V, and II, and fibrinogen) abnormalities. It is also used for a quantification of intrinsic coagulation factor activity, which is a detailed test for APTT abnormalities, a detection of acquired hemophilia and lupus anticoagulant, a cross-mixing test, which is a differential test, or monitoring of heparin administration.

[0006]

The performance required for APTT is that it is highly sensitive to blood coagulation factors, and anticoagulants such as heparin. Since APTT is an item that needs to be diagnosed based on the absolute value of coagulation time, differences in production lots are more likely to appear compared to items for which a general calibration curve is created to obtain a diagnostic value. Therefore, in particular, a reagent with a small difference in production lots is a clinically highly preferred performance.

[0007]

Various studies have been conducted on the difference in production lots of APTT. With respect to conventional APTT reagents, naturally occurring phospholipids such as soybeans were extracted and used to prepare APTT reagents. By converting phospholipids from natural sources to synthetic products, uniform phospholipids can be obtained, which has contributed to the reduction of the difference in production lots (Non-patent literature 1). However, the difference in production lots has not completely disappeared, and there is still room for improvement in order to meet clinical demands.

[0008]

For example, Patent literature 1 describes that a liposome-containing liquid was obtained by filtering through a 0.6 μm polycarbonate membrane to uniform the particle size of liposome. Since this is an operation before reconstitution of tissue factor into synthetic liposomes, and it is an operation before freeze-drying, it is unlikely that the effect of making the particle size uniform by filtering a final product through the polycarbonate membrane is obtained. Furthermore, the effect shown in Patent literature 1 is a reduction of variation (difference) in measured prothrombin time before and after lyophilization, and the absolute value of coagulation time for each production lot is not controlled.

CITATION LIST

PATENT LITERATURE

[0009]

[Patent literature 1] Japanese Unexamined Patent Publication (Kokai) No. 2017-181265

NON-PATENT LITERATURES

[0010]

[Non-patent literature 1] Okuda M, Kikukawa N, Uemura Y, “Development of new APTT reagent using synthetic phospholipid”, Journal of the Japanese Society for Laboratory Hematology, February 28, 2002, vol. 3, no. 1, p. 124-131, reprint

SUMMARY

TECHNICAL PROBLEM

[0011]

The present invention has been made in view of these problems, and an object of the present invention is to provide a liposome-containing liquid reagent for measuring blood coagulation ability with a small difference in production lots.

SOLUTION TO PROBLEM

[0012]

The present inventor conducted intensive studies in view of the object to find a surprising result that, contrary to conventional expectations, the coefficient of variation between lots changed significantly depending on the particle size of liposomes. Based on this finding, the present invention has succeeded in producing a liposome-containing liquid reagent for measuring blood coagulation ability with a small difference in production lots by controlling the cumulative integrated value of liposomes with particle sizes of 351 nm to the maximum particle size to 0% or more and less than 35% relative to the cumulative integrated value of total liposomes.

[0012a]

In one aspect, the present disclosure refers to a liposome-containing liquid reagent for measuring blood coagulation ability, wherein a cumulative integrated value of liposomes with particle sizes of 351 nm to a maximum particle size is 0% or more and less than 35% relative to a cumulative integrated value of total liposomes. In another aspect, the present disclosure refers to a process of manufacturing a liposome-containing liquid reagent for measuring blood coagulation ability, said process comprising: step A: the step of mixing phospholipids; step B: the step of forming liposomes by dispersing the mixed phospholipids in an aqueous solution; and step C: the step of preparing uniform liposomes from the liposomes using a liposome particle size adjusting means, wherein a cumulative integrated value of liposomes with particle sizes of 351 nm to a maximum particle size is 0% or more and less than 35% relative to a cumulative integrated value of total liposomes. In yet another aspect, the present disclosure refers to a method for reducing a difference in production lots of a liposome-containing liquid reagent for measuring blood coagulation ability, wherein a cumulative integrated value of liposomes with particle sizes of 351 nm to a maximum particle size is 0% or more and less than 35% relative to a cumulative integrated value of total liposomes.

[0013]

The present invention relates to:

[1] a liposome-containing liquid reagent for measuring blood coagulation ability, wherein a cumulative integrated value of liposomes with particle sizes of 351 nm to a maximum particle size is 0% or more and less than 35% relative to a cumulative integrated value of total liposomes,

[2] the reagent of [1], wherein the reagent is an activated partial thromboplastin time measuring reagent, a prothrombin time measuring reagent, a complex factor measuring reagent, a specific factor activity measuring reagent, or a blood coagulation factor inhibitor measuring reagent,

[3] a process of manufacturing a liposome-containing liquid reagent for measuring blood

coagulation ability, said process comprising:
(step A): the step of mixing phospholipids;
(step B): the step of forming liposomes by dispersing the mixed phospholipids in an aqueous solution; and
(step C): the step of preparing uniform liposomes from the liposomes using a liposome particle size adjusting means, wherein a cumulative integrated value of liposomes with particle sizes of 351 nm to a maximum particle size is 0% or more and less than 35% relative to a cumulative integrated value of total liposomes, and
[4] a method for reducing a difference in production lots of a liposome-containing liquid reagent for measuring blood coagulation ability, wherein a cumulative integrated value of liposomes with particle sizes of 351 nm to a maximum particle size is 0% or more and less than 35% relative to a cumulative integrated value of total liposomes.

ADVANTAGEOUS EFFECTS OF INVENTION

[0014]

In a reagent for measuring blood coagulation ability in which phospholipids are contained