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Description

The present invention relates to a multilayered medicament delivery device of the sustained release type for orally administering a predetermined selective dose of a medicament. In another aspect, it relates to a method of preparing the medicament delivery device of the present invention. In a further aspect, it relates to an apparatus for preparing said delivery device.

The convenience of administering a single dose of medication which releases an active medicament over an extended period of time so as to achieve a constant rate of release of medicament has long been recognized in the pharmaceutical field. Since oral administration of single dose medicinals is simple and desirable, considerable interest has been expressed in increasing the residence time of medicaments in the stomach.

One way to retain medication in the stomach is to close off the pylorus, the opening from the stomach into the first part of the small intestine, before or during the adminstration of a drug. Tablets or other drug dispensing devices which swell, inflate, or unfold when in contact with gastric juices and thus become too large to enter the pylorus are known in the art.

Sustained release devices which are buoyant in gastric juices have been disclosed. U.S. Patent Nos. 4,140,755 and 4,167,558 relate to a sustained release, hydrodynamically balanced hydrocolloid-medicament tablet having a bulk density of less than 1.0 which is capable of floating in gastric fluid. U.S. Patent No. 3,976,764 teaches a solid therapeutic preparation for gastric diseases, in which an empty globular shell, granular lump, or oval shaped nucleus of polystyrol foam of high buoyancy is coated on the external surface with a medicament and additives. Alternatively the medicament may be within the hard capsule as a disc shaped tablet.

Drug administering vehicles that are divisible into unit dosage forms are taught in U.S. Patent Nos. 3,444,858, 4,126,503, and 4,136,145.

The present invention provides a flexible, sustained release medicament device for oral administration which: (1) releases medication approaching a zero order release rate, (2) releases medication for a prolonged period of time, (3) remains buoyant in the stomach for an extended period of time during release of medicament, (4) comprises a multilayered polymer film which both controls the rate of release and aids in the buoyancy of the medicament, (5) is in a linear form suitably marked for facile measurement of prescribed medical dosage according to length and capable of being easily cut to the desired length and (6) can be dispensed and administered in a compact form which extends in the stomach to remain buoyant.

The orally administered, sustained release, flexible medicament device of multilayer composite construction is comprised of at least one carrier film and at least one barrier film, the carrier film(s) containing medicament and the barrier film(s) comprising at least one water-insoluble and permeable polymer and additives to control release of medicament. The barrier film(s) is sealed or affixed to the carrier film(s) along its periphery in such a way as to entrap air onto one or more surfaces of the carrier film(s) and render the sustained release medicament device buoyant in the gastric juices of the stomach during release of medication.

Since the ratio of effective dose to toxic dose for some medicinals is very small, e.g. dicoumarin, the sustained release medicament delivery device of the present invention has the desirable property of being capable of fine adjustment to the needs of the recipient. It is capable of being administered in a predetermined selective dose that is not necessarily a unit dose but one that can be accurately measured and dispensed according to linear measurement.

Release of medicament through the barrier and carrier films appears to be achieved by a combination of leaching, diffusion (permeability), and erosion. Initial erosion of the films and subsequent leaching of medicament occurs when the excipient or water soluble plasticizer dissolves in the gastric juices. Permeability depends upon the reservoir concentration (conc. of medicament in the device), membrane thickness, polymer stiffner, co-diffusants, molecular weight of diffusants, and chemical functionality of the transport of active ingredients. For example, varying the thickness and stiffness of the barrier film enables incorporation therein of tailor-made properties for a specific controlled release application. It is desirable that the device maintain its integrity for a period up to several weeks, preferably 4 to 24 hours, before exiting the stomach or degrading.

In the accompanying drawing:

Fig. 1 is a top plan view of a medicament containing device in strip form showing entrapped air pockets;

Fig. 2 is an enlarged cross-sectional view of the device of Fig. 1 taken along lines 2—2;

Fig. 3 is an enlarged cross-sectional view of a device similar to that shown in Fig. 2 showing another embodiment of the present invention;

Fig. 4 is an enlarged perspective view of an open gelatin capsule having the device of the invention in pleated strip form contained therein;

Fig. 5 is a top plan view of a modified embodiment of the invention showing perforations for division into unit dosages;

Fig. 6 is a perspective view of an apparatus for forming devices of the present invention.

