US005756123A

United States Patent [19]

Yamamoto et al.

[11] Patent Number: 5,756,123

[45] Date of Patent: May 26, 1998

[54] **CAPSULE SHELL**

[75] Inventors: **Taizo Yamamoto**, Osaka; **Seinosuke Matsuura**, Souraku-gun; **Kazukiyo Akai**, Kashihara, all of Japan

[73] Assignee: **Japan Elanco Co., Ltd.**, Osaka, Japan

[21] Appl. No.: **797,622**

[22] Filed: **Feb. 7, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 548,265, Oct. 25, 1995, abandoned.

[30] **Foreign Application Priority Data**

Dec. 1, 1994 [JP] Japan 6-323581
Dec. 16, 1994 [JP] Japan 6-333965

[51] **Int. Cl.**[6] **A61K 9/48**

[52] **U.S. Cl.** **424/451**; 424/452; 424/455; 424/494

[58] **Field of Search** 424/451, 494, 424/452, 455

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,617,588	11/1971	Langman	264/486
4,001,211	1/1977	Sarkar	536/84
4,993,137	2/1991	Muto et al.	29/451
5,032,074	7/1991	Muto et al.	425/272
5,264,223	11/1993	Yamamoto et al.	424/451
5,431,917	7/1995	Yamamoto et al.	424/451

FOREIGN PATENT DOCUMENTS

0592130	4/1994	European Pat. Off. .
2029402	6/1970	Germany .
47-4310	2/1972	Japan .
61-100519	5/1986	Japan .
62-266060	11/1987	Japan .
3-279325	12/1991	Japan .

Primary Examiner—Amy Hulina
Attorney, Agent, or Firm—Birch, Stewart, Kolasch & Birch, LLP

[57] **ABSTRACT**

A capsule shell comprising 79.6–98.7% by weight of a hydroxypropylmethyl cellulose, 0.03–0.5% by weight of carrageenan, and 0.14–3.19% by weight of a potassium ion and/or a calcium is prepared by drying an solution comprising 18–28% by weight of hydroxypropylmethyl cellulose whose 2% aqueous solution has a viscosity of 2.4–5.4 centistokes at 20° C. as a base, 0.01–0.09% by weight of carrageenan as a gelling agent, and 0.05–0.6% by weight of a potassium ion and/or calcium ion as a co-gelling agent. The capsule shell exhibits disintegrating ability equivalent to gelatin shells without degrading that ability even under special conditions containing much calcium ions.

8 Claims, 2 Drawing Sheets

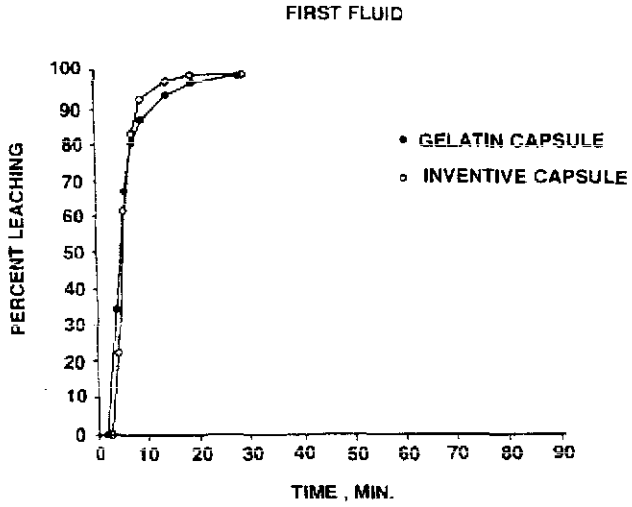


FIG.1(A) FIG.1(B) FIG.1(C)

