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United States Patent [19]

Edgren et al.

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[45] Date of Patent: * Nov. 3, 1992

[54] **ANNEALED COMPOSITION FOR PHARMACEUTICALLY ACCEPTABLE DRUG**

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[73] Assignee: **Alza Corporation**, Palo Alto, Calif.

[*] Notice: The portion of the term of this patent subsequent to Apr. 9, 2008 has been disclaimed.

[21] Appl. No.: **647,321**

[22] Filed: **Jan. 28, 1991**

Related U.S. Application Data

[60] Continuation-in-part of Ser. No. 350,482, May 11, 1989, Pat. No. 5,006,346, which is a division of Ser. No. 187,621, Apr. 28, 1988, Pat. No. 4,931,285.

[51] **Int. Cl.**[5] **A61K 9/24**

[52] **U.S. Cl.** **424/473;** 427/3; 427/214; 424/468; 424/472

[58] **Field of Search** 424/473, 472, 468; 427/3, 214

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Assistant Examiner—Leon R. Horne
Attorney, Agent, or Firm—Paul L. Sabatine; Jacqueline S. Larson; Jean M. Duvall

[57] **ABSTRACT**

A dosage form is disclosed comprising a coat that surrounds a drug. The coat comprises a subcoat and an overcoat thermally annealed to provide a single unit coat around the drug.

