Antimicrobial clonidine compositions are provided. These antimicrobial clonidine compositions can be applied to medical devices or be part of a drug depot. Through the administration of an effective amount of clonidine at or near a target site, one can reduce, prevent, or treat infections. When appropriate clonidine compositions are provided within biodegradable polymers, the infection may be treated for extended periods of time.
CLONIDINE FORMULATIONS HAVING ANTIMICROBIAL PROPERTIES

BACKGROUND

Infections continue to pose a serious threat to public health as indicated by a worldwide resurgence of infectious diseases. In some instances, common infections, such as bacterial infections have become more difficult because of increasing bacterial resistance to antibiotics.

Every year, lives are lost because of the spread of infections. Infections result from the body's inability to fight off foreign microorganisms or pathogens that may cause damage or disease if left untreated. The infecting organism or pathogen can be bacteria, viruses, fungi or some other parasites. Sometimes the infecting organism can invade an implanted medical device (e.g., catheter, implanted device, etc.). After its invasion into the body, the infecting organism or pathogen begins to spread and seeks to utilize the host's resources to multiply (usually at the expense of the host). The infecting organism or pathogen interferes with the normal functioning of the host and can lead to the patient having complications, for example, chronic wound infections, gangrene, loss of an infected limb or, in severe cases, death.

There are many common infections and some very rare ones, all with varying causes and treatments. Common bacterial infections include strep throat, tuberculosis, urinary tract infections and microbial infections such as *E. coli* or *Staphylococcus aureus*. Bacterial infections are generally treated with an antibiotic specifically chosen to destroy the infectious bacteria and to be delivered systemically, however, antibiotics are sometimes not effective.

Common viral infections include a cold, influenza, hepatitis A, hepatitis B, hepatitis C, and hepatitis E viruses, herpes viruses, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus, adenovirus, or severe acute respiratory syndrome (SARS)-associated coronavirus, swine flu, etc. Viral and bacterial infections differ in that viral infections are caused by viruses which are smaller than a bacterium or fungus. When a virus infects healthy cells, it prevents the cells from doing their job and causes sickness. Viruses usually infect a specific type of cell which causes viral infections to affect certain parts of the body. Viral infections in some cases can be treated with antiviral drugs to stop the virus from replication, however, antiviral drugs are not always effective at preventing...
or stopping replication of the virus. Antibiotics are not effective against viral infections. As such, viral infections must generally run a natural course and be fought off by the body. However, the body sometimes has trouble fighting off the virus and the virus could promote subsequent infection by a bacterium or fungus.

Common fungal infections include ringworm, Athlete's foot, vaginal yeast infections, Candida infections, etc. Fungal infections are caused by a fungus that has either been transmitted through contact or has grown as a result of certain conditions of the body. Fungal infections are treated with anti-fungal medications that may be applied as a cream or taken orally, however, these medications are also sometimes not effective.

Infections can occur in many ways including during or following surgery and the implications can be very serious. Antibiotics have been used prior to and after surgery to treat infections, however, as stated above, antibiotics are not always effective and if the pathogen is not bacterial, the antibiotic will not be effective. In addition, if an infection occurs during surgery, a systemically administered antibiotic may not be effective quickly enough and a physician may need to access the site of infection to try to treat the infection.

One pharmaceutical that is known to the medical profession is clonidine, which is widely recognized as an antihypertensive agent that acts as an agonist on the alpha-2-adrenergic receptor and as a neural receptor agonist. In general, clonidine, also referred to as 2,6-dichloro-N-2-imidazolidinylidenebenzenamine (C₉H₉Cl₂N₃) may be represented by the following chemical structure:

![Chemical structure of clonidine]

However, to date it has not been widely appreciated for its antimicrobial properties. Thus, there is a need to develop effective clonidine compositions that have antimicrobial properties.

**SUMMARY**

New clonidine compositions and methods are provided that have antimicrobial properties. In some embodiments, the clonidine compositions can effectively prevent, treat or reduce infections. The clonidine compositions can be provided as a drug depot.
The drug depot can be a film, coating or strip alone or can be applied to a medical device (e.g., catheter, artificial implant, valve, hardware, etc.). In some embodiments, the drug depot(s) can be easily delivered to the target site (e.g., wound site, abdomen, synovial joint, at or near the spinal column, etc.) and reduce, prevent or treat infections.

In one embodiment, there is an antimicrobial pharmaceutical formulation comprising: clonidine, wherein the clonidine comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer. The pharmaceutical composition may, for example, be part of a drug depot.

The drug depot may: (i) consist of only the clonidine (or one or more of its pharmaceutically acceptable salts) and the biodegradable polymer(s); or (ii) consist essentially of the clonidine (and/or one or more of its pharmaceutically acceptable salts) and the biodegradable polymer(s); or (iii) comprise the clonidine (and/or one or more of its pharmaceutically acceptable salts), the biodegradable polymer(s) and one or more other active ingredients, surfactants, excipients or other ingredients, medical devices or combinations thereof. When there are other active ingredients, surfactants, excipients or other ingredients or combinations thereof in the formulation, in some embodiments these other compounds or combinations thereof comprise less than 50 wt.% less than 40 wt.%, less than 30 wt.%, less than 20 wt.%, less than 19 wt.%, less than 18 wt.%, less than 17 wt.%, less than 16 wt.%, less than 15 wt.%, less than 14 wt.%, less than 13 wt.%, less than 12 wt.%, less than 11 wt.%, less than 10 wt.%, less than 9 wt.%, less than 8 wt.%, less than 7 wt.%, less than 6 wt.%, less than 5 wt.%, less than 4 wt.%, less than 3 wt.%, less than 2 wt.%, less than 1 wt. % or less than 0.5 wt.%.

In another embodiment, a method of making an antimicrobial coated medical device is provided, the method comprising coating the medical device with clonidine in an amount from about 0.1 wt.% to about 30 wt.% based on the total weight of the polymer coating or film, wherein the coating or film is capable of releasing the clonidine over a period of at least one day.

According to another embodiment, there is a pharmaceutical formulation comprising: clonidine, wherein the clonidine is in the form of a base and/or hydrochloride salt, and comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer, wherein the at least one biodegradable polymer comprises poly(lactic-co-glycolide) (or poly(lactic-co-glycolic acid)) or poly(orthoester) or a
combination thereof, and said at least one biodegradable polymer comprises at least 70 wt.% of said formulation.

According to another embodiment, there is an implantable drug depot for reducing, preventing or treating infection in a patient in need of such treatment, the implantable drug depot comprising clonidine in an amount from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer.

According to another embodiment, there is an implantable drug depot for reducing, preventing or treating infection in a patient in need of such treatment, the implantable drug depot comprising clonidine hydrochloride in an amount of from about 1 wt.% to about 20 wt.% of the drug depot, and at least one biodegradable polymer, wherein the at least one biodegradable polymer comprises poly(lactic-co-glycolic acid) (or poly(lactic-co-glycolic acid)) or poly(orthoester) or a combination thereof, and said at least one biodegradable polymer comprises at least 80 wt.% of said formulation.

According to another embodiment, there is an implantable drug depot for reducing, preventing or treating infection in a patient in need of such treatment, the implantable drug depot comprising clonidine hydrochloride in an amount of from about 0.5 wt.% to about 20 wt.% of the drug depot, and at least one polymer, wherein the at least one polymer comprises one or more of poly(lactide-co-glycolide), poly(orthoester), D-lactide, D,L-lactide, L-lactide, D,L-lactide-caprolactone, and D,L-lactide-co-glycolide-co-caprolactone.

According to another embodiment there is a method for treating infection, wherein said method comprises implanting a drug depot in an organism to reduce, prevent or treat infection, wherein said drug depot comprises clonidine in an amount from about 0.1 wt.% to about 30 wt.% of the drug depot, and at least one biodegradable polymer.

According to another embodiment, there is a method of making an antimicrobial implant, the method comprising coating the implant with a polymer containing clonidine.

According to another embodiment, there is a method for treating infection, wherein said method comprises: administering a pharmaceutical composition comprising clonidine and at least one biodegradable polymer to an organism, wherein said clonidine comprises from about 0.1 wt.% to about 30 wt.% of the drug depot.

According to another embodiment, an implantable drug depot for reducing, preventing or treating infection in a patient in need of such treatment is provided, the implantable drug depot comprising clonidine in an amount from about 0.1 wt.% to about
30 wt.% of the drug depot, and at least one biodegradable polymer, wherein the drug depot is capable of releasing clonidine over a period of at least three days to one or more months.

Additional features and advantages of various embodiments will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of various embodiments. The objectives and other advantages of various embodiments will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

**BRIEF DESCRIPTION OF THE DRAWINGS**

In part, other aspects, features, benefits and advantages of the embodiments will be apparent with regard to the following description, appended claims and accompanying drawings where:

- Figure 1 is a graphic representation of an *in vitro* release of clonidine from three pellet doses as measured by percentage release.
- Figure 2 is a graphic representation of the calculated daily release of clonidine from three pellet doses as measured by micrograms released *in vitro*.
- Figure 3 is a graphic representation of clonidine HCl release for various formulations as measured by the cumulative clonidine released percentage.
- Figure 4 is a graphic representation of the cumulative *in vitro* release profile for certain clonidine formulations.
- Figure 5 is a graphic representation of the cumulative release profiles for certain irradiated clonidine HCl formulations.
- Figure 6 is a graphic representation of certain calculated daily release measurements of clonidine from 2/3/4 pellets doses.
- Figure 7 is a graphic representation of the calculated daily release of clonidine from certain three pellet doses.
- Figure 8 is a graphic representation of the cumulative *in vitro* release profile of clonidine from certain coaxial formulations.
- Figure 9 is a graphic representation of the cumulative *in vitro* release profile for certain irradiated clonidine formulations.
Figure 10 is a graphic representation of the calculated daily release of clonidine for certain three pellet dose formulations.

Figure 11 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 12 is a graphic representation of the micrograms of clonidine released for certain 3/4/5 pellet dose formulations.

Figure 13 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 14 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 15 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 16 is a graphic representation of the cumulative release percentage of clonidine for one formulation.

Figure 17 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 18 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 19 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 20 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations.

Figure 21 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations.

Figure 22 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations.

Figure 23 is a graphic representation of the cumulative elution percentage of clonidine for one formulation.

Figure 24 is a graphic representation of the cumulative release percentage of clonidine for one formulation.

Figure 25 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations.
Figure 26 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations.

Figure 27 is a graphic representation of the cumulative elution percentage of clonidine for one formulation.

Figure 28 is a graphic representation of the cumulative release percentage of clonidine for certain formulations.

Figure 29 is a graphic representation of the cumulative release percentage of clonidine for one formulation.

Figure 30 is a graphic representation of the cumulative release percentage of clonidine for one formulation.

It is to be understood that the figures are not drawn to scale. Further, the relation between objects in a figure may not be to scale, and may in fact have a reverse relationship as to size. The figures are intended to bring understanding and clarity to the structure of each object shown, and thus, some features may be exaggerated in order to illustrate a specific feature of a structure.

**DETAILED DESCRIPTION**

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing quantities of ingredients, percentages or proportions of materials, reaction conditions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be
understood to encompass any and all subranges subsumed therein. For example, a range of "1 to 10" includes any and all subranges between (and including) the minimum value of 1 and the maximum value of 10, that is, any and all subranges having a minimum value of equal to or greater than 1 and a maximum value of equal to or less than 10, e.g., 5.5 to 10.

Definitions

It is noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the," include plural referents unless expressly and unequivocally limited to one referent. Thus, for example, reference to "a drug depot" includes one, two, three or more drug depots.

A "drug depot" is the composition in which the clonidine is administered to the body. Thus, a drug depot may comprise a physical structure to facilitate implantation and retention in a desired site (e.g., a disc space, a spinal canal, a tissue of the patient, particularly at or near a site of infection, etc.). In some embodiments, the drug depot may be a coating, film, or strip alone or it may be on or in another medical device to impart antimicrobial properties to it. The drug depot may also comprise the drug itself. The term "drug" as used herein is generally meant to refer to any substance that alters the physiology of a patient. The term "drug" may be used interchangeably herein with the terms "therapeutic agent," "therapeutically effective amount," and "active pharmaceutical ingredient" or "API." It will be understood that unless otherwise specified a "drug" formulation may include more than one therapeutic agent, wherein exemplary combinations of therapeutic agents include a combination of two or more drugs. The drug provides a concentration gradient of the therapeutic agent for delivery to the site. In various embodiments, the drug depot provides an optimal drug concentration gradient of the therapeutic agent at a distance of up to about 0.01 cm to about 5 cm from the administration site and comprises clonidine. This will impart antimicrobial properties and inhibit, or kill the growth of microbes. A drug depot may also include a pump or pellet.

A "therapeutically effective amount" or "effective amount" is such that when administered, the drug results in alteration of the biological activity, such as, for example, inhibition of infection, reduction or alleviation of infection, etc. The dosage administered to a patient can be as single or multiple doses depending upon a variety of factors, including the drug's administered pharmacokinetic properties, the route of administration, patient conditions and characteristics (sex, age, body weight, health, size, etc.), extent of
symptoms, concurrent treatments, frequency of treatment and the effect desired. In some embodiments the formulation is designed for immediate release. In other embodiments the formulation is designed for sustained release. In other embodiments, the formulation comprises one or more immediate release surfaces and one or more sustained release surfaces.

In various embodiments, the effective amount is an antimicrobial amount, which refers to the use of the compounds, products, or compositions wherein the clonidine has antimicrobial activity to create a composition or solution capable of fulfilling its original purpose, based upon the other ingredients, and also of providing antimicrobial protection when coated or part of a medical device (e.g., film, coating, strip, depot, etc.).

As used herein, the term "antimicrobial" is used in its general sense to refer to the property of the described compound, product, composition or article to prevent or reduce the growth, spread, formation or other livelihood of organisms such as bacteria, viruses, protozoa, molds, fungi (including algae), or other organisms. The term antimicrobial includes clonidine that kills (deactivate) or slows the growth of microbes. The clonidine may have antibacterial activity (which kill or inhibit bacteria), antiviral activity (which kills or inhibits viruses), antifungal activity (which kills or inhibits fungi), and antiparasitic activity (which kills or inhibits parasites). In various embodiments, the antimicrobial comprises clonidine in a polymer in an amount of from about 0.1 wt.% to about 30 wt.% based on the total weight of the polymer.

In various embodiments, the effective amount of clonidine imparts antimicrobial activity to compositions or solutions where no such activity previously existed, or to the increase of antimicrobial activity wherein the starting compositions or solutions inherently possessed antimicrobial activity. In various embodiments, the effective amount inhibits or kills microbes (e.g., bacteria, viruses, fungi, yeast, protozoa, parasites, and/or molds). In various embodiments, the antimicrobial composition comprises clonidine in a polymer in an amount of from about 0.1 wt.% to about 30 wt.% based on the total weight of the polymer.

