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3,017,668

METHOD OF PREPARING PEARLS

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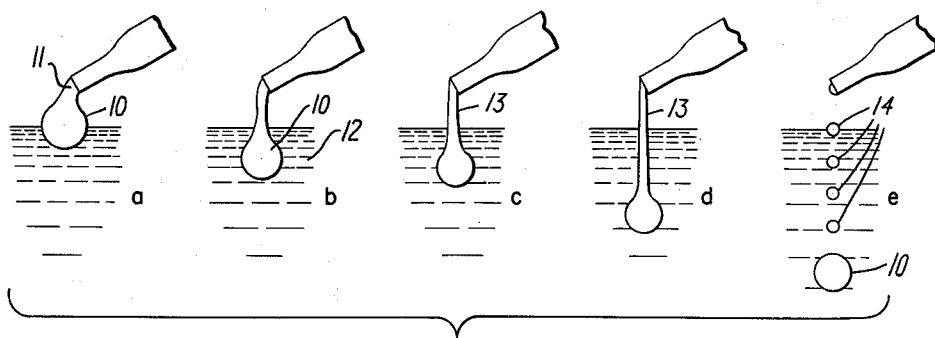


FIG. 1

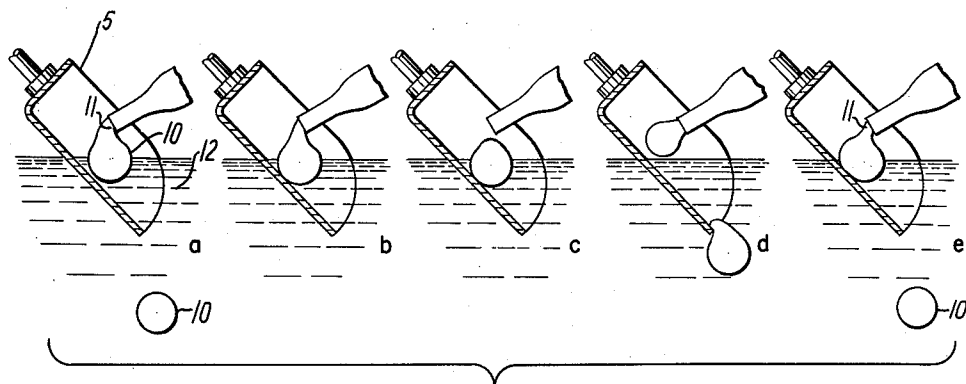


FIG. 2

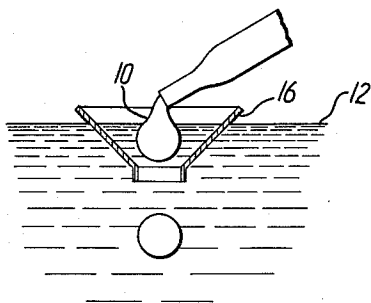


FIG. 3

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METHOD OF PREPARING PEARLS

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This invention relates to the manufacture of medicated pearls and has particular reference to a continuous method of making homogeneous medicated pearls each having a uniform size and shape and containing a uniform quantity of the medicament.

Heretofore, medicines and other materials have been dissolved, dispersed in or otherwise mixed with a gelable colloid, such as gelatin, and droplets of the mixture deposited in a congealing liquid under such conditions that the droplets congeal into individual pellets, or pearls, containing the medicine.

Notwithstanding that medicated pearls are relatively simple to produce in the foregoing manner, they have not been widely adopted as a means for dosage medication, because the methods heretofore used do not produce pearls which contain the requisite uniform dosage of the medicine largely because no way has been found to continuously make them of uniform size and shape. Thus one such prior method comprises dispersing the medicine in a solution of a gelable colloid which is then suspended in a congealing liquid and agitated so as to subdivide the mixture into droplets and then cool them to form pearls, which are not of uniform size or dosage. Another such method comprises dispersing or dissolving the medicine in a gelatin solution and then introducing droplets of the solution into a congealing liquid to cause them to congeal into pearls, which, because of the formation of a "tail" which usually breaks off, leaves pearls of non-uniform size, shape and dosage. Moreover, the dislodged tails tend to coalesce with other pearls, thus augmenting the disparity in size, shape and dosage.

