Advanced Patent Prosecution Workshop 2021:

*Claim Drafting & Amendment Writing*

**Chemical / Pharmaceutical**

In-Class Problems 9-12

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# PLI Chemical/Pharmaceutical Practice In Class Problem 9

The scientists at Relaxa Pharma invented a new compound, RP-1001, which miraculously alleviates child-induced headaches for a week at a time. Relaxa Pharma filed a provisional application to this genus on April 1, 2018.

In attempting to produce a direct compression tablet product of RP-1001 hydrochloride, the scientists at Relaxa Pharma encountered two problems: (1) chemical instability of RP-1001 hydrochloride, and (2) stickiness of the tablet blend of RP-1001 hydrochloride.

The scientists began testing other acid addition salts of RP-1001. In December 2018, the scientists invented the besylate salt of RP-1001. The besylate salt showed improved stability, and did not exhibit the stickiness of the hydrochloride salt.

Relaxa Pharma files a provisional application to the besylate salt of RP-1001 on March 16, 2019.

On April 1, 2019, Relaxa Pharma filed a U.S. non-provisional application (the ‘111 Application) directed to RP-1001, and included new biological data for the besylate salt of RP-1001 without identifying the compound as the besylate salt. Claim 1 of the ‘111 Application reads:

1. A compound selected from [the chemical name of RP-1001] and pharmaceutical acceptable salts thereof.

The patent counsel at Relaxa Pharma intentionally did not disclose the besylate salt of RP-1001 in the ‘111 Application. This was done in order to delay filing a non-provisional application to the besylate salt until March 2020, and obtain an additional 11½ months of patent term.

On March 16, 2020, Relaxa Pharma filed a U.S. non-provisional application directed to the besylate salt of RP-1001.

The ’111 Application is rejected for failure to disclose the best mode of RP-1001. The Examiner argues that the inventors knew the besylate salt of RP-1001 was the best mode of the claimed invention when the ‘111 Application was filed on April 1, 2019, as evidenced by the provisional application on March 16, 2019.

**1. Is the best mode rejection proper?**

**2. The ‘111 Application publishes on October 8, 2019. Assume the provisional application to the besylate salt of RP-1001 is filed November 1, 2019. Is the besylate salt obvious over the ‘111 Application?**

# PLI Chemical/Pharmaceutical Practice In Class Problem 10

Below is a specification and set of claims which were filed on August 1, 2019. Please respond to the problems provided after the specification and claims.

**Technical Field**

The present invention relates to pharmaceutical compositions of erythromycin derivatives with an extended release of an active compound in the gastrointestinal environment. More particularly, it relates to pharmaceutical compositions of clarithromycin which are ingested daily as a single oral administration.   
  
**Background of the Invention**

Erythromycin and its derivatives are known for their antibacterial activity against a number of organisms or activity in a number of indications and are typically administered as immediate release (IR) compositions, two or three times a day, for a regimen of 10 to 14 days. These compounds have a bitter taste. In particular, the 6-O-methoxyerythromycin A (clarithromycin) has a bitter metallic taste which can result in poor compliance of the regimen or selection of another, possibly less effective, therapeutic agent.   
  
One approach to improve the possible non-compliance with the regimen has been to develop controlled release solid preparations containing these erythromycin derivatives in an alginate matrix comprising a water-soluble alginate and a complex salt of alginic acid, having one cation that yields a soluble alginate salt and another cation that alone yields an insoluble alginate salt. These formulations are described in U.S. Pat. No. 4,842,866. However, *in-vivo* animal studies showed that reproducibly bioavailable controlled release formulation were not possible using alginates or any other monolithic hydrogel tablets.   
  
To overcome some of the problems associated with the formulations described in U.S. Pat. No. 4,842,866, improved controlled release formulations for poorly soluble basic drugs such as erythromycin derivatives including clarithromycin, have been developed and are described in U.S. Patent No. 5,705,190 . . . . However, these controlled release compositions do not purport to minimize the adverse effects related to gastrointestinal (GI) disorders including nausea and vomiting and a phenomenon described as taste perversion.   
  
One approach to address taste perversion has been to develop acceptable palatable liquid oral dosage forms of these drugs as described in U.S. Pat. No. 4,808,411. However, these formulations are administered twice-a-day for a period of 10 to 14 days and do not address the frequency and duration of the administration regimen, or the adverse effects related to GI disorders. Therefore, there still exists a need for developing a pharmaceutical composition which minimizes the adverse effects described above and provides a degree of drug plasma concentration control which is equivalent to or better than the (IR) tablet or liquid formulations currently used.   
  
**Summary of the Invention**

It has been discovered that the extended release (ER) formulations of the present invention which comprise a pharmaceutically acceptable polymer, provide extended release clarithromycin in vivo when given once daily. Maximum concentrations (Cmax) of clarithromycin in plasma are statistically significantly lower than the IR formulation given twice daily, and area under the plasma concentration-time curve (AUC) and the minimum plasma concentration are maintained over 24 hours. . . . The compositions of the invention have surprisingly a two-to three-fold reduction in incidence rates for taste perversion compared to the IR formulation.   
  
In one aspect, the present invention relates to a pharmaceutical composition for extended release of an erythromycin derivative in the gastrointestinal environment, comprising an erythromycin derivative and a pharmaceutically acceptable polymer, so that when ingested orally, the composition induces statistically significantly lower mean fluctuation index in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability substantially equivalent to that of the immediate release composition of the erythromycin derivative.   
  
In another aspect, the present invention relates to a pharmaceutical composition for extended release of an erythromycin derivative in the gastrointestinal environment, comprising an erythromycin derivative and a pharmaceutically acceptable polymer, so that upon oral ingestion, maximum peak concentrations of the erythromycin derivative are statistically significantly lower than those produced by an immediate release pharmaceutical composition, and an area under the concentration-time curve and the minimum plasma concentration are substantially equivalent to that of the immediate release pharmaceutical composition.   
  