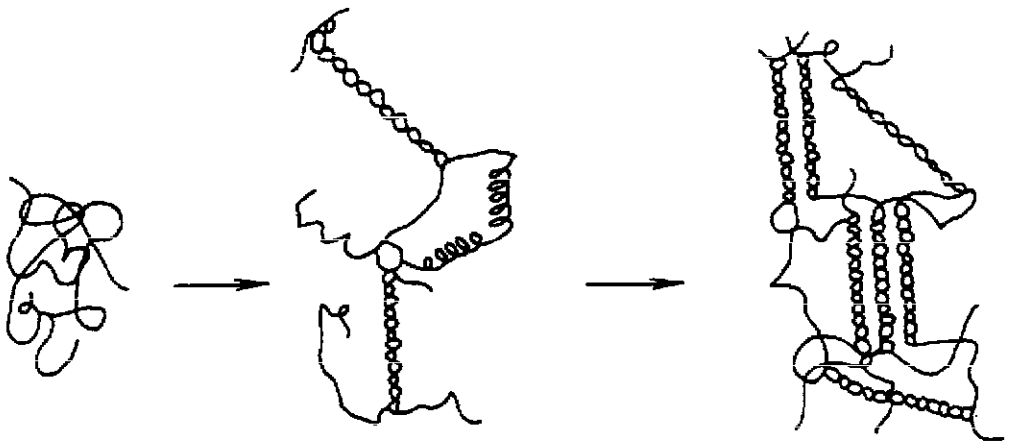


FIG.2

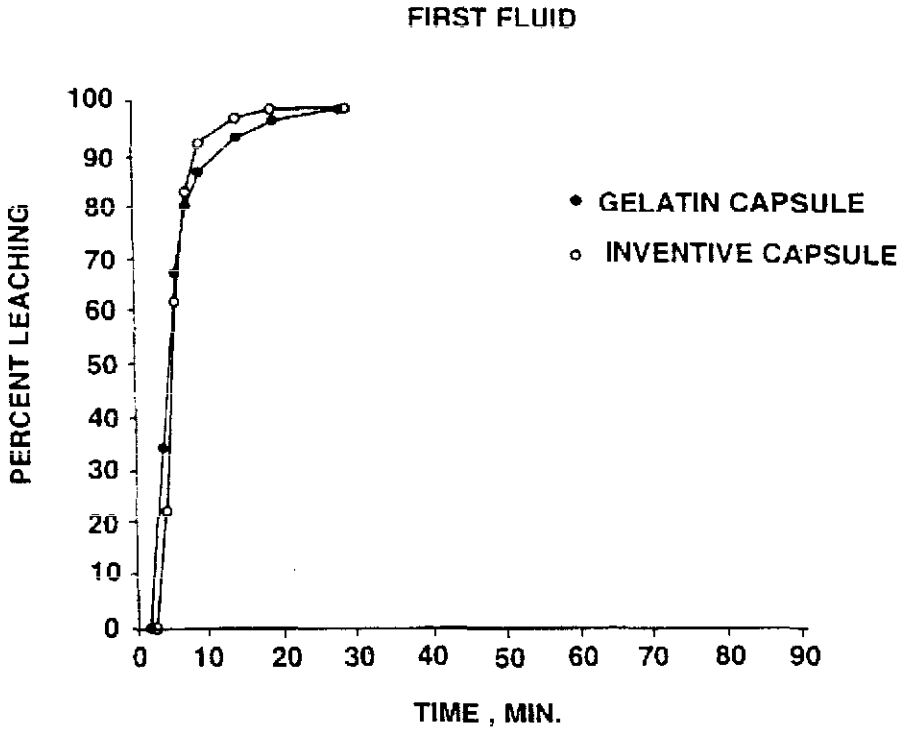
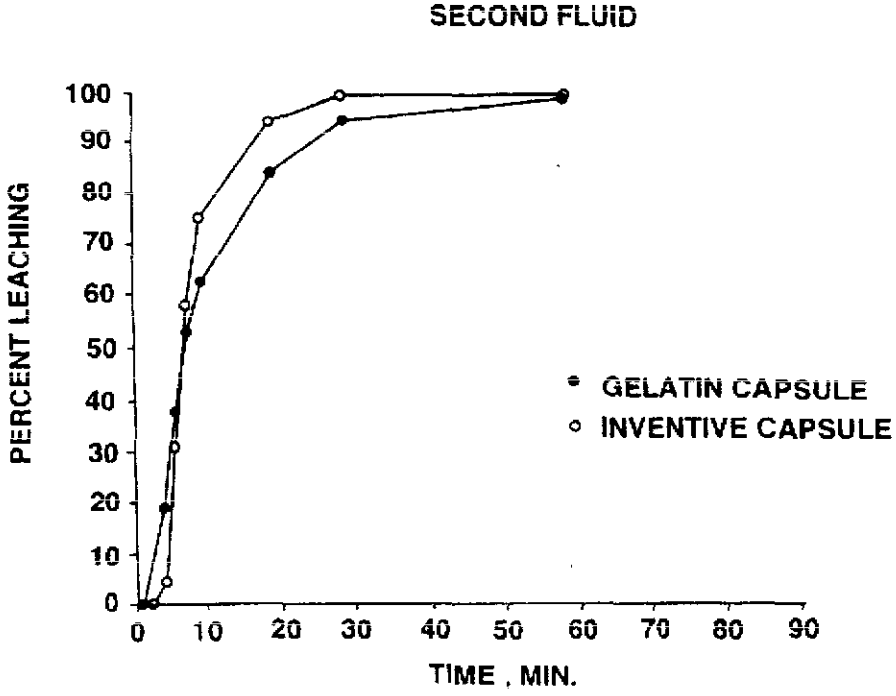