This activity extends to antimicrobial kill of organisms like bacteria, fungi, and viruses, e.g., HIV (human immunodeficiency virus), hepatitis B virus (HBV), influenza A virus, the rhinovirus, hepatitis C virus (HCV), tuberculosis, Avian influenza, SARS, Staphylococcus aureus including methicillin resistant Staphylococcus aureus, (MRSA),...
Streptococcus species, vancomycin-resistant enterococci (VRE), Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Fusarium species, Salmonella species, Shigella species, Yersinia species, Bacillus species, Norwalk virus, Campylobacteria, Clostridium botulinum, C. perfringens, Listeria monocytogenes, Penicillium, Aspergillus, and, tuberculosis other pathogens. In some embodiments, the clonidine inhibits gram positive bacteria and/or gram negative bacteria, including anaerobic and/or aerobic bacteria.

Some examples of parasites include, but are not limited to, Toxoplasma sp. e.g., Toxoplasma gondii, Trypanosomes, Leishmania parasites, Plasmodium falciparum, or the like.

In some embodiments, the infection is caused by eukaryotic cells. In some embodiments, the infection is a fungal infection. A fungal infection includes any infection caused by fungi. Fungi include any eukaryotic single celled organism characterized by the absence of chlorophyll and by the presence of a rigid cell wall. The fungi of interest in the present specification are clinically significant fungi, i.e. fungi which grow in or on mammals. Examples of clinically significant fungi include Cryptococcus species, Candida albicans, Rhizopus species, Aspergillus fumigatus, Penicillium species, Absidia species, Scedosporium apiospermum, Phialophora verrucosa, Cunninghamella species, Tricotherium species, Ulocladium species, and Fonsecaea species. In some embodiments, the fungus comprises Candidas or Aspergillus or Magnaporthe or Fusarium infections. More specifically, in some embodiments, the infection can be caused by Candidas or Aspergillus or Magnaporthe or Fusarium, for example, Candida albicans, Candida tropicalis, Candida parapsilokis, Candida krusei, Candida dubliniensis, Cryptococcus neoformans, A. fumigatus, A. flavus, A. niger, Magnaporthe grisea or Fusarium moniforme or combinations thereof.

In various embodiments, the microbes that the clonidine may inhibit growth of or kill are the microorganisms listed in Table A.

Table A

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Bacteria</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus niger</td>
<td>Aspergillus fumigatus</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Aspergillus versicolor</td>
<td>Stapylococcus epidermidis</td>
<td>Avian Flu</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>Enterobacter agglomerans</td>
<td>HIV B</td>
</tr>
<tr>
<td></td>
<td>Acinetobacter calcoaceticus</td>
<td>SARS</td>
</tr>
</tbody>
</table>
Aspergillus terreus Stapylococcus aureus H1N1
Penicillium chrysogenum Stapylococcus aureus Swine Flu
Penicillium albicans Klebsiella pneumoniae Influenza
Penicillium citrinum Pseudomonas aeruginosa
Penicillium elegans Pseudomonas aeruginosa
Penicillium funiculosum Streptococcus faecalis
Penicillium humicola Pseudomonas aeruginosa
Penicillium notatum Escherichia coli
Penicillium variabile Escherichia coli
Mucor sp. Proteus mirabilis
Candida sp. (e.g., canidia albicans) Streptococci sp.
Trichophyton mentagrophytes Citrobacter diversus 1
Trichophyton interdigitalis Salmonella typhosa
Trichoderma flavus Proteus mirabilis 1
Ch suntium globusum Salmonella choleraesuis
Rhizopus nigricans Corynebacterium bovis
Cladosporium herbarum Mycobacterium smegmatis
Aureobasidium pullulans Mycobacterium tuberculosis
Fusarium nigrum Brucella canina
Fusarium solani Brucella abortus
Gliocladium roseum Brucella suis
Oosopa lactis Streptococcus mutans
Stachybotrys chartarum Bacillus subtilis
                Bacillus cereus
Algae Clostridium perfringens
Oscillatoria borneti LB 143 Haemophilus influenzae
Anabaena cylindrica B-1446-1C Haemophilus suis
Selenastrum gracile B-325 Lactobacillus casei
Pleurococcus sp. LB 11 Leuconostoc lactis
Schenedesmus quadricauda Listeria monocytogenes
Gonium sp. LB 9c Propionibacterium acnes
Volvox sp. LB 9 Proteus vulgaris
Chlorella vulgaris Pseudomonas cepacia
                Pseudomonas fluorescens
Yeast Xanthomonas campestris
Saccharomyces cerevisiae
Candida albicans

A “depot” includes but is not limited to capsules, microspheres, microparticles, microcapsules, microfibers particles, nanospheres, nanoparticles, coating, film, strip, matrices, wafers, pills, pellets, emulsions, liposomes, micelles, gels, or other delivery compositions or a combination thereof. Suitable materials for the depot are ideally
pharmaceutically acceptable biodegradable and/or any bioabsorbable materials that are preferably FDA approved or GRAS materials. These materials can be polymeric or non-polymeric, as well as synthetic or naturally occurring, or a combination thereof.

The term "biodegradable" includes that all or parts of the drug depot will degrade over time by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body. In various embodiments, "biodegradable" includes that the depot (e.g., microparticle, microsphere, strip, coating, film, etc.) can break down or degrade within the body to non-toxic components after or while a therapeutic agent has been or is being released. By "bioerodible" it is meant that the depot will erode or degrade over time due, at least in part, to contact with substances found in the surrounding tissue, fluids or by cellular action. By "bioabsorbable" it is meant that the depot will be broken down and absorbed within the human body, for example, by a cell or tissue. "Biocompatible" means that the depot will not cause substantial tissue irritation or necrosis at the target tissue site.

In some embodiments, the drug depot has pores that allow release of the drug from the depot. The drug depot will allow fluid in the depot to displace the drug. However, cell infiltration into the depot will be prevented by the size of the pores of the depot. In this way, in some embodiments, the depot should not function as a tissue scaffold and allow tissue growth. Rather, the drug depot will solely be utilized for drug delivery. In some embodiments, the pores in the drug depot will be less than 250 to 500 microns. This pore size will prevent cells from infiltrating the drug depot and laying down scaffolding cells. Thus, in this embodiment, drug will elute from the drug depot as fluid enters the drug depot, but cells will be prevented from entering. In some embodiments, where there are little or no pores, the drug will elute out from the drug depot by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the human body.

The phrases "sustained release" and "sustain release" (also referred to as extended release or controlled release) are used herein to refer to one or more therapeutic agent(s) that is introduced into the body of a human or other mammal and continuously or continually releases a stream of one or more therapeutic agents over a predetermined time period and at a therapeutic level sufficient to achieve a desired therapeutic effect (e.g., inhibiting microorganism growth) throughout the predetermined time period. Reference to a continuous or continual release stream is intended to encompass release that occurs as
the result of biodegradation in vivo of the drug depot, or a matrix or component thereof, or as the result of metabolic transformation or dissolution of the therapeutic agent(s) or conjugates of therapeutic agent(s).

The phrase "immediate release" is used herein to refer to one or more therapeutic agent(s) that is introduced into the body and that is allowed to dissolve in or become absorbed at the location to which it is administered, with no intention of delaying or prolonging the dissolution or absorption of the drug.

The two types of formulations (sustain release and immediate release) may be used in conjunction. The sustained release and immediate release may be in one or more of the same depots. In various embodiments, the sustained release and immediate release may be part of separate depots. For example a bolus or immediate release formulation of clonidine may be placed at or near the target site where the infection is or where prevention of microbial growth is desired and a sustain release formulation may also be placed at or near the same site. Thus, even after the bolus becomes completely accessible, the sustain release formulation would continue to provide the active ingredient for the intended tissue.

In various embodiments, the drug depot can be designed to cause an initial burst dose of therapeutic agent within the first twenty-four to seventy-two hours after implantation. "Initial burst" or "burst effect" or "bolus dose" refers to the release of therapeutic agent from the depot during the first twenty-four hours to seventy-two hours after the depot comes in contact with an aqueous fluid (e.g., synovial fluid, cerebral spinal fluid, etc.). The "burst effect" is believed to be due to the increased release of therapeutic agent from the depot. In alternative embodiments, the depot (e.g., gel) is designed to avoid or reduce this initial burst effect (e.g., by applying an outer polymer coating to the depot).

"Treating" or "treatment" of a disease or condition refers to executing a protocol that may include administering one or more drugs to a patient (human, other normal or otherwise or other mammal), in an effort to alleviate signs or symptoms of the infection disease or condition. Alleviation can occur prior to signs or symptoms of the disease or condition appearing, as well as after their appearance. Thus, treating or treatment includes preventing or prevention of disease or undesirable condition (e.g. infection). In addition, treating or treatment does not require complete alleviation of signs or symptoms, does not
require a cure, and specifically includes protocols that have only a marginal effect on the patient. "Reducing infection" includes a decrease in infection and does not require complete alleviation of infection signs or symptoms, and does not require a cure. In various embodiments, reducing infection includes even a marginal decrease in infection.

By way of example, the administration of the effective dosage of clonidine may be used to prevent, treat or relieve the symptoms of infection for different diseases or conditions. These disease/conditions may comprise oral-facial diseases, bursitis, tendonitis, chronic inflammatory diseases, including, but not limited to autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, osteoarthritis, insulin dependent diabetes (type I diabetes), systemic lupus erythematosis and psoriasis, immune pathologies induced by infectious agents, such as helminthic (e.g., leishmaniasis) and certain viral infections, including HIV, and bacterial infections, including Lyme disease, tuberculosis and lepromatous leprosy, tissue transplant rejection, graft versus host disease and atopic conditions, such as asthma and allergy, including allergic rhinitis, gastrointestinal allergies, including food allergies, eosinophilia, conjunctivitis or glomerular nephritis.

In various embodiments, the clonidine may be used to reduce, treat, or prevent infection by locally administering the clonidine at one or more target tissue sites (e.g., nerve root, dorsal root ganglion, focal sites of pain, at or near the spinal column, etc.).

In some embodiments, the drug depot can be used to treat one or more target tissue sites that are involved in the infection, such as for example, rheumatoid arthritis, osteoarthritis, sciatica, carpal tunnel syndrome, lower back pain, lower extremity pain, upper extremity pain, cancer, tissue pain and pain associated with injury or repair of cervical, thoracic, and/or lumbar vertebrae or intervertebral discs, rotator cuff, articular joint, TMJ, tendons, ligaments, muscles, a surgical wound site or an incision site or the like.

In some embodiments the compositions and methods can be used to "reduce the risk of infection", which as used herein, means to lower the likelihood or probability of an infection occurring due to, for example, a surgical or invasive medical procedure, for example when the patient or subject is predisposed to an infection or at risk of contracting an infection. Infections can be detected by the patient exhibiting its signs and symptoms, such as for example, aches, chills, fever, nausea, vomiting, weakness, redness, swelling, pain, discharge or the like. After the clonidine composition is implanted, in some
embodiments, these signs and symptoms of infection will reduce and/or resolve. In some embodiments, the clonidine can be used to reduce, prevent, or treat a bone infection, such as for example, osteomyelitis.

The terms "surgical procedure" or "invasive medical procedure", as used herein mean any surgical procedure, as understood by one of ordinary skill in the art or other medical procedure that involves an entry or contact with the patient or subject, or that potentially compromises the integrity of the skin or other tissues. Nonlimiting examples of surgical procedures include: cardiothoracic surgery, vascular surgery, colon surgery, hip or knee arthroplasty, biliary surgery, vaginal or abdominal hysterectomy, percutaneous gastronomy, repair of long bone fractures, dental surgery, oral surgery, ear, nose or throat surgery, spinall surgeries, Cesarean section, etc. Nonlimiting examples of invasive medical procedures include: non-surgical dental procedures (e.g., tooth repairs and cleanings), bladder catheter insertions, insertion of nasal cannulas, biopsies, dermatological procedures, hair transplants, removal of a foreign object from the skin, eye, nasal, ear, or other body cavities, etc. It should be understood that the distinction between surgical procedures and invasive medical procedures can be somewhat arbitrary and is meant to provide a general guideline for defining procedures where a patient or subject could be at risk of contracting an infection from the procedure.

The term "implantable" as utilized herein refers to a biocompatible device (e.g., drug depot, or other medical device) retaining potential for successful placement within a mammal. The expression "implantable device" and expressions of the like import as utilized herein refers to an object implantable through surgery, injection, or other suitable means whose primary function is achieved either through its physical presence or mechanical properties.

"Medical device" includes any device adapted for use in the medical or surgical fields that has a contact surface repeatedly exposed to bodily fluid and/or tissue. Examples of medical devices include, but are not limited to devices insertable into or implantable within the body at a targeted site, or otherwise devices that come into contact with tissue or bodily fluid on or within the body. Specific examples of medical devices include surgical needles, stents, catheters, orthopedic implants, sponges, screws, rods, drug depots (e.g., film, sheet, strip, or the like). The medical device can be any shape as desired (e.g., cube, rhomboid, cone, pyramid, sphere, ellipsoid, tetrahedron, pellet, polyhedron,
other regular shapes, other irregular shapes, and the like), with the shape generally
depending on the application for which the medical device is to be used.

"Localized" delivery includes delivery where one or more drugs are deposited
within a tissue either via drug depot alone or as a coating, film, strip on another medical
device, for example, a nerve root of the nervous system or a region of the brain, or in close
proximity (within about 0.1 cm, or preferably within about 10 cm, for example) thereto.
For example, the drug dose delivered locally from the drug depot may be, for example,
10% , 20% , 30% , 40% , 50% , 60% , 70% , 80% , 90% , 95% , 99% , or 99.9% less than the oral
dosage or injectable dose. In turn, systemic side effects, such as for example, liver
transaminase elevations, hepatitis, liver failure, myopathy, constipation, etc. may be
reduced or eliminated.

The term "mammal" refers to organisms from the taxonomy class "mammalian,"
including but not limited to humans, other primates such as chimpanzees, apes, orangutans
and monkeys, rats, mice, cats, dogs, cows, horses, etc.

The phrase "release rate profile" refers to the percentage of active ingredient that is
released over fixed units of time, e.g., mcg/hr, mcg/day, 10% per day for ten days, etc. As
persons of ordinary skill know, a release rate profile may, but need not, be linear. By way
of a non-limiting example, the drug depot may be a ribbon-like fiber that releases the
clonidine over a period of time (see Figures 1-30). These release rate profiles would
impart antimicrobial properties and prevent, or inhibit microbial growth (e.g., inhibit the
growth of gram positive bacteria, gram negative bacteria, fungi, parasites and/or viruses).

The term "solid" is intended to mean a rigid material, while, "semi-solid" is
intended to mean a material that has some degree of flexibility, thereby allowing the depot
to bend and conform to the surrounding tissue requirements.