These difficulties are obviated by this invention which provides a continuous method of making pearls which are of a single uniform size and shape and which contain a uniform dosage of the medicament.

In accordance with the present invention, a mixture of gelable colloid and the medicinal material, hereinafter referred to as the gelating paste, is forced drop by drop through an orifice spaced above a bath of a congealing liquid under such conditions that the falling droplets as they fall through the air assume a pear shape before they reach the congealing liquid. As each droplet sinks slowly in the bath of congealing liquid, it is precluded from developing an attached "tail" so that as it congeals while sinking in the bath, it has formed into a round solid pearl by the time it reaches the bottom of the bath tank and all of the pearls are of uniform sized dosage. Preclusion of "tail" development is effected according to the invention by momentarily retaining the droplet of gelating paste just below the surface of the congealing bath for a sufficient time to permit the tail-forming connection between the droplet and the orifice to break before the droplet is substantially congealed in the bath.

FIGURES 1a to 1e of the drawings are diagrams showing the various stages in which the "tail" initially formed on the pearl droplet is then separated and subdivided into small particles as the descent of the pearl-forming droplet is retarded according to the invention;

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FIGURES 2a to 2c are diagrams showing various stages by which a trough-like device is used to retain the droplets at the surface of the liquid and thus retard its descent, for the purpose described;

FIGURE 3 illustrates still another mode of retarding the pearl formation, this mode utilizing a funnel-like device.

In carrying out the process of the present invention, an aqueous solution of gelatin or other gelable colloids, such as agar-agar, gum arabic, pectins, starch, gum tragacanth, casein alginates, cellulose derivatives, dextran, albumin, wares, polyvinyl pyrrolidene, synthetic hydrophilic colloids (such as Carbopol 934) etc., their derivatives or mixtures of these materials, is prepared. The solution is such that it will either remain liquid at increased temperature, above about 45° C., but will solidify at normal ambient temperatures, or will remain liquid until congealed by neutralization.

To this aqueous solution of the gelable colloid is added the quantity of medicine or medicines in the desired amounts so that each pearl will have the proper dosage of medicament. The method of adding the medicine, or medicines, to the aqueous solution of the gelable colloid depends upon the nature of the medicine itself. If the medicine to be added is water-soluble, it is dissolved directly in the colloidal solution or in a solvent miscible with the colloidal solution, for example, water. If the medicine occurs in the form of a water-insoluble oil, it can be dispersed in the colloidal solution and stirred vigorously to form a stable emulsion. In this process, emulsifiers, such as lecithin or surface-active agents, such as Tween, can be used. Alternately, the water-insoluble oil can be mixed with oil and this oil mixture dispersed in the gelable colloid solution. When a solid water-insoluble medication is to be added, it can be dissolved in a suitable oil and then the solution dispersed in the colloidal solution as outlined above, or it can be sufficiently pulverized to form a fine powder which can then be dispersed in the colloidal solution. This latter method can also be employed if a solid completely insoluble medicine is concerned.

Additional ingredients can be added to this gelable paste. For example, it may be necessary or desirable to add a plasticizing agent, such as glycerin glucose, sorbitol, ethylene glycol, honey, etc., in a quantity adjusted so as to give the desired hardness to the finished product. Such a plasticizing agent is preferably added prior to the addition of the medication. If desired, it is also possible to add taste correctives, such as peppermint oil or lemon oil, or to color the solution as desired. Moreover, in order to obtain clear pearls, it is possible to adjust the refractive index of the two phases to practically the same value. This can be done, for example, by adding to the oil phase a suitable quantity of resin. Furthermore, one or several aseptic agents can be added to the solution.

It has also been noted that it is possible to obtain pearls having the highest gel strength and gelating pastes having a low viscosity when hot when the colloidal solution of the dispersion is adjusted at or close to the isoelectric point of the gelable colloid.