In yet still another aspect, the present invention relates to a method of using an extended release, pharmaceutical composition comprising an erythromycin derivative and a pharmaceutically acceptable polymer, comprising administering the composition in an effective amount for the treatment of bacterial infection in a mammal, whereby an area under the concentration-time curve equivalent to that for an immediate release pharmaceutical composition of the erythromycin derivative is maintained.   
  
In yet another aspect, the present invention is an extended release pharmaceutical composition comprising an erythromycin derivative and a pharmaceutically acceptable polymer, wherein the composition has an improved taste profile relative to the immediate release formulation.   
  
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**Detailed Description of the Invention**

"500 mg or 1000 mg" as used herein, means the strength of tablet composition containing 500 mg clarithromycin, or the dose administered as 2x 500 mg of clarithromycin, respectively.   
  
"Cmax " as used herein, means maximum plasma concentration of the erythromycin derivative, produced by the ingestion of the composition of the invention or the IR comparator.   
  
"Cmin " as used herein, means minimum plasma concentration of the erythromycin derivative, produced by the ingestion of the composition of the invention or the IR comparator.   
  
"Cavg " as used herein, means the average concentration within the 24-hour interval.   
  
"Tmax " as used herein, means time to the maximum observed plasma concentration.   
  
"AUC" as used herein, means area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the complete 24-hour interval for all the formulations.   
  
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"Erythromycin derivative" as used herein, means erythromycin having no substituent groups, or having conventional substituent groups, in organic synthesis, in place of a hydrogen atom of the hydroxy groups and/or a methyl group of the 3'-dimethylamino group, which is prepared according to the conventional manner.   
  
"Pharmaceutically acceptable" as used herein, means those compounds which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, in keeping with a reasonable benefit/risk ratio, and effective for their intended use in the chemotherapy and prophylaxis of antimicrobial infections.   
  
"Adverse effects" as used herein, means those physiological effects to various systems in the body such as cardiovascular systems, nervous system, digestive system, and body as a whole, which cause pain and discomfort to the individual subject.   
  
"Taste perversion" as used herein, means the perception of a bitter metallic taste normally associated with the erythromycin derivatives, particularly, with clarithromycin.   
  
The pharmaceutical composition of the invention comprise a pharmaceutically active compound and a pharmaceutically acceptable polymer. The pharmaceutically active compound is an erythromycin derivative. Preferably, the erythromycin derivative is 6-O-methoxy erythromycin A, known as clarithromycin. The amount of the erythromycin derivative varies from about 45% to about 60% by weight of the composition. Preferably, the composition comprises about 50% by weight of the erythromycin derivative.   
  
The pharmaceutically acceptable polymer is a water-soluble hydrophilic polymer selected from the group consisting of polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof. Preferably, the polymer is selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and methyl cellulose. More preferably, the polymer is hydroxypropylmethyl cellulose. Most preferably, the polymer is a low viscosity hydroxypropyl-methyl cellulose with viscosity ranging from about 50 cps to about 200 cps. The most preferred low viscosity polymer is a hydroxypropylmethyl cellulose with a viscosity of about 100 cps, commercially available under the Tradename MethocelTM K 100 LV from The Dow Chemical Company.   
  
The amount of the polymer in the composition generally varies from about 5% to about 50% by weight of the composition. Preferably, the amount of polymers varies from about 10% to about 35% by weight of the composition. Most preferably, the amount of polymer varies from about 10% to about 30% by weight of the polymer.   
  
The composition of the invention further comprise pharmaceutically acceptable excipients and/or fillers and extenders, such as lactose, starches, glucose, sucrose, mannitol, and silicic acid, lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof.   
  
The amount of the lubricants generally varies from about 0.5% to about 10% by weight of the composition. Preferably, the lubricants used are magnesium stearate and talc in the total amounts ranging from about 1.0% to about 4.0% by weight of the composition. The amount of fillers and extenders varies from about 10% to about 40% by weight of the composition.   
  
A particularly preferred composition for the extended release of the active compound therefrom comprises:   
  
about 500 mg of clarithromycin; and   
  
from 100 to 300 mg of Methocel K 100 LV.   
  
The formulations are generally prepared by dry blending the polymer, filler, erythromycin derivative, and other excipients followed by granulating the mixture using water until proper granulation is obtained. The granulation is done by methods known in the art. The wet granules are dried in a fluid bed dryer, sifted and ground to appropriate size. Lubricating agents are mixed with the dried granulation to obtain the final formulation.   
  
The compositions of the invention can be administered orally in the form of tablets, pills, or suspensions. The tablets can be prepared by techniques known in the art and contain a therapeutically useful amount of erythromycin derivative and such excipients as are necessary to form the tablet by such techniques. Tablets and pills can additionally be prepared with enteric coatings and other release-controlling coatings for the purpose of light protection, and swallowability. The coating may be colored with a pharmaceutically accepted dye. The amount of dye and other excipients in the coating liquid may vary and will not impact the performance of the extended release tablets. The coating liquid generally comprises film forming polymers such as hydroxy-propyl cellulose, hydroxypropylmethyl cellulose, cellulose ester or ether, an acrylic polymer or a mixture of polymers. The coating solution is generally an aqueous solution further comprising propylene glycol, sorbitan monoleate, sorbic acid, fillers such as titanium dioxide, a pharmaceutically acceptable dye.   
  
Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants, such as wetting agents; emulsifying and suspending agents; and sweetening, flavoring and perfuming agents.   
  
The daily dose of the composition of this invention administered to a host in single dose can be in the amounts from 500 mg to 1000 mg once-a-day for five to fourteen days.   
  
Pharmacokinetic Study   
  
The bioavailability study for the formulations of the invention can be done by administering the ER formulation in a tablet form to healthy subjects and measuring the levels of erythromycin derivative in the plasma at different time intervals over a period of twenty four hours.   
  