"Targeted delivery system" provides delivery of one or more drugs depots, gels or
depots dispersed in the gel having a quantity of therapeutic agent that can be deposited at
or near the target site as needed for reduction, prevention and/or treatment of infection.

The abbreviation "DLG" refers to poly(DL-lactide-co-glycolide).

The abbreviation "DL" refers to poly(DL-lactide).

The abbreviation "LG" refers to poly(L-lactide-co-glycolide).

The abbreviation "CL" refers to polycaprolactone.

The abbreviation "DLCL" refers to poly(DL-lactide-co-caprolactone).
The abbreviation "LCL" refers to poly(L-lactide-co-caprolactone).
The abbreviation "G" refers to polyglycolide.
The abbreviation "PEG" refers to poly(ethylene glycol).
The abbreviation "PLGA" refers to poly(lactide-co-glycolide) also known as poly(lactic-co-glycolic acid), which are used interchangeably.
The abbreviation "PLA" refers to polylactide.
The abbreviation "POE" refers to poly(orthoester).

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying drawings. While the invention will be described in conjunction with the illustrated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents that may be included within the invention as defined by the appended claims.

In one embodiment, an implantable drug depot having antimicrobial properties for reducing, preventing or treating an infection is provided in a patient in need of such treatment, the implantable drug depot comprising clonidine in an amount from about 0.1 wt.% to about 30 wt.% of the drug depot, and at least one biodegradable polymer, wherein the drug depot is capable of releasing clonidine over a period of at least one day to prevent or inhibit microbial growth.

In another embodiment, an implantable drug depot is provided having antimicrobial properties for reducing, preventing or treating infection in a patient in need of such treatment, the implantable drug depot comprising clonidine hydrochloride or base in an amount of from about 0.1 wt.% to about 30 wt.% of the drug depot, and at least one polymer, wherein the at least one polymer comprises one or more of poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, polyorthoester (POE), D,L-lactide, L-lactide, D,L-lactide-co-e-caprolactone, D,L-lactide-co-glycolide-co-e-caprolactone or a combination thereof.

In another embodiment, a method of making an antimicrobial coated medical device is provided, the method comprising coating the medical device with a drug depot having antimicrobial properties, the drug depot comprising clonidine in an amount from about 0.1 wt.% to about 30 wt.% of the drug depot and at least one biodegradable
polymer, wherein the drug depot is capable of releasing the clonidine over a period of at least one day.

**Clonidine**

When referring to clonidine, unless otherwise specified or apparent from context it is understood that the inventors are also referring to pharmaceutically acceptable salts. One well-known commercially available salt for clonidine is its hydrochloride salt. Some other examples of potentially pharmaceutically acceptable salts include those salt-forming acids and bases that do not substantially increase the toxicity of a compound, such as, salts of alkali metals such as magnesium, potassium and ammonium, salts of mineral acids such as hydriodic, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycolic, gluconic, gulonic, succinic, arylsulfonic, e.g., p-toluenesulfonic acids, and the like. In some embodiments, the clonidine is clonidine chlorohydrate.

Further, when referring to clonidine the active ingredient may not only be in the salt form, but also in the base form (e.g., free base or clonidine base). In various embodiments, the clonidine may be combined with polymers under conditions in which there is not severe polymer degradation, as may be seen upon heat or solvent processing that may occur with PLGA or PLA. By way of a non limiting example, when formulating clonidine with poly(orthoesters) (POE) it may be desirable to use the clonidine base formulation. By contrast, when formulating clonidine with PLGA, it may be desirable to use the HCl salt form. In some embodiments, the clonidine may be incorporated into a polymer core with a polymer and then coated with the same or different polymer.

The clonidine or its pharmaceutically acceptable salt may be administered with a muscle relaxant. Exemplary muscle relaxants include by way of example and not limitation, alcuronium chloride, atracurium besylate, baclofen, carbamate, carbolonium, carisoprodol, chlorphenesin, chlorzoxazone, cyclobenzaprine, dantrolene, decamethonium bromide, fazadinium, gallamine triethiodide, hexafluorenium, meladrazine, mephenisin, metaxalone, methocarbamol, metocurine iodide, pancuronium, pridinol mesylate, styramate, suxamethonium, suxethonium, thiocolchicoside, tizanidine, tolperisone, tubocurarine, vecuronium, or combinations thereof.
The drug depot may comprise other therapeutic agents in addition to the clonidine as well. These therapeutic agents, in various embodiments, block the transcription or translation of TNF-a or other proteins in the inflammation cascade. Suitable therapeutic agents include, but are not limited to, integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, CTLA4-Ig agonists/antagonists (BMS-188667), CD40 ligand antagonists, Humanized anti-IL-6 mAb (MRA, Tocilizumab, Chugai), HMGB-1 mAb (Critical Therapeutics Inc.), anti-IL2R antibodies (daclizumab, basilicimab), ABX (anti IL-8 antibodies), recombinant human IL-10, or HuMax IL-15 (anti-IL 15 antibodies).

Other suitable therapeutic agents include IL-1 inhibitors, such Kineret® (anakinra) which is a recombinant, non-glycosylated form of the human inerleukin-1 receptor antagonist (IL-IRa), or AMG 108, which is a monoclonal antibody that blocks the action of IL-1. Therapeutic agents also include excitatory amino acids such as glutamate and aspartate, antagonists or inhibitors of glutamate binding to NMDA receptors, AMPA receptors, and/or kainate receptors. Interleukin-1 receptor antagonists, thalidomide (a TNF-a release inhibitor), thalidomide analogues (which reduce TNF-a production by macrophages), bone morphogenetic protein (BMP) type 2 and BMP-4 (inhibitors of caspase 8, a TNF-a activator), quinapril (an inhibitor of angiotensin II, which upregulates TNF-a), interferons such as IL-11 (which modulate TNF-a receptor expression), and aurin-tricarboxylic acid (which inhibits TNF-a), may also be useful as therapeutic agents for reducing inflammation. It is further contemplated that where desirable a pegylated form of the above may be used. Examples of still other therapeutic agents include NF kappa B inhibitors such as glucocorticoids, antioxidants, such as dithiocarbamate, and other compounds, such as, for example, sulfasalazine.

Examples of therapeutic agents suitable for use also include, but are not limited to an anti-inflammatory agent, an analgesic agent, or an osteoinductive growth factor or a combination thereof. Anti-inflammatory agents include, but are not limited to, apazone, celecoxib, diclofenac, diflunisal, enolic acids (piroxicam, meloxicam), etodolac, fenamates (mefenamic acid, meclofenamic acid), gold, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, nimesulide, salicylates, sulfasalazine [2-hydroxy-5-[4-[C2-pyridinylamino)sulfonyl]azo]benzoic acid, sulindac, tepoxalin or tolmetin; as well as antioxidants, such as dithiocarbamate, steroids, such as fluocinolone, Cortisol, cortisone,
hydrocortisone, fludrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, beclomethasone, fluticasone or a combination thereof.

Suitable anabolic growth or anti-catabolic growth factors include, but are not limited to, a bone morphogenetic protein, a growth differentiation factor, a LIM mineralization protein, CDMP or progenitor cells or a combination thereof.

Suitable analgesic agents include, but are not limited to, acetaminophen, bupivacaine, lidocaine, opioid analgesics such as buprenorphine, butorphanol, dextromoramide, dezocine, dextropropoxyphene, diamorphine, fentanyl, alfentanil, sufentanil, hydrocodone, hydromorphone, ketobemidone, levomethadyl, meperidine, methadone, morphine, nalbuphine, opium, oxycodone, papaveretum, pethidine, phenoperidine, piritramide, dextropropoxyphene, remifentanil, tilidine, tramadol, codeine, dihydrocodeine, meptazinol, dezocine, eptazocine, flupirtine, amitriptyline, carbamazepine, gabapentin, pregabalin, or a combination thereof.

The clonidine may also be administered with non-active ingredients. These non-active ingredients may have multi-functional purposes including the carrying, stabilizing and controlling the release of the therapeutic agent(s). The sustained release process, for example, may be by a solution-diffusion mechanism or it may be governed by an erosion-sustained process. Typically, the depot will be a solid or semi-solid formulation comprised of a biocompatible material that can be biodegradable.

Exemplary excipients that may be formulated with clonidine in addition to the biodegradable polymer include but are not limited to MgO (e.g., 1 wt.%), 5050 DLG 6E (Lakeshore Biomaterials, Birmingham, AL), 5050 DLG 1A (Lakeshore Biomaterials, Birmingham, AL), mPEG, TBO-Ac, mPEG, Span-65, Span-85, pluronic F127, TBO-Ac, sorbitol, cyclodextrin, maltodextrin, pluronic F68, CaCl, 5050 DLG-7A (Lakeshore Biomaterials, Birmingham, AL) and combinations thereof. In some embodiments, the excipients comprise from about 0.001 wt.% to about 50 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 40 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 30 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 20 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 10 wt.% of the formulation. In some
embodiments, the excipients comprise from about 0.001 wt.% to about 50 wt.% of the formulation. In some embodiments, the excipients comprise from about 0.001 wt.% to about 2 wt.% of the formulation.

In various embodiments, the non-active ingredients will be durable within the tissue site for a period of time equal to or greater than (for biodegradable components) or greater than (for non-biodegradable components) the planned period of drug delivery.

In some embodiments, the depot material may have a melting point or glass transition temperature close to or higher than body temperature, but lower than the decomposition or degradation temperature of the therapeutic agent. However, the pre-determined erosion of the depot material can also be used to provide for slow release of the loaded therapeutic agent(s). Non-biodegradable polymers include but are not limited to PVC and polyurethane.

In some embodiments, the drug depot may not be fully biodegradable. For example, the drug depot may comprise polyurethane, polyurea, polyether(amide), PEBA, thermoplastic elastomeric olefin, copolyester, and styrenic thermoplastic elastomer, steel, aluminum, stainless steel, titanium, metal alloys with high non-ferrous metal content and a low relative proportion of iron, carbon fiber, glass fiber, plastics, ceramics, methacrylates, poly (N-isopropylacrylamide), PEO-PPO-PEO (pluronics) or combinations thereof. Typically, these types of drug depots may need to be removed after a certain amount of time.

In some instances, it may be desirable to avoid having to remove the drug depot after use. In those instances, the depot may comprise a biodegradable material. There are numerous materials available for this purpose and having the characteristic of being able to breakdown or disintegrate over a prolonged period of time when positioned at or near the target tissue. As a function of the chemistry of the biodegradable material, the mechanism of the degradation process can be hydrolytical or enzymatical in nature, or both. In various embodiments, the degradation can occur either at the surface (heterogeneous or surface erosion) or uniformly throughout the drug delivery system depot (homogeneous or bulk erosion).

In various embodiments, the depot may comprise a bioerodible, a bioabsorbable, and/or a biodegradable biopolymer that may provide immediate release, or sustained release of the clonidine. Examples of suitable sustained release biopolymers include but
are not limited to poly (alpha-hydroxy acids), poly (lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyethylene glycol (PEG) conjugates of poly (alpha-hydroxy acids), poly(orthoester)s (POE), polyaspirins, polyphosphagens, collagen, starch, pre-gelatinized starch, hyaluronic acid, chitosans, gelatin, algamates, albumin, fibrin, vitamin E analogs, such as alpha tocopheryl acetate, d-alpha tocopheryl succinate, D,L-lactide, or L-lactide, -caprolactone, dextran, vinylpyrrolidone, polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer (polyactive), PEO-PPO-PAA copolymers, PLGA-PEO-PLGA, PEG-PLG, PLA-PLGA, poloxamer 407, PEG-PLGA-PEG triblock copolymers, SAIB (sucrose acetate isobutyrate) or combinations thereof. As persons of ordinary skill are aware, mPEG may be used as a plasticizer for PLGA, but other polymers/excipients may be used to achieve the same effect. mPEG imparts malleability to the resulting formulations. In some embodiments, these biopolymers may also be coated on the drug depot or other medical device to provide the desired release profile to reduce or prevent microbial growth. In some embodiments, the coating thickness may be thin, for example, from about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 microns to thicker coatings 60, 65, 70, 75, 80, 85, 90, 95, 100, 250, 500, 750, or 1000 microns to delay release of the clonidine from the depot or other medical device (for example, when the clonidine is coated on it). In some embodiments, the range of the coating on the drug depot or other medical device ranges from about 5 microns to about 250 microns or 5 microns to about 200 microns to delay release from the drug depot or other medical device.

In various embodiments, the drug depot comprises poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-e-caprolactone, D,L-lactide-co-glycolide-co-e-caprolactone or a combination thereof.

As persons of ordinary skill in the art are aware, an implantable depot compositions having a blend of polymers with different end groups are used the resulting formulation will have a lower burst index and a regulated duration of delivery. For example, one may use polymers with acid (e.g., carboxylic acid) and ester end groups (e.g., methyl or ethyl ester end groups).

Additionally, by varying the comonomer ratio of the various monomers that form a polymer (e.g., the L/G (lactic acid/glycolic acid) or G/CL (glycolic acid/polycaprolactone)
ratio for a given polymer) there will be a resulting depot composition having a regulated burst index and duration of delivery. For example, a depot composition having a polymer with a L/G ratio of 50:50 may have a short duration of delivery ranging from about two days to about one month; a depot composition having a polymer with a L/G ratio of 65:35 may have a duration of delivery of about two months; a depot composition having a polymer with a L/G ratio of 75:25 or L/CL ratio of 75:25 may have a duration of delivery of about three months to about four months; a depot composition having a polymer ratio with a L/G ratio of 85:15 may have a duration of delivery of about five months; a depot composition having a polymer with a L/CL ratio of 25:75 or PLA may have a duration of delivery greater than or equal to six months; a depot composition having a terpolymer of CL/G/L with G greater than 50% and L greater than 10% may have a duration of delivery of about one month and a depot composition having a terpolymer of CL/G/L with G less than 50% and L less than 10% may have a duration months up to six months. In general, increasing the G content relative to the CL content shortens the duration of delivery whereas increasing the CL content relative to the G content lengthens the duration of delivery. Thus, among other things, depot compositions having a blend of polymers having different molecular weights, end groups and comonomer ratios can be used to create a depot formulation having a lower initial burst and a regulated duration of delivery.

The depot may optionally contain inactive materials such as buffering agents and pH adjusting agents such as potassium bicarbonate, potassium carbonate, potassium hydroxide, sodium acetate, sodium borate, sodium bicarbonate, sodium carbonate, sodium hydroxide or sodium phosphate; degradation/release modifiers; drug release adjusting agents; emulsifiers; preservatives such as benzalkonium chloride, chlorobutanol, phenylmercuric acetate and phenylmercuric nitrate, sodium bisulfate, sodium bisulfite, sodium thiosulfate, thimerosal, methylparaben, polyvinyl alcohol and phenylethyl alcohol; solubility adjusting agents; stabilizers; and/or cohesion modifiers. If the depot is to be placed in the spinal area, in various embodiments, the depot may comprise sterile preservative free material.