With colloidal solutions which gel upon cooling the gelating paste is kept at an elevated temperature, above about 45° C., until it is dropped into a bath containing a congealing liquid. Colloidal solutions which are congealed by neutralization require that the immiscible liquid

be either an alkali or an acid. As used herein, the term "congealing liquid" refers to liquids which are not miscible with the gelating paste or which neutralize the paste. Examples of liquids which are suitable for congealing pastes by cooling are mineral oil, vegetable oil, animal oil, an organic solvent immiscible with the solvent used for the colloidal solution, or mixtures of the substances mentioned. The use of paraffin oil or mineral oil is preferred.

FIGURES 1a to 1e of the drawing show the steps in the formation of a "tail" and small pearls. According to the method of this invention a drop 10 of gelating paste is forced through an orifice 11. As the drop 10 sinks rapidly into the liquid 12, the "tail" 13 is left behind (FIGURE 1d) and breaks forming small pearls 14 (FIGURE 1e).

In order to prevent the formation of small pearls, the drops of gelating paste are momentarily retained at the surface of the congealing liquid. The length of time which the drops must be held just below the surface of the congealing liquid varies depending upon the constitution of the gelable colloid and the weight of the drops. The more viscous the drops the longer the period of time they must be retained just below the surface of the liquid. The length of time for any particular paste formulation is easily determined by dropping the paste into the liquid and noting the length of time that it must be held at the surface so that small pearls will not be formed. The holding time is usually 1 second or less.

The drops can be delayed at the surface as illustrated in FIGURES 2a to 2e of the drawing by placing means, such as a conduit 15, at the surface of the congealing liquid 12 so that the drop 10 is momentarily retained thereon to give the connection 17 between the pearl and the mouthpiece time to break before a "tail" has been formed. The conduit is preferably placed at an angle of 45° to the liquid surface. The slope of the trough can be varied so as to shorten or lengthen the time the drops are retained just below the surface. It is also possible to use a funnel 16 with a short lip as illustrated in FIGURE 3.

In the case of gelating pastes congealed by cooling, the temperature of the congealing liquid in the bath is varied so that at the surface the temperature is kept at the same temperature as the gelating paste, and is then decreased successively so as the drops fall through the liquid they will be cooled and caused to congeal. This is easily accomplished by having the liquid in a high vertical tube, for example, where the temperature is higher at the top and successively decreases towards the bottom. As the drops solidify and sink through the congealing liquid they will congeal when they reach the cool regions of the liquid.

Colloids which are congealed by neutralization require only that the congealing liquid neutralize the colloid; there is no necessity that the congealing liquid be maintained with zones of varying temperature.

The congealed pearls are then collected and the bath liquid is removed by washing with a suitable solvent. If a paraffin oil has been used as the immiscible liquid, benzene, methyl chloride, trichloroethylene, etc., are suitable solvents. The pearls are then dried. The water may be removed from the pearls by extracting with a suitable water-soluble solvent, such as, acetone, methyl-, ethyl-, or propyl alcohol, dioxane, etc. In order to prevent the pearls from sticking together or being deformed by too rapid a drying, it is preferred to leave on a thin film of the bath liquid during the washing step and not to finish the complete washing off of the liquid until after the pearls have been completely dried.

The pearls can be further processed by coating them or, if desired, it is possible to coat them with other medications.

The following examples are given by way of illustration to show specific embodiments of the invention.

Example 1

A vitamin containing pearl is prepared according to the following formula:

	Gms.
5 Glycerin -----	400.0
Partially hydrolyzed starch (water soluble) -----	945.0
Gelatin -----	1140.0
Thiamine hydrochloride -----	27.3
Riboflavin -----	9.0
10 Pyridoxine hydrochloride -----	21.0
Panthenol -----	25.2
Nicotinamide -----	210.0
Vitamin A palmitate 1 million u.i./gm. -----	60.0
Vitamin D ₃ palmitate 2 million u.i./gm. -----	30.0
15 Vitamin E acetate -----	22.1
Vegetable oil -----	500.0
Peppermint oil -----	15.0
Methylparaben -----	5.4
Ethylene diamine tetracetic acid -----	5.0
20 Hydrochloric acid 5% to make pH=4.3.	
Distilled water, to make 5400.0 gms.	

