Abstract:
The present invention is directed to a process for producing pharmaceutically acceptable aqueous poloxamer gels in a cost efficient manner. The process involves pre-melting the poloxamer prior to mixing with cold water.
DESCRIPTION

PROCESS FOR PRODUCING A POLOXAMER GEL

BACKGROUND OF THE INVENTION

This application claims benefit of priority to U.S. Provisional Application Serial No. 60/981,670, filed October 22, 2007, the entire contents of which are hereby incorporated by reference.

A. Field of the Invention

The present invention relates generally to methods of producing poloxamer gels. In particular, the invention is directed to a process of producing pharmaceutically acceptable aqueous-based poloxamer gels in a cost efficient manner. These gels are particularly useful for topical delivery of pharmaceutical active ingredients.

B. Background

Aqueous poloxamer gels comprise at a minimum water and poloxamer. Many other ingredients are commonly added to the gels including pharmaceutical active ingredients, cosmetic ingredients, surfactants, humectants, moisturizers, emollients, preservatives, antioxidants, buffers, rheology modifiers, colorants, and fragrances. The poloxamers used to make these gels are typically in solid form as a flake or granule (i.e. prilled).

Aqueous poloxamer gels are generally temperature sensitive, i.e. the gel can be in a liquid flowable state or a semi-solid state (gel) depending on the temperature. Temperature sensitive gels can be thermoreversible or thermo-irreversible. Temperature sensitive gels can be formulated to remain in a liquid state during
processing at cold temperatures, e.g. 0°C - 15°C and change into a semi-solid when
the formulation warms to room temperature, e.g. 20°C - 25°C, or above. Some gels
can be formulated to change to a semi-solid when the formulation reaches body
temperature, e.g. 37°C.

Two manufacturing processes for aqueous poloxamer gels are known in the art
and are commonly used to produce these gels ("Technical Data on PLURONIC®
Polyols", BASF Wyandotte Corporation, herein incorporated by reference). One
method is known as the "hot" process in which water and solid (flaked or granular)
poloxamer are mixed and then heated to about 80°C allowing the poloxamer to melt
into the hot water. The formulation is subsequently cooled to room temperature
allowing a gel to form. A disadvantage of the "hot" process is that the entire batch
must be heated, thus a large amount of energy is required for heating and subsequent
cooling.

The other method is known as the "cold" process in which water and solid
(flaked or granular) poloxamer are mixed in cold water, e.g. from 5°C - 10°C.
Mixing continues at that temperature until the poloxamer is completely dissolved. In
this process, the poloxamer and water mixture remains liquid below the gel point until
the temperature raises to room temperature or above, at which time the solution
changes to a gel. The disadvantage of this process is that the dissolution of the solid
poloxamer in water at cold temperatures is extremely difficult resulting in long
processing times. In some cases, processing times can be several hours or even days
making this a very inefficient process requiring large amounts of energy to maintain
the cold temperatures and long mixing times.

Another process is disclosed in US patent 5,635,540, herein incorporated by
reference, whereby water and either solid flaked or granular poloxamer are mixed and
subjected to freezing temperatures in the range of 0°F to 10°F (-12°C to -17°C) for 14 to 16 hours. This process results in gels with depressed congealing points relative to other processes, the benefit of which is that ingredients suspended in the gels do not settle out during storage even at very low temperatures. However, the energy requirements for obtaining and maintaining freezing temperatures during processing, especially for large-scale processes, are very high.

The manufacturing costs for the prior art processes are restrictive and can even be cost prohibitive due to requirements for extended mixing periods and concomitant heating, cooling and/or freezing. Additional costs are also incurred by the need for specialized equipment such as large refrigeration units and/or large capacity steam heating units. Thus, there is a need for scalable processes for the production of aqueous poloxamer gels in a cost efficient manner.

SUMMARY OF THE INVENTION

The present invention is directed to a process of efficiently producing an aqueous poloxamer gel with minimal energy. The process comprises pre-melting the poloxamer in a separate vessel and then mixing the molten poloxamer with cold water and maintaining the resulting mixture at the cold temperature until the poloxamer is dissolved. The molten poloxamer may be added to the water or the water may be added to the molten poloxamer. The resulting solution is subsequently warmed to its gel point such as room temperature.

