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(54) Title: CAPSULES CONTAINING AQUEOUS FILL COMPOSITIONS STABILIZED WITH DERIVATIZED CYCLODEXTRIN

(57) Abstract: A capsule containing an aqueous fill composition that comprises water, a derivatized cyclodextrin, such as sulfoalkyl ether cyclodextrin (SAE-CD) or hydroxypropyl cyclodextrin (HPCD), optionally one or more active agents and optionally one or more excipients is stabilized from degradation, erosion, swelling or dissolution of its shell during storage. The derivatized cyclodextrin is present in an amount sufficient to reduce, eliminate or inhibit degradation, erosion, swelling and/or dissolution of the shell by water present in the fill composition. Alternatively, the derivatized cyclodextrin and another shell-stabilizing material together stabilize the shell from degradation, erosion, swelling and/or dissolution by water present in the fill composition. The derivatized cyclodextrin can reduce the water activity of the fill composition.

Capsules Containing Aqueous Fill Compositions Stabilized with Derivatized Cyclodextrin

By:

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FIELD OF THE INVENTION

The present invention relates to a capsule containing a derivatized cyclodextrin in an aqueous fill, wherein the cyclodextrin is present in an amount sufficient to stabilize the shell of the capsule from erosion, dissolution, swelling or degradation by water in the fill.

BACKGROUND OF THE INVENTION

Liquid, or semi-solid filled capsules are widely known. These fill compositions are generally preferred over solid filled capsules, since it is easier to obtain a higher content uniformity for liquid or semi-solid filled capsules than it is for solid filled capsules.

Capsule fill compositions can be aqueous or non-aqueous. Materials generally used for capsule fill compositions include: 1) water-immiscible, volatile and nonvolatile liquids, 2) water miscible, volatile and nonvolatile liquids, and 3) miscellaneous carriers such as glycerin, propylene glycol, water, and low-molecular weight alcohols, ketones, acids, amines, and esters. Suspensions of the active are often included in vegetable or mineral oils, triglycerides, glycols such as polyethylene glycols and propylene glycol, surfactants such as polysorbates, or combinations of these.

The shell-forming material of the capsule is chosen so as to maximize the stability of the shell toward the fill composition, while at the same time maintaining the desired release profile for the active agent. Non-aqueous fill compositions are used widely because the shell of a capsule must be water soluble, erodible or degradable in order to be useful for use in an aqueous environment, e.g., for oral administration to a subject. Quite often, however, it is desirable to include water in the fill composition in order to obtain the desired active agent release profile, increase dissolution of active agent in the fill composition and/or maximize stability of the ingredients in the fill composition. When an aqueous fill composition is used, the shell of the capsule is generally made of material that is more resistant to water dissolution, erosion or degradation.

A number of different relatively water stable shell compositions are known. Those shell compositions generally include materials or are made by processes that reduce the instability of the shell toward water in the fill composition. For example, Banner Pharmacaps and Cardinal Health provide capsules that are somewhat stabilized for a lipophilic fill and other for a hydrophilic fill. However, using such a shell results in altered performance of the capsule formulation. Accordingly, the pharmaceutical scientist must carefully balance the amount of water included in the fill composition against the aqueous stability properties of the shell. Moreover, the known aqueous fill compositions are limited in the amounts of water and the combination of active agents and excipients that can be included therein. In other words, known shells containing fill compositions with high amounts of water still degrade, dissolve, swell or erode during storage.

A number of references disclose capsule dosage forms filled with an aqueous liquid or semi-solid vehicle, an active agent, and another component added to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

Kuentz et al. (*International Journal of Pharmaceutics* (2002), 236(1-2), 145-152) disclose capsules filled with a liquid composition comprising water, PEG and poly(vinylpyrrolidone) or comprising water, glycerides (LABRASOL®) and colloidal silicon dioxide (AEROSIL®). The components were added to determine which combination thereof would be able to reduce or stop dissolution, erosion or degradation of the shell by the fill composition. Kuentz et al. do not disclose the use of cyclodextrins.