The depot can be different sizes, shapes and configurations. There are several factors that can be taken into consideration in determining the size, shape and configuration of the drug depot. For example, both the size and shape may allow for ease in positioning the drug depot at the target tissue site that is selected as the implantation or
injection site. In addition, the shape and size of the system should be selected so as to minimize or prevent the drug depot from moving after implantation or injection. In various embodiments, the drug depot can be shaped like a sphere, a cylinder such as a rod or fiber, a flat surface such as a disc, film or sheet (e.g., ribbon-like) or strip or the like. Flexibility may be a consideration so as to facilitate placement of the drug depot. In various embodiments, the drug depot can be different sizes, for example, the drug depot may be a length of from about 0.5 mm to 5 mm and have a diameter of from about 0.01 to about 4 mm. In various embodiments, as the diameter decreases, the surface area that comes in contact with the bodily fluid of the depot increases and therefore release of the drug from the depot increases. In various embodiments, the drug depot may have a layer thickness of from about 0.005 to 1.0 mm, such as, for example, from 0.05 to 0.75 mm.

Radiographic markers can be included on the drug depot to permit the user to position the depot accurately into the target site of the patient. These radiographic markers will also permit the user to track movement and degradation of the depot at the site over time. In this embodiment, the user may accurately position the depot in the site using any of the numerous diagnostic imaging procedures. Such diagnostic imaging procedures include, for example, X-ray imaging or fluoroscopy. Examples of such radiographic markers include, but are not limited to, barium, calcium phosphate, bismuth, iodine, tantalum, tungsten, and/or metal beads or particles. In various embodiments, the radiographic marker could be a spherical shape or a ring around the depot.

**Gel**

In various embodiments, the clonidine is administered in a gel to the target tissue site or on a medical device and then implanted. The gel may have a pre-dosed viscosity in the range of about 1 to about 2000 centipoise (cps), 1 to about 200 cps, or 1 to about 100 cps. After the gel is administered to the target site, the viscosity of the gel will increase and the gel will have a modulus of elasticity (Young's modulus) in the range of about 1 x 10^2 to about 6 x 10^5 dynes/cm^2, or 2 x 10^4 to about 5 x 10^5 dynes/cm^2, or 5 x 10^4 to about 5 x 10^5 dynes/cm^2.

In one embodiment, a depot comprises an adherent gel comprising clonidine that is evenly distributed throughout the gel. The gel may be of any suitable type, as previously indicated, and should be sufficiently viscous so as to prevent the gel from migrating from the targeted delivery site once deployed; the gel should, in effect, "stick" or adhere to the
targeted tissue site or to the medical device. The gel may, for example, solidify upon contact with the targeted tissue or after deployment from a targeted delivery system. The targeted delivery system may be, for example, a syringe, a catheter, needle or cannula or any other suitable device. The targeted delivery system may inject the gel into or on the targeted tissue site. The therapeutic agent may be mixed into the gel prior to the gel being deployed at the targeted tissue site. In various embodiments, the gel may be part of a two-component delivery system and when the two components are mixed, a chemical process is activated to form the gel and cause it to stick or to adhere to the target tissue.

In various embodiments, a gel is provided that hardens or stiffens after delivery. Typically, hardening gel formulations may have a pre-dosed modulus of elasticity in the range of about 1 x 10^2 to about 3 x 10^5 dynes/cm^2, or 2 x 10^4 to about 2 x 10^5 dynes/cm^2, or 5 x 10^4 to about 1 x 10^5 dynes/cm^2. The post-dosed hardening gels (after delivery) may have a rubbery consistency and have a modulus of elasticity in the range of about 1 x 10^2 to about 2 x 10^6 dynes/cm^2, or 1 x 10^5 to about 7 x 10^5 dynes/cm^2, or 2 x 10^5 to about 5 x 10^5 dynes/cm^2.

In various embodiments, for those gel formulations that contain a polymer, the polymer concentration may affect the rate at which the gel hardens (e.g., a gel with a higher concentration of polymer may coagulate more quickly than gels having a lower concentration of polymer). In various embodiments, when the gel hardens, the resulting matrix is solid but is also able to conform to the irregular surface of the tissue or the medical device (e.g., recesses and/or projections in bone).

The percentage of polymer present in the gel may also affect the viscosity of the polymeric composition. For example, a composition having a higher percentage by weight of polymer is typically thicker and more viscous than a composition having a lower percentage by weight of polymer. A more viscous composition tends to flow more slowly. Therefore, a composition having a lower viscosity may be preferred in some instances. In some embodiments, the polymer comprises 20 wt.% to 90 wt.% of the formulation.

In various embodiments, the molecular weight of the gel can be varied by many methods known in the art. The choice of method to vary molecular weight is typically determined by the composition of the gel (e.g., polymer, versus non-polymer). For example in various embodiments, when the gel comprises one or more polymers, the degree of polymerization can be controlled by varying the amount of polymer initiators.
(e.g. benzoyl peroxide), organic solvents or activator (e.g. DMPT), crosslinking agents, polymerization agent, incorporation of chain transfer or chain capping agents and/or reaction time.

Suitable gel polymers may be soluble in an organic solvent. The solubility of a polymer in a solvent varies depending on the crystallinity, hydrophobicity, hydrogen-bonding and molecular weight of the polymer. Lower molecular weight polymers will normally dissolve more readily in an organic solvent than high-molecular weight polymers. A polymeric gel that includes a high molecular weight polymer tends to coagulate or solidify more quickly than a polymeric composition that includes a low-molecular weight polymer. Polymeric gel formulations that include high molecular weight polymers, also tend to have a higher solution viscosity than a polymeric gel that includes low-molecular weight polymers. In various embodiments, the molecular weight of the polymer can be a wide range of values. The average molecular weight of the polymer can be from about 1000 to about 10,000,000; or about 1,000 to about 1,000,000; or about 5,000 to about 500,000; or about 10,000 to about 100,000; or about 20,000 to 50,000.

When the gel is designed to be a flowable gel, it can vary from low viscosity, similar to that of water, to high viscosity, similar to that of a paste, depending on the molecular weight and concentration of the polymer used in the gel. The viscosity of the gel can be varied such that the polymeric composition can be applied to a patient's tissues or to the medical device, by any convenient technique, for example, by brushing, dripping, injecting, or painting. Different viscosities of the gel will depend on the technique used to apply the composition.

In various embodiments, the gel has an inherent viscosity (abbreviated as "I.V." and units are in deciliters/gram), which is a measure of the gel's molecular weight and degradation time (e.g. a gel with a high inherent viscosity has a higher molecular weight and may have a longer degradation time). Typically, when the polymers have similar components but different MWs, a gel with a high molecular weight provides a stronger matrix and the matrix takes more time to degrade. In contrast, a gel with a low molecular weight degrades more quickly and provides a softer matrix. In various embodiments, the gel has a molecular weight, as shown by the inherent viscosity, from about 0.10 dL/g to about 1.2 dL/g or from about 0.10 dL/g to about 0.40 dL/g. Other IV ranges include but
are not limited to about 0.05 to about 0.15 dL/g, about 0.10 to about 0.20 dL/g, about 0.15 to about 0.25 dL/g, about 0.20 to about 0.30 dL/g, about 0.25 to about 0.35 dL/g, about 0.30 to about 0.35 dL/g, about 0.35 to about 0.45 dL/g, about 0.40 to about 0.45 dL/g, about 0.45 to about 0.50 dL/g, about 0.50 to about 0.70 dL/g, about 0.60 to about 0.80 dL/g, about 0.70 to about 0.90 dL/g, and about 0.80 to about 1.00 dL/g.

In some embodiments, when the polymer materials have different chemistries (e.g., high MW DLG 5050 and low MW DL), the high MW polymer may degrade faster than the low MW polymer.

In various embodiments, the gel can have a viscosity of about 300 to about 5,000 centipoise (cp). In other embodiments, the gel can have a viscosity of from about 5 to about 300 cps, from about 10 cps to about 50 cps, or from about 15 cps to about 75 cps at room temperature. The gel may optionally have a viscosity enhancing agent such as, for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, carboxymethylcellulose and salts thereof, Carbopol, poly-(hydroxyethylmethacrylate), poly-(methoxyethylmethacrylate), poly(methoxymethoxyethyl methacrylate), polymethylmethacrylate (PMMA), methylmethacrylate (MMA), gelatin, polyvinyl alcohols, propylene glycol, mPEG, PEG 200, PEG 300, PEG 400, PEG 500, PEG 600, PEG 700, PEG 800, PEG 900, PEG 1000, PEG 1450, PEG 3350, PEG 4500, PEG 8000 or combinations thereof.

In various embodiments, the gel is a hydrogel made of high molecular weight biocompatible elastomeric polymers of synthetic or natural origin. A desirable property for the hydrogel to have is the ability to respond rapidly to mechanical stresses, particularly shears and loads, in the human body.

Hydrogels obtained from natural sources are particularly appealing because they are more likely to be biocompatible for in vivo applications. Suitable hydrogels include natural hydrogels, such as for example, gelatin, collagen, silk, elastin, fibrin and polysaccharide-derived polymers like agarose, and chitosan, glucosamannan gel, hyaluronic acid, polysaccharides, such as cross-linked carboxyl-containing polysaccharides, or a combination thereof. Synthetic hydrogels include, but are not limited to those formed from polyvinyl alcohol, acrylamides such as polyacrylic acid and poly (acrylonitrile-acrylic acid), polyurethanes, polyethylene glycol (e.g., PEG 3350, PEG 4500, PEG 8000), silicone, polyolefins such as polysobutylene and polyisoprene, copolymers of silicone and
polyurethane, neoprene, nitrile, vulcanized rubber, poly(N-vinyl-2-pyrrolidone), acrylates such as poly(2-hydroxy ethyl methacrylate) and copolymers of acrylates with N-vinyl pyrrolidone, N-vinyl lactams, polyacrylonitrile or combinations thereof. The hydrogel materials may further be cross-linked to provide further strength as needed. Examples of different types of polyurethanes include thermoplastic or thermoset polyurethanes, aliphatic or aromatic polyurethanes, polyetherurethane, polycarbonate-urethane or silicone polyether-urethane, or a combination thereof.

In various embodiments, rather than directly admixing the therapeutic agent into the gel, microspheres may be dispersed within the gel, the microspheres being loaded with clonidine. In one embodiment, the microspheres provide for a sustained release of the clonidine. In yet another embodiment, the gel, which is biodegradable, prevents the microspheres from releasing the clonidine; the microspheres thus do not release the clonidine until they have been released from the gel. For example, a gel may be deployed around a target tissue site (e.g., a nerve root). Dispersed within the gel may be a plurality of microspheres that encapsulate the desired therapeutic agent. Certain of these microspheres degrade once released from the gel, thus releasing the clonidine.

Microspheres, much like a fluid, may disperse relatively quickly, depending upon the surrounding tissue type, and hence disperse the clonidine. In some situations, this may be desirable; in others, it may be more desirable to keep the clonidine tightly constrained to a well-defined target site. The present invention also contemplates the use of adherent gels to so constrain dispersal of the therapeutic agent. These gels may be deployed, for example, in a disc space, in a spinal canal, or in surrounding tissue.

**Delivery**

In some embodiments, it will be appreciated by those with skill in the art that the depot (e.g. coating, film, strips, etc.) can be administered to the target site using a "cannula" or "needle" that can be a part of a drug delivery device e.g., a syringe, a gun drug delivery device, or any medical device suitable for the application of a drug to a targeted organ or anatomic region. The cannula or needle of the drug depot device is designed to cause minimal physical and psychological trauma to the patient.

Cannulas or needles include tubes that may be made from materials, such as for example, polyurethane, polyurea, polyether(amide), PEBA, thermoplastic elastomeric
olefin, copolyester, and styrenic thermoplastic elastomer, steel, aluminum, stainless steel, titanium, metal alloys with high non-ferrous metal content and a low relative proportion of iron, carbon fiber, glass fiber, plastics, ceramics or combinations thereof. The cannula or needle may optionally include one or more tapered regions. In various embodiments, the cannula or needle may be beveled. The cannula or needle may also have a tip style vital for accurate treatment of the patient depending on the site for implantation. Examples of tip styles include, for example, Trephine, Cournand, Veress, Huber, Seldinger, Chiba, Francine, Bias, Crawford, deflected tips, Hustead, Lancet, or Tuohy. In various embodiments, the cannula or needle may also be non-corning and have a sheath covering it to avoid unwanted needle sticks.

The dimensions of the hollow cannula or needle, among other things, will depend on the site for implantation. For example, the width of the epidural space is only about 3-5 mm for the thoracic region and about 5-7 mm for the lumbar region. Thus, the needle or cannula, in various embodiments, can be designed for these specific areas. In various embodiments, the cannula or needle may be inserted using a transforaminal approach in the spinal foramen space, for example, along an inflamed nerve root and the drug depot implanted at this site for treating the condition. Typically, the transforaminal approach involves approaching the intervertebral space through the intervertebral foramina.

Some examples of lengths of the cannula or needle may include, but are not limited to, from about 50 to 150 mm in length, for example, about 65 mm for epidural pediatric use, about 85 mm for a standard adult and about 110 mm for an obese adult patient. The thickness of the cannula or needle will also depend on the site of implantation. In various embodiments, the thickness includes, but is not limited to, from about 0.05 to about 1.655 (mm). The gauge of the cannula or needle may be the widest or smallest diameter or a diameter in between for insertion into a human or animal body. The widest diameter is typically about 14 gauge, while the smallest diameter is about 22 gauge. In various embodiments the gauge of the needle or cannula is about 18 to about 22 gauge.

In various embodiments, like the drug depot and/or gel, the cannula or needle includes dose radiographic markers that indicate location at or near the site beneath the skin, so that the user may accurately position the depot at or near the site using any of the numerous diagnostic imaging procedures. Such diagnostic imaging procedures include, for example, X-ray imaging or fluoroscopy. Examples of such radiographic markers
include, but are not limited to, barium, bismuth, tantalum, tungsten, iodine, calcium, and/or metal beads or particles.

In various embodiments, the needle or cannula may include a transparent or translucent portion that can be visualizable by ultrasound, fluoroscopy, X-ray, or other imaging techniques. In such embodiments, the transparent or translucent portion may include a radiopaque material or ultrasound responsive topography that increases the contrast of the needle or cannula relative to the absence of the material or topography.

The drug depot, and/or medical device to administer the drug may be sterilizable. In various embodiments, one or more components of the drug depot, and/or medical device to administer the drug are sterilized by radiation in a terminal sterilization step in the final packaging. Terminal sterilization of a product provides greater assurance of sterility than from processes such as an aseptic process, which require individual product components to be sterilized separately and the final package assembled in a sterile environment.