Plasma samples are assayed for erythromycin derivative at BAS Analytics (West Lafayette, Ind.) using a validated high-performance liquid chromatographic procedure similar to that described in the literature. See for example, Chu S-Y, et al., "Simultaneous determination of clarithromycin and 14(R)-hydroxyclarithromycin in plasma and urine using high-performance liquid chromatography with electrochemical detection", J. Chromatog., 571, pp 199-208 (1991).   
  
Adverse Effects and Taste Profile   
  
Adverse effects including those related to the digestive system, nervous system, respiratory system and special senses, including taste perversion, are measured by dosing subjects with multiple doses of 1000 mg of ER and IR tablets per day, respectively. The adverse effects are monitored, reported spontaneously by subjects and recorded on case report forms for the study database.   
  
The invention will be understood more clearly from the following Examples, which are given solely by way of illustration and serve to provide a clear understanding of the invention and to illustrate its different embodiments as well as its various advantages.   
  
Examples   
  
Example 1   
  
Preparation of Formulation   
  
MethocelTM (K 100 LV) available from The Dow Chemical Company was loaded into a mixer, and dry blended with clarithromycin. The mixture was granulated using water until proper granulation was obtained. The granulation was then dried, sifted and ground to appropriate size.   
  
Talc and magnesium stearate were screened and blended with dry granulation. The granulation was then loaded into hopper and compressed into tablets. The tablets were then coated with an aqueous coating.   
  
. . .

Example 2   
  
Pharmacokinetic Study of the Extended Release Formulation   
  
The bioavailability study to determine the concentration-time plasma profile was done on healthy subjects. The study was conducted as a Phase I, single-dose, open, randomized, four-period, balanced cross-over study described below.   
  
Single-Dose Study   
  
Twenty-four (24) healthy adult subjects were enrolled and 23 completed all phases of the study. For the 23 subjects who completed all phases of the study (12 males, 11 females), the mean age was 29 years (range: 19 to 49 years), the mean weight was 69.0 kg (range: 51.5 to 85 kg) and the mean height was 172 cm (range: 157 to 192 cm).   
  
Clarithromycin 500 mg extended release tablets corresponding to the formulations A, B, and C of Example 1 and the 500 mg IR clarithromycin tablet (Reference Formulation), currently sold by Abbott Laboratories under the Tradename BIAXINTM, were administered to the 23 healthy subjects.   
  
The study was conducted according to a single-dose, open-label, randomized four-period crossover design in which each subject received a single 500 mg dose of clarithromycin during each 30 minutes period after starting breakfast. Wash-out periods of one week separated the doses.   
  
. . .

Multiple-Dose Study   
  
Twenty-four (24) healthy adult subjects were enrolled and 23 completed all phases of the study. Of the 23 who completed the study (19 males, 4 females), the mean age was 30 years (range: 20 to 47 years), the mean weight was 72 kg (range: 51 to 87 kg) and the mean height was 176 cm (range: 159 to 189.5 cm).   
  
The clarithromycin dosage forms included 500 mg ER tablets of Example 1 containing 10% or 20% by weight of K 100 LV, respectively, and a reference 500 mg IR tablet (BIAXIN).   
  
The study was conducted according to a single- and multiple-dose, open-label, randomized three-period crossover design.   
  
. . .

**Claims**

1. A method of reducing gastrointestinal adverse side effects comprising administering an effective amount of an extended release pharmaceutical composition comprising an erythromycin derivative and a pharmaceutically acceptable polymer.

2. The method according to claim 1, wherein the erythromycin derivative is clarithromycin.

3. The method according to claim 2, wherein the composition comprises about 50% by weight of clarithromycin.

4. The method according to claim 3, wherein the composition comprises from about 10 to about 30% by weight of hydroxypropylmethylcellulose having a viscosity of about 100 cps.

5. A pharmaceutical composition for extended release of an erythromycin

derivative in the gastrointestinal environment, comprising an erythromycin derivative and from about 5 to about 50% by weight of a pharmaceutically acceptable polymer, so that when ingested orally, the composition induces statistically significantly lower mean fluctuation index in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability substantially equivalent to that of the immediate release composition of the erythromycin derivative.   
  
 6. The pharmaceutical composition of claim 5, wherein the polymer is a hydrophilic water-soluble polymer.   
  
 7. The pharmaceutical composition of claim 6, wherein the polymer is selected from the group consisting of polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof.   
  
 8. A pharmaceutical composition for extended release of an erythromycin derivative in the gastrointestinal environment, comprising an erythromycin derivative and from about 5 to about 50% by weight of a pharmaceutically acceptable polymer, so that upon oral ingestion, maximum peak concentrations of the erythromycin derivative are lower than those produced by an immediate release pharmaceutical composition, and area under the concentration-time curve and the minimum plasma concentration are substantially equivalent to that of the immediate release pharmaceutical composition.   
 9. A method of using an extended release, pharmaceutical composition comprising an erythromycin derivative and from about 5 to about 50% by weight of a pharmaceutically acceptable polymer, comprising administering the composition in an effective amount for the treatment of bacterial infection in a mammal, whereby an area under the concentration-time curve substantially equivalent to that for an immediate release pharmaceutical composition of the erythromycin derivative is maintained.

**PROBLEM**

1. All the claims are rejected as anticipated by or, in the alternative, as obvious over Quack, which was published in February 2018. Quack discloses an extended release formulation of erythromycin. Quack does not provide any pharmacokinetic data for its formulations. However, it would have been obvious to formulate the clarithromycin to have the claimed pharmacokinetic profile in order to reduce side effects. It was well known that extended release formulations reduce side effects compared to similar immediate release formulations.

Claims 1 and 5-9 are rejected for lack of written description. There is no written description of any erythromycin derivatives other than erythromycin and clarithromycin. Not all erythromycin derivatives will necessarily have the desired activity. Furthermore, the term “derivative” is open ended.

Claims 1 and 5-9 are rejected for lack of enablement. While the examples provide enablement for clarithromycin, the specification does not reasonably enable all erythromycin derivatives. Not all erythromycin derivatives can be formulated into extended release formulations.

