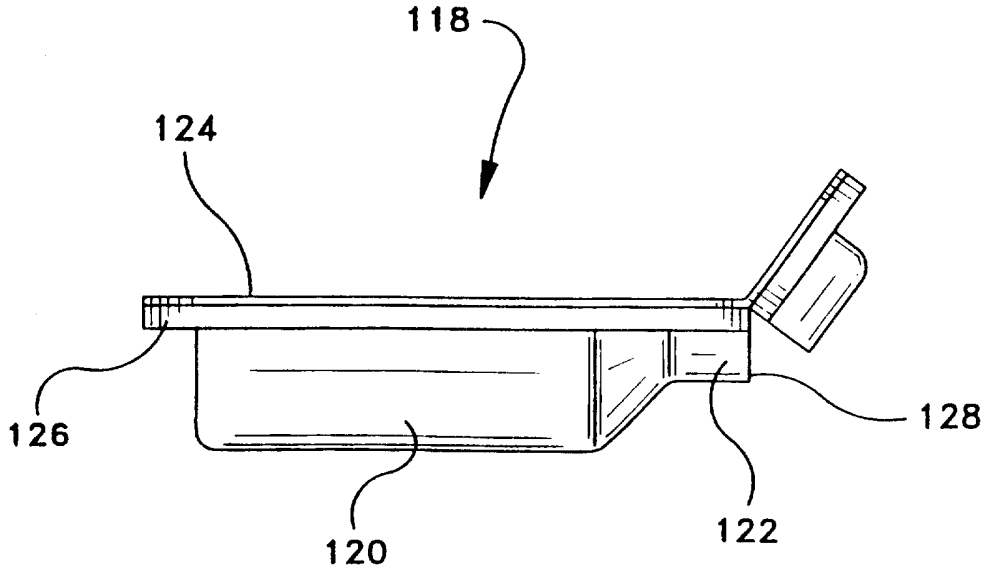


FIG-9

FIG-10

FIG-11

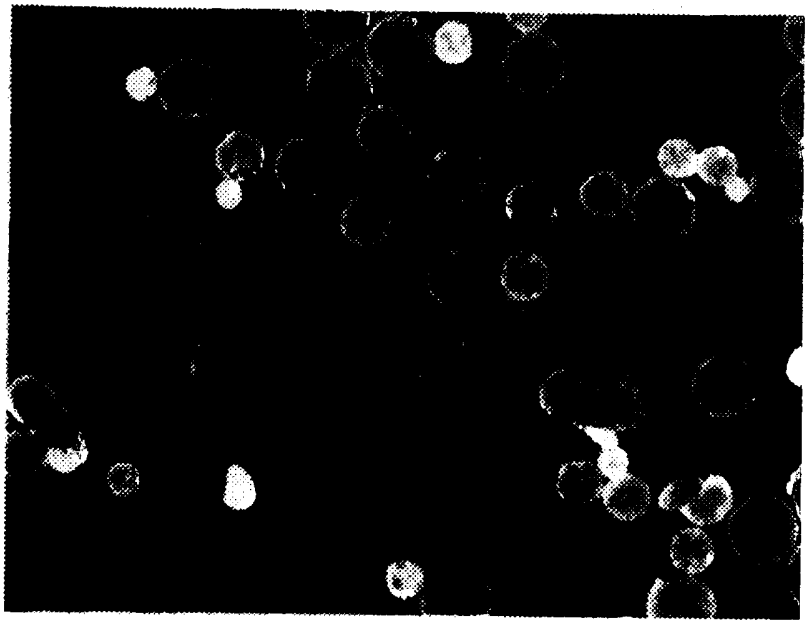


FIG-12A

FIG-12B

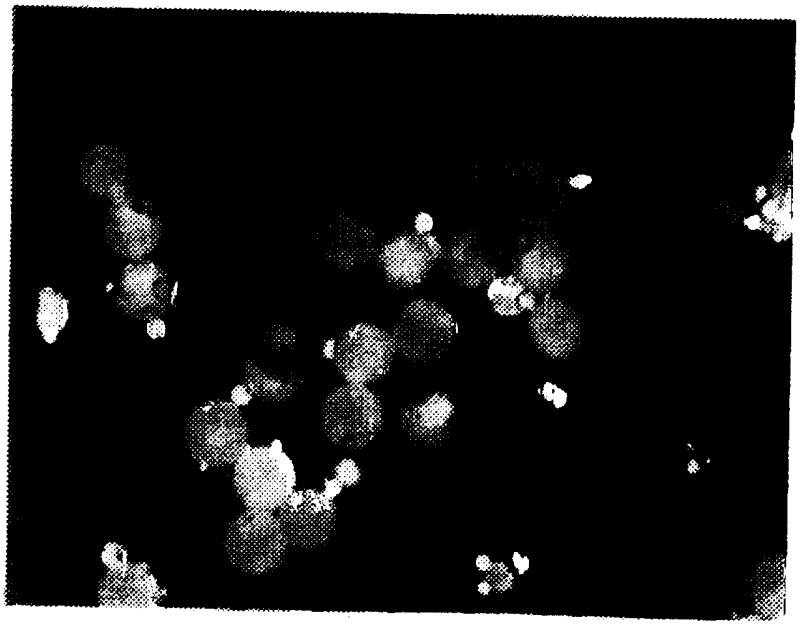


FIG-13

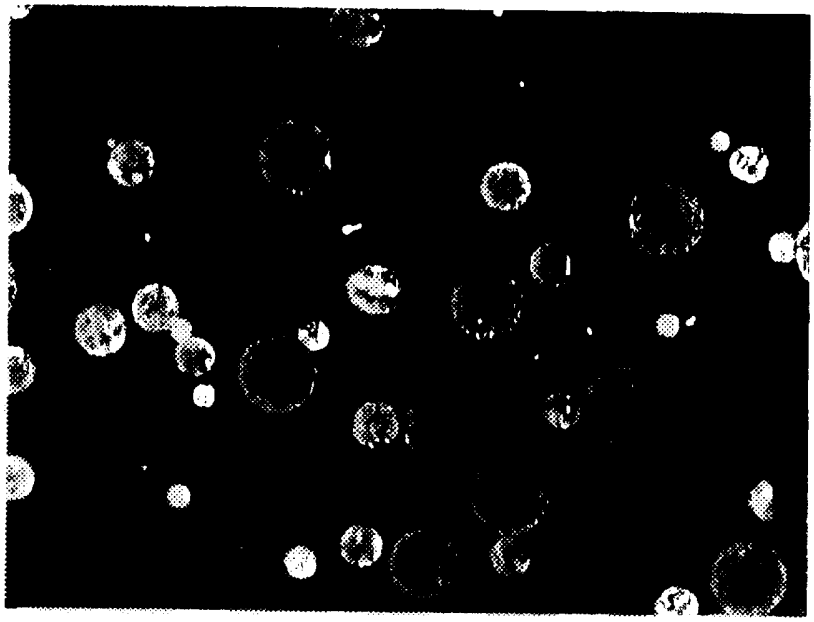


FIG-14

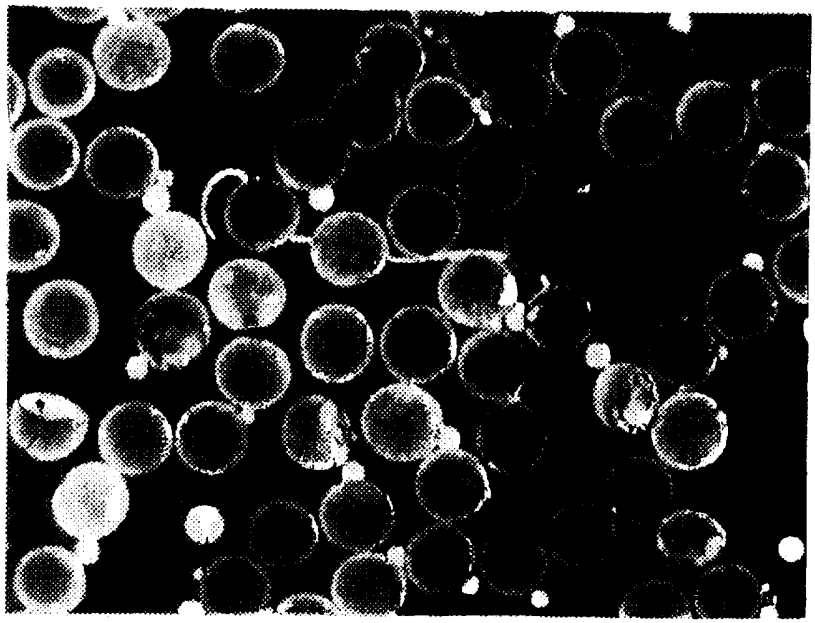


FIG-15

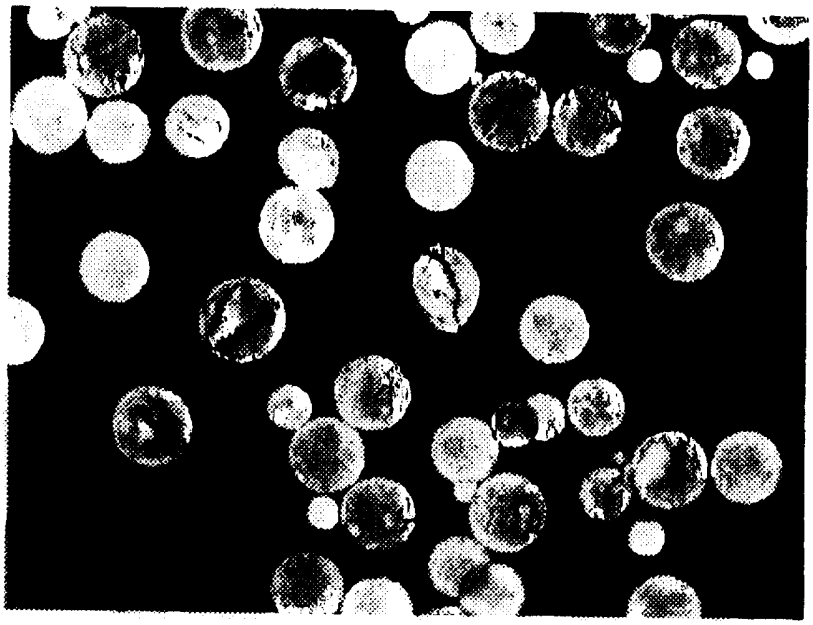


FIG-16