In the process of the present invention, the molten poloxamer dissolves more rapidly in the water than the flaked or granular poloxamers as in the "cold" process, so process times are reduced resulting in a more efficient process. This process is surprisingly efficient when used to make gels with high concentrations of poloxamer,
i.e. greater than about 45% w/w. Additionally, it is not required to heat the entire batch of the poloxamer and water mixture as in the "hot" process, but only the poloxamer itself, therefore less mass is subjected to heating which results in less energy being expended for heating.

A "cold temperature" in various embodiments is a temperature from about 0 °C to about 15 °C, or from about 0 °C to about 12 °C, or from about 0 °C to about 10 °C, or from 0 °C to about 8 °C, or from 0 °C to about 6 °C, or from about 0 °C to about 5 °C, or from about 0 °C to about 4 °C, or from about 0 °C to about 3 °C, or from about 0 °C to about 2 °C, or from about 2 °C to about 15 °C, or from about 2 °C to about 12 °C, or from about 2 °C to about 10 °C, or from 2 °C to about 8 °C, or from 2 °C to about 6 °C, or from 2 °C to about 5 °C, or from about 2 °C to about 4 °C, or from about 4 °C to about 15 °C, or from about 4 °C to about 12 °C, or from about 4 °C to about 10 °C, or from about 4 °C to about 8 °C, or from about 4 °C to about 6 °C, or from about 4 °C to about 5 °C, or from about 5 °C to about 15 °C, or from about 5 °C to about 12 °C, or from about 5 °C to about 10 °C, or from 5 °C to about 8 °C, or from 5 °C to about 6 °C, or about 5 °C. "Room temperature" is defined as from about 20 °C to about 25 °C. The "gel point" or "congealing point" is the temperature at which a formulation converts from a liquid flowable state to a semi-solid gel state.

The use of the word "a" or "an" when used in conjunction with the term "comprising" or "containing" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device obtaining the value, the method
being employed to determine the value, or the variation that exists among the objects being evaluated.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION

One aspect of the present invention provides for a manufacturing process for producing an aqueous poloxamer gel. The process comprises pre-melting the poloxamer in a separate vessel and then mixing the molten poloxamer with cold water and maintaining the resulting mixture at the cold temperature until the poloxamer is dissolved. In one embodiment, the molten poloxamer is added to the water. In
another embodiment, the water is added to the molten poloxamer. The resulting solution of poloxamer and water is subsequently warmed to the gel point or above.

The process of the present invention can be used to produce several types of aqueous poloxamer gels including temperature sensitive (i.e. thermoreversible or thermo-irreversible) and non-temperature sensitive gels. In some embodiments, the process produces gels with depressed congealing points whereby ingredients suspended in the gels do not settle out during storage even at very low temperatures. The gels comprise poloxamer and water. The gels can also include additional ingredients. Non-limiting examples of additional ingredients are pharmaceutical active ingredients, cosmetic ingredients, humectants, moisturizers, emollients, preservatives, antioxidants, buffers, colorants, and fragrances. Additional ingredients may be added at various times in the process. For example, an additional ingredient could be added to the cold water or to the molten poloxamer prior to mixing, or to the resulting poloxamer/water solution, or even to the resulting gel after the poloxamer/water solution has risen to its gel point (e.g. room temperature). Different additional ingredients of a given formulation may be added at different times throughout the process.