Please provide appropriate arguments for responding to these rejections.

2. (For those students familiar with pharmaceuticals) This patent has issued with all of its original claims, and the patent is assigned to PlaceboPharma. PlaceboPharma sells its extended release clarithromycin product under the tradename Clarit. Clarit is sold for treating tonsillitis due to *S. pyogenes*. Clarit contains 57% of the polymer hydroxypropyl methyl cellulose (HPMC). Is this patent listable in the FDA Orange Book? If so, which claims render the patent listable?

Draft new pharmaceutical composition and method of treatment claims which if included in a patent would render the patent listable in the Orange Book.

Assuming claim 9 is listable in the Orange Book, what would be an appropriate use code for it?

3. This patent has issued with all of its original claims, and the patent is assigned to PlaceboPharma. DumbCo submits an abbreviated new drug application (ANDA) for a generic extended release clarithromycin product. The generic product includes 48% glyceryl monostearate as its release controlling ingredient. Glyceryl monostearate has the formula:

|  |  |  |
| --- | --- | --- |
|  |  | Glyceryl monostearate, 2,3-Dihydroxypropyl octadecanoate, Monostearin, GMS, CAS #: 31566-31-1 |
|  | | |
| Molecular Formula |  | C21H42O4 |

Glyceryl monostearate is used as a thickening, emulsifying, antisticking agent; emulsifying agent for oils, waxes and solvents; protective coating for hygroscopic powders; solidifier and control release agent in pharmaceuticals.

PlaceboPharma sues DumbCo for infringement of the claims of this patent. DumbCo argues that it does not infringe the claims, either literally or under the doctrine of equivalents, because its product does not contain a "pharmaceutically acceptable polymer." Provide arguments supporting DumbCo’s position of non-infringement.

DumbCo replaces the glyceryl monostearate with polyethylene oxide. Provide arguments supporting DumbCo’s position of non-infringement.

# PLI Chemical/Pharmaceutical Practice In Class Problem 11

Your client has filed an application which describes a process for dehydrating liposomes to form a storage stable powder. A liposome is a microscopic sphere of vesicle. It is like a bubble. However, whereas in a bubble, a thin membrane surrounds a gas, in a liposome, the membrane surrounds a liquid. A liposome’s membrane is a lipid bilayer, a lamella, and is approximately five nanometers thick. As one can make a bubble within a bubble, one can make a liposome within a liposome, so that one sphere of liquid with a lipid bilayer is contained in a larger sphere of liquid with a lipid bilayer. These liposomes with several bilayers are known as multilamellar vesicles. Liposomes with one bilayer are unilamellar and are termed large or small unilamellar vesicles. Small unilamellar liposomes typically have diameters of from about 40 to 100 nanometers, while large ones typically have diameters of from about one half to one micron.

The liposome’s bilayers are composed predominantly of phospholipids, a class of lipids present in plants and animals that have a hydrophilic (or water-loving) head and a hydrophobic (or water-having) tail. When placed in water, the phospholipids organize to form a sphere (or liposome) with a bilayer in which the polar heads align to face the water inside and outside of the bilayer and the hydrophilic tails align to face each other.

Due to their structure, liposomes are valuable as agents for delivering products such as enzymes and drugs to organisms.

The specification includes the following descriptions:

Thus, an object of the present invention is a process for the dehydration of a liposome colloidal dispersion in a aqueous liquid medium, which comprises mixing a hydrophilic compound with the liposome dispersion and subjecting the obtained mixture to a dehydration operation leading to the formation of liposomes in the form of a stable powder which can be stored for a long period and from which, and with an aqueous medium, a liposome dispersion can be reconstituted.

The hydrophilic compound used for carrying out the process of the invention can be advantageously selected among various high molecular weight compounds. For instance, very satisfactory results have been obtained with different hydrophilic polymers such a dextran, ox-albumin, polyvinyl alcohol (PVA), polyvinyl-pyrrolidone and gum arabic. Lower molecular weight compounds, such as sucrose, can also be used. Therefore, said hydrophilic compound is actually a stabilizing additive which protects the liposomes of the dehydrated product and keeps them in a condition suitable for further use. Further, the presence of such a hydrophilic compound in the liposome powder is not likely to cause any particular inconvenience, especially if natural polymers chosen among those described above are used. Thus, when dextran is used, any kind of subsequent use of the liposome powder according to the invention can be contemplated.

[Example 1] A liposome dispersion in water was prepared which comprised 25 mg of lecithin per mL of dispersion; the encapsulated solution was 100mg/mL aqueous insulin solution. Dextran (Pharmacia T-70) (25 mg/mL) was added as a stabilizer to the liposome dispersion and was thoroughly mixed therein.

**Problem 11.1:** Draft a broad method claim.

**Problem 11.2:** The examiner rejects the claim you drafted for Problem 11.1 on the grounds that the term “hydrophilic compound” is indefinite and lacking enablement as required by 35 U.S.C. §112, first and second paragraphs. She says that the term “hydrophilic compound” as used in the patent is extraordinarily broad in that the patentee gives no guidance to determine which compounds to use beyond the compounds referred to in the patent. She contends failure to be more specific renders the patent invalid as indefinite and lacking enablement, since an experimenter would receive no guidance as to how to identify which compounds would work.

(a) Draft a short argument in response to the Examiner’s rejection of the claim you drafted for Problem 11.1.

(b) Redraft your claim for Problem 11.1 to overcome the rejection.

**Problem 11.3:** Your patent issues with the broad method claim you drafted for Problem 11.1.

A competitor markets a lyophilized (dehydrated) cake or powder that provides amphotericin B (an antibiotic) encapsulated in a liposome. The competitor’s dehydrated product contains sucrose, which functions to preserve the structural integrity of the liposomes. The dehydrated powder is rehydrated with sterile water for injection. When rehydrated, the competitor’s liposomes are small unilamellar vesicles.