1 Claim, 2 Drawing Sheets

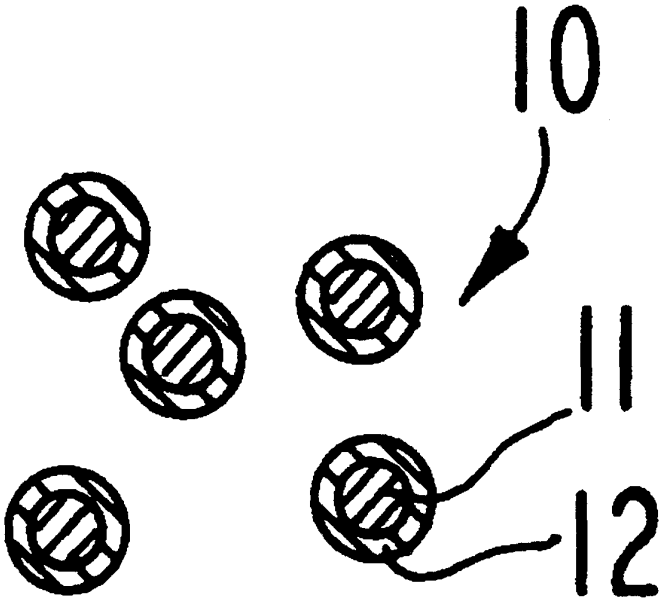


FIG. 1

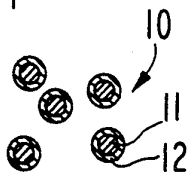


FIG. 2

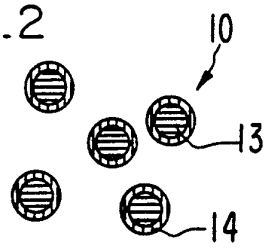


FIG. 3

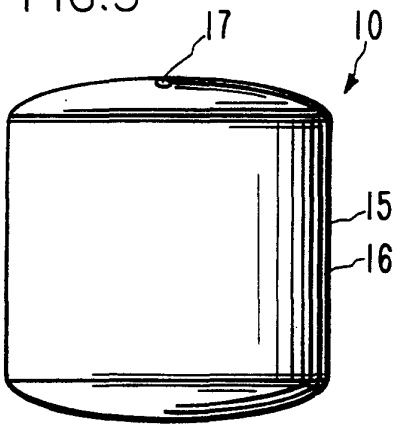


FIG. 4

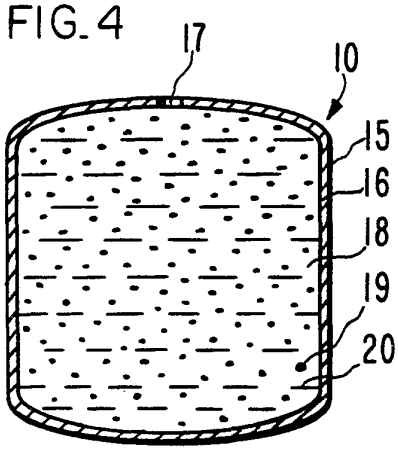


FIG. 5

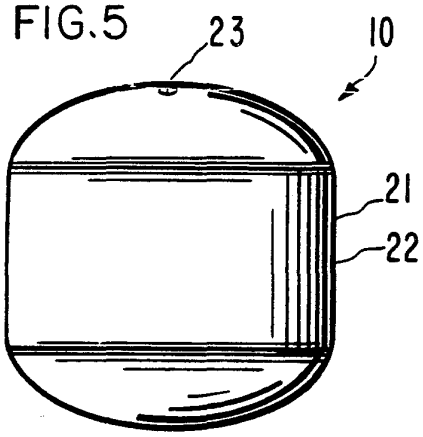


FIG. 6

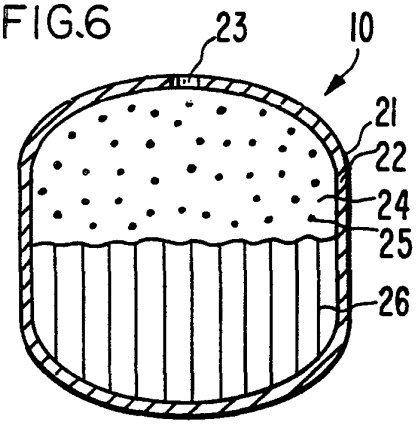


FIG_7

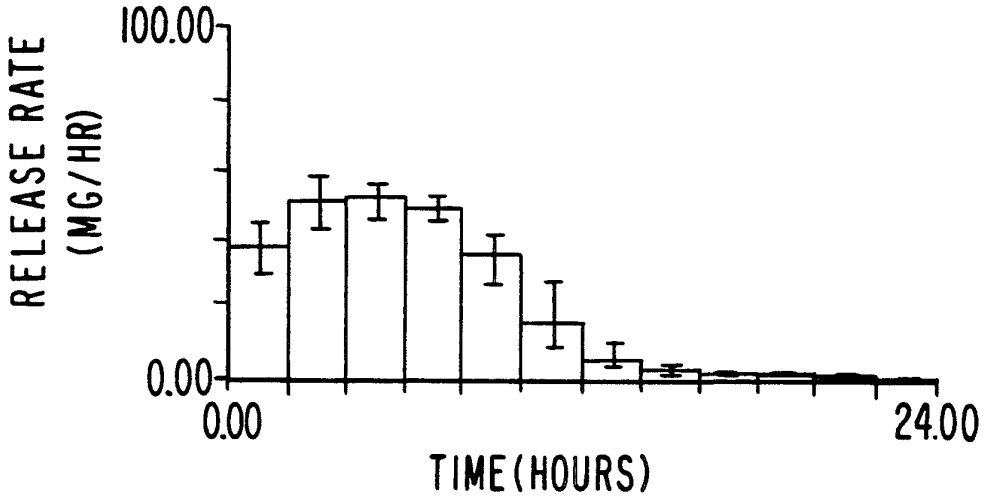
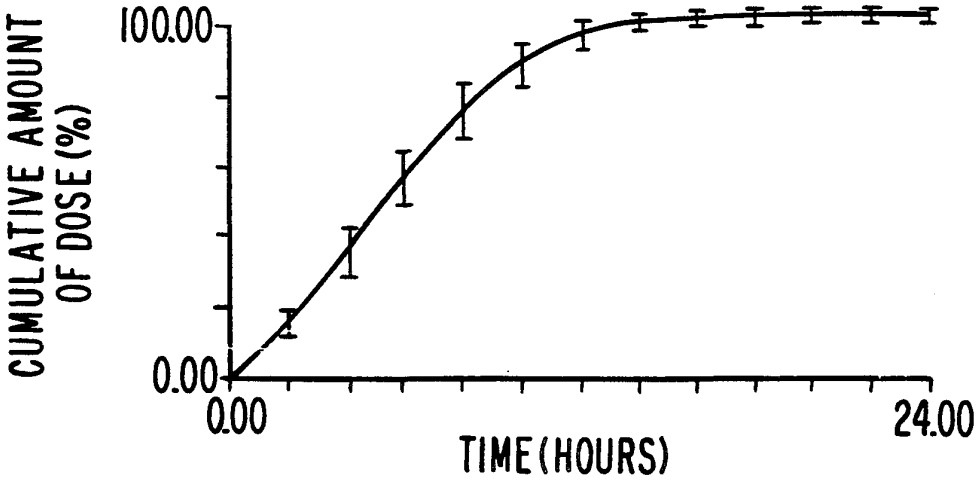


