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(54) **Title:** SINGLE PHARMACEUTICAL COMPOSITION CONTAINING ANTIBIOTICS AND PROBIOTICS

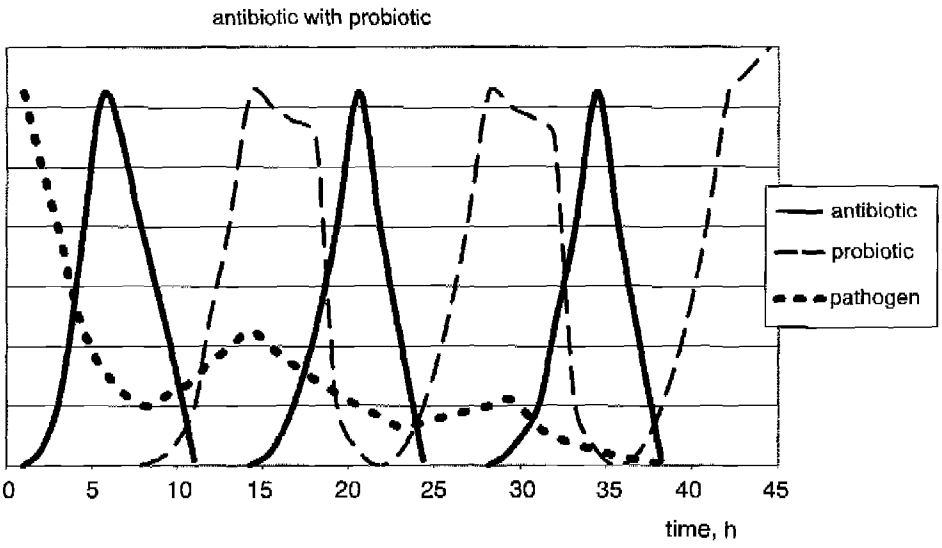

FIG 2

(57) **Abstract:** The present invention discloses a method of use antibiotic and probiotic combination in a time-controlled manner in single pharmaceutical composition, wherein in use of the pharmaceutical composition at first step of the pharmaco-cinetic cycle the antibiotic deploys its effect against infection achieving the maximum level followed by time-controlled release of the probiotics. After achieving the maximum level, shortly before the end of the pharmaco-cinetic cycle of the single dose the probiotic population is released, wherein the time of releasing the probiotic depends on the antibiotic/probiotic ratio, which enables rapid multiplication of the probiotics to suppress further pathogenic activity between two pharmaco-cinetic cycles.

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Description

Single pharmaceutical composition containing antibiotics and probiotics

Technical Field

[0001] The present invention provides novel method of use antibiotic and probiotic combination in single pharmaceutical composition, whereas the release of the probiotics is time-controlled. The single pharmaceutical composition is useful for the effective treatment of infection and in addition minimizing of the side effect of the antibiotic treatment.

Background Art

[0002] It is well-known that treatment of the diseases caused by pathogens (for example pathogenic microorganisms etc) with antibiotics where the effect of the treatment is achieved by the concept of rapid action antibiotics, which steep increase its concentration/efficacy in organism and then very rapidly decreases in time, to avoid long-lasting influence of one antibiotic consumption on the human organism, which in it case can be one of the main reason of antibiotic resistance development.

[0003] At the present when bacteriological infection occurs it is typically required and used the antibiotic treatment to have quick results of the recovery from the infection. Such a treatment is described in the Fig. 1. Beginning from the first antibiotic intake (continuous curves) pathogen bacteria concentration (dotted line curves) decreases rapidly till known concentration, which is determined with decreasing antibiotic concentration.

[0004] Between the antibiotic intakes residue pathogenic microorganisms (dotted line curves) has opportunity to re-populate, because the concentration of antibiotic in the human organism is low or insufficient. This growth continues till next antibiotic intake, when increasing antibiotic concentration is capable to suppress pathogen growth.

[0005] This cycle continues till maximum suppression of photogenic bacteria to the end of antibiotic treatment. After antibiotic treatment (last intake) human intestine is relatively sterile and in this case it is unprotected from contamination with fungal infection or new pathogenic bacteria (see *Fig. 1.* right end, dotted line curve). Such organisms can start rapid development

in absence of natural (protective) intestine microflora and cause new bacterial or fungal infection, which might need a following treatment.