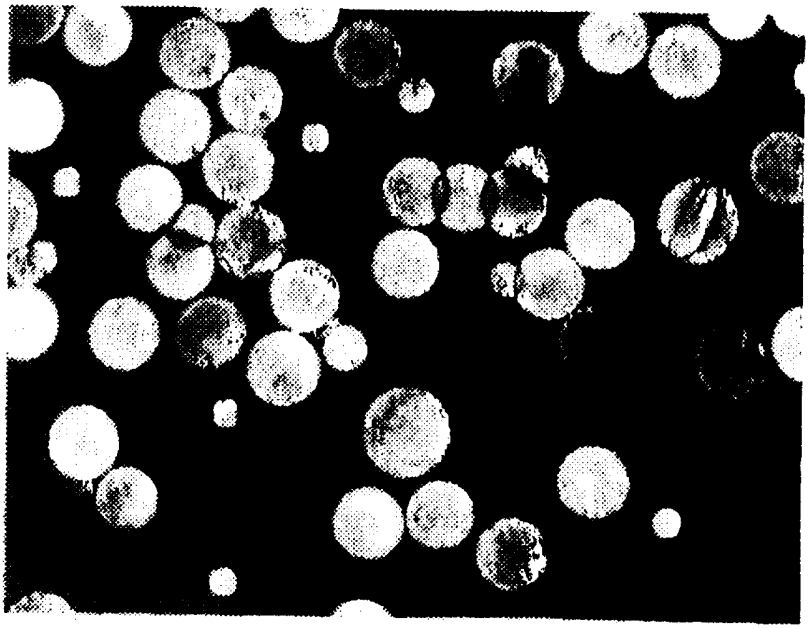


FIG-17

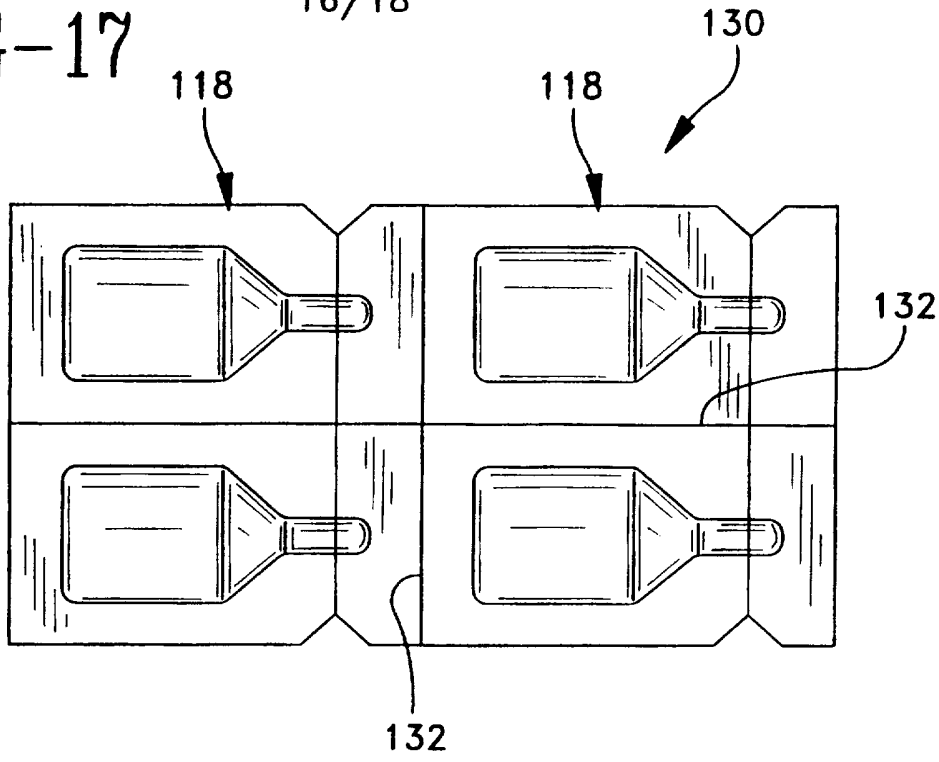


FIG-18

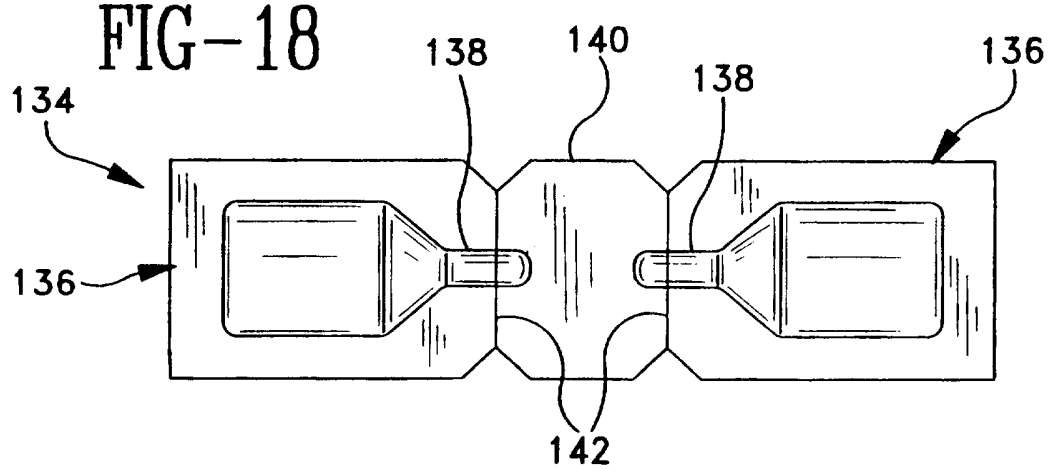


FIG-19

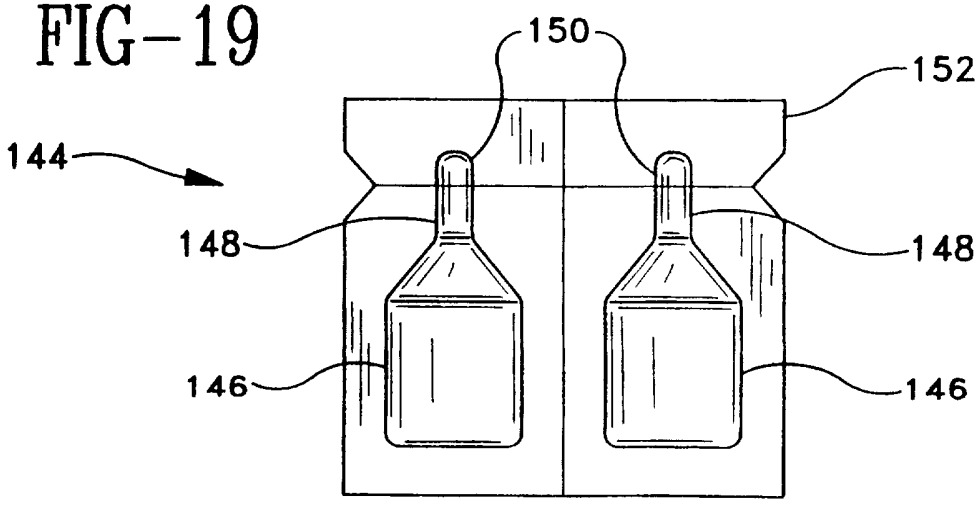


FIG-20

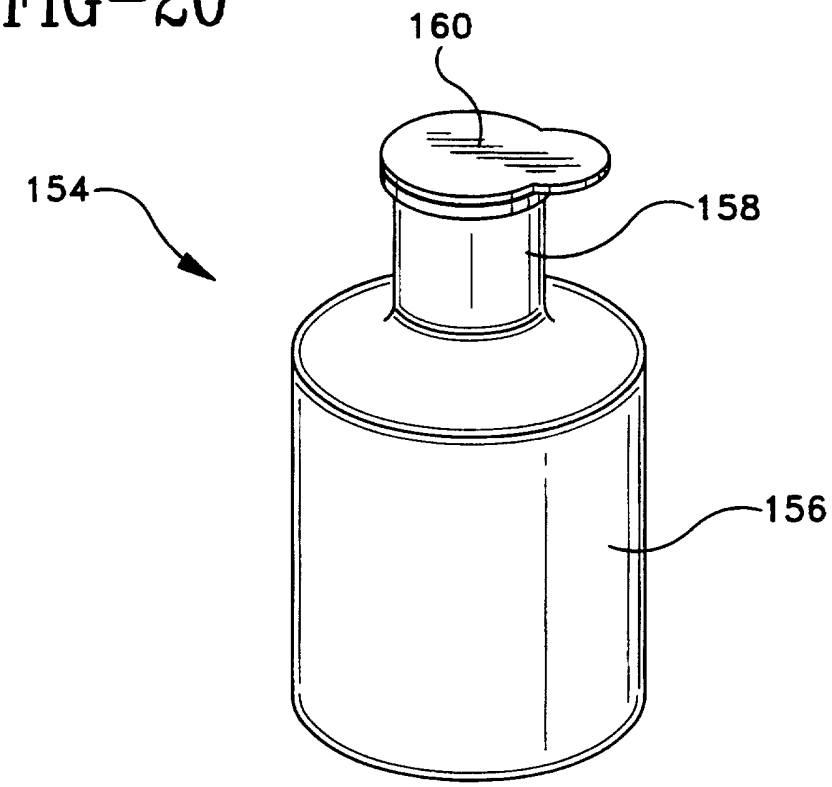


FIG-20a

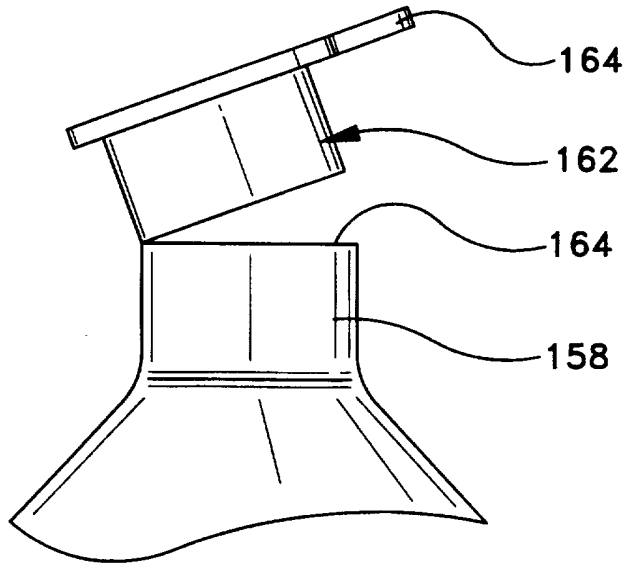


FIG-21

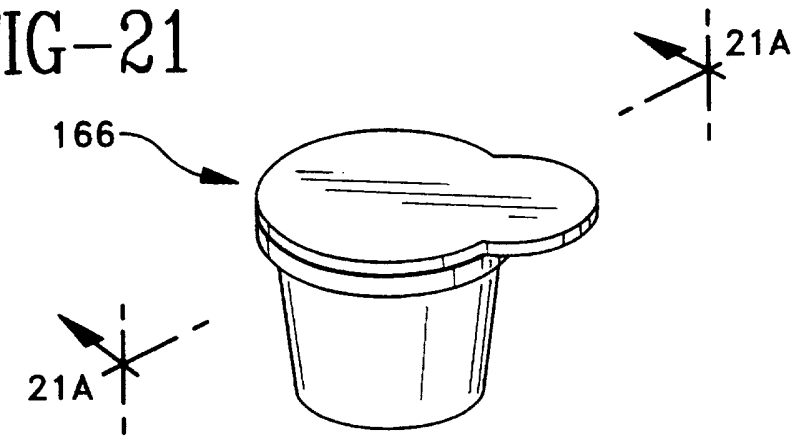