Bowtle (Presentation entitled "Liquid-encapsulation technology for oral delivery") discloses the use of hydrogenated glucose syrup as a material suitable for use in liquid-filled capsules. Bowtle does not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

Japanese Patent No. JP 61207329 to Mochizuki et al. discloses a soft gelatin capsule filled with an aqueous liquid vehicle, a sugar and an active agent. The sugar is present in amounts of ≥ 55% wt. with respect to the fill composition. Sugars such as sucrose, glucose, fructose, and maltose are disclosed. The sugar is present in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by the fill

composition. Mochizuki et al. do not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

German Patent No. DE 19545043 to Lucks et al. discloses a liquid-filled soft gelatin capsule. The liquid is present in a single phase. The fill composition comprises 1-20% wt. polyol (such as glycerol, propanediol or PEG) or benzyl alcohol, 1-20% wt. surfactant, 79-98% wt. co-surfactant (such as glycerides), <5% wt. ethanol and <10% wt. water. Lucks et al. do not disclose cyclodextrins. Water is present in an amount low enough to minimize dissolution, erosion or degradation of the shell by the fill composition. Lucks et al. do not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

U.S. Patent No. 5,037,698 to Brunel discloses a solid or semi-solid filled capsule wherein the fill composition comprises water (0.1-10% wt.), a thickening agent (≥35% wt.), a hygroscopic or deliquescent agent (0.1-50% wt.) and optionally an equilibrium protecting agent (0.1-15% wt.). The water is present at or near stoichiometric amounts with respect to the hygroscopic or deliquescent agent so that a hydrate can form but degradation of the shell by water is minimized. The thickening agent is a thermosoftening solid or semi-solid excipient. The equilibrium protecting agent includes compounds such as aliphatic or aromatic hydroxy compounds including for example demulcents (glycerin) and oils. Brunel does not disclose the use of cyclodextrins.

U.S. Patent No. 5,707,648 to Yiv discloses a biphasic liquid-filled capsule containing an oil phase and an aqueous phase. The aqueous phase includes water (2-30% wt.) and PEG (60-95% wt.), wherein the ratio of PEG to water is ≥2:1 or 2:1-99:1. The formulation also requires a surfactant and an active agent. The PEG is present in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by the fill composition. Yiv does not disclose the use of cyclodextrins.

U.S. Patent Pregrant Publication No. 2003/0133974 to Curatolo et al. discloses an encapsulated dosage form containing sertraline; however, that dosage form comprises a water immiscible carrier medium.

Cyclodextrins and their derivatives are widely used in liquid formulations to enhance the aqueous solubility of hydrophobic compounds. Cyclodextrins are cyclic

carbohydrates derived from starch. The unmodified cyclodextrins differ by the number of glucopyranose units joined together in the cylindrical structure. The parent cyclodextrins contain 6, 7, or 8 glucopyranose units and are referred to as α-, β-, and γ-cyclodextrin respectively. Each cyclodextrin subunit has secondary hydroxyl groups at the 2 and 3-positions and a primary hydroxyl group at the 6-position. The cyclodextrins may be pictured as hollow truncated cones with hydrophilic exterior surfaces and hydrophobic interior cavities. In aqueous solutions, these hydrophobic cavities provide a haven for hydrophobic organic compounds, which can fit all, or part of their structure into these cavities. This process, known as inclusion complexation, may result in increased apparent aqueous solubility and stability for the complexed drug. The complex is stabilized by hydrophobic interactions and does not involve the formation of any covalent bonds.

Chemical modification of the parent cyclodextrins (usually at the hydroxyl moieties) has resulted in derivatives with sometimes improved safety while retaining or improving the complexation ability of the cyclodextrin. A number of different cyclodextrin derivatives are currently available including sulfobutyl ether derivatives such as SBE1-β-CD and SBE4-β-CD (degree of substitution~4), SBE7-β-CD (degree of substitution~7; CAPTISOL® cyclodextrin); hydroxypropyl derivatives such as ENCAPSIN™ (degree of substitution~4; HP4-β-CD) and MOLECUSOL™ (degree of substitution~8; HP8-β-CD); carboxylated derivatives; sulfated derivatives; alkylated derivatives; hydroxyalkylated derivatives; methylated derivatives; and carboxy-β-cyclodextrins, e.g. succinyl-β-cyclodextrin, 6^A-amino-6^A-deoxy-N-(3-carboxypropyl)-β-cyclodextrin.

The SAE-CDs are a class of negatively charged cyclodextrins, which vary in the nature of the alkyl spacer, the salt form, the degree of substitution and the starting parent cyclodextrin. The sodium salt of the sulfobutyl ether derivative of beta-cyclodextrin, with an average of about 7 substituents per cyclodextrin molecule (SBE7-β-CD), is being commercialized by CyDex, Inc. (Kansas) as CAPTISOL® cyclodextrin.

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