The present invention provides a flexible, sheet-like, sustained release medicament device for orally

administering a predetermined selective dose of a medicament, which device is of a multilayer composite construction comprising

(a) at least one carrier film comprising at least one water-insoluble polymer and containing medicament, and

(b) at least one barrier film overlaying said carrier film on at least one surface thereof and sealed to said carrier film along its periphery and in such a way as to entrap small quantities of air between said carrier and barrier films, said barrier film comprising at least one water-insoluble and water- and medicament-permeable polymer or copolymer and optionally additives to control the release of medicament, said multilayer composite construction having a bulk density of less than 1.0 g/cc and being facilely divisible into any desired length.

As used in this application:

"flexible" means pliant or conforming under stress to a new shape, yet still maintaining its integrity;

"sustained release" means a technique or method in which active chemicals are made available to a specified target at a rate and duration designed to accomplish an intended effect;

"film" means a sheet-like material having a thickness up to 0.05 cm;

"permeable polymer" means one that allows migration or transport of substances, such as water, medicament, excipient, or water-soluble plasticizer therethrough;

"zero order" release rate means a rate of release that is constant;

"medicament" means any composition or substance which will produce a pharmacologic response; and

"facilely divisible" means readily and easily subdivided, as for example by cutting with a scissors, into any dosage which is not necessarily a unit dose.

Referring to the accompanying drawing, Fig. 1 shows one embodiment of the multilayered sustained release medicament containing device 10 with outer barrier film 12 enclosing pockets of air 14. Fig. 2 is an enlarged cross-sectional view of device 10 taken along line 2—2 of Fig. 1. Barrier films 12 are shown overlying air pockets 14 and carrier film 16 which has medicament therein. Films 12 and 16 sealably adhere at surfaces 13.

Fig. 3 is an enlarged cross-sectional view of another embodiment of the present invention 10 showing barrier films 12, air pockets 14, and a plurality of carrier films 16, each of which can carry therein the same medicament, different medicaments, or, when desired, no medicament at all. Films 12 and 16 sealably adhere at surfaces 13 and and films 16 adhere to each other at surfaces 15.

Fig. 4 shows open gelatin capsule 20 having the device 10 of the present invention in pleated form contained therein.

Fig. 5 shows another embodiment of the device 10 having barrier film 12, air pockets 14, and perforations 22 which are located at intervals so as to provide unit dosages.

Fig. 6 shows an apparatus 30 for forming the devices of the present invention. Piston 32 moves heater block 34 which has an embossing die of suitable pattern on its undersurface. Carrier film 16 unwinds from spool 36 and is overlaid on both surfaces by barrier films 12 which unwind from spools 38 and 42. Device 10, which has been embossed by the die on the lower surface of block 34 so as to provide air pockets 14 in some areas and sealing of the films in other areas, is shown moving in the direction of the arrow. Device 10 has perforations 22 therein.

The device of the present invention is an orally administered sustained release drug delivery device which is suitable for facile measurement and divisibility for prescribed medical dosage according to length and has a bulk density of less than 1.0 g/cm^3 so as to remain buoyant in the stomach for an extended period of time during which substantially all of the medicament is released therefrom. The device of the invention can be prepared with a known amount of medicament per linear measurement. Perforations may be provided at regular intervals to provide unit dosages. When it is desirable to very accurately dispense medicament, the device of the present invention may be cut, as with a scissors for example, to the precisely predetermined length according to the prescribed dosage. The medicament device may be dispensed and administered in a compact form which extends in the stomach. For example, the device, in flexible, preferably strip form, may be rolled or folded as by pleating so as to easily fit in a gelatin capsule for oral administration. The gelatin capsule dissolves in gastric juices at physiological temperatures in a short time to allow the constrained medicament device to unroll or unfold.

The overall dimensions of the drug delivery device are 0.004 to 0.08 cm thick with a preferred thickness between 0.02—0.03 cm, with a length dispensed according to prescribed medical dosage; a length of 14 cm is preferred. The width of the device can be from 0.5 cm to 7.5 cm, with a preferred width of 2.1 to 6.1 cm. For veterinary use, for example, the size of the sustained release medicament device can be much larger, depending on medical and physical requirements of the animals.

The medicament delivery device of the present invention is a laminated multilayered structure comprising two polymeric films having different functions. One film is a carrier film and a second is a barrier film. The carrier film is overlaid on at least one surface thereof by an outside barrier film but is not limited to this number or arrangement of films. Polymers forming carrier and barrier films are, and remain, physiologically inert during the time of complete drug delivery.

The carrier film, of which there is at least one, is comprised of a film-forming polymer or matrix containing a medicament or active agent or drug dispersed or dissolved therein or applied thereon. By

incorporating multiple carrier films in the device it is possible to vary the number and kind of medicaments released and their rates of release. Other additives such as fillers, colorants, excipients, and plasticizers may be added to the polymer by simple mixing. The polymeric material or matrix is water insoluble and capable of forming a flexible, self-supporting film when containing medicament in the concentration of up to 65 percent by weight. The matrix does not swell to any appreciable degree in water and has a softening point above 37°C, the normal physiological temperature.