FIG.3



CAPSULE SHELL

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of copending application Ser. No. 08/548,265 filed on Oct. 25, 1995 the entire contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a capsule shell for forming medical hard capsules. More particularly, it relates to such a capsule shell using hydroxypropylmethyl cellulose as a base.

2. Prior Art

Medical hard capsules are conventionally formed from compositions comprising gelatin as a base with a plasticizer such as glycerin and sorbitol, opaque agent, dye, pigment and other additives blended therein. After molding pins are immersed in a gelatin aqueous solution with such components blended and withdrawn therefrom, the gelatin solution adhering to the pins is dried, obtaining capsule shells.

The shell-forming compositions based on gelatin have the problem that the plasticity and other properties of shells largely depend on a water content. With a too low water content, shells are less resistant against shocks as encountered on drug filling. Also, as the water content lowers due to drying during shelf storage, shells can contract to loosen the cap-body engagement of capsules.

For gelatin capsules, it is thus critical to maintain the water content constant. However, since the optimum water content is as high as about 10 to 15% by weight, there is a likelihood that the water in the capsule shell can affect the drug fill to lower its titer, degrade its quality, and change its color, and inversely, the capsule shell can be insolubilized if the drug fill is susceptible to hydrolysis or is a mixture of interacting ingredients. Therefore, there is a demand to have capsules based on a substance other than gelatin so that the material of capsules can be selected in accordance with a particular drug fill.

Medical capsules using a base other than gelatin are known in the art. Typically, capsules based on water- soluble cellulose derivatives were proposed. For example, Japanese Patent Publication (JP-B) No. 4310/1972 discloses a method for preparing capsules based on water-soluble cellulose ether from an aqueous solution of water-soluble cellulose ether. Japanese Patent Application Kokai (JP-A) Nos. 100519/1986 and 266060/1987 discloses to prepare capsules from an aqueous solution of water-soluble cellulose ether and polyvinyl alcohol (PVA) blended therewith.

The former shell-forming method involves the steps of immersing molding pins in an aqueous solution of water-soluble cellulose derivative and heating the pins and hence, the coating adhered thereto for gelation. The coating is not gelled or solidified and can fall down from the pins if heating is insufficient. The coating can be wrinkled during gelation if the heating temperature is too high. In the latter method of preparing capsules from an aqueous solution of water-soluble cellulose derivative and PVA, the water-soluble cellulose derivative adhered to the molding pins is gelled by immersing it in hot water. Some of the gelled coating can be dissolved in the hot water at this point, hindering formation of uniform shells. In addition, due to low jelly strength, the dried shells can be often cracked upon removal from the molding pins. In either of these methods, it is difficult to produce capsule shells having a low water content.

Additionally, these methods require a special apparatus or operation of heating the molding pins or immersing the molding pins with cellulose coating in hot water. Unfortunately, it is impossible to utilize the current manufacturing apparatus for gelatin capsules without a substantial change.

To solve these problems, the applicant previously proposed in U.S. Pat. No. 5,264,223 a medical hard capsule having a low water content which is shaped from a capsule shell composition comprising a water-soluble cellulose derivative as a base, a gelling agent and a co-gelling agent. This capsule has equivalent performance to conventional gelatin capsules and can be produced by utilizing the current manufacturing apparatus for gelatin capsules as such.