FIG_8



ANNEALED COMPOSITION FOR PHARMACEUTICALLY ACCEPTABLE DRUG

CROSS-REFERENCE TO RELATED APPLICATON

This application is a continuation-in-part of U.S. Appln. Ser. No. 07/350,482 filed on May 11, 1989, now U.S. Pat. No. 5,006,346 issued Apr. 9, 1991 which application Ser. No. 07/350,482 is a division of U.S. Pat. Appln. Ser. No. 07/187,621, filed Apr. 28, 1988 now U.S. Pat. No. 4,931,285 issued Jun. 5, 1990, which applications are incorporated herein by reference and benefit is claimed of its filing date. These applications are assigned to the ALZA Corporation of Palo Alto, Calif.

FIELD OF THE INVENTION

This invention pertains to both a novel and useful pharmaceutical coating composition. More particularly, the invention relates to a pharmaceutically acceptable coating composition on dosage forms such as delivery devices comprising a core comprising a therapeutically active drug; osmotic delivery systems; tablets; capsules; powders; granules; and beads.

BACKGROUND OF THE INVENTION

In Remington's *Pharmaceutical Sciences,* 14th Ed., p 1681, published in 1970, it is reported that pill coating has been a pharmaceutical technique for well over ten centuries. For example, Rhazes (850–932 A.D.) used a mucilage for coating pills in the ninth century and Avicenna (980–1037 A.D.) is credited with the introduction of silver and gold pill coatings into medicine. The coating of pills with finely powdered talcum, called pearl coating, was popular at one time. Gelatin coating of pills was introduced by Garot in 1838. The first sugar-coated pills in the United States were imported from France in about 1842. The first sugar-coated pill manufactured in the United States was in 1856 by Warner, a Philadelphia pharmacist. The coating of pills with tolu was done in about 1860, and twenty-four years later Unna introduced enteric coated pills.

Various pharmaceutically indicated articles of manufacture have been coated by the drug dispensing art. For example, tablets were coated to provide a more attractive dosage form, to protect its drug content from moisture and to enhance its taste. Then too, tablets were provided with a coat for releasing a drug by enteric dissolution in the intestine of a warm-blooded animal. Recently osmotic dosage forms were coated with a semipermeable rate controlling wall for delivering a drug at a known rate per unit time.