The competitor’s product is made by a two step process: hydration and lyophilization. During the hydration step, a spray-dried powder containing lipids and amphotericin B is introduced into a mixing tank that contains an aqueous solution of sucrose and a buffering agent, disodium succinate. Liposomes are formed at this stage, both multilamellar large vesicles and unilamellar small vesicles. Because the liposomes are formed in the presence of dissolved sucrose, sucrose is found both on the inside and the outside of the resulting liposomes.

(a) Does the competitor’s process infringe your broad claim? Why or why not?

(b) Draft a claim which covers the infringer’s process.

# PLI Chemical/Pharmaceutical Practice In Class Problem 12

You are presented with an invention disclosure entitled “Lubricating oil compositions containing ashless dispersant, zinc dihydrocarbyldithiophosphate, metal detergent and a copper compound.” The information disclosure teaches as follows:

The present invention relates to lubricating compositions, especially crankcase lubricants for automobiles and trucks, containing copper in an amount sufficient to retard or inhibit oxidation of the lubricant during use, without interfering with the function of other components of the lubricant composition.

There is currently a great need to improve the efficiency and useful life of lubricants, particularly those used as crankcase lubricants in internal combustion engines in automobiles and trucks. Limited oil resources and rapidly increasing prices for crude oil have made it imperative to obtain a longer useful life from oil-based products.

One of the factors which substantially shorten the life of lubricating compositions is oxidation of the oil component. Oxidation results in increased acidity of the lubricant, leading to greater corrosion of engine parts and undesirably increased viscosity, which degrades its lubricant qualities.

While high quality oil itself is relatively resistant to oxidation, contaminants, such as iron, which inevitably are present in internal combustion engines and common lubricant additives, such as magnesium and calcium detergents and polyisobutenyl succinic acid/polyamine or polyester dispersants, have the undesirable effect of greatly accelerating the oxidation process, to the extent that oxidation is one of the major contributors to reduced lubricant life. In addition, there has been an increasing need to utilize lower quality lubricating oil base stocks, as oil fields producing the higher quality oils are depleted. These lower quality oil base stocks exhibit a greater tendency to oxidize.

Therefore, effective inhibition or retardation of oxidation is important in obtaining the maximum life from a lubricant composition and has become more important as demands increase for longer intervals between oil changes, to reduce oil consumption and to lessen the environmental impact resulting from disposal of large volumes of used oil.

It has been known for some time that some compounds have the ability to inhibit or retard oxidation when incorporated into the lubricating composition. For example, hindered phenols and sulfurized phenols have been used for that purpose. Zinc dialkyldithiophosphates, which are primarily anti-wear agents, are also known to have antioxidant activity. The known agents are typically used in large amounts in order to obtain the desired effect, which increases the cost of the composition and, in the case of zinc dialkyldithiophosphate, produces an undesirably high level of phosphorus in the oil. Even in such large amounts, adequate antioxidant performance may not be achieved when the composition contains other additives which can be oxidation promoters. Moreover, modem lubricants are complex mixtures of various additives, each serving a particular purpose. For example, they may contain one or more viscosity modifiers, detergents, dispersants, antacids, corrosion inhibitors, anti-rust agents and anti-wear agents, for protecting and promoting the efficiency of the engine in which the composition is used. An effective antioxidant should retard oxidation of the lubricant without interfering with the function of other additives and without contributing undesirable contaminants. Obviously, extending the life of the lubricant through retardation of oxidation would be of no value if it were accompanied by damage to the engine, by increased corrosion or wear.

In accordance with the present invention, it is possible to retard or inhibit oxidation of a lubricant composition containing dispersant and anti-wear additives without adversely affecting the performance of those additives, by incorporating in the lubricant composition an oil-soluble copper compound, within a specified range of concentrations.

In accordance with its preferred aspects, this invention provides novel, oxidation-stable lubricant compositions comprising a major amount of a lubricating oil, one or more ashless and/or polymeric viscosity index improver dispersants, one or more zinc dihydrocarbyldithiophosphates (ZDDPS) as extreme pressure and anti-wear agents and an oil-soluble copper compound present in the amount of about 5 to about 500 parts per million (ppm) of copper by weight, based on the total composition.

In particularly preferred embodiments of the invention, the lubricant composition will also contain one or more overbased additives which function as antacid and anti-rust agents, such as overbased calcium or magnesium sulfonates or phenates.

The amount of copper compound employed is critical in obtaining the benefits of this invention. At unduly low concentrations, the anti-oxidant effect will not be sufficiently realized. At unduly high concentrations, interference with the performance of the anti-wear additive may occur and a pronounced increase in wear may be observed on high stress points, such as camshafts and lifters. In general, the amount of added copper compound employed will be such to give a copper concentration of about 5 to about 500 ppm by weight of copper in the lubricant composition and preferably about·10 to 200, e.g. 60 to about 200 ppm. The amount of copper compound employed, within the above ranges, will also preferably be correlated with the amount of zinc dihydroxcarbyldithiophosphate, as indicated by the phosphorus concentration.

The ability of the oil-soluble copper compound to function as an anti-oxidant in lubricating compositions is surprising. Copper is known to act, in many cases, as an oxidation promoter or catalyst. Moreover, closely related metals, such as cobalt and chromium, are not effective lubricant antioxidants.

It is also surprising that the copper compound functions effectively in compositions which contain other metal compounds, such as zinc dialkyldithiophosphates and calcium or magnesium overbased additives, which might be expected to inactivate it through interchange of the metal components.

The copper anti-oxidants of this invention are inexpensive and are effective at low concentrations and therefore do not add substantially to the cost of the product. The results obtained are frequently better than those obtained with previously used anti-oxidants, which are expensive and used in higher concentrations. In the amounts employed, the copper compounds do not interfere with the performance of other components of the lubricant composition. In many instances, completely satisfactory results are obtained when the copper compound is the sole anti-oxidant in addition to the ZDDP. The copper compounds can be utilized to replace part or all of the need for supplementary antioxidants. Thus, for particularly severe conditions it may be that the amount of supplementary anti-oxidant required is small, far less than the amount required in the absence of the copper compound. There have previously been isolated references to the inclusion of copper compounds in lubricant compositions, but none of those references disclose the composition of the present invention.