Typically, in various embodiments, gamma radiation is used in the terminal sterilization step, which involves utilizing ionizing energy from gamma rays that penetrates deeply in the device. Gamma rays are highly effective in killing microorganisms, they leave no residues nor have sufficient energy to impart radioactivity to the device. Gamma rays can be employed when the device is in the package and gamma sterilization does not require high pressures or vacuum conditions, thus, package seals and other components are not stressed. In addition, gamma radiation eliminates the need for permeable packaging materials.

In various embodiments, electron beam (e-beam) radiation may be used to sterilize one or more components of the device. E-beam radiation comprises a form of ionizing energy, which is generally characterized by low penetration and high-dose rates. E-beam irradiation is similar to gamma processing in that it alters various chemical and molecular bonds on contact, including the reproductive cells of microorganisms. Beams produced for e-beam sterilization are concentrated, highly-charged streams of electrons generated by the acceleration and conversion of electricity. E-beam sterilization may be used, for example, when the drug depot is included in a gel.
Other methods may also be used to sterilize the depot and/or one or more components of the device, including, but not limited to, gas sterilization, such as, for example, with ethylene oxide or steam sterilization.

In various embodiments, a kit is provided that may include additional parts along with the drug depot and/or medical device combined together to be used to implant the drug depot. The kit may include the drug depot device in a first compartment. The second compartment may include a canister holding the drug depot and any other instruments needed for the localized drug delivery. A third compartment may include gloves, drapes, wound dressings and other procedural supplies for maintaining sterility of the implanting process, as well as an instruction booklet. A fourth compartment may include additional cannulas and/or needles. A fifth compartment may include an agent for radiographic imaging. Each tool may be separately packaged in a plastic pouch that is radiation sterilized. A cover of the kit may include illustrations of the implanting procedure and a clear plastic cover may be placed over the compartments to maintain sterility.

In various embodiments, a method for delivering a therapeutic agent into a site of a patient is provided, the method comprising inserting a cannula at or near a target tissue site and implanting the drug depot at the target site beneath the skin of the patient and brushing, dripping, injecting, or painting the gel in the target site to hold or have the drug depot adhere to the target site. In this way unwanted migration of the drug depot away from the target site is reduced or eliminated.

In various embodiments, to administer the gel having the drug depot dispersed therein to the desired site, first the cannula or needle can be inserted through the skin and soft tissue down to the target tissue site and the gel administered at or near the target site. In those embodiments where the drug depot is separate from the gel, first the cannula or needle can be inserted through the skin and soft tissue down to the site of injection and one or more base layer(s) of gel can be administered to the target site. Following administration of the one or more base layer(s), the drug depot can be implanted on or in the base layer(s) so that the gel can hold the depot in place or reduce migration. If required, a subsequent layer or layers of gel can be applied on the drug depot to surround the depot and further hold it in place. Alternatively, the drug depot may be implanted first and then the gel placed around the drug depot to hold it in place. By using the gel, accurate and precise implantation of a drug depot can be accomplished with minimal
physical and psychological trauma to the patient. The gel also avoids the need to suture the drug depot to the target site reducing physical and psychological trauma to the patient.

In various embodiments, when the target site comprises a spinal region, a portion of fluid (e.g., spinal fluid, etc.) can be withdrawn from the target site through the cannula or needle first and then the depot administered (e.g., placed, dripped, injected, or implanted, etc.). The target site will re-hydrate (e.g., replenishment of fluid) and this aqueous environment will cause the drug to be released from the depot. In some embodiments, when several drug depots are to be implanted, they are implanted in a manner that optimizes location, accurate spacing, and drug distribution. The drug depot can be delivered to any site beneath the skin, including, but not limited to, at least one muscle, ligament, tendon, cartilage, spinal disc, spinal foraminal space, near the spinal nerve root, or spinal canal. In some embodiments, the drug depot or medical device coated with clonidine can be implanted next to infected tissue.

The clonidine-based formulation of the present application may be used as medicaments in the form of pharmaceutical preparations. The preparations may be formed in an administration with a suitable pharmaceutical carrier that may be solid or liquid and organic or inorganic, and placed in the appropriate form for parenteral or other administration as desired. As persons of ordinary skill are aware, known carriers include but are not limited to water, saline solution, gelatin, lactose, starches, stearic acid, magnesium stearate, sicaryl alcohol, talc, vegetable oils, benzyl alcohols, gums, waxes, propylene glycol, polyalkylene glycols and other known carriers for medicaments.

Parenteral administration may additionally include, for example, an infusion pump that administers a pharmaceutical composition (e.g., analgesic and anti-inflammatory combination) through a catheter near the spine or one or more inflamed joints, an implantable mini-pump that can be inserted at or near the target site, an implantable controlled release device or sustained release delivery system that can release a certain amount of the statin per hour or in intermittent bolus doses. One example of a suitable pump for use is the SynchroMed® (Medtronic, Minneapolis, Minnesota) pump. This pump has three sealed chambers. One contains an electronic module and battery. The second contains a peristaltic pump and drug reservoir. The third contains an inert gas that provides the pressure needed to force the pharmaceutical composition into the peristaltic pump. To fill the pump, the pharmaceutical composition is injected through the reservoir
fill port to the expandable reservoir. The inert gas creates pressure on the reservoir, and the pressure forces the pharmaceutical composition through a filter and into the pump chamber. The pharmaceutical composition is then pumped out of the device from the pump chamber and into the catheter, which will direct it for deposit at the target site. The rate of delivery of pharmaceutical composition is controlled by a microprocessor. This allows the pump to be used to deliver similar or different amounts of pharmaceutical composition continuously, continually, at specific times, or at set intervals between deliveries.

Another embodiment is directed to a method for treating a mammal suffering from infection, said method comprising administering a therapeutically effective amount of clonidine at a target site beneath the skin. The clonidine (or pharmaceutically acceptable salt) may for example be administered locally to the target tissue site as a drug depot.

In some embodiments, the clonidine is encapsulated in a plurality of depots comprising microparticles, microspheres, microcapsules, and/or microfibers.

In some embodiments there is a method for making an implantable drug depot. The method may comprise combining a biocompatible polymer and a therapeutically effective amount of clonidine or a pharmaceutically acceptable salt thereof and forming the implantable drug depot from the combination.

In some embodiments, the clonidine is suitable for parenteral administration. The term "parenteral" as used herein refers to modes of administration that bypass the gastrointestinal tract, and include for example, intravenous, intramuscular, continuous or intermittent infusion, intraperitoneal, intrasternal, subcutaneous, intra-operatively, intrathecal, intradiscally, peridiscally, epidurally, perispinally, intraarticular injection or combinations thereof. In some embodiments, the injection is intrathecal, which refers to an injection into the spinal canal (intrathecal space surrounding the spinal cord). An injection may also be into a muscle or other tissue.

**Method of Making**

In various embodiments, a method of antimicrobially coating an implant is provided, comprising contacting the implant with an effective amount of clonidine in a polymer for a period of time sufficient to antimicrobially coat the implant. In some embodiments, the clonidine is in an amount from about 0.1 wt.% to about 30 wt.% based on the total weight of the polymer and is coated on the implant.
In various embodiments, the drug depot comprising the clonidine can be made by combining a biocompatible polymer and a therapeutically effective amount of clonidine or pharmaceutically acceptable salt thereof and forming the implantable drug depot from the combination.

Various techniques are available for forming at least a portion of a drug depot from the biocompatible polymer(s), therapeutic agent(s), and optional materials, including solution processing techniques and/or thermoplastic processing techniques. Where solution processing techniques are used, a solvent system is typically selected that contains one or more solvent species. The solvent system is generally a good solvent for at least one component of interest, for example, biocompatible polymer and/or therapeutic agent. The particular solvent species that make up the solvent system can also be selected based on other characteristics, including drying rate and surface tension.

Solution processing techniques include solvent casting techniques, spin coating techniques, web coating techniques, solvent spraying techniques, dipping techniques, techniques involving coating via mechanical suspension, including air suspension (e.g., fluidized coating), ink jet techniques and electrostatic techniques. Where appropriate, techniques such as those listed above can be repeated or combined to build up the depot to obtain the desired release rate and desired thickness.

In various embodiments, a solution containing solvent and biocompatible polymer are combined and placed in a mold of the desired size and shape. In this way, polymeric regions, including barrier layers, lubricious layers, and so forth can be formed. If desired, the solution can further comprise, one or more of the following: clonidine and other therapeutic agent(s) and other optional additives such as radiographic agent(s), etc. in dissolved or dispersed form. This results in a polymeric matrix region containing these species after solvent removal. In other embodiments, a solution containing solvent with dissolved or dispersed therapeutic agent is applied to a pre-existing polymeric region, which can be formed using a variety of techniques including solution processing and thermoplastic processing techniques, whereupon the therapeutic agent is imbibed into the polymeric region.

Thermoplastic processing techniques for forming the depot or portions thereof include molding techniques (for example, injection molding, rotational molding, and so
(forth), extrusion techniques (for example, extrusion, co-extrusion, multi-layer extrusion, and so forth) and casting.

Thermoplastic processing in accordance with various embodiments comprises mixing or compounding, in one or more stages, the biocompatible polymer(s) and one or more of the following: clonidine, optional additional therapeutic agent(s), radiographic agent(s), and so forth. The resulting mixture is then shaped into an implantable drug depot. The mixing and shaping operations may be performed using any of the conventional devices known in the art for such purposes.

During thermoplastic processing, there exists the potential for the therapeutic agent(s) to degrade, for example, due to elevated temperatures and/or mechanical shear that are associated with such processing. For example, clonidine may undergo substantial degradation under ordinary thermoplastic processing conditions. Hence, processing is preferably performed under modified conditions, which prevent the substantial degradation of the therapeutic agent(s). Although it is understood that some degradation may be unavoidable during thermoplastic processing, degradation is generally limited to 10% or less. Among the processing conditions that may be controlled during processing to avoid substantial degradation of the therapeutic agent(s) are temperature, applied shear rate, applied shear stress, residence time of the mixture containing the therapeutic agent, and the technique by which the polymeric material and the therapeutic agent(s) are mixed.

Mixing or compounding biocompatible polymer with therapeutic agent(s) and any additional additives to form a substantially homogenous mixture thereof may be performed with any device known in the art and conventionally used for mixing polymeric materials with additives.

Where thermoplastic materials are employed, a polymer melt may be formed by heating the biocompatible polymer, which can be mixed with various additives (e.g., therapeutic agent(s), inactive ingredients, etc.) to form a mixture. A common way of doing so is to apply mechanical shear to a mixture of the biocompatible polymer(s) and additive(s). Devices in which the biocompatible polymer(s) and additive(s) may be mixed in this fashion include devices such as single screw extruders, twin screw extruders, banbury mixers, high-speed mixers, ross kettles, and so forth.
Any of the biocompatible polymer(s) and various additives may be premixed prior to a final thermoplastic mixing and shaping process, if desired (e.g., to prevent substantial degradation of the therapeutic agent among other reasons).

For example, in various embodiments, a biocompatible polymer is precompounded with a radiographic agent (e.g., radio-opacifying agent) under conditions of temperature and mechanical shear that would result in substantial degradation of the therapeutic agent, if it were present. This precompounded material is then mixed with therapeutic agent under conditions of lower temperature and mechanical shear, and the resulting mixture is shaped into the clonidine containing drug depot. Conversely, in another embodiment, the biocompatible polymer can be precompounded with the therapeutic agent under conditions of reduced temperature and mechanical shear. This precompounded material is then mixed with, for example, a radio-opacifying agent, also under conditions of reduced temperature and mechanical shear, and the resulting mixture is shaped into the drug depot.

The conditions used to achieve a mixture of the biocompatible polymer and therapeutic agent and other additives will depend on a number of factors including, for example, the specific biocompatible polymer(s) and additive(s) used, as well as the type of mixing device used.

As an example, different biocompatible polymers will typically soften to facilitate mixing at different temperatures. For instance, where a depot is formed comprising PLGA or PLA polymer, a radio-opacifying agent (e.g., bismuth subcarbonate), and a therapeutic agent prone to degradation by heat and/or mechanical shear (e.g., clonidine), in various embodiments, the PGLA or PLA can be premixed with the radio-opacifying agent at temperatures of about, for example, 150°C to 170°C. The therapeutic agent is then combined with the premixed composition and subjected to further thermoplastic processing at conditions of temperature and mechanical shear that are substantially lower than is typical for PGLA or PLA compositions. For example, where extruders are used, barrel temperature, volumetric output are typically controlled to limit the shear and therefore to prevent substantial degradation of the therapeutic agent(s). For instance, the therapeutic agent and premixed composition can be mixed/compounded using a twin screw extruder at substantially lower temperatures (e.g., 100-105°C), and using substantially reduced volumetric output (e.g., less than 30% of full capacity, which generally corresponds to a volumetric output of less than 200 cc/min). It is noted that this
processing temperature is well below the melting points of clonidine because processing at or above these temperatures will result in substantial therapeutic agent degradation. It is further noted that in certain embodiments, the processing temperature will be below the melting point of all bioactive compounds within the composition, including the therapeutic agent. After compounding, the resulting depot is shaped into the desired form, also under conditions of reduced temperature and shear.

In other embodiments, biodegradable polymer(s) and one or more therapeutic agents are premixed using non-thermoplastic techniques. For example, the biocompatible polymer can be dissolved in a solvent system containing one or more solvent species. Any desired agents (for example, a radio-opacifying agent, a therapeutic agent, or both radio-opacifying agent and therapeutic agent) can also be dissolved or dispersed in the solvents system. Solvent is then removed from the resulting solution/dispersion, forming a solid material. The resulting solid material can then be granulated for further thermoplastic processing (for example, extrusion) if desired.

As another example, the therapeutic agent can be dissolved or dispersed in a solvent system, which is then applied to a pre-existing medical device (e.g. catheter, screw, rod, artificial hip, valve, heart valve, hardware, etc.) the drug depot (the pre-existing drug depot can be formed using a variety of techniques including solution and thermoplastic processing techniques, and it can comprise a variety of additives including a radio-opacifying agent and/or viscosity enhancing agent), whereupon the therapeutic agent is imbibed on or in the drug depot or other medical device.

Typically, an extrusion process may be used to form the drug depot (coating, film, strip, etc.) comprising a biocompatible polymer(s), therapeutic agent(s) and radio-opacifying agent(s). Co-extrusion may also be employed, which is a shaping process that can be used to produce a drug depot comprising the same or different layers or regions (for example, a structure comprising one or more polymeric matrix layers or regions that have permeability to fluids to allow immediate and/or sustained drug release). Multi-region depots can also be formed by other processing and shaping techniques such as co-injection or sequential injection molding technology.

In various embodiments, the depot that may emerge from the thermoplastic processing (e.g., pellet) is cooled. Examples of cooling processes include air cooling and/or immersion in a cooling bath. In some embodiments, a water bath is used to cool
the extruded depot. However, where a water-soluble therapeutic agent such as clonidine is used, the immersion time should be held to a minimum to avoid unnecessary loss of therapeutic agent into the bath.