Mixture A: The riboflavin and nicotinamide are dissolved by heating in 1800 gms. of distilled water. Then methylparaben is added and the heating is continued till the methylparaben is dissolved. The heating is then discontinued, and ethylene diamine tetracetic acid, glycerin is added with stirring and the mixture is kept at 60° C. so that the gelatin will remain dissolved.

30 Mixture B: The vitamin A palmitate, vitamin D₃ palmitate, vitamin E and peppermint oil are dissolved in vegetable oil.

Then thiamine hydrochloride, pyridoxine hydrochloride and panthenol are added to mixture A and dissolved. 35 The mixture B is emulsified with A by vigorous stirring. Hydrochloric acid is added with stirring till the pH of the solution is 4.3, after which distilled water is added to make full weight, and the paste is stirred until it is homogeneous.

40 The gelable paste is then expelled from an orifice so that it falls drop by drop into a liquid bath of paraffin oil. The drops, which weigh about 0.4 gm. each, are retained just below the surface of the paraffin oil for a period of about 1/2 second and then cooled as they fall to the bottom of the bath to form congealed pearls.

45 The pearls are of a uniform size and shape and contain a uniform dosage of the vitamins. There was no "tail" formation and no resultant small or deformed pearls.

Example 2

A vitamin containing pearl is prepared according to the following formula:

	Gms.
Gelatin -----	800.0
55 Partially hydrolyzed starch (water soluble) -----	500.0
Glycerin -----	530.0
Methylparaben -----	4.0
Ethylene diamine tetracetic acid -----	4.0
Vitamin A palmitate 1 million u.i./gm. -----	575.0
60 Vegetable Oil -----	175.0
Distilled Water, to make 4000.0 gms.	

The methylparaben is dissolved by heating in 1400 gm. distilled water. The solution is put on a water bath at 60° C., and ethylene diamine tetracetic acid, hydrolyzed starch and glycerin are added. When the solution is homogeneous, the gelatin is pressed carefully into the same, letting as little air as possible come into the solution. It is then stirred every now and then until the gelatin is dissolved. The vitamin A palmitate is dissolved in the oil, and the solution added with stirring to the gelatin paste. Distilled water is added to make full weight, and the paste is vigorously stirred till it is completely emulsified.

75 The paste is then formed into pearls by following the

procedure set forth in Example 1 with the drops being retained for only $\frac{1}{4}$ of a second.

Uniform pearls are formed which contained 5,000 u.i. of vitamin A.

Example 3

A hormone containing pearl is prepared according to the following formula:

	Gms.
Gelatin -----	760.0
Syrup -----	400.0
Glycerin -----	500.0
Vegetable Oil -----	940.0
Chlortrianisene -----	60.0
Methylparaben -----	4.0
Erythrosine -----	2.0
Distilled Water, to make 4000.0 gms.	

The methylparaben is dissolved in 1300 gm. distilled water by heating. The solution is put on a water bath at 60° C., and erythrosine, syrup, glycerin and gelatin are added and dissolved. Then chlortrianisene is dissolved in vegetable oil by careful heating to 80° C., and emulsified with the gelatin solution to form a paste.

The paste is then formed into pearls by following the procedure set forth in Example 1 with the drops being retained just below the surface of the congealing liquid for $\frac{1}{4}$ of a second.

Uniform pearls are formed which contain 0.006 gm. of chlortrianisene.

The chlortrianisene pearls are an example of a preparation where the active ingredients are in the state of an over-saturated oil solution. This solution is emulsified into the gelatin paste where it retains its oversaturated character, in the form of microscopical drops. By preparing oversaturated oil solutions after this method, the gross weight of a preparation can be reduced, which is of importance if the preparation in question—when prepared in a conventional method—would have to be taken in large gross doses.

It is to be understood that the present invention contemplates the use of a large variety of medicines aside from the one specifically illustrated in the specific examples. It is possible to incorporate antibiotics, antispasmodics, alkaloids, etc., into the gelable colloids to form pearls having these medicines dispersed there-through.