U.S. Pat. Nos. 2,343,756 and 2,356,662 disclose the addition of copper compounds in conjunction with sulfur compounds, to lubricant oils. In U.S. Pat. No. 2,552,570, cuprous thiophosphates are included in lubricant compositions at relatively high levels, which results in undesirably high sulfated ash content. In U.S. Pat No. 3,346,493, a wide variety of polymeric amine-metal reactants are employed as detergents in lubricant compositions. In the two isolated instances in which the metal is copper and the composition contains zinc dihydrocarbyl-dithiophosphate, either the amount of copper employed is outside the range of the present invention or it is necessary that the oil insoluble copper compound be complexed with the dispersant. U.S. Pat. No. 3,652,616 discloses a wide variety of polymeric amine-metal reactants for addition to lubricant compositions. U.S. Pat. No. 4,122,033 discloses the entire group of transition metal compounds as additives for lubricants.

None of these references discloses the use of copper compounds which are oil soluble per se in the range of 5-500 ppm in conjunction with a zinc dihydrocarbyl dithiophosphate polymeric viscosity index improver dispersant, in the range of about 0.01 and 5 parts. The hydrocarbyl groups of the zinc dihydrocarbyl dithiophosphate contain from 1 to 18 carbon atoms. None of these references teaches such a composition with the copper either in the complexed form with the dispersant or non-complexed, in the preferred range of 10-200 ppm. None discloses the ability of such a composition to resist oxidation while providing good anti-wear properties and none discloses that such compositions can also include overbased additives without impairment of their oxidation resistance.

The present invention therefore provides a lubricating composition comprising a major amount of a lubricating oil containing 1 to 10 wt% ashless dispersant compounds.

The lubricating oil includes the mineral lubricating oils and the synthetic lubricating oils and mixtures thereof. The synthetic oils will include diester oils such as di(2-ethylhexyl) sebacate, azelate and adipate; complex ester oils such as those formed from dicarboxylic acids, glycols and either monobasic acids or monohydric alcohols; silicone oils; sulfide esters; organic carbonates; hydrocarbon oils and other synthetic oils known to the art. The invention is particularly useful in mineral lubricating oils and has the added benefit that it may allow use of basestock oils that have inferior antioxidant properties to those currently used.

The oils of the present invention contain from 0.01 to 0.5 wt% phosphorus and from 0.01 to 0.5 wt% zinc, preferably 0.03 to 0.3 wt %, more preferably 0.04 to 0.14 wt % of phosphorus and zinc, these weight percents and all subsequent weight percents used herein are based upon the total weight of the lubricant composition or additive concentrate composition. All parts by weight as used herein are based upon 100 parts by weight of the total lubricant or additive concentrate composition unless other specified. The phosphorus and zinc are most conveniently provided by a zinc dihydrocarbyl dithiophosphate. Generally 0.01 to 5 parts, preferably 0.2 to 2.0 parts,. and mote preferably 0.5 to 1.5 parts by weight per 100 parts of the lubricating oil composition is a zinc dihydrocarbyldithiophosphate.

Zinc dihydrocarbyl dithiophosphates which may be used in the compositions of the present invention may be prepared in accordance with known techniques by first forming a dithiophosphoric acid, usually by reaction of an alcohol or a phenol with P2S5 and then neutralizing the dithiophosphoric acid with a suitable zinc compound.

Mixtures of alcohols may be used including mixtures of primary and secondary alcohols, secondary generally for imparting improved antiwear properties, with primary giving improved thermal stability properties. Mixtures of the two are particularly useful. In general, any basic or neutral zinc compound could be used but the oxides, hydroxides and carbonates are most generally employed. Commercial additives frequently contain an excess of zinc due to use of an excess of the basic zinc compound in the neutralization reaction.

The zinc dihydrocarbyl dithiophosphates useful in the present invention are oil soluble salts of dihydrocarbyl esters of dithiophosphoric acids and may be represented by the following formula:



wherein R and R’ may be the same or different hydrocarbyl radicals containing 1 to 18 and preferably 2 to 12 carbon atoms and including radicals such as alkyl, alkenyl, aryl, aralkyl, alkaryl and cycloaliphatic radicals. Particularly preferred as R and R' groups are alkyl groups of 2 to 8 carbon atoms. Thus, the radicals may, for example, be ethyl, n-propyl, I-propyl, n-butyl, I-butyl, sec-butyl, amyl, n-hexyl, n-octyl, decyl, dodecyl, octadecyl, 2-ethylhexsyl, phenyl, butylphenyl, cyclohexyl, methylcyclopentyl, propenyl, butenyl etc. In order to obtain oil solubility, the total number of carbon atoms (i.e. R and R') in the dithiophosphoric acid will generally be about 5 or greater.

The copper may be blended into the oil as any suitable oil soluble copper compound, and by oil soluble we mean the compound is soluble under normal blending conditions in the oil or additive package. The copper compound may be in the cuprous or cupric form. The copper may be in the form of the copper dihydrocarbyl thio- or dithio-phosphates wherein copper may be substituted for zinc in the compounds and reactions described above although one mole of cuprous or cupric oxide may be reacted with one or two moles of the dithiophosphoric acid respectively. Alternatively the copper may be added as the copper salt of a synthetic or natural carboxylic acid. Examples include C10 to C18 fatty acids such as stearic or palmitic, but unsaturated acids such as oleic or branched carboxylic acids such as naphthenic acids of molecular weight from 200 to 500 or synthetic carboxylic acids are preferred because of the improved handling and solubility properties of the resulting copper carboxylates.

Oil soluble copper dithiocarbamates of the general formula (RR'NCSS)nCu (where n is 1 or 2 and R and R' are the same or different as described above for the zinc dihydrocarbyl dithiophosphate). Copper sulphonates, phenates, and acetyl acetonates may also be used.