In various embodiments, immediate removal of water or moisture by use of ambient or warm air jets after exiting the bath will also prevent re-crystallization of the drug on the depot surface, thus controlling or minimizing a high drug dose "initial burst" or "bolus dose" upon implantation or insertion if this is release profile is not desired.

In various embodiments, the drug depot can be prepared by mixing or spraying the drug with the polymer and then molding the depot to the desired shape. In various embodiments, clonidine is used and mixed or sprayed with the PLGA or PEG550 polymer, and the resulting depot may be formed by extrusion and dried.

In various embodiments, there is a pharmaceutical formulation comprising: clonidine, wherein the clonidine comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer. In some embodiments, the pharmaceutical the clonidine comprises from about 3 wt.% to about 20 wt.%, about 3 wt.% to about 18 wt.%, about 5 wt.% to about 15 wt.% or about 7.5 wt.% to about 12.5 wt.% of the formulation. By way of example, when using a 5% - 15% clonidine composition, the mole ratio of clonidine to polymer would be from approximately 16 - 53 when using an approximately 80 kDalton polymer that has a 267 grams/mole ratio. By way of another example, when using a 5% - 15% clonidine base in the composition, the mole ratio of clonidine base to polymer would be from approximately 18 - 61 with a mole mass of 230g/mol.

In some embodiments, the drug depot comprises at least one biodegradable material in a wt% of about 99.5%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 65%, 60%, 55%, 50%, 45%, 35%, 25%, 20%, 15%, 10%, or 5% based on the total weight of the depot and the remainder is active and/or inactive pharmaceutical ingredients.

In some embodiments, the at least one biodegradable polymer comprises poly(lactic-co-glycolide) (PLGA) or poly(orthoester) (POE) or a combination thereof. The poly(lactic-co-glycolide) may comprise a mixture of polyglycolide (PGA) and polylactide and in some embodiments, in the mixture, there is more polylactide than
polyglycolide. In various embodiments there is 100% polylactide and 0% polyglycolide; 95% polylactide and 5% polyglycolide; 90% polylactide and 10% polyglycolide; 85% polylactide and 15% polyglycolide; 80% polylactide and 20% polyglycolide; 75% polylactide and 25% polyglycolide; 70% polylactide and 30% polyglycolide; 65% polylactide and 35% polyglycolide; 60% polylactide and 40% polyglycolide; 55% polylactide and 45% polyglycolide; 50% polylactide and 50% polyglycolide; 45% polylactide and 55% polyglycolide; 40% polylactide and 60% polyglycolide; 35% polylactide and 65% polyglycolide; 30% polylactide and 70% polyglycolide; 25% polylactide and 75% polyglycolide; 20% polylactide and 80% polyglycolide; 15% polylactide and 85% polyglycolide; 10% polylactide and 90% polyglycolide; 5% polylactide and 95% polyglycolide; and 0% polylactide and 100% polyglycolide.

In various embodiments that comprise both polylactide and polyglycolide; there is at least 95% polylactide; at least 90% polylactide; at least 85% polylactide; at least 80% polylactide; at least 75% polylactide; at least 70% polylactide; at least 65% polylactide; at least 60% polylactide; at least 55%; at least 50% polylactide; at least 45% polylactide; at least 40% polylactide; at least 35% polylactide; at least 30% polylactide; at least 25% polylactide; at least 20% polylactide; at least 15% polylactide; at least 10% polylactide; or at least 5% polylactide; and the remainder of the biopolymer is polyglycolide.

In various embodiments, the drug particle size (e.g., clonidine) is from about 5 to 30 micrometers, however, in various embodiments ranges from about 1 micron to 250 microns may be used. In some embodiments, the biodegradable polymer comprises at least 50 wt.%, at least 60 wt.%, at least 70 wt.%, at least 80 wt.% of the formulation, at least 85 wt.% of the formulation, at least 90 wt.% of the formulation, at least 95 wt.% of the formulation or at least 97 wt.% of the formulation. In some embodiments, the at least one biodegradable polymer and the clonidine are the only components of the pharmaceutical formulation.

In some embodiments, at least 75% of the particles have a size from about 10 micrometer to about 200 micrometers. In some embodiments, at least 85% of the particles have a size from about 10 micrometer to about 200 micrometers. In some embodiments, at least 95% of the particles have a size from about 10 micrometer to about 200 micrometers. In some embodiments, all of the particles have a size from about 10 micrometer to about 200 micrometers.
In some embodiments, at least 75% of the particles have a size from about 20 micrometer to about 180 micrometers. In some embodiments, at least 85% of the particles have a size from about 20 micrometers to about 180 micrometers. In some embodiments, at least 95% of the particles have a size from about 20 micrometer to about 180 micrometers. In some embodiments, all of the particles have a size from about 20 micrometer to about 180 micrometers.

In some embodiments, there is a pharmaceutical formulation comprising: clonidine, wherein the clonidine is in the form of a hydrochloride salt, and comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer, wherein the at least one biodegradable polymer comprises poly(lactide-co-glycolide) (or poly(lactic-co-glycolic acid)) or poly(orthoester) or a combination thereof, and said at least one biodegradable polymer comprises at least 70 wt.% of said formulation.

In some embodiments, the formulation comprises a drug depot that comprises a biodegradable polyorthoester. The mechanism of the degradation process of the polyorthoester can be hydrolytical or enzymatical in nature, or both. In various embodiments, the degradation can occur either at the surface of the drug depot (heterogeneous or surface erosion) or uniformly throughout the drug delivery system depot (homogeneous or bulk erosion). Polyorthoester can be obtained from A.P. Pharma, Inc. (Redwood City, CA) or through the reaction of a bis(ketene acetal) such as 3,9-diethylidene-2,4,8,10-tetraoxospiro[5,5]undecane (DETOSU) with suitable combinations of diol(s) and/or polyol(s) such as 1,4-trans-cyclohexanediethanol and 1,6-hexanediol or by any other chemical reaction that produces a polymer comprising orthoester moieties.

In some embodiments, there are methods for treating infection. These methods comprise: administering a pharmaceutical composition to an organism, wherein said pharmaceutical composition comprises from about 0.1 wt.% to about 30 wt.% of the formulation, and at least one biodegradable polymer. In some embodiments, the loading is
from about 1 wt% to about 25 wt%, or about 5 wt% to about 10 wt%. In some embodiments, the loading is from about 10 wt% to about 20 wt%.

In some embodiments there is a higher loading of clonidine, e.g., at least 20 wt%, at least 30 wt%, at least 40 wt%, at least 50 wt%, at least 60 wt%, at least 70 wt%, at least 80 wt%, or at least 90 wt%.

A strategy of triangulation may be effective when administering these pharmaceutical formulations. Thus, a plurality (at least two, at least three, at least four, at least five, at least six, at least seven, etc.) of drug depots comprising the pharmaceutical formulations may be placed around the target tissue site (e.g., infected tissue or tissue that may become infected) such that the target tissue site falls within a region that is either between the formulations when there are two, or within an area whose perimeter is defined by a set of plurality of formulations.

In some embodiments, the formulations are slightly rigid with varying length, widths, diameters, etc. For example, certain formulations may have a diameter of 0.50 mm and a length of 4 mm. It should be noted that particle size may be altered by techniques such as mort and pestle, jet-drying or jet milling.

In some embodiments, clonidine is released at a rate of 2-3 µg per day for a period of at least three days. In some embodiments, this release rate continues for, at least ten days, at least fifteen days, at least twenty-five days, at least fifty days, at least ninety days, at least one hundred days, at least one-hundred and thirty-five days, at least one-hundred and fifty days, or at least one hundred and eighty days. For some embodiments, 300-425 micrograms of clonidine as formulated with a biopolymer are implanted into a person at or near a target tissue site. If clonidine is implanted at multiple sites that triangulate the target site then in some embodiments, the total amount of clonidine at each site is a fraction of the total 300-425 micrograms. For example, one may implant a single dose of 324 micrograms at one site, or two separate doses of 162 micrograms at two sites, or three separate dose of 108 micrograms at three sites that triangulate the tissue site. It is important to limit the total dosage to an amount less than that which would be harmful to the organism.

The dosage of clonidine may be from approximately 0.0005 to approximately 960 µg/day. Additional dosages of clonidine include from approximately 0.0005 to approximately 900 µg/day; approximately 0.0005 to approximately 500 µg/day;
approximately 0.0005 to approximately 250 µg/day; approximately 0.0005 to approximately 100 µg/day; approximately 0.0005 to approximately 75 µg/day; approximately 0.001 to approximately 70 µg/day; approximately 0.001 to approximately 65 µg/day; approximately 0.001 to approximately 60 µg/day; approximately 0.001 to approximately 55 µg/day; approximately 0.001 to approximately 50 µg/day; approximately 0.001 to approximately 45 µg/day; approximately 0.001 to approximately 40 µg/day; approximately 0.001 to approximately 35 µg/day; approximately 0.0025 to approximately 30 µg/day; approximately 0.0025 to approximately 25 µg/day; approximately 0.0025 to approximately 20 µg/day; approximately 0.0025 to approximately 15 µg/day; approximately 0.0025 to approximately 10 µg/day; approximately 0.0025 to approximately 5 µg/day; and approximately 0.0025 to approximately 2.5 µg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 15 µg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 10 µg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 5 µg/day. In another embodiment, the dosage of clonidine is from approximately 0.005 to approximately 2.5 µg/day. In some embodiments, the amount of clonidine is between 40 and 600 µg/day. In some embodiments, the amount of clonidine is between 200 and 400 µg/day.

In some embodiments, the therapeutically effective dosage amount (e.g., clonidine dose) and the release rate profile are sufficient to reduce, prevent or treat infection for a period of at least one day, for example, 1-90 days, 1-10 days, 1-3 days, 3-7 days, 3-12 days; 3-14 days, 7-10 days, 7-14 days, 7-21 days, 7-30 days, 7-50 days, 7-90 days, 7-140 days, 14-140 days, 3 days to 135 days, 3 days to 180 days, or 3 days to 6 months or 1 year or longer.

In some embodiments the clonidine depot is designed for a bolus dose or burst dose within 1, 2, or 3 days after implantation to provide an immediate release of the clonidine for treatment of infection.

In some embodiments, the clonidine depot is administered parenterally, e.g., by injection. In some embodiments, the injection is intrathecal, which refers to an injection into the spinal canal (intrathecal space surrounding the spinal cord). An injection may also be into a muscle or other tissue. In other embodiments, the clonidine depot is
administered by placement into an open patient cavity during surgery. These embodiments may be used to prevent or treat a post-operative wound infection.

In some embodiments, the drug depot (i) comprises one or more immediate release layer(s) that is capable of releasing about 5% to about 20% of the clonidine or pharmaceutically acceptable salts thereof relative to a total amount of the clonidine or pharmaceutically acceptable salt thereof loaded in the drug depot over a first period of up to 48 hours and (ii) one or more sustain release layer(s) that is capable of releasing about 21% to about 99% of the clonidine or pharmaceutically acceptable salt thereof relative to a total amount of the clonidine or pharmaceutically acceptable salt thereof loaded in the drug depot over a subsequent period of up to 3 days to 90 days, 150 days, 180 days, or 6 months to 1 year.

In some embodiments, there is a drug depot comprising clonidine or clonidine hydrochloride and a polymer, wherein the polymer is one more of various embodiments, the drug depot comprises poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-e-caprolactone, D,L-lactide-co-glycolide-co-e-caprolactone or a combination thereof.

In one exemplary dosing regimen, a rat may be provided with sufficient clonidine in a biodegradable polymer to provide sustain release of 0.240 μg/day for 135 days. The total amount of clonidine that is administered over this time period would be approximately 32.4 μg. In another exemplary dosing regimen, a human is provided with sufficient clonidine in a biodegradable polymer to provide sustain release of 2.4 μg/day for 135 days. The total amount of clonidine that is administered over this time period would be approximately 324 μg.

When using a plurality of pellets, the pellet number is based on the amount of drug loading into a pellet of appropriate size (i.e., 0.5 mm diameter x 4 mm length) and how much drug is needed (e.g., approximately 325 μg clonidine (3 pellets)). In some embodiments there is a polymer that releases a bolus amount of compound over the first few (~5) days before it settles down and releases 2.5 mg/day for 135 days. An exemplary formulation is 5% wt. clonidine, 100 DL 5E (Lakeshore Biomaterials, Birmingham, AL).

In some embodiments, the polymer depots of present invention enable one to provide efficacy of the active ingredient that is equivalent to subcutaneous injections that
deliver more than 2.5 times as much drug. These doses may be useful to reduce, prevent or treat infections.

Having now generally described the invention, the same may be more readily understood through the following reference to the following examples, which are provided by way of illustration and are not intended to limit the present invention unless specified.

EXAMPLES

The examples below show certain particularly advantageous results wherein the initial burst is not too large (i.e., not more than 7% of the load drug in the first five days) and the daily does is approximately 2.4 µg/day ± 0.5 µg/day for 135 days. See e.g., figures 12, 13, 14, and 19. The figures further demonstrate that drug loadings 5 wt.% to 8 wt.% provide advantageous results and levels useful to prevent, treat or inhibit microorganisms.

In Vitro

The In-Vitro Elation Studies were carried out at 37°C in phosphate-buffered saline (PBS, pH 7.4). Briefly, the rods (n = 3) were weighed prior to immersion in 5 mL of PBS. At regular time intervals, the PBS was removed for analysis and replaced with 5 mL of fresh PBS. The PBS-elution buffer was analyzed for clonidine content using UV-Vis spectrometry.

Example 1: Formulation Testing

The inventors prepared a number of clonidine formulations in which they varied the polymer type, drug load, excipient (including some formulations in which there was no excipient), pellet size and processing. These formulations are described below in Table 1, Table 2 and Table 3. A number of tests were performed on these formulations, including in vitro release tests in which the number of micrograms released was measured, as well as the cumulative percentage release of clonidine. The results of these tests appear in Figures 1-30. These levels in vitro elution levels from clonidine shown in Figures 1-30 may be useful in preventing, treating, or inhibiting microorganisms, whether in a depot, film, coating, sheet, or strip alone or on a medical device.

Figure 1 is a graphic representation of a study of the cumulative release by percentage of clonidine HCl sterilized formulations. In Figure 1, the formulations (first three of Table 3) contained: 8.1 wt% clonidine, the remainder 100 DL 5E (the inherent viscosity of the 100 DL was 0.45-0.55 and had an ester end group), or 7.2 wt% clonidine,
the remainder 100 DL 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group) or 5 wt% clonidine, the remainder 100 DL 5E (the inherent viscosity of the 100 DL was 0.45-0.55 and had an ester end group). The formulations with the higher drug loads released the fastest over 70 days, with a cumulative release of 45% and 80%. The formulation with 5% clonidine drug load released drug the longest for over 160 days and had a cumulative release of 95% of the drug.

