MACROCYCLIC POLYMORPHS, COMPOSITIONS COMPRISING SUCH POLYMORPHS, AND METHODS OF USE AND MANUFACTURE THEREOF

1. RELATED APPLICATIONS

This application is a U.S. National Phase Application of International Application Number PCT/US2008/000735 filed Jan. 22, 2008, which claims the benefit of U.S. Provisional Patent Application No. 60/881,950, filed Jan. 22, 2007, each of which is incorporated by reference in its entirety.

2. FIELD OF THE INVENTION

The invention encompasses novel forms of compounds displaying broad spectrum antibiotic activity, especially crystalline polymorphic forms and amorphous forms of such compounds, compositions comprising such crystalline polymorphic forms and amorphous forms of such compounds, processes for manufacture and use thereof. The compounds and compositions of the invention are useful in the medical and pharmaceutical industry, for example, in the treatment or prevention of diseases or disorders associated with the use of antibiotics, chemotherapies, or antiviral therapies, including, but not limited to, colitis, for example, pseudo-membranous colitis; antibiotic associated diarrhea; and infections due to *Clostridium difficile* ("*C. difficile*"), *Clostridium perfringens* ("*C. perfringens*"), *Staphylococcus* species, for example, methicillin-resistant *Staphylococcus*, or *Enterococcus* including Vancomycin-resistant *enterococci.*

3. BACKGROUND OF THE INVENTION

Antibiotic-associated diarrhea ("AAD") diseases are caused by toxin producing strains of *C. difficile, Staphylococcus aureus* ("*S. aureus*") including methicillin-resistant *Staphylococcus aureus* ("MRSA") and *C. perfringens*. AAD represents a major economic burden to the healthcare system that is conservatively estimated at $3-6 billion per year in excess hospital costs in the United States alone.

AAD is a significant problem in hospitals and long-term care facilities. *C. difficile* is the leading cause of AAD in the hospital setting, accounting for approximately 20% of cases of AAD and the majority of cases of antibiotic-associated colitis ("AAC"). The rising incidence of *C. difficile* associated diarrhea ("CDAD") has been attributed to the frequent prescribing of broad-spectrum antibiotics to hospitalized patients.

The tiacumicins are a group of 18-membered macrolide antibiotics originally isolated from the fermentation broth of *Dactylosporangium aurantiacum*. The tiacumicins are effective Gram-positive antibiotics. In particular, tiacumicins, specifically Tiacumicin B, show activity against a variety of bacterial pathogens and in particular against *C. difficile*, a Gram-positive bacterium (*Antimicrob. Agents Chemother.*, 1991, 1108-1111). A purification of tiacumicins was carried out in suitable solvents, wherein tiacumicin B exhibited a

melting point of 143-145° C. (See, e.g., J. E. Hochlowski, et al., *J. Antibiotics*, vol. XL, no. 5, pages 575-588 (1987)).

The polymorphic behavior of a compound can be of crucial importance in pharmacy and pharmacology. Polymorphs are, by definition, crystals of the same molecule having different physical properties as a result of the order of the molecules in the crystal lattice. The differences in physical properties exhibited by polymorphs affect pharmaceutical parameters such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rates (an important factor in determining bio-availability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of a crystal may be important in processing: for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (i.e., particle shape and size distribution might be different between one polymorph relative to the other).

Each pharmaceutical compound has an optimal therapeutic blood concentration and a lethal concentration. The bio-availability of the compound determines the dosage strength in the drug formulation necessary to obtain the ideal blood level. If the drug can crystallize as two or more polymorphs differing in bio-availability, the optimal dose will depend on the polymorph present in the formulation. Some drugs show a narrow margin between therapeutic and lethal concentrations. Thus, it becomes important for both medical and commercial reasons to produce and market the drug in its most thermodynamically stable polymorph, substantially free of other kinetically favored or disfavored polymorphs.

Thus, there is a clear need to develop safe and effective polymorphs of drugs that are efficacious at treating or preventing disorders associated with bacterial pathogens. The present inventors have identified novel crystalline and amorphous forms of 18-membered macrolide compounds that exhibit broad spectrum antibiotic activity.

4. SUMMARY OF THE INVENTION

The invention encompasses novel crystalline and amorphous forms of the macrolide compounds that are useful in treating or preventing bacterial infections and protozoal infections. In an illustrative embodiment, the novel crystalline and amorphous forms of the macrolide compounds of the invention exhibit broad spectrum antibiotic activity. Thus, surprisingly novel crystalline and amorphous forms of the macrolide compounds have been identified, which act as antibiotics possessing a broad spectrum of activity in treating or preventing bacterial infections and protozoal infections, especially those associated with Gram-positive and Gram-negative bacteria and in particular, Gram-positive bacteria.