

Soft-shelled Gelatin Encapsulated Particles

Background of the Invention

This invention relates to a soft-shelled gelatin capsule filled with beadlets which contain at least one beneficial agent. This presentation makes the capsule more tamper evident.

Introduction

Soft elastic capsules derived from liquid gelatin which has been plasticized with a polyol, or another plasticizer, have been used successfully for both oral and suppository drug presentation. These capsules are soft and have a globular, gelatin shell into which is filled a liquid, paste or powder. Capsules can be prepared in many forms, for example these capsules are produced commercially in round, oval, oblong, tube and suppository form. Commercial processes usually produce the capsule with a seam transcribing the long axis of the capsule. In oral dosage forms this seam is produced by a heat sealing process in such a way as to insure this seam is the point of opening and that this occurs rapidly in the stomach, i.e. in less than five minutes. Capsules for suppository use usually are formulated so that this seam breaks down in the presence of the moisture present in the body cavity. This form of drug delivery and the associated technology for manufacturing them is well documented and available from research and commercial sources.

This invention involves a modification to the soft gelatin capsule technology so as to be able to incorporate beadlets directly into the soft capsule without degrading or deforming the beadlets.

Summary of the Invention

This invention comprises a partially or wholly transparent soft gelatin capsule preparation wherein the internal volume is filled with beadlets or beadlets in a hard-shelled gelatin skin wherein the beadlets contain a beneficial agent.

Detailed Description of the Invention

The finished product consists of a soft gelatin shell which has been filled with beadlets which contain at least one beneficial agent where the gelatin coating is transparent over-all or over a major portion of the product. The finished capsule will be sufficiently translucent so as to allow the particles to be seen through the soft gelatin wall under normal lighting conditions no matter how the capsule is oriented. In one embodiment, all of the soft gel capsule wall will be translucent. In another variation a portion of the soft gel capsule will have a different refractive index or will transmit more light than another portion of the capsule. In yet a third iteration, one portion of the capsule will be opaque while the other portion will be transparent. As a further example of this invention, one can prepare a capsule where one-half of an elliptical capsule is opaque, either the as measured by its long axis or its short axis.

A preferred form of this capsule will be one where the capsule is filled with beadlets and all parts of the soft gel wall are transparent to essentially the same extent. Another preferred variation is one in which beadlets have been filled into a hard-shelled gelatin capsule and are then coated with soft gelatin to provide a transparent preparation where the hard-shelled capsule and its contents are visible to the naked eye under normal lighting conditions.

As regards the soft gelatin wall-forming materials, any materials known to the art may be used to form the shell. Such materials may contain cross-linking or polymerizing agents, stabilizers, antioxidants, light absorbing agents for protecting light-sensitive fills, preservatives and the like. Soft gelatin capsule wall-forming materials are well documented in the literature and are well known to manufacturers and technicians alike. In addition, formulating and mixing ingredients in preparation for manufacturing SGCs may follow any route or utilize any technique known to the art.

Any sort of beadlet can be used in this formulation, so long as it contains or comprises at least one beneficial agent, is stable during the capsule-manufacturing process and during storage, and is visible to the naked eye.

The term "beneficial agent" means any compound or material which acts on a mammal in one fashion or another when consumed for its intended use in the manner prescribed. For example, a drug is a beneficial agent for the purposes of this definition. But in addition there are numerous other compounds which can have a subjective or objective beneficial effect on the user and which are to be included within the meaning of this term. For example an antacid or anti-gas agent can have a beneficial effect when used to treat indigestion. A breath freshener provides an objective and a subjective beneficial effect to many people. Nutritional agents such as vitamins, minerals, or amino acid supplements are beneficial to those needing to supplement their diet. Flavors and sweeteners provide a subjective benefit and a source of energy as well, and are also included. These examples illustrate but a few of the many different kinds of materials which are intended to be included within the scope of the term beneficial agent. Others will be apparent to the practitioner of this art.

Drugs and drug delivery are of greatest interest herein. The word "drug" is used in its broadest sense and includes any agent which exhibits a pharmacological effect on the user and which can be administered via SGC technology utilizing particles as described herein. Any solid or liquid form of a drug can be used provided it can be manufactured into a particulate, as is true for any compound which constitutes a beneficial agent for the purposes of this invention. Both fat soluble and water soluble drugs may be used. Drugs for treating cough, cold, and allergy symptoms are of most interest. They include antihistamines; drugs for treating inflammation, pain and pyrexia; nasal decongestants; expectorants; sedatives as used in cough and cold remedies, and the like. Phenylpropanolamine hydrochloride, caramiphen edisylate, acetaminophen, aspirin or another non-steroidal anti-inflammatory, pseudoephedrine hydrochloride, dextromethorphan hydrobromide, and chlorpheniramine maleate are most

preferred.

The beadlets and stability are the primary concerns. So far as size is concerned, the principal consideration will be that of creating a particle of a size such that the particles are visible to the naked eye under normal lighting conditions. Preferred beadlets will have a diameter in the range of about 149 to 1190 microns. Beadlet size can vary in any given capsule. The preferred particle size is between about 420 and 840 microns (about 20-40 mesh).