However, through the continuing research works of the inventors, it was found that this capsule is inferior to conventional gelatin capsules in solubility or disintegrating ability under certain conditions. More particularly, one preferred formulation of this capsule shell composition uses hydroxypropylmethyl cellulose as a water-soluble cellulose derivative base, carrageenan as a gelling agent and a potassium ion as a co-gelling agent. Shells of this preferred formulation take a long time to disintegrate under special conditions where calcium ions are present. Then, if a capsule of this composition filled with drugs is administered after having a food or beverage containing much calcium ions, for example, milk, then the capsule is retarded from disintegration. Then the drugs are not fully released or absorbed within a proper time, failing to fully exert their pharmaceutical effect. Therefore, it is desired to further improve the properties of the capsule based on a water-soluble cellulose derivative.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a capsule shell based on a water-soluble cellulose derivative which does not degrade its disintegration ability under special conditions where much calcium ions are present, that is, exerts its performance under any condition.

In connection with the capsule shell composition comprising hydroxypropylmethyl cellulose (to be abbreviated as HPMC, hereinafter) as a water-soluble cellulose derivative base, carrageenan as a gelling agent, and a potassium ion as a co-gelling agent wherein the shapability of HPMC is improved by blending carrageenan as a gelling agent and gelling this carrageenan with the co-gelling agent, we found that the disintegration ability of this composition is degraded in the presence of calcium ions because the calcium ions inhibit dissolution of the carrageenan blended in the composition as the gelling agent.

Continuing research works, we have found that degradation of the disintegration ability due to the presence of calcium ions is restrained by using a larger proportion of a EPMC having a relatively low viscosity as a base, increasing the amount of the co-gelling agent blended, and minimizing the proportion of carrageenan gelling agent within a sufficient range to insure good shapability. More particularly, by using a HPMC having a viscosity of 2.4 to 5.4 centistokes as measured in a 2t aqueous solution at 20° C., blending the HPMC with carrageenan as a gelling agent and a co-gelling agent in the water to form an aqueous solution comprising 18 to 28% by weight of the HPMC, 0.01 to 0.09% by weight of carrageenan and 0.05 to 0.6% by weight of a co-gelling agent, and drying the aqueous solution to form a capsule

shell comprising 79.6 to 98.7% by weight of the HPMC, 0.03 to 0.5% by weight of carrageenan, and 0.14 to 3.19% by weight of a co-gelling agent, there is obtained a capsule shell which maintains satisfactory disintegration ability even in the presence of calcium ions and exerts performance equivalent to conventional gelatin capsules. A hard capsule for pharmaceutical drugs of the capsule shell can be securely and efficiently produced according to the conventional immersion molding.

Accordingly, the present invention provides a capsule shell comprising 79.6 to 98.7% by weight of a hydroxypropyl-methyl cellulose, 0.03 to 0.5% by weight of carrageenan, and 0.14 to 3.19% by weight of a potassium ion and/or a calcium ion, said capsule shell being prepared by drying an aqueous solution comprising 18 to 28% by weight of hydroxypropyl-methyl cellulose having a viscosity of 2.4 to 5.4 centistokes as measured in a 2% aqueous solution at 20° C. as a base, 0.01 to 0.09% by weight of carrageenan as a gelling agent, and 0.05 to 0.6% by weight of at least one ion selected from the group consisting of potassium and calcium ions as a co-gelling agent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1(A), 1(B) and 1(C) schematically illustrate the gelation mechanism of carrageenan.

FIG. 2 is a graph showing the percent leaching of the contents from a capsule of Example 1 and a conventional gelatin capsule when they were immersed in the first solution prescribed in the Pharmacopoeia of Japan.

FIG. 3 is a graph showing the percent leaching of the contents from a capsule of Example 1 and a conventional gelatin capsule when they were immersed in the second solution prescribed in the Pharmacopoeia of Japan.

BEST MODE FOR CARRYING OUT THE INVENTION

In a capsule shell consisting essentially of HPMC as a base, carrageenan as a gelling agent, a co-gelling agent for assisting in gelation of carrageenan and water, the present invention optimizes the viscosity of HPMC and the blending proportion of the respective components such that the capsule shell may maintain satisfactory disintegration ability even under special conditions where much calcium ions are present.