FIG-21A

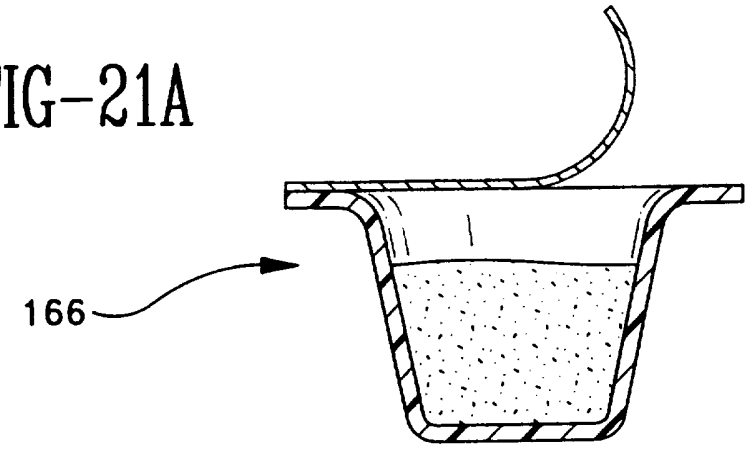


FIG-22

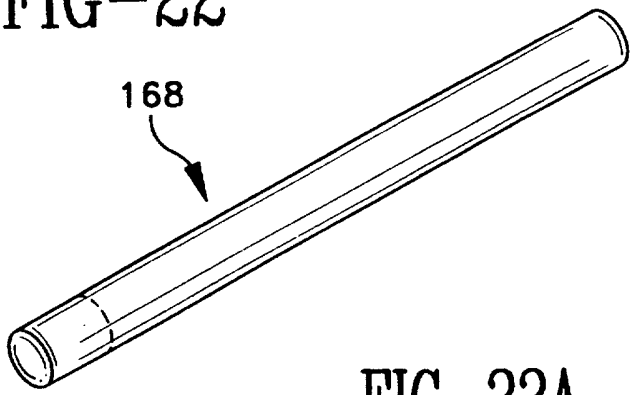
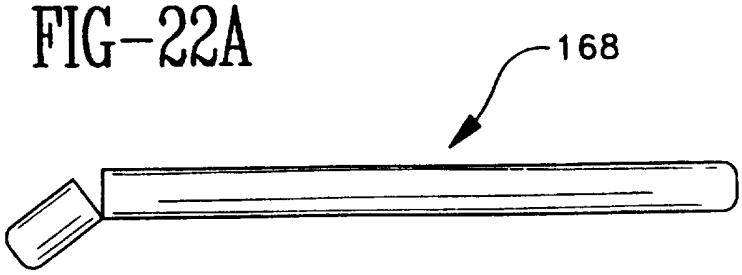


FIG-22A



INTERNATIONAL SEARCH REPORT

Inter. ..nal Application No
PCT/US 97/07101

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16 B01J2/00 B01J2/02 A61J1/00 A61J7/00
B65D75/58 B65D75/42

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 B01J A61J B65D

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

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FR 1 465 545 A (MAUVERNAY) 24 March 1967 see the whole document ---	1,3,9, 10,25
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1997	22.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Baert, F

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Inten. ..nal Application No
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A	GB 2 246 555 A (CHRISTOPHER GEORGE) 5 February 1992 see page 2, line 1 - line 15 see page 2, line 25 - page 3, line 19 see page 5, line 8 - page 6, line 17; figures 1-6	1,3,6, 16,25
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A	EP 0 667 147 A (FUISZ TECHNOLOGIES LTD.) 16 August 1995 see page 8; example 1 see page 6, line 31 - line 35 see page 12, line 1 - line 21	18-21, 27,28

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