Figure 2 is an in vitro graphic representation of studies of the percentage daily release profiles of sterilized clonidine formulations of Figure 1 (first three of Table 3) and their cumulative average daily release of the three formulations in micrograms per day. Each drug depot had an initial burst effect with a release of clonidine over 50 meg for the first day. These calculations are based on 3 pellets implanted (which would approximate the dose of clonidine in humans). The pellets ranged in size from 0.5 mm to about 1 mm in diameter and 3-4 mm in length, which would be small enough to place in a needle. The formulations with the higher drug loads released the fastest over 70 days, where the drug dose released was about 5 meg to about 0.1 meg/day after about the first 30 days and the formulation with the lowest drug load of about 5% clonidine released the longest for a period of over 160 days, where the release was consistently between about 5 meg to 0.1 meg/day after about day 30. The target daily dose was 2.4 meg/day and the formulation with the 5% clonidine drug load came closest to this target daily dose.

The In-Vitro Elation Studies were carried out at 37°C in phosphate-buffered saline (PBS, pH 7.4). The rods (n = 3) were weighed prior to immersion in 5 mL of PBS. At regular time intervals, the PBS was removed for analysis and replaced with 5 mL of fresh PBS. The PBS-elution buffer was analyzed for clonidine content using UV-Vis spectrometry.

[0001] Table 1

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<th>Notebook ID</th>
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<th>Processing</th>
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| 13699-31-4 | 7E | 10 | N/A | N/A | Melt extrusion, spray dried drug;

1,6-Hexanediol / 12702-13-4-atCHDM 10 N/A 3 x 3 Melt extrusion
12702-13-4-b75/25 PLGA 10 N/A 3 x 3 Melt extrusion

12702-68-12 75/25 PLGA 5 mPEG 1 x 1 Melt extrusion
12702-68-13 75/25 PLGA 5 TBO-Ac 1 x 1 Melt extrusion
12702-72-1 75/25 PLGA 5 mPEG 1 x 1 Melt extrusion
12702-80-7 75/25 PLGA 10 mPEG 0.75 x 0.75 Melt extrusion
12702-80-8 75/25 PLGA 15 mPEG 0.75 x 0.75 Melt extrusion
13395-3-1 85/15 PLGA 10 mPEG 0.75 x 0.75 Melt extrusion
13395-3-2 85/15 PLGA 15 mPEG 0.75 x 0.75 Melt extrusion
13395-3-3 85/15 PLGA 5 mPEG 0.75 x 0.75 Melt extrusion
13395-15 85/15 PLGA 15 mPEG 0.75 x 0.75 Melt extrusion
13395-20-1 85/15 PLGA 5 Span-85 0.75 x 0.75 Melt extrusion
13395-20-2 85/15 PLGA 5 Pluronic-F127 0.75 x 0.75 Melt extrusion
13395-20-3 85/15 PLGA 5 N/A 0.75 x 0.75 Melt extrusion
13395-21-1 D,L-PLA 5 mPEG 0.75 x 0.75 Melt extrusion
13395-21-2 85/15 PLGA 5 TBO-Ac 0.75 x 0.75 Melt extrusion
13395-24-1 85/15 PLGA 5 Span-65 0.75 x 0.75 Melt extrusion
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Table 2
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Table 3

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<td></td>
<td>100 DL 7E core with 100 DL 5E core8</td>
<td></td>
<td>coaxial extrusion, 4 different coating thicknesses</td>
</tr>
<tr>
<td>00178-76- R1</td>
<td>100DL 5E coating</td>
<td>7.76</td>
<td>coaxial extrusion, 4 different coating thicknesses</td>
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<tr>
<td>00178-76- R2</td>
<td>100 DL 7E core with 100DL 5E</td>
<td>6.92</td>
<td>coaxial extrusion, 4 different coating thicknesses</td>
</tr>
<tr>
<td>00178-76- R3</td>
<td>100 DL 7E core with 100DL 5E</td>
<td>6.76</td>
<td>coaxial extrusion, 4 different coating thicknesses</td>
</tr>
</tbody>
</table>

Notebook: D,L-PLA
with 100DL 5E coating
100 DL 5E core with
00178-79- R1 100DL 5E coating 12.1 coaxial extrusion, thin coat
100 DL 5E core with
00178-80- R1 100DL 5E coating 7.54 coaxial extrusion, different coating thicknesses
100 DL 5E core with
00178-80- R3 100DL 5E coating 8.9 coaxial extrusion, different coating thicknesses
100 DL 5E core with
00178-80- R4 100DL 5E coating 10.0 coaxial extrusion, different coating thicknesses
100 DL 5E core with
00178-77 100 DL 5E repeat of 178-35 (1.0 mm diameter)
00178-78 100 DL 5E repeat of 178-35 (0.8 mm diameter)
00178-81 100 DL 5E repeat of 178-23
00178-87 100 DL 5E Repeat 178-35 (1.0 mm diam)
Repeat 178-35, mechanical mixing, single screw melt extrusion (0.8mm and 1.0 mm diameter)
00178-90 100 DL 5E 5 Coaxial extrusion, thick coating
100 DL 5E core with
00178-91-R1 100DL 5E coating 3.5 Coaxial extrusion, thin coating
100 DL 5E core with
00178-91-R6 100DL 5E coating 7.4 Coaxial extrusion, thin coating
100 DL 5E core with
00178-93-R3 100DL 7E coating 5 Coaxial extrusion, mechanical mixing, thin coating layer
100 DL 5E core with
00178-93-R4 100DL 7E coating 3.8 Coaxial extrusion, mechanical mixing, thick coating layer

The codes within the table for the polymer are explained as follows. The first number or numbers refer to monomer mole percentage ratio of DL-lactide (e.g., polylactide) to glycolide (e.g., poly-glycolide). The letter code that follows the first number refers to the polymer(s) and is the polymer identifier. The second number, which follows the letter code for the polymer, is the target IV designator and is 10 times the midpoint of a range in dl/g. The meanings of certain IV designators are reflected in Table 4.

Table 4

<table>
<thead>
<tr>
<th>IV Target</th>
<th>IV Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designator</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.05 - 0.15</td>
</tr>
<tr>
<td>1.5</td>
<td>0.10 - 0.20</td>
</tr>
<tr>
<td>2</td>
<td>0.15 - 0.25</td>
</tr>
<tr>
<td>2.5</td>
<td>0.20 - 0.30</td>
</tr>
<tr>
<td>3</td>
<td>0.25 - 0.35</td>
</tr>
<tr>
<td>3.5</td>
<td>0.30 - 0.40</td>
</tr>
<tr>
<td>4</td>
<td>0.35 - 0.45</td>
</tr>
<tr>
<td>4.5</td>
<td>0.40 - 0.50</td>
</tr>
</tbody>
</table>
The final letter within the code of the polymer is the end group designator. For examples "E" refers to an ester end group, while "A" refers to an acid end group.

By way of example, 100 DL7E is a polymer that has an inherent viscosity of 0.60-0.80 dL/g. It contains 100% poly(DL-lactide) that has ester end groups. It is available from Lakeshore Biomaterials, Birmingham, Alabama.

Figure 3 is a graphic representation of clonidine HCl release for various formulations (identified in Table 3) as measured by the cumulative clonidine released percentage. In Figure 3, the formulations contained: 10 wt% clonidine, the remainder 100 DL 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group) or 7 wt% clonidine, the remainder 8515 DLG or 5 wt% clonidine, the remainder 100 DL 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group), or 10 wt% clonidine, the remainder 100 DL 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group) and the pellets had small diameters of 0.5 mm. The clonidine formulation with the 10% drug load had a faster release also because it had a smaller diameter, but increased surface area, which allowed a faster drug release. This formulation was dispersed better in the polymer as indicated by the fine mixing legend. The 10% clonidine formulation that was thicker in diameter and was less dispersed throughout the polymer and had a slower release profile. The lower drug load formulation of 7% had a longest release period of over 60 days. In general, increasing the drug load was found to cause a more rapid release of the drug, while the lower drug loads produce a more sustained release effect. All formulations had an initial burst release within 1-2 days of between 5% and 35% cumulative clonidine release.

Figure 4 is a graphic representation of the cumulative in vitro release profile for certain clonidine formulations having different processing. The depots had PLG polymer coatings (poly soin), solvent coating with ethyl acetate (EtOAC), glacial acetic acid (glacial HoAc), or was processed in a nitrogen environment and coated with ethyl acetate as indicated in the legend. The coatings can be applied by methods known in the art (e.g., spray coating, dip coating, etc.) The solvents used to coat the depot can be solvents.
known in the art, for example, acetone, methyl chloride, chloroform, EtOAC, etc. The coatings produced a release from 12 to 35 days, with the fastest release (over 100%) in the formulation that was placed in a nitrogen environment. The longest release was observed for the formulation with the polymer coating and high drug load of clonidine 7 wt%, where drug was released for over 35 days.

Figure 5 is a graphic representation of the cumulative release profiles for certain irradiated clonidine HCl formulations produced as indicated in Table 3. The slowest release was seen for clonidine formulations that were double extruded, where a first batch was mixed and then extruded and then that batch was mixed again and extruded to form the double extruded composition. These formulations had a slower polymer degradation and drug release at about day 30, when compared to formulations that were not double extruded. The formulations with the DLG 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group) polymer had a rapid release and a second burst about day 30.

Figure 6 is a graphic representation of certain calculated daily release measurements of clonidine from 2/3/4 pellets doses. The slowest release was seen for clonidine formulations that were double extruded, where a first batch was mixed and then extruded and then that batch was mixed again and extruded to form the double extruded depot. These formulations had a slower polymer degradation and drug release at about day 30, when compared to formulations that were not double extruded. The formulations with the DLG 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group) polymer had a rapid release and a second burst about day 30. All formulations had an initial burst release on day one from about 10 mcg-50 mcg and the daily release ranged from 0.5 meg to 20 meg/day over about 48 days. The formulations that were not double extruded had a second initial burst at around day 25 to day 35 as indicated by the large peaks. These formulations did not have polymer coatings on the depot and, thus, had high initial bursts ranging from 30 meg- 50 meg.

Figure 7 is a graphic representation of the calculated daily release of clonidine from certain three pellet doses produced as indicated in Table 3. Each pellet (drug depot) had an inner core of drug and polymer and an outer coating with varying degrees of thickness (a thick coating is about 50 ~ 100 microns and a thin coating is about 5 microns to about ~ 20 microns). The thinnest coating (about 20 microns) had the highest initial
burst ranging from about 9-14 meg, which was much less than the uncoated depots from Figure 6. The formulations in Figure 7 were designed to decrease the initial burst with the outer coating. In general, the thicker the coating on the polymer drug core, the slower the drug release from the depot.

Figure 8 is a graphic representation of the cumulative in vitro release profile of clonidine from certain coaxial formulations (Table 3). The formulations containing clonidine loads having 7.76 wt %, 6.92 wt %, 6.76 wt %, or 8.0 wt % had polymer and drug core with no outer coating. In general, with respect to these 4 formulations, the higher the drug loads, the faster the drug release and more release of the drug from the depot. For example, the drug depot having an 8.0 wt % drug load (the highest load in the core group) released about 90 wt % of the drug from the depot at about 70 days. In the second group, the formulations containing clonidine loads having 12.1 wt %, 7.6 wt %, 8.9 wt %, or 10.0 wt % had polymer and drug core with an outer coating to delay release. The higher the drug load the thinner the coating and the lower the drug load, the thicker the coating. These results show that by varying the drug load, and changing the polymer from DL 7E (the inherent viscosity of the 100 DL was 0.60-0.80 and had an ester end group) to DL 5E (the inherent viscosity of the 100 DL was 0.45-0.55 and had an ester end group) and the coating thickness (a thick coating is about 50 ~ 100 microns and a thin coating would be 5 to about ~ 20 microns) changed the release profile of the drug depot, where the higher drug loads (12.1 wt % and 10 wt %) had a higher % cumulative release, while the lower drug loads (8.9 wt % and 7.6 wt %) had a lower % cumulative release.

Figure 9 is a graphic representation of the cumulative in vitro release profile for certain irradiated clonidine formulations in Table 3. The formulations contained 5 wt % clonidine drug loads and the drug depot was either 1 mm or 0.8 mm. One formulation had a drug load of 7 wt %. None of the formulations had a polymer coating. In general, the smaller the diameter of the pellet, the more rapid release of the drug from the drug depot as the smaller diameter pellets had increased surface area, which can lead to a higher % cumulative release of drug from the drug depot.

Figure 10 is a graphic representation of the calculated daily release of clonidine for certain three pellet dose formulations of Figure 9 that did not have coatings on them. All formulations had a high initial burst release on day one from about 28 mcg-32 meg and daily release ranged from 0.5 meg to 4 meg/day over about 75-95 days. There was no
coating on these pellets, which lead to a high initial burst. All formulations had consistent release after the initial burst period.

Figure 11 is a graphic representation of the cumulative release percentage of clonidine for certain formulations. The formulations containing clonidine loads having 3.54 wt %, 7.38 wt %, 5.0 wt %, or 3.8 wt % had polymer and drug core and polymer DL coating. The polymer for the drug core was 100 DL 5E (the inherent viscosity of the 100 DL was 0.45-0.55 and had an ester end group) and some had this polymer for the coating (sheath) as indicated in the legend. Others had the drug core polymer as DL 5E (the inherent viscosity of the DL was 0.45-0.55 and had an ester end group) and the polymer coating (sheath) on the core as indicated in the legend was DL 7E (the inherent viscosity of the DL was 0.60-0.80 and had an ester end group). The thinnest coating and highest drug load (7.38 wt % clonidine) had the fastest release and thicker coating and lowest drug load (3.54 wt % clonidine) had the slower drug release considering both groups had the same polymer and coating 100 DL 5E (a thick coating is about 50 ~ 100 microns and a thin coating would be 5 to about ~ 20 microns). The other group having 5.0 wt % clonidine load and 3.8 wt % clonidine load had a polymer core of DL 5E and a polymer coating of DL 7E (sheath), which delayed drug release. The drug depot with the higher drug load released the fastest. In general, the higher the drug loads, the faster the drug release and more release of the drug from the depot, also the thicker the coating the slower the drug release.

Figure 12 is a graphic representation of the micrograms of clonidine released for certain 3/4/5 pellet dose formulations of Figure 11. All formulations had either a 100 DL 5E coating on the core or a DL 7E coating on the core. All formulations had a lower initial burst effect as compared to uncoated pellets on day one, which was from about 3 meg- 5 meg and daily release ranged from 0.1 meg to 5 meg/day over about 55 -92 days. Except there was one formulation that had a high drug load of 7.38 wt % clonidine that had the fastest release over about 25 days and a peak release of about 13 meg. This formulation may be useful where a fast release is needed. All other formulations had consistent release after the initial burst period, with some having a release over 90 days with a release of from about 0.1 meg/day to about 3 meg/day.