While the above mentioned dosage forms are useful in the management of health and disease, serious disadvantages are associated with them. That is, usually organic solvents are used for applying the coating to the drug and drawbacks accompany the use of organic solvents. For example, organic solvents generally are toxic and they must be substantially removed, usually by vacuum or by air ciruclation, from the dosage form to avoid hazard to health the dosage form's recipient. Another drawback is that most organic solvents are flammable thereby possibly providing the danger of fire to the manufacturer. Also, organic solvents present an environmental problem and they require complicated recovery systems to avoid contaminating the environment, which systems are expensive to operate. It will be appreciated by those skilled in the drug dispensing art that if a coating is provided that is substantially-free of organic solvents for coating drugs, drug granules, drug powders, drug delivery devices, and the like, such a coating would have an immediate positive value and, concomitantly, represent an advancement in the drug coating art. Likewise, it will be appreciated by those versed in the dispensing art that if a delivery device is made available comprising a coating applied from a non-organic solvent, and which delivery device possesses the thermodynamic ability to deliver a beneficial drug at a controlled rate, such a delivery device would have a practical application in the fields of human and veterinary medicine.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a novel and useful coating composition for dosage forms and which coating overcomes the disadvantages associated with the prior art.

Another object of this invention is to provide a new coating composition comprising pharmaceutically acceptable ingredients, and which coating composition is innocuous and useful for manufacturing dosage forms.

Another object of this invention is to provide a non-toxic coating composition free of organic solvents and which coating composition is useful for making dosage forms by standard manufacturing techniques.

Another object of the invention is to provide an aqueous coating composition which is relatively uncomplicated, capable of application without difficulty, and is applied at a relatively low cost.

Another object of the invention is to provide an aqueous polymeric coating that exhibits stability and resistance to sedimentation.

Another object of the invention is to provide an aqueous coating composition useful for manufacturing a drug delivery device possessing drug release rate controlling properties.

Another object of this invention is to provide a drug delivery device that can be manufactured by standard manufacturing techniques into various sizes, shapes and forms that comprise an improvement in the dispensing art, which comprises a non-toxic, aqueous coated wall that surrounds a drug.

Another object of this invention is to provide an aqueous-solvent coating composition that is non-flammable and is not an environmental hazard during formulation and not a hazard when applied to a drug core.

Another object of the invention is to provide a novel coating composition comprising a water carrier useful for coating a drug.

Other objects, features and advantages of this invention will be more apparent to those versed in the dispensing art from the following detailed specification taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

FIG. 1 is an opened view depicting a powdered drug coated with the coating composition provided by this invention;

FIG. 2 is an opened view illustrating granules of a beneficial drug coated with a coating composition provided by this invention;

FIG. 3 is a view of an osmotic device designed and shaped for orally administering a beneficial drug to the gastrointestinal tract;

FIG. 4 is an opened view of the osmotic device of FIG. 3 depicting the wall of the osmotic device comprising the wall-forming coating composition of this invention;

FIG. 5 is a view of another embodiment of an osmotic device provided by this invention, which osmotic device is adapted and sized for oral admittance into the gastrointestinal tract of a host;

FIG. 6 is an opened view of the osmotic system of FIG. 5 for illustrating a wall formed from the coating composition provided by this invention;

FIG. 7 is a graph that depicts the drug delivery rate per unit time from a device comprising a wall coated by the process of the invention; and,

FIG. 8 is a graph that depicts the cumulative amount of drug released per unit time by the delivery device of FIG. 7.

In the drawings and in the specification like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which figures are examples of a dosage form comprising a coating composition provided by this invention and which examples are not to be considered as limiting the invention, one example of a dosage form is illustrated in FIG. 1. In FIG. 1, a dosage form **10** is seen in opened section. Dosage form **10** comprises a powdered drug **11**, generally exhibiting a powder size that passes through a sieve having an opening of from 0.074 mm to 0.250 mm, surrounded by coating composition **12**. Coating composition **12** comprises a subcoat and an overcoat. The subcoat comprises a finely divided membrane forming polymer dispersed in an oil-in-water emulsion, wherein the oil, generally present as an oily plasticizer, lowers the glass transition temperature of the membrane forming polymer. The overcoat comprises a water soluble composition wherein the glass transition temperature of the overcoat is higher than that of the subcoat. The subcoat and the overcoat are annealed, with the subcoat forming an insoluble membrane that surrounds powdered drug **11**. The annealed overcoat forms a membrane that dissolves in an aqueous environment of use, leaving a continuous, insoluble membrane coating **12**.