Examples of polymers that may be used in the carrier film, which may comprise a plurality of layers, are ethyl cellulose, poly(γ-benzyl glutamate), polyvinyl acetate, cellulose acetate phthalate, a copolymer of methyl vinyl ether with maleic anhydride, and the above polymers to which polyvinylpyrrolidone may be added. Other useful polymers and a discussion of controlled release systems in general is given in *Controlled Release Technologies; Methods, Theory, and Applications,* Vol. I, editor A. F. Kydonieus, CRC Press Inc., Boca Raton, Florida, pp. 1—14, (1980).

Table I, below, summarizes some mechanical properties and sources for polymers and polymer films that are used in the examples of this invention.

The medicament or therapeutic agent or drug can be dispersed homogeneously into the matrix, or it may be desirable to increase the concentration of the medicament from the outer wall to the interior of the carrier film to approach a zero order release behavior. Any medicament which can be given orally, and for which a sustained release action is beneficial or desirable, can be incorporated into the carrier film. The medicament can be any substance which is at least partially water-soluble and may comprise acidic, basic, neutral, or amphoteric substances. Concentration of medicament in the carrier layer may typically vary from 0.05 to 65 percent. The carrier may comprise a plurality of layers, generally each having at least one medicament incorporated therein, although designated carrier layers may contain no medicament.

Suitable medicaments used with the device of this invention are those mentioned in, for example, U.S. Patent Nos. 3,625,214, 4,248,857 and 4,167,558 and in British Patent No. 1,428,426. Some of these medicaments are, for example: acetazolamide; antacids such as calcium carbonate and aluminum hydroxide; aspirin; belladonna alkaloids; benztropine; bromocriptine; cephalothin; chloropromazine; cimetidine; dipyridamole; disopyramide; isoephedrine; isosorbide dinitrate; ephedrine; estrogens; lithium carbonate; methadone; naloxone; nitroglycerin; papavarine; penicillin; phenylpropanolamine; potassium chloride; probucol; prochlorperazine; progesterone; quinidine; terbutaline; tetracycline; theophylline; tolazoline; and trihexylphenidyl.

Plasticizers suitable for use in the carrier film of the sustained release formulations of the invention include those well known in the art of preparing coatings used in the pharmaceutical industry. Examples are acetylated monoglycerides; esters of phthalic acid such as dimethyl phthalate, dibutyl phthalate, and dioctyl phthalate; propyleneglycol; glycerol; castor oil; D-sorbitol; diacetin; triacetin; dibutyl tartarate; and the like. The preferred percentage of plasticizer varies up to 30 percent by weight with desired percentages from 1—15% of the carrier film.

An excipient is usually incorporated into the matrix of the carrier film. The excipient is a water-soluble material which gradually dissolves in the gastric juices. This gradual dissolution creates regions of porosity within the matrix. Penetration of gastric juices or water into these porous regions results in the controlled release of medicament. Excipients generally comprise from 1.0 to 30 percent by weight of the carrier film. Typical excipients are those used in the pharmaceutical industry and some examples are salt, sugar, polyvinylpyrrolidone, and polyethylene glycol (molecular weight of these latter two polymers ranges from 300—20,000).

The thickness of the carrier film is in the range of 0.001 to 0.05 cm, and preferably it is 0.015 to 0.02 cm thick.

As mentioned above, the barrier film overlays the carrier film on at least one surface. Obviously, if the medicament is dispersed homogeneously in a single carrier film, the barrier film will overlay both surfaces of the carrier film, unless it is desired to have more rapid release of medicament from one surface of the device than from the other. The purpose of the barrier film is to control the rate of release of medicament that is present in the carrier film. Another purpose of the barrier film is to control the rate of release of medicament such that the control rate profile approaches that of a zero order release profile or any other desired release rate profile. In addition, the barrier film provides buoyancy of the medicament release device in the stomach by entrapping air in small pockets between it and the carrier film.