Figure 13 is a graphic representation of the cumulative release percentage of clonidine for certain formulations produced as indicated in Table 1. The formulation
containing 10 wt% clonidine drug load and the polymer 8515 DLG 7E had about 90 cumulative release % of drug released from the depot as long as 120 days, which is suitable for many chronic conditions of pain, inflammation and/or infection.

Figure 14 is a graphic representation of the cumulative release percentage of clonidine for certain formulations produced as indicated in Table 1. The formulation containing 20 wt% clonidine drug load and the polymer 8515 DLG 7E had about 90 cumulative release % of drug released from the depot as long as 140 days, which is suitable for many chronic conditions of pain, inflammation and/or infection.

Figure 15 is a graphic representation of the cumulative release percentage of clonidine for certain formulations produced as indicated in Table 1. The formulation containing 7.5 wt% clonidine drug load and the polymer 8515 DLG 7E had about 90 cumulative release % of drug released from the depot as long as 145 days, which is suitable for many chronic conditions of pain, inflammation and/or infection.

Figure 16 is a graphic representation of the cumulative release percentage of clonidine for one formulation produced as indicated in Table 1. The formulation containing 5 wt% clonidine drug load and the polymer 100 DL 7E had about 100 cumulative release % of drug released from the depot as long as 175 days, which is suitable for many chronic conditions of pain and/or inflammation.

Figure 17 is a graphic representation of the cumulative release percentage of clonidine for certain formulations produced as indicated in Table 1. The formulation containing 5 wt% clonidine drug load and the polymer 8515 DLG 7E and mPEG as a plasticizer had about 80 cumulative release % of drug released from the depot as long as 150 days, which is suitable for many chronic conditions of pain and/or inflammation.

Figure 18 is a graphic representation of the cumulative release percentage of clonidine for certain formulations produced as indicated in Table 1. The formulation containing 5 wt% clonidine drug load and the polymer 8515 DLG 7E had about 75 cumulative release % of drug released from the depot as long as 135 days, which is suitable for many chronic conditions of pain, inflammation and/or infection.

Figure 19 is a graphic representation of the cumulative release percentage of clonidine for certain formulations produced as indicated in Table 1. All formulations had about 50 to 75 cumulative release % of drug released from the depot as long as 160 days, which is suitable for many chronic conditions of pain, inflammation and/or infection.
Figure 20 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations produced as indicated in Table 1. All formulations had about 90 cumulative release % of drug released from the depot for 7 days. The formulations here had smaller size (0.75 mm x 0.75 mm), which increases surface area for release as compared to deports with larger diameters.

Figure 21 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations produced as indicated in Table 1. All formulations had over 100 cumulative release % of drug released from the depot for over 30 days.

Figure 22 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations produced as indicated in Table 1. Span 85 is a plasticizer for one formulation. All formulations had about 30 to 50 cumulative release % of drug released from the depot for over 50 days.

Figure 23 is a graphic representation of the cumulative release percentage of clonidine for one formulation produced as indicated in Table 1. The formulation containing 5 wt% clonidine drug load and the polymer 8515 PLGA had about 100 cumulative release % of drug released from the depot as long as over 75 days, which is suitable for many chronic conditions of pain, inflammation, and/or infection.

Figure 24 is a graphic representation of the cumulative release percentage of clonidine for one formulation produced as indicated in Table 1. The formulation containing 5 wt% clonidine drug load and the polymer 8515 PLGA and Span 65 as a plasticizer had about 65 cumulative release % of drug released from the depot as long as 70 days, which is suitable for many chronic conditions of pain, inflammation, and/or infection.

Figure 25 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations produced as indicated in Table 1. All formulations had about 90 to 110 cumulative release % of drug released from the depot for over 100 days, except one, which had about 90 cumulative release % of drug released from the depot for about 20 days.

Figure 26 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations produced as indicated in Table 1. All formulations had about 55 to 85 cumulative release % of drug released from the depot for over 28 days.
Figure 27 is a graphic representation of the cumulative release percentage of clonidine for one formulation produced as indicated in Table 1. The formulation containing 10 wt% clonidine drug load and the polymer DL-PLA had about 45 cumulative release % of drug released from the depot for about 18 days, which may be suitable for acute conditions of pain, inflammation, and/or infection.

Figure 28 is a graphic representation of the cumulative elution percentage of clonidine for certain formulations produced as indicated in Table 2. All formulations had POE and 10% or 20% clonidine drug load. All formulations had about 80 to 90 cumulative release % of drug released from the depot for over 120 days, except one formulation, which released drug within about 35 days.

Figure 29 is a graphic representation of the cumulative release percentage of clonidine for one formulation produced as indicated in Table 2. The formulation containing 10 wt% clonidine drug load and the polymer POE had about 100% cumulative release % of drug released from the depot for about 100 days, which may be suitable for chronic conditions of pain, inflammation, and/or infection.

Figure 30 is a graphic representation of the cumulative release percentage of clonidine for one formulation produced as indicated in Table 2. The formulation had about 35% cumulative release % of clonidine released from the depot for about 23 days.

**Example 2:**

This example illustrates that clonidine inhibited growth of gram negative bacteria (*E. coli*), gram positive bacteria (*S. aureus*) and fungus (*C. albicans*), as no growth was seen after 4 days.

**Control Films**

1: 13903-24-6 (Control Film) 1-A, 2: 13903-24-6 (Control Film) 1-B, and 3: 13903-24-6 (Control Film) 1-C: the films contained 80 wt% 5050DLG 8E, which contains poly(DL-lactide-co-glycolide) that has ester end groups and the polymer has an inherent viscosity of 0.70 - 0.90 dL/g; 10 wt% PEG (400MW), and 20 wt% mannitol. No clonidine was present in these films.

**Sample Films**

4: 14386-32-3 (Sample Film) 2-A; 5. 14386-32-3 (Sample Film) 2-B, and 6. 14386-32-3 (Sample Film) 2-C, the films contained 79.5 wt% 5050DLG 8E, which contains poly(DL-lactide-co-glycolide) that has ester end groups and the polymer has an
inherent viscosity of 0.70 - 0.90 dL/g; 10 wt% PEG (400MW), and 20 wt% mannitol, and 0.5 wt% clonidine HCl. All films had a length of 25 mm, width of 9 mm and thickness of 0.5 mm.

Test Codes: 110790, 110790A

Each film sample was individually placed on the surface of a Tryptic Soy Agar (TSA) plate in an aseptic manner. Each film was individually inoculated with 1mL of one of the three (3) challenge organisms shown below. For each challenge organism, one "Sample Film" and one "Control Film" were inoculated. Due to the anticipated slow absorption of the challenge inoculum by the test samples, the inoculum was dispensed onto each film sample very slowly. After inoculation, each sample was carefully moved to incubation at the temperature range appropriate for the inoculated challenge organism and incubated for four (4) days. Each day of incubation, all plates were removed from incubation for visual and stereoscopic evaluation. Upon evaluation, the presence or absence of growth on the plate and/or on the sample was noted. In addition, the sample was evaluated for the presence or absence of a zone of inhibition around the sample. The presence or absence of a zone was reported as "Z" for Zone (size in mm) or "NZ" for no zone present.

<table>
<thead>
<tr>
<th>Inoculum Concentration (CFU / 1.0 mL)</th>
<th>Escherichia coli ATCC 8739</th>
<th>Staphylococcus aureus ATCC 6538</th>
<th>Candida albicans ATCC 10231</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.1 x 10⁴</td>
<td>3.9 x 10⁴</td>
<td>1.9 x 10³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 1</th>
<th>Growth on the Plate</th>
<th>Growth on the Sample</th>
<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli ATCC 8739</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td>S. aureus ATCC 6538</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td>C. albicans</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td>ATCC 10231</td>
<td>Control</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>---</td>
<td>----</td>
</tr>
</tbody>
</table>

**DAY 2**

<table>
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<th>Growth on the Plate</th>
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<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong> ATCC 8739</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td><strong>S. aureus</strong> ATCC 6538</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td><strong>C. albicans</strong> ATCC 10231</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
</tbody>
</table>

**DAY 3**

<table>
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<th>Growth on the Plate</th>
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<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong> ATCC 8739</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td><strong>S. aureus</strong> ATCC 6538</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td><strong>C. albicans</strong> ATCC 10231</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
</tbody>
</table>

**DAY 4**

<table>
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<tr>
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<th>Growth on the Plate</th>
<th>Growth on the Sample</th>
<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong> ATCC 8739</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td><strong>S. aureus</strong> ATCC 6538</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
<tr>
<td><strong>C. albicans</strong> ATCC 10231</td>
<td>Test Sample</td>
<td>G</td>
<td>NG</td>
</tr>
</tbody>
</table>
Note: Due to the inoculum volume selected (1.0mL), the inoculum failed to remain on top of the sample for the duration of the test. Liquid inoculum did not adhere to or absorb into the test samples or control samples. The movement of the liquid inoculum over the sample and the test plate made definitive observation of the organisms' growth pattern difficult for all samples tested.

Additional Test Information:

G = Growth
NG = No Growth
Z = Zone (in mm)
NZ = No Zone

Additional Information/Observations:

At the conclusion of the testing period, all test samples were individually removed from the agar surface and gently shaken to remove any excess moisture remaining on the surface of the sample. The samples were then individually examined under the stereoscope by a laboratory technician. The technician recorded the following general observations:

E. coli Test Sample - Growth touching the sides of the sample on the plate; no growth on sample along sides or on top of sample; growth under sample

E. coli Control Sample - Growth touching the sides of the sample on the plate; small amount of growth along the sides of the sample; growth under the sample

S. aureus Test Sample - Growth under the sample on the plate; growth along the sides of the sample, but not touching the sample; no growth on the sample

S. aureus Control Sample - Growth under the sample on the plate; growth along the sides of the sample, but not touching the sample; no growth on the sample
C. albicans Test Sample - Growth under the sample on the plate; growth along and on the sides of the sample; no growth on top of sample.

C. albicans Control Sample - Growth under the sample on the plate; growth touching the side of the test sample; no growth on top or side of sample.

Following the documentation of the observations above, each sample was scraped with an inoculating loop on the inoculated, top side of each sample to determine whether macroscopic growth could be visually observed. The loops were then streaked onto agar medium plates and incubated at the appropriate temperature for the applicable challenge organism and the plates were observed for the presence or absence of the challenge organism. The following is a summary of findings from this portion of the test:

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Macroscopic Microbial Growth from Scraping</th>
<th>Growth of Challenge Organism on Streaked Plate</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli ATCC 8739</td>
<td>Test Sample: No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Control: No</td>
<td>Yes</td>
</tr>
<tr>
<td>S. aureus ATCC 6538</td>
<td>Test Sample: No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Control: No</td>
<td>Yes</td>
</tr>
<tr>
<td>C. albicans ATCC 10231</td>
<td>Test Sample: No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Control: No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

It was surprising that a drug depot is not susceptible to microorganisms. It was assumed that implants or drug depots are inherently susceptible to microbial attachment, as they provide a source for the microorganism to attach.

It will be apparent to those skilled in the art that various modifications and variations can be made to various embodiments described herein without departing from the spirit or scope of the teachings herein. Thus, it is intended that various embodiments cover other modifications and variations of various embodiments within the scope of the present teachings.
WHAT IS CLAIMED IS:

1. An implantable drug depot having antimicrobial properties for reducing, preventing or treating an infection in a patient in need of such treatment, the implantable drug depot comprising clonidine in an amount from about 0.1 wt.% to about 30 wt.% of the drug depot, and at least one biodegradable polymer, wherein the drug depot is capable of releasing clonidine over a period of at least one day.

2. An implantable drug depot according to claim 1, wherein said clonidine comprises from about 0.5 wt.% to about 15 wt.% of the drug depot and the drug depot is in the form of a coating, film or strip or a film, coating or strip on a medical device.

3. An implantable drug depot according to claim 1, wherein the infection is caused by gram positive bacteria, gram negative bacteria, parasites, viruses, fungi or a combination thereof.

4. An implantable drug depot according to claim 1, wherein said at least one biodegradable polymer comprises at least 70 wt% or 90 wt.% of the drug depot.

5. An implantable drug depot according to claim 1, wherein the at least one biodegradable polymer comprises one or more of poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PGA), D-lactide, D,L-lactide, L-lactide, D,L-lactide-co-e-caprolactone, D,L-lactide-co-glycolide-co-e-caprolactone or a combination thereof.

6. An implantable drug depot according to claim 1, wherein the drug depot is implanted locally at a site of the infection beneath the skin.

7. An implantable drug depot according to claim 6, wherein the depot is implanted to prevent a postoperative infection.
8. An implantable drug depot according to claim 1, wherein the drug depot releases:
(i) a bolus dose of the clonidine at a site beneath the skin; and (ii) an effective amount of
the clonidine over a period of at least fifty days or at least sixty days.

9. An implantable drug depot according to claim 1, wherein the at least one
biodegradable polymer comprises poly(lactic-co-glycolide) or poly(orthoester) or a
combination thereof, and said at least one biodegradable polymer comprises at least 70
wt.% of said drug depot.

10. An implantable drug depot having antimicrobial properties for reducing,
preventing or treating infection in a patient in need of such treatment, the implantable drug
depot comprising clonidine hydrochloride or base in an amount of from about 0.1 wt.% to
about 30 wt.% of the drug depot, and at least one polymer, wherein the at least one
polymer comprises one or more of poly(lactide-co-glycolide) (PLGA), polylactide (PLA),
polyglycolide (PGA), D-lactide, polyorthoester (POE), D,L-lactide, L-lactide, D,L-lactide-
co-e-caprolactone, D,L-lactide-co-glycolide-co-e-caprolactone or a combination thereof.

11. A method of making an antimicrobial coated medical device, the method
comprising coating the medical device with a drug depot having antimicrobial properties,
the drug depot comprising clonidine in an amount from about 0.1 wt.% to about 30 wt.%
based on a total weight of the drug depot and at least one biodegradable polymer, wherein
the drug depot is capable of releasing the clonidine over a period of at least one day.

12. A method according to claim 11, wherein said clonidine comprises from about 5
wt.% to about 15 wt.% of the drug depot and the drug depot is in the form of a coating,
film or strip or a coating on the medical device.

13. A method according to claim 11, wherein said biodegradable polymer comprises at
least 70 wt.% or at least 90 wt.% of the drug depot.
14. A method according to claim 11, wherein the antimicrobial properties comprise inhibiting gram positive bacteria, gram negative bacteria, parasites, viruses, fungi or a combination thereof.

15. An implantable drug depot according to claim 1, wherein the infection is caused by a fungus.
IRRADIATED CLONIDINE HCL FORMULATIONS

![Graph showing cumulative clonidine released over time for different formulations.]

**FIG. 1**

CALCULATED DAILY RELEASE OF CLONIDINE FROM 3 PELLET DOSE

![Graph showing clonidine release over time for different formulations.]

**FIG. 2**
FIG. 17

FIG. 18
FIG. 25

FIG. 26