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Release profiles of the active core from the compositions in an aqueous physiological environment are described in Example 2, and plotted as cumulative percentage release versus time and presented in FIG. 3.

Burst-free, variable release from 28–70 days is achieved by varying the polymer concentration in the oil phase.

EXAMPLE 6

Microcapsule compositions are prepared as described in Example 5, wherein polymer molecular weight is 28,000–40,000 and polymer concentrations vary between 5% to ~12% w/w. Compositions 5 and 6 are listed in Table 1.

Release profiles of the active core from the compositions in an aqueous physiological environment are described in Example 2 and are plotted as cumulative percentage release versus time, and presented in FIG. 5.

Burst-free, variable release from 28–70 days is achieved by varying the polymer concentration.

EXAMPLE 7

Microcapsule compositions are prepared as described in Example 6, wherein the aqueous/oil ratio varies between 1/5 to 1/25 (v/v). Compositions 3 and 7 are listed in Table 1.

Release profiles of the active core from the compositions in an aqueous physiological environment are described in Example 2, and plotted as cumulative percentage release versus time, and presented in FIG. 5.

Burst-free, variable release from 28–70 days is achieved by varying the aqueous/oil ratios.

EXAMPLE 8

Microcapsule compositions are prepared as described in Example 5, wherein the copolymer ratio is 75/25 and polymer concentrations vary between 5% to ~25% w/w. Compositions 8 and 9 are listed in Table 1.

Release profiles of the active core from the compositions in an aqueous physiological environment are described in Example 2, and are plotted as cumulative percentage release versus time, and presented in FIG. 3.

Burst-free, variable release from 56->90 days is achieved by varying the polymer concentration in the oil phase.

EXAMPLE 9

Microcapsule compositions are described in Example 2, wherein the active core is leutinizing hormone releasing hormone (LHRH, a decapeptide of molecular weight 1182) and the polymer concentration is ~40% w/w. Release profiles of the active core from the composition in an aqueous physiological environment are described in Example 2, They are plotted as cumulative percentage release versus time, and presented in FIG. 7.

Burst-free, continuous and complete release is achieved within 35 days, similar to Histatin acetate.

EXAMPLE 10

Microcapsule compositions are prepared as described in Example 2, wherein an additive such as sodium salt (car-

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bonate or bicarbonate) is added to the inner aqueous phase at concentrations of 1–10% w/w to maintain the biological activity of the released polypeptide.

Burst-free, variable release from 1–28 days is achieved similar to Examples 2 & 3, and the released polypeptide is biologically active until 30 days, due to the presence of the sodium salt.

EXAMPLE 11

Microcapsule compositions are prepared as described in Example 2, wherein an additive such as a nonionic surfactant, polyoxyethylene/polyoxypropylene block copolymer (Pluronic F68 and F127) is added to either the inner oil or the aqueous phase at concentrations from 10–100% w/w, to maintain the biological activity of the released polypeptide.

Burst-free, continuous release from 1–35 days is achieved similar to Examples 2 & 3, and the released polypeptide is bioactive due to the presence of the surfactant.

EXAMPLE 12

Cumulative histatin release from the microcapsule compositions described in Examples 1 through 11 and release profiles plotted in FIGS. 3 and 5 show the burst-free, programmable peptide release for variable duration from 1–100 days. Virtually any pattern of cumulative release is achievable over a 100 day duration by a judicious blending of several compositions, as shown in FIG. 6.

We claim:

1. A process for preparing controlled release microcapsule formulations characterized by burst-free, sustained, programmable release of biologically active agents comprising: Dissolving biodegradable poly (lactide/glycolide), polymer in a form of uncapped/end-capped blend in a ratio of from 50/50 to 1/99 in methylene chloride, and dissolving a biologically active agent or active core in water; adding the aqueous layer to the polymer solution and emulsifying to provide an inner water-in-oil (w/o) emulsion; stabilizing said inner w/o emulsion in a solvent-saturated aqueous phase containing an oil-in-water (o/w) emulsifier; emulsifying said inner w/o emulsion in an external aqueous layer containing oil-in-water emulsifier to form a ternary emulsion; and stirring the resulting water-in-oil-in-water (w/o/w) emulsion for sufficient time to remove said solvent to harden microcapsules, and rinsing the hardened microcapsules with water and lyophilizing said hardened microcapsules.

2. The process of claim 1 wherein a solvent-saturated external aqueous phase is added to emulsify the inner w/o emulsion prior to addition of the external aqueous layer, to provide microcapsules of narrow size distribution range between 0.05–500 μm .

3. The process of claim 1 wherein a low temperature of about 0–4° C. is provided during preparation of the inner w/o emulsion, and a low temperature of about 4–20° C. is provided during preparation of the w/o/w emulsion to provide a stable emulsion and high encapsulation efficiency.

4. The process of claim 1 wherein a the blend of uncapped and end-capped polymer is used to provide release of the active core in a continuous and sustained manner without a lag phase.

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