We have found that when used in combination with the zinc dialkyl dithiophosphates the quantity of copper in the oil is important to obtaining the combination of antioxidant and antiwear properties needed for extended life lubricants.

We prefer that the lubricant contain 60 to 200, especially 80 to 180 and most preferably 90 to 120 although generally it contains from 5 to 500, more preferably 10 to 200, more especially 10 to 180, and even more especially 20 to 130 parts per million of copper based on the weight of the lubricant composition. The preferred amount may depend amongst other factors on the quality of the basestock oil.

The lubricating compositions of the present invention may and usually will contain other traditional lubricant additives such as rust inhibitors such as lecithin, sorbitan mono-oleate, dodecyl succinic anhydride or ethoxylated alkyl phenols; pour point depressants such as copolymers of vinyl acetate with fumaric acid esters of coconut oil alcohols; viscosity index improvers such as olefin copolymers, polymethacrylates; etc.

In copper-free oils other antioxidants in addition to the zinc dialkyldithiophosphate are sometimes required to improve the oxidative stability of the oil. These supplementary antioxidants are included especially when the basestock has poor oxidative stability, and typically the supplementary antioxidant is added to the oil in amounts from 0.5-2.5 wt %. The supplementary antioxidants that are used include phenols, hindered-phenols, bis-phenols, and sulfurized phenols, catechol, alkylated catechols and sulfurized alkyl catechols, diphenylamine and alkyl diphenylamines, phenyl-1-naphthylamine and its alkylated derivatives, alkyl borates and aryl borates, alkyl phosphites and alkyl phosphates, aryl phosphites and aryl phosphates, O,O,S-trialkyl dithiophosphates, O,O,S-triaryl dithiophosphates and O,O,S-trisubstituted dithiophosphates containing both alkyl and aryl groups.

The inclusion of small amounts of copper generally removes the need for these supplementary antioxidants. It would, however, still be within the scope of our invention that a supplementary antioxidant can be included especially for oils operating under particularly severe conditions where the presence of such supplementary antioxidants may be beneficial.

The prime benefit of our invention is that the use of copper permits replacing part or all of the need for supplementary antioxidants, that is an antioxidant in addition to the ZDDP. Frequently, it enables lubricating compositions having the desired antioxidant properties to be obtained with either no additional supplementary antioxidant or with less than normal concentrations, for example with less than 0.5 wt % and frequently less than about 0.3 wt % of the supplementary antioxidant. The presence of small amounts of copper according to our invention has the added advantage that smaller amounts of a zinc dialkyldithiophosphate may be used.

The dispersancy can be provided by a traditional lubricating oil ashless dispersant compound such as derivatives of long chain hydrocarbon substituted carboxylic acids in which the hydrocarbon groups contains 50 to 400 carbon atoms. These will generally be a nitrogen containing ashless dispersant having a relatively high molecular weight aliphatic hydrocarbon oil solubilizing group attached thereto or an ester of a succinic acid/anhydride with a high molecular weight aliphatic hydrocarbon attached thereto and derived from monohydric and polyhydric alcohols, phenols and naphthols. The ashless dispersants are susceptible to change, and do not stay ashless for a significant amount of time.

The nitrogen containing dispersant additives are those known in the art as sludge dispersants for crankcase motor oils. These dispersants include mineral oil-soluble salts, amides, imides, oxazolines and esters of mono-and dicarboxylic acids (and where they exist the corresponding acid anhydrides) of various amines and nitrogen containing materials having amino nitrogen or heterocyclic nitrogen and at least one amido or hydroxy group capable of salt, amide, imide, oxazoline or ester formation. Other nitrogen containing dispersants which may be used in this invention include those wherein a nitrogen containing polyamine is attached directly to the long chain aliphatic hydrocarbon as shown in U.S. Pat. Nos. 3,275,554 and 3,565,804 where the halogen group on the halogenated hydrocarbon is displaced with various alkylene polyamines.

Another class of nitrogen containing dispersants which may be used are those containing Mannich base or Mannich condensation products as they are known in the art. Such Mannich condensation products generally are prepared by condensing about 1 mole of an alkyl substituted phenol with about 1 to 2.5 moles of formaldehyde and about 0.5 to 2 moles polyalkylene polyamine as disclosed, e.g. in U.S. Pat. No. 3,442,808. Such Mannich condensation products may include a long chain, high molecular weight hydrocarbon on the phenol group or may be reacted with a compound containing such a hydrocarbon, e.g. alkenyl succinic anhydride as shown in said aforementioned U.S. Pat. No. 3,442,808.

Monocarboxylic acid dispersants have been described in U.K. Patent Specification 983,040. Here, the high molecular weight monocarboxylic acid can be derived from a polyolefin, such as polyisobutylene, by oxidation with nitric acid or oxygen, or by addition of halogen to the polyolefin followed by hydrolyzing and oxidation. Another method is taught in Belgian Pat. No. 658,236 where polyolefins, such as polymers of C2 to C5 monoolefins, e.g. polypropylene or polyisobutylene, are halogenated, e.g. chlorinated, and then condensed with an alpha-beta-unsaturated, monocarboxylic acid of from 3 to 8, preferably 3 to 4, carbon atoms, e.g. acrylic acid, α-methyl-acrylic acid, etc. Esters of such acids, e.g. ethyl methacrylate, may be employed if desired in place of the free acid.

The most commonly used dicarboxylic acid is alkenyl succinic anhydride wherein the alkenyl group contains about 50 to about 400 carbon atoms. Primarily because of its ready availability and low cost, the hydrocarbon portion of the mono-or dicarboxylic acid or other substituted group is preferably derived from a polymer of a C2 to C5 monoolefin, said polymer generally having a molecular weight of about 700 to about 5000. Particularly preferred is polyisobutylene.