The HPMC used as the base may be a commercially available powder product. According to the invention, the HPNC should be a low viscosity one such that a 2% aqueous solution of HPMC has a viscosity of 2.4 to 5.4 centistokes at 20° C., preferably 3.0 to 4.6 centistokes at 20° C. As defined herein, the viscosity of HPMC is not the viscosity of HPMC itself, but the viscosity of a 2% aqueous solution of HPMC throughout the specification. With a viscosity of less than 2.4 centistokes, an immersion solution of HPMC from which a capsule shell is to be obtained by a dipping technique has a too low viscosity to shape the capsule shell. With a viscosity of more than 5.4 centistokes, an immersion solution has a too high viscosity, which requires to reduce the amount of HPMC blended which in turn, requires to increase the proportion of the gelling agent blended, failing to achieve the object of the invention.

Such low viscosity EPMC is commercially available as TC-5M type HPMC (2% aqueous solution viscosity 4.5 centistokes at 20° C.) and TC-5E type HPMC (2% aqueous solution viscosity 3.0 centistokes at 20° C.) from Shin-Etsu Chemical Co., Ltd. These HPMC products may be used alone or suitably blended to form a mixture having a viscosity of 3.0 to 4.6 centistokes. Alternatively, such a EPMC product may be blended with another HPMC product having higher or lower viscosity (by itself outside the scope of the invention) to form a mixture having an optimum viscosity as defined above.

Carrageenan is blended as the gelling agent. Carrageenan generally includes three types, iota (ι), kappa (κ) and lambda (λ). Among these, ι-carrageenan and κ-carrageenan having a gelling ability may be used, with the carrageenan being preferred.

The co-gelling agent for assisting in gelation of carrageenan is a potassium ion, a calcium ion or both. As a general rule, a calcium ion is used for ι-carrageenan and a potassium ion is used for κ-carrageenan. It is most preferred to use κ-carrageenan as the gelling agent and a potassium ion as the co-gelling agent. The potassium ion may be blended in the form of a water-soluble compound such as potassium chloride, potassium phosphate and potassium citrate. The calcium ion may also be blended in the form of a water-soluble compound such as calcium chloride.

In the capsule shell of the invention containing the above-defined HRMC base, carrageenan gelling agent and co-gelling agent in the above-defined proportion, there may be further blended various additives such as coloring agents (e.g., dyes and pigments), opaque agents, and flavors in conventional amounts.

The capsule shell of the present invention is prepared by drying an aqueous solution comprising the above-defined HPMC base, carrageenan gelling agent, co-gelling agent and optional additives.

The amount of HPMC blended in the aqueous solution is 18 to 28% by weight, preferably 19 to 25% by weight. Several inconvenient problems occur if the amount of HPMC blended is outside this range. The capsule shell of the invention is prepared by dissolving the HPMC, gelling agent, co-gelling agent and optional additives in water to form an aqueous immersion solution, immersing molding pins in the immersion solution, withdrawing the pins from the solution with the solution adhering to the periphery of the pins, and drying the adhering solution. If the amount of HPMC blended is less than 18% by weight, the proportion of the gelling agent blended becomes relatively high, failing to achieve the object of the invention. If the amount of HPMC blended is more than 28% by weight, the proportion of the gelling agent blended becomes relatively low, but the immersion solution has a too high viscosity to shape capsule shells by the dipping technique.

The amount of carrageenan blended in the aqueous solution is 0.01 to 0.09% by weight, preferably 0.05 to 0.07% by weight. If the amount of carrageenan blended is less than 0.01% by weight, no satisfactory degree of gelation is achieved and shells of sufficient gage cannot be formed by the dipping technique. If the amount of carrageenan blended exceeds 0.09% by weight, the capsule shell loses disintegration ability in the presence of calcium ions, failing to achieve the object of the invention.

The amount of co-gelling agent blended in the aqueous solution is 0.05 to 0.6% by weight, preferably 0.06 to 0.1% by weight in ionic amount. If the amount of co-gelling blended is less than 0.05% by weight, no satisfactory gelation of carrageenan is achieved and shells of sufficient gage cannot be formed by the dipping technique. If the amount of co-gelling agent blended exceeds 0.6% by weight, a gelled film forms in an aqueous immersion solution, shell formation by the dipping technique is difficult, and shells, even formed, are low in disintegration ability.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.