The barrier film is comprised of at least one water-insoluble, permeable, film-forming polymer or copolymer, and optionally a water-soluble polymer or copolymer, or a mixture thereof, a plasticizer, and generally an excipient. In certain instances, the barrier film may also contain medicament. Useful water-insoluble, permeable, film-forming polymers, after leaching of the excipient or water-soluble plasticizer therefrom have a pore size, as determined by scanning electron microscopy, in the range of 0.1 to 10 microns, and preferably 0.5 to 5 microns. Portions of the surface of the outermost barrier film of the drug delivery device are fixed, sealed, or laminated onto the carrier film in such a manner that a pocket, or pockets, of air or "bubbles" are entrapped between this external film and the remainder of the drug delivery device to provide the device with buoyancy sufficient to float in the stomach (i.e., apparent specific gravity of the device is less than that of the gastric juices, which have a specific gravity of between 1.004 and 1.01) for an extended period of time during which substantially all of the medicament is released. The bulk density of the device is less than 1.0 g/cc. The barrier film has suitable flexibility and mechanical

strength to allow pleating and sealing or affixing of said film onto the drug delivery device in such a manner as to become the air-entrapped or "bubble" polymer film. The barrier film comprises in the range of 17 to 60 percent by weight, and preferably 25 to 45 percent by weight, of the sustained release device.

A judicious selection of the polymers or copolymers having the required degree of permeability for forming the barrier film can dictate the rate of release of medicament from the drug delivery system. The required degree of permeability of the barrier film can be obtained by starting with a permeable polymer or by adding from 0.5 to 30 percent by weight of a water-soluble polymer to the film-forming polymer. Examples of water-insoluble, permeable film-forming polymers are ethylcellulose, polyvinyl acetate, cellulose acetate phthalate, polyesters laminated with low-density and medium-density polyethylene and copolymers of polyethylene and polyvinyl acetate. Examples of water-soluble polymers are polyvinyl pyrrolidone and hydroxypropylmethyl cellulose. Table I summarizes some mechanical properties and sources for some of the polymers and polymeric films that are used as examples in this invention.

TABLE I
Data on polymers and polymer films

Polymer or copolymer	Physical properties: Molecular weight[a] or viscosity[b, c]	Film tensile strength: Pascal (Pa)	Film tensile strength: lb.sq. in. (PSI)
Ethyl cellulose	0.045—0.11 Pa · S, 45—110 cP	5.87×10^7	8,520
	0.063—0.085 Pa · S, 63—85 cP (preferred for carrier film)	—	—
	0.041—0.085 Pa · S, 41—85 cP (preferred for barrier film)	—	—
Poly(-benzyl glutamate)[d]	50,000—100,000[e]	1.65×10^7	2,400[f]
Copoly(ethylenevinyl-acetate)[g]	50,000—100,000	3.8×10^7	5,500
Cellulose acetate phthalate	50,000—100,000	—	—
Copolymer of methyl vinyl ether—maleic anhydride[h]	High viscosity type	—	—
Polyethylene terephthalate polyester laminated with polyethylene[i]	20,000 (mol. wt. of polyester) 5,000—100,000 (mol. wt. of laminated polyethylene)	5.17×10^7	7,500[j]
	10,000—50,000 (preferred)	4.14×10^7	6,000[k]

[a] Number average molecular weight; flow rate and pressure limit data for cellulose ester membrane materials are given in Millipore Corp. Bulletin PB085, incorporated herein by reference
[b] Viscosity reported in Pascal-second (Pa · S) and Centipoise (cP)
[c] Viscosity of Methocel® E-15 (Dow Chemical Co.) determined as a 2% solution in water at 20°C. Viscosity of Ethocel®-45 (Dow Chemical Co.) determined as a 5% solution in toluene-ethanol (80:20, vol/vol) at 25°C. Viscosity of Ethocel®-70 (Dow Chemical Co.) determined as a 5% solution in toluene-ethanol (60:40, vol/vol) at 25°C.
[d] Prepared according to directions of S. B. Mitra, N. K. Patel and J. M. Anderson, Int. J. Biol. Macromolecules *1*, 55 (1979)
[e] Molecular weight determined in dichloroacetic acid, see P. Doty, J. H. Bradbury and A. M. Holtzer, J. Am. Chem. Soc. *78*, 947 (1956)
[f] Stress at failure reported by J. M. Anderson et al, J. Biomed. Mater. Res. Symposium, No. 3, 25 (1972)
[g] Scotchpak® laminated copolymer (3M) heat sealable polyester film Nos. 112, 113, 115, 125
[h] Gantrez® AN-169 copolymer (GAF)
[i] Scotchpak® laminated copolymer (3M) Nos. 5, 6
[j] Laminated with low density polyethylene
[k] Laminated with medium density polyethylene

Plasticizers suitable for use in barrier films of the invention include those well known in the art for preparing coatings used in the pharmaceutical industry and can be those plasticizers that are listed above as suitable for use in the carrier film of the invention. The percentage of plasticizer can be in the range of 0.5 to 30 percent, preferably 20 to 25 percent, by weight of the barrier film.

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