In FIG. 2, another embodiment of dosage form **10** is seen in opened view. In FIG. 2 dosage form **10** comprises granules of drug **13**. The drug granules generally exhibit a granule size that passes through a sieve having an opening from greater than 0.250 mm to 9.50 mm. Drug granules **13** are surrounded by aqueous-applied coating composition **14**. Coating composition **14** is applied in two steps, first a subcoat followed by an overcoat. The two coats are annealed, which annealing process coalesces the polymer in the subcoat thereby providing a continuous membrane or film. The overcoat protects the subcoat during the annealing process and the overcoat additionally prevents the subcoat of one dosage form from fusing with the subcoat of a neighboring dosage form.

In FIG. 3, another embodiment of dosage form **10** is illustrated manufactured as an osmotic drug delivery device. In FIG. 3 osmotic dosage form **10** comprises a body **15** comprising a wall **16** that surrounds and forms an internal compartment, not seen in FIG. 3. Osmotic dosage form **10** comprises at least one passageway **17** for connecting the interior of osmotic dosage form **10** with the exterior of osmotic dosage form **10** when in a biological environment of use.

In FIG. 4 osmotic dosage form **10** of FIG. 3 is seen in opened view. In FIG. 4 osmotic dosage form **10** comprises body member **15**, aqueous coated wall **16** and exit passageway **17**. Wall **16** surrounds and forms an internal compartment **18**. Internal compartment **18** comprises a dispensable drug **19**, represented by dots, and an optional osmagent, represented by dashes. Wall **16** is permeable to the passage of an exterior fluid present in the environment of use, and wall **16** is substantially impermeable to the passage of drug **19** and osmagent **20**.

In FIG. 5 another embodiment of dosage form **10** is illustrated and made as an osmotic drug delivery device. In FIG. 5 osmotic dosage form **10** comprises a body member **21** comprising a wall **22** that surrounds and forms an internal compartment, not seen in FIG. 5. Dosage form **10** comprises at least one passageway **23**, formed during the manufacture of dosage form **10** or, optionally, formed when dosage form **10** is in a fluid environment of use. Passageway **23** connects the interior of dosage form **10** with its exterior for delivering a drug to an environment of use.

In FIG. 6 dosage form **10** of FIG. 5 is seen in opened view. In FIG. 6 dosage form **10** comprises body member **21**, aqueous coated annealed wall **22** and exit passageway **23**. Wall **22** surrounds, forms and defines an internal compartment **24**. Internal compartment **24** comprises a first composition identified by dots **25**, and a second composition **26** identified by vertical lines. First composition **25** comprises a beneficial drug and second composition **26** comprises an expandable hydrogel. First composition **25** and second composition **26** are in laminar arrangement and they cooperate with wall **22** for the effective delivery of a drug through exit passageway **23** to an environment of use.

FIG. 7 and FIG. 8 exemplify the release of an active agent from a delivery system made according to this invention. The release rate per unit time and the cumulative amount release of the drug potassium chloride are depicted, respectively, for a delivery system made according to this invention.

While FIGS. 1 through 8 illustrate different embodiments of dosage forms that can be coated with the coating composition of this invention, it is to be understood that the coating composition can be applied to a wide variety of dosage forms, which dosage forms comprise various shapes, sizes and forms. The coating composition can be applied to devices not limited to but including uses for buccal, implant, artificial gland, cervical, intrauterine, nose, and the like. In these forms the device coated with the coat of this invention can be adapted for administering a beneficial medicine to animals, warmblooded mammals, humans, farm and zoo animals, avians and reptiles.

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