**Processing Equipment**

Various types of processing equipment can be used to manufacture the aqueous poloxamer gels following the process of the present invention. The poloxamer can be melted in a jacketed vessel, such as a kettle or tank, by passing steam or hot water (above the melting point of the poloxamer) through the vessel jacket. Mixers known in the art, e.g., COWLES dissolvers, LIGHTNIN mixers, or SILVERSON homogenizers, can be used to mix the molten poloxamer with the cold water in a jacketed vessel. A LEE TRI-MIX Turbo-Shear Mixer, which includes a
high shear homogenizer and a low shear side-scraping mixer integrated in one jacketed vessel, can also be used. The cold temperature can be attained and maintained by passing water or a cooling fluid such as DOWTHERM through a refrigeration system and then through the vessel jacket. The poloxamer and water solution can be warmed to its congealing point using room temperature water or allowing the batch to stand at room temperature. The gels can be made in vacuum conditions, at atmospheric pressure, or at pressures greater than atmospheric. Various batch sizes can be employed typically ranging from 3 Liters to 3400 Liters depending on the vessel/mixer size. Laboratory size batches (e.g. 100 grams to 2000 grams) can be made using laboratory mixers with COWLES type dissolver blades in glass or stainless steel beakers. Steam baths or hot water baths can be used for heating and ice baths can be used for cooling.

**Poloxamers**

The aqueous poloxamer gels made by the process of the present invention comprise poloxamer and water. Poloxamers are water-soluble block copolymers of propylene oxide and ethylene oxide. Poloxamers are represented by the following chemical formula:

$$\text{HO(C}_2\text{H}_4\text{O)}_a\text{(C}_3\text{H}_6\text{O)}_b\text{(C}_2\text{H}_4\text{O)}_2\text{H}$$

In the above formula $a$ and $b$ represent whole integers. Generally $a$ is from 2 to 150 and $b$ is from 15 to 70 depending on the particular poloxamer. Poloxamers are generally known as being non-toxic and non-irritating.

The poloxamers used to make aqueous poloxamer gels are in solid form at room temperature, typically as a flake or granule (i.e. prilled). Depending on the particular poloxamer, the melting point is from about 48 °C to about 57 °C, and the molecular weight is from about 5000 to 14,000. For solid poloxamers, $a$ is generally
from 46 to 128 and $b$ is generally from 16 to 67 in the chemical formula above. For the purposes of this invention, the term "poloxamer" will refer to poloxamers that are in solid form at room temperature unless otherwise specified.

The poloxamers can be pharmaceutical grade (i.e. NF grade) or non-pharmaceutical grade. Examples of pharmaceutical grade poloxamers that can be used to make aqueous poloxamer gels are poloxamer 407, poloxamer 338, and poloxamer 188, available commercially from the BASF Corporation under the tradenames PLURONIC F 127, PLURONIC F 108, and PLURONIC F 68 respectively. These tradenames are synonymous with the tradenames PLURACARE F 127, PLURACARE F 108, and PLURACARE F 68; and also LUTROL F 127, LUTROL F 108 and LUTROL F 68 all from the BASF Corporation. Non-pharmaceutical grade poloxamers would generally be cosmetic or technical grades such as poloxamer 108, poloxamer 217, poloxamer 237, poloxamer 238, and poloxamer 288, also available commercially from the BASF Corporation under the tradenames PLURONIC F 38, PLURONIC F 77, PLURONIC F 87, PLURONIC F 88, and PLURONIC F 98 respectively. Poloxamers are also commercially available from the Uniqema Corporation under the trademark SYNERONIC.

In various embodiments, the concentration of poloxamer in a gel formulation ranges from about 5% w/w to about 60% w/w. In other embodiments, the concentration of poloxamer in a gel formulation ranges from about 45% w/w to about 55% w/w.

**Additional Formulation Ingredients**

The aqueous poloxamer gels can contain additional formulation ingredients. Non-limiting examples of additional ingredients that can be included in the aqueous
poloxamer gels are pharmaceutical active ingredients, cosmetic ingredients, surfactants, humectants, moisturizers, emollients, preservatives, antioxidants, buffers, rheology modifiers, colorants, and fragrances.

Non-limiting examples of pharmaceutical active ingredients include anti-acne agents (including those for the treatment of rosacea), analgesics, anesthetics, anorectals, antihistamines, anti-inflammatory agents including non-steroidal anti-inflammatory drugs, antibiotics, antifungals, antimitotics, antivirals, antimicrobials, anti-cancer actives, scabicides, pediculicides, antineoplastics, antiperspirants, antipruritics, antipsoriatic agents (including anthralin), antiseborrheic agents, biologically active proteins and peptides, burn treatment agents (including silver sulfadiazine), cancer treatment agents, cauterizing agents, depigmenting agents, diaper rash treatment agents, enzymes, hair growth stimulants, hemostatics, kerotolytics, canker sore treatment agents, cold sore treatment agents, dental and periodontal treatment agents, photosensitizing actives, skin protectant/barrier agents, steroids including hormones and corticosteroids, sunburn treatment agents, sunscreens, transdermal actives, nasal actives, vaginal actives, wart treatment agents, wound debriding agents, wound treatment agents, wound healing agents, wound antimicrobial agents and retinoids (including retinol, retinoic acid and retinoic acid derivatives).