Beadlets can be comprised of pure agent or, as will more often be the case, the agent can be coated with a protective layer which may or may not affect how fast the particle dissolves and releases the active ingredient. Creating beadlets of pure agent is mostly a matter of shaping the raw material by some means, usually a mechanical means. A coating of some sort may be added to protect the neat compound. More often than not, one will want to coat the particles for both functional and aesthetic reasons. There are a number of ways to coat particles. Pan coating, for example, is a well established technology that provides a basic pellet. A more sophisticated approach is to create a core and then to add one or more layers of a coating to the core. If the "seeds" are differentially coated, that is some have a thicker coating layer, any particles with different coating thicknesses are loaded into one capsule, drug can be delivered over an extended period to time. This technology was pioneered by R. H. Blythe in U.S. patent 2,738,303. He describes there a therapeutic preparation in unit dosage form prepared from non-pareil seeds (sugar pellets), screened, placed in a coating pan, wetted with syrup, then treated with a 80:20 mixture of dextro-amphetamine sulfate and calcium sulfate dihydrate, then dried. This process was repeated several times to build up drug on the non-pareil seed; it is treated with talc to create the core pellet. These pellets were then treated with a wax-fat coating solution one or more times to create pellets with one or more fatty layers surrounding the core pellet. Later developments include placing an osmotic wall around the core pellet, and preparations where the drug dissolves in the wall-forming material of the particle and passes through it to the exterior on exposure to water. Reference to such particles can be found in the literature, for example in U.S. patent 4,434,153; the relevant parts are incorporated herein by reference. See also U.S. patent 4,961,932 which contains a substantial list of patents said to relate to tiny or small pills, and dosage forms comprising same.

Color variations in the particles can be used to make capsules esthetically more pleasing. Dyes or lakes of any sort may be used so long as they are not toxic or do not have an untoward or deleterious effect on the user and do not adversely affect stability of the beneficial agent.

Beadlet stability, as compared with stability of the agent, is another factor which must be taken into consideration when formulating beadlets. Beadlets must remain chemically inert when in contact with the gelatin wall-forming materials and whatever materials may leach out

of the wall-forming materials. It is not possible to identify all of the combinations which could lead to particle-carrier interactions. Beadlet coatings known to be soluble in soft gelatin wall-forming materials should not be used to formulate coated beads if that vehicle is the vehicle of choice. Also, it should be kept in mind that gelatin materials used to make SGC contain substantial amounts of water which may migrate into the spaces between the beadlets or be absorbed by the beadlets and have a deleterious effect on the particulates.

Stability of the beneficial agent is a consideration as well, just as it is with any formulation, not just these preparations. There is no single recipe for formulating a product which will not degrade chemically. Each formulation must be addressed on a case-by-case basis; this is within the skill of one trained in the formulation arts. Beadlets which do not require a sustained release coat will implicitly require a suitable coat to maintain stability within the finished product.

An alternative is to first fill the beadlets into a hard-shelled gelatin capsule then coat this capsule with a soft gelatin material which dries to a soft film; in other words coats the hard shelled gelatin capsule with a soft gelatin shell. This can be done by first preparing the hard-shelled gelatin capsule preparation where the fill is beadlets, then passing the finished hard gel capsules through a manufacturing process which coats the capsule with soft gelatin. This provides a second seal for the hard shelled capsule and renders it tamper resistant and tamper evident.

Examples of useful manufacturing techniques which can be modified to accommodate this invention are the plate process, the rotary-die process pioneered by R. P. Scherer, the process using the Norton capsule machine, and the Accogel machine and process developed by Lederle or the process of U.S. patent 5,146,730 for enrobing a unitary core. Each of these processes are mature technologies and are all widely available to any one wishing to prepare soft gelatin capsules. No preference is stated for any one of these processes as all will meet the needs of one practicing this invention.

Any form or shape can be used in this invention, so long as it can be prepared. Capsules may be oval, square, rectangular, have a dumbbell shape, look like an hour-glass, or have multiple sides, e.g. octagonal, hexagonal, pentagonal or the like.

The following examples are provided to illustrate the invention. They are not to be read as limiting the invention in any manner.

Examples

Example 1

Capsule Preparation

Large soft gelatin capsules containing vitamin E were purchased from the local pharmacy store. Individual capsules were slit on one end such that there was enough opening to empty the contents. Contents of these capsules were squeezed out through the opening. These empty capsules were then washed in absolute ethanol several times, such that all traces

of previous contents were removed and dried at room temperature for a few hours. Beadlets obtained from Central Pharmaceuticals, Inc., Seymour, Indiana, were carefully poured into the empty soft gelatin capsules through the opening until the capsule was full. The edges of the gelatin capsule around the slit were carefully wet with a small amount of water and pushed together by holding the capsule firmly between the fingers (5 to 10 minutes) until the edges sealed.

The active ingredients in the beadlets were chlorpheniramine maleate 12.0 mg and phenylpropanolamine HCl 75.0 mg. These beadlets were differentially coated so that some beadlets would release the actives immediately, and others would release their active ingredients at several time points over a 12 hour period.

CLAIMS

1. A gelatin capsule comprising a partially or wholly transparent soft gelatin capsule preparation wherein the internal volume is filled with beadlets or beadlets in a hard-shelled gelatin capsule wherein the beadlets contain a beneficial agent.
- 5 2. The capsule of claim 1 wherein capsule if filled with beadlets having diameters between about 149 and 1190 microns.
3. The capsule of claim 2 wherein the beneficial agent is a drug.
4. The capsule of claim 3 wherein the beadlets are time released or immediate release beadlets which contain medicaments for treating cough, cold and/or allergy
10 symptoms.
5. The capsule of claim 1 where the capsule is filled with beadlets in a hard shelled gelatin capsule.
6. The capsule of claim 5 wherein capsule if filled with beadlets having diameters between about 149 and 1190 microns.
- 15 7. The capsule of claim 6 wherein the beneficial agent is a drug.
8. The capsule of claim 7 wherein the beadlets are time released or immediate release beadlets which contain medicaments for treating cough, cold and/or allergy symptoms.