The present invention makes it possible to produce pearls of a single uniform size and shape which contain a standard dose of medicinal material by a continuous method.

There are many other different embodiments of the invention which may be made without departing from the spirit and scope hereof and it is to be understood that this invention is not limited hereto except as defined in the appended claims.

I claim:

1. A method of preparing homogeneous medicated pearls which comprises, dispersing a predetermined quantity of a medicinal preparation in a solution of a gelable colloid, adding said dispersion from an orifice by drops into a congealing liquid, momentarily retaining said drops just below the surface of said liquid after separation of said drops from said orifice and congealing said drops as they sink in said liquid to form pearls with said medicine dispersed therethrough.

2. A method of preparing homogeneous medicated pearls which comprises, dispersing a predetermined quantity of medicinal material in a solution of a gelable colloid, adding said dispersion from an orifice drop by drop through the air into a congealing liquid, momentarily retaining said drops just below the surface of said liquid after separation of said drops from said orifice, causing said drops to travel down through said liquid and congealing said drops in the course of said travel to form said drops into pearls containing said medicinal preparation dispersed therein.

3. A method of preparing homogeneous medicated pearls which comprises, dispersing a predetermined quantity of medicinal material in a solution of a gelable colloid, heating said dispersion of medicinal material and colloid to maintain the same in a liquid state, adding said dispersion from an orifice by drops into a congealing liquid having an upper part of substantially the same temperature as that of said dispersion, momentarily retaining said drops at the upper part of said liquid after separation of said drops from said orifice, causing said drops to sink through said liquid and gradually decreasing the temperature of said liquid in said bath in a downward direction to cause said colloid drops to congeal and to form pearls containing said medicinal preparation dispersed therein.

4. A method of preparing medicated pearls which comprises, dispersing a predetermined quantity of medicinal material in a solution of a gelable colloid, adding said dispersion from an orifice by drops into a congealing liquid, momentarily retaining said drops at the upper part of said liquid after separation of said drops from said orifice, causing said drops to sink through said liquid to neutralize said drops and cause them to congeal.

5. A method of preparing homogeneous medicated pearls which comprises, dispersing a predetermined quantity of a water-soluble medicinal material in an aqueous solution of a gelable colloid, adding said dispersion from an orifice by drops into a congealing liquid, momentarily retaining said drops just below the surface of said liquid after separation of said drops from said orifice and causing said drops to travel down through said liquid and congealing the same in the course of said travel to form pearls of said colloid in congealed form containing said medicinal preparations dispersed therein.

6. A method of preparing homogeneous medicated pearls which comprises, dissolving a predetermined quantity of a water-insoluble medicinal preparation in an oil in which it is soluble, dispersing said oil solution in an aqueous solution of a gelable colloid, adding said dispersion from an orifice by drops into a congealing liquid, momentarily retaining said drops just below the surface of said liquid after separation of said drops from said orifice, allowing said drops to travel down through said liquid and congealing the same in the course of said travel to form said drops into pearls containing said medicinal preparation dispersed therein.

7. The method as set forth in claim 3 which includes the steps of incompletely removing the immiscible liquid adhering to said congealed pearls by washing with a solvent, drying said pearls and thereafter removing the remaining adherent immiscible liquid.

8. A method of preparing homogeneous medicated pearls which comprises, dispersing a predetermined quantity of medicinal material in a solution of a gelable colloid, heating said dispersion and maintaining the same at a temperature above 45° C., adjusting the pH of said dispersion closely to the isoelectric point of said colloid, adding said dispersion from an orifice by drops into an immiscible liquid having substantially the same temperature as said dispersion, momentarily retaining said drops just below the surface of said liquid after separation of said drops from said orifice, congealing said drops as they slowly sink through said liquid to form pearls, removing said pearls from said liquid bath, washing said pearls with a solvent to remove the adherent immiscible liquid and drying said pearls.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,017,668

January 23, 1962

Knut Jacobus Sundman

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 4, line 27, after "glycerin" insert -- and hydrolyzed starch are added and dissolved. The gelatin --.

Signed and sealed this 29th day of May 1962.

(SEAL)

Attest:

ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of Patents