In regard to other additional ingredients generally, the CTFA International Cosmetic Ingredient Dictionary and Handbook, Eleventh Edition (2006) describes a wide variety of non-limiting ingredients commonly used in the skin care industry, generally suitable for use in the aqueous poloxamer gel compositions. Examples of these ingredient classes include: fragrances, colorants (e.g. Blue 1, Blue 1 Lake, Red 40, and titanium dioxide), antioxidants (e.g. BHT and tocopherol), chelating agents
(e.g. disodium EDTA and tetrasodium EDTA), preservatives (e.g. methylparaben, propylparaben, and phenoxyethanol), pH adjusters (e.g. sodium hydroxide, triethanolamine, phosphoric acid, and citric acid), buffers (e.g. citrate and phosphate), absorbents (e.g. aluminum starch octenylsuccinate, kaolin, corn starch, oat starch, cyclodextrin, talc, and zeolite), skin bleaching and lightening agents (e.g., hydroquinone and niacinamide lactate), humectants (e.g. glycerin, propylene glycol, butylene glycol, pentylene glycol, sorbitol, urea, and manitol), emollients (e.g. mineral oil, petrolatum, isopropyl myristate, cyclomethicone, and vegetable oil), exfoliants (e.g. alpha-hydroxyacids, and beta-hydroxyacids such as lactic acid, glycolic acid, and salicylic acid; and salts thereof) waterproofing agents (e.g. magnesium/aluminum hydroxide stearate), skin conditioning/moisturizing agents (e.g. aloe extracts, allantoin, bisabolol, ceramides, dimethicone, hyaluronic acid, and dipotassium glycyrrhizate), surfactants (e.g. ethoxylated alcohol, ethoxylated fatty esters and oils, quaternary surfactants, and sulfates of alcohols), and rheology modifiers (e.g. sodium polyacrylates, carbomers, natural gums, natural gum derivatives, clays, modified clays, cellulose, microcrystalline cellulose, cellulose derivatives, magnesium aluminum silicates, gellan gums, xanthan gums, starches and modified starches).

Additional ingredients may be incorporated into the aqueous poloxamer gel pursuant to various methods, including methods known in the art, depending on the characteristics of the additional ingredient to be added. For example, additional agents may be combined with poloxamer prior to or following heating the poloxamer to a molten state, and prior to mixing the poloxamer with a cold aqueous solution. Alternatively, the agent may be incorporated with an aqueous solution prior to its
combination with molten poloxamer. The agent could also be incorporated with the aqueous poloxamer gel after the aqueous poloxamer gel has been formulated.

**Formulations**

Because of the low toxicity profile of poloxamers, the aqueous poloxamer gels are particularly suitable as wound and burn dressings. Aqueous poloxamer gels containing silver sulfadiazine as a pharmaceutical active ingredient are particularly suited as wound or burn treatments. Such a treatment is exemplified below.

**EXAMPLES**

**EXAMPLE 1 - Poloxamer Gel**

Poloxamer 188 45.0 grams  
Purified Water 55.0 grams

The composition of Example 1 was prepared by heating the Poloxamer 188 to approximately 70°C in beaker using a hot water bath. The molten poloxamer was slowly added to cold Purified Water while mixing with a laboratory mixer with a COWLES-type dissolver blade and was mixed for about an hour while in an ice bath until dissolved. The resulting solution was allowed to reach room temperature. A gel was formed.