Polyalkyleneamines are usually the amines used to make the dispersant. These polyalkyleneamines include those represented by the general formula: H2N(CH2)n-[NH(CH2)n]m-NH(CH2)nNH2 wherein n is 2 or 3, and m is 0 to 10. Examples of such polyalkyleneamines include diethylene triamine, tetraethylene pentamine, octaethylene nomimine, and tetrapropylene pentamine, as well as various cyclic polyalkyleneamines.

Dispersants formed by reacting alkenyl succinic anhydride, e.g. polyisobutenyl succinic anhydride and an amine, are described in U.S. Pat. Nos. 3,202,678, 3,154,560, 3,172,892, 3,024,195, 3,024,237, 3,219,666, and 3,216,936 and Belgium Pat. No. 662,875.

Alternatively the ashless dispersants may be esters derived from any of the aforesaid long chain hydrocarbon substituted carboxylic acids and from hydroxy compounds such as monohydric and polyhydric alcohols or aromatic compounds such as phenols and naphthols etc. The polyhydric alcohols are the most preferred hydroxy compound and preferably contain from 2 to about 10 hydroxy radicals, for example, ethylene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, diproplyene glycol, and other alkylene glycols in which the alkylene radical contains from 2 to about 8 carbon atoms. Other useful polyhydric alcohols include glycerol, monooleate of glycerol, monostearate of glycerol, monomethyl ether of glycerol, pentaerythritol.

The ester dispersant may also be derived from unsaturated alcohols such as allyl alcohol, cinnamyl alcohol, propargyl alcohol, 1-cyclohexane-3-ol, and oleyl alcohol. Still other classes of the alcohols capable of yielding the esters of this invention comprise the ether-alcohols and ammo-alcohols including, for example, the oxy-alkylene, oxy-arylene, amino alkylene, and amino-arylene-substituted alcohols having one or more oxy-alkylene, amino-alkylene or aminoarylene oxy-arylene radicals. They are exemplified by Cellosolve, Carbitol, N,N,N’,N’-tetrahydroxy-trimethylene di-amine, and the like. For the most part, the ether-alcohols having up to about 150 oxy-alkylene radicals in which the alkylene radical contains from 1 to about 8 carbon atoms are preferred.

The ester dispersant may be di-esters of succinic acids or acidic esters, i.e., partially esterified succinic acids, as well as partially esterified polyhydric alcohols or phenols, i.e., esters having free alcohols or phenolic hydroxyl radicals. Mixtures of the above illustrated esters likewise are contemplated within the scope of this invention.

The ester dispersant may be prepared by one of several known methods as illustrated for example in U.S. Pat. No. 3,522,179.

Hydroxyamines which can be reacted with any of the aforesaid long chain hydrocarbon substituted carboxylic acids to form dispersants include 2-amino-1-butanol, 2-amino-2-methyl-l-propanol, p-(beta-hydroxyethyl)-aniline, 2-anrino-l-propanol, 3-amino-l-propanol, 2-amino-2-methyl-l, 3-propane-diol, 2-amino-2-ethyl-l, 3-propanediol, N’-(beta-hydroxy-propyl)-N’-(beta-aminoethyl)-piperazine, tris(hydroxmethyl) amino-methane (also known as trismethylol-aminomethane), 2-amino-l-butanol, ethanolamine, beta-(beta-hydroxyethoxy)-ethylamine, and the like. Mixtures of these or similar amines can also be employed.

The preferred dispersants are those derived from polyisobutenyl succinic anhydride and polyethylene amines, e.g., tetraethylene pentamine, polyoxyethylene and polyoxypropylene amines, e.g. polyoxypropylene diamine, trismethylolartlinomethane and pentaerythritol, and combinations thereof. One particularly preferred dispersant combination involves a combination of (A) polyisobutenyl succinic anhydride with (B) a hydroxy compound, e.g, pentaerythritol, (C) a polyoxyalkylene polyamine, e.g. polyoxypropylene diamine, and (D) a polyalkylene polyamine, e.g. polyethylene diamine and tetraethylene pentamine using about 0.01 to about 4 equivalents of (B) and (D) and about 0.01 to about 2 equivalents of (C) per equivalent of (A) as described in U.S. Pat No. 3,804,763.

Another preferred dispersant combination involves the combination of (A) polyisobutenyl succinic anhydride with (B) a polyalkylene polyamine, e.g., tetraethylene pentamine, and (C) a polyhydric alcohol or polyhydroxy-substituted aliphatic primary amine, e.g., pentaerythritol or trismethyloaminomethane as described in U.S. Pat No. 3,632,511.

The alkenyl succinic polyamine type dispersants can be further modified with a boron compound such as boron oxide, boron halides, boron acids and esters of boron acids in an amount to provide about 0.1 to about 10 atomic proportions of boron per mole of the acylated nitrogen compound as generally taught in U.S. Pat Nos. 3,087,936 and 3,254,025. Mixtures of dispersants can also be used such as those described in U.S. Pat. No. 4,113,639.

The oils may contain from 1.0 to 10 wt %, preferably 2.0 to 7.0 wt % of these dispersants.

The composition of the present invention also contains a detergent additive, which is a magnesium or a calcium salt of sulfonic acids, alkyl phenols, sulfurized alkyl phenols, alkyl salicylates and naphthenates.

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**1.** Draft a broad claim to the invention.

**2.** A year after the patent you drafted issues, your client’s competitor markets a motor oil, which your client has analyzed. The motor oil contains lubricating oil, 1 part zinc polyalkenyl succinate, 200 ppm copper diethyldithiophosphate, and calcium sulfonate. Your client wants to know: does it infringe claim (1)?

**3.** Six months later, your client learns that the competitor’s motor oil is manufactured by mixing lubricating oil with polyalkenyl succinic anhydride, followed by “zinc diethyldithiophosphate, an oil soluble copper compound, followed by calcium sulfonate.” She asks you again: does it infringe claim (1)?

**4.** Your client decides to file for reissue. Draft new claims which cover your competitor’s product and process.