**EXAMPLE 2 - 1% Silver Sulfadiazine Wound or Burn Treatment**

500 gram batch

<table>
<thead>
<tr>
<th></th>
<th>%w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 188</td>
<td>50.0</td>
</tr>
<tr>
<td>Citrate/Phosphate Buffer Solution*</td>
<td>48.5</td>
</tr>
</tbody>
</table>
*(50% w/w Purified Water,
28% w/w 0.2M Dibasic Sodium Phosphate solution,
and 22% w/w 0.1M Citric Acid solution)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoxyethanol</td>
<td>0.50</td>
</tr>
<tr>
<td>Silver Sulfadiazine USP</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The composition of Example 2 was prepared by heating the Poloxamer 188 in beaker using a hot water bath until molten. Phenoxyethanol was added to the Citrate/Phosphate Buffer Solution in a beaker and mixed with a laboratory mixer with a COWLES-type dissolver blade at 390 RPM until dissolved. The Silver Sulfadiazine was added to the Buffer Solution and mixed at 390 RPM until dissolved. The resulting Buffer Solution was cooled to 0 - 5 °C using an ice bath. The molten Poloxamer 188 was slowly added to the cold Buffer Solution while mixing with a laboratory mixer with a COWLES-type dissolver blade for approximately 1 hour at 780 RPM until dissolved while maintaining a temperature of 0 - 5 °C using an ice bath. The batch was removed from the ice bath and allowed to reach room temperature while continuing to mix at 600 RPM. A gel was formed.

While this disclosure is made with reference to specific embodiments, other embodiments and variations of this disclosure can be devised by others skilled in the art without departing from the true spirit and scope of the disclosure.
CLAIMS

1. A process for producing an aqueous poloxamer gel comprising:
   (a) melting poloxamer,
   (b) mixing the molten poloxamer with water at a cold temperature,
   (c) maintaining the cold temperature until the poloxamer is dissolved, and
   (d) warming the resulting solution of poloxamer and water to the gel point or above.

2. The process of claim 1 wherein the molten poloxamer is added to the water.

3. The process of claim 1 wherein the water is added to the molten poloxamer.

4. The process of claim 1 wherein the poloxamer is poloxamer 407, poloxamer 338, or poloxamer 188.

5. The process of claim 4 wherein the poloxamer is poloxamer 188.

6. The process of claim 1 wherein the poloxamer is at a concentration of about 45% w/w to about 55% w/w.

7. A process for producing a wound or burn treatment comprising:
   (a) melting about 45% w/w to about 55% w/w of poloxamer 188,
   (b) mixing the molten poloxamer 188 with water at a temperature of about 0 - 5 °C,
(c) maintaining a temperature of about 0 - 5 °C until the poloxamer 188 is dissolved,
(d) warming the resulting solution to the gel point or above, and
(e) adding 1% w/w silver sulfadiazine.

8. The process of claim 7 wherein a buffer is added.

9. The process of claim 8 wherein the buffer is citric acid and dibasic sodium phosphate.

10. The process of claim 7 wherein a preservative is added.

11. The process of claim 10 wherein the preservative is phenoxyethanol.

12. The process of claim 7 wherein a humectant is added.

13. The process of claim 12 wherein the humectant is glycerin.
**INTERNATIONAL SEARCH REPORT**

**A CLASSIFICATION OF SUBJECT MATTER**

IPC(8) - A61K 47/30 (2008.04)

USPC - 514/772.3

According to International Patent Classification (IPC) or to both national classification and IPC

**B FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 47/30 (2008 04)
USPC - 514/772 3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC*: 424/78 02, 78 06, 514/772 3 (text search - see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST(USPT,PGPB, EPAB,JPAB), Google Patent, Google Scholar Search Terms Poloxamer, nonionic, copolymer, polyoxymethylene, polyoxymethylene, cold, chilly, melt, molten, water, gel, hydrogel, dissolve, burn and treat

**C DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
</table>

**D**

Further documents are listed in the continuation of Box C

Date of the actual completion of the international search

10 December 2008 (10 12 2008)

Date of mailing of the international search report

23 DEC 2008

Name and mailing address of the ISA/US

Lee W Young

P O Box 1450, Alexandria, Virginia 22313-1450

Authorized officer

PCT/US 08/80310

Form PC17ISA/2 10 (second sheet) (April 2007)