[0006] Probiotics are currently used in several indications together with antibiotic (not in a single pharmaceutical composition), either in an attempt to ameliorate the antibiotic effect of the treatment itself, or to mitigate mainly gastrointestinal side effects often associated with application of antibiotics.

[0007] Mainly probiotics are used to reduce the development of antibiotic associated diarrhea, but also to eliminate other side effects which can occur during or after antibiotic treatment.

Disclosure of Invention

[0008] To minimize problems related with antibiotic consumption, time controlled ANTIPRO concept is developed (see *Fig. 2.*) by the authors of the present invention. There are developed the concept of combining a fast-acting antibiotic (e.g. clarithomycin) with a probiotic (e.g. lactobacillus). The objective of current invention is to merge the antibiotic and probiotic into a single pharmaceutical composition or product, separated by a time-controlled protective layer so that the antibiotic deploys its effect first against infection, then the probiotic exert its protective action between two separate intakes (double mechanism of action) of the pharmaceutical composition according to the present invention.

[0009] After rapid antibiotic action, the probiotic bacteria initiate rapid multiplication between two antibiotic doses. The probiotic warrants competitive exclusion conditions against pathogens through production of bacteriocins (for example lactic acid) helping to minimize pathogenic bacteria activity between two intakes, thus playing a protective role.

[0010] The effect is to be achieved through the utilization of multi layer tablets or capsules where the probiotic, or a mixture of probiotic and a carrier (e.g. fish oil, gum and etc), would constitute the core of the pharmaceutical form. This core would be coated with an antibiotic-resistant layer allowing time-controlled release. The antibiotic, alone or together with a carrier, is formulated around the core containing the probiotic (with or without carrier) and then coated with an additional protective layer, which may or may not provide time-controlled release, depending on target application. The

pharmaceutical composition according to the present invention can be in the form of tablet, capsule, suppositories or other known forms of the pharmaceutical dosage or application forms.

[0011] Once the external coating is dissolved after administration the fast acting antibiotic is released to exert its primary activity. Thereafter the layer between the antibiotic and probiotic dissolves at a point in time when the antibiotic activity has faded out allowing the probiotic bacteria to initiate rapid multiplication by colonizing the microflora and thus inhibiting the growth of remaining pathogens via a number of mechanisms: including competitive inhibition (occupation of specific environmental niches), production of inhibitory factors, modification of the local environment (production of organic acids, volatile fatty acids, hydrogen peroxide and other compounds), or effects on local inflammatory and immune responses. Time of releasing the probiotic depends on the predetermined antibiotic/probiotic ratio, which enables rapid multiplication of the probiotics to suppress further pathogenic activity between two intakes of the pharmaceutical compositions according to present invention.

[0012] Combination of a specific fast-acting antibiotic with a specific probiotic into a single pharmaceutical composition, separated by a time-controlled protective layer foresees several benefits, e.g.:

- reduced development of allergies to antibiotics
- reduced digestive upsets that can appear during the antibiotic treatment
- reduction of stomach irritations caused by antibiotics
- minimizing residue pathogen reproduction
- reduced possibility of fungal colonization at the end of antibiotic treatment
- reduced time between two fast acting antibiotic intakes when the intestine is not protected
- reduced development of antibiotic resistant bacteria
- faster recovery after antibiotic treatment.

[0013] Decreasing of the antibiotic side effects by ANTIPRO concept

[0014] The integrity of the normal gut flora is ensured by a quality called colonization resistance, which prevents the overgrowth of pathogens. The

most common disruption of the flora is a side effect of antibiotic treatment that can cause diarrhea (antibiotic associated diarrhea (AAD)), and an appealing area for the use of probiotics is in the prevention of ADD.

[0015] The incidence of AAD varies, but studies show that it can occur in up to 39% of hospitalized patients under treatment by antibiotics. The consequences of AAD include a longer hospital stay, a higher cost of care, a fivefold increase in the incidence of other nosocomial infections and a threefold increase in mortality (up to 38%) (McFarland 1998).

[0016] Bacteria and yeast have been studied in meta-analysis for prevention of AAD. The meta-analysis concluded that probiotics can be used to prevent antibiotic associated diarrhoea and that *S.boulardii* and lactobacilli have the potential to be used in this situation (D´Souza et al., 2002). Lactobacilli, bifidobacteria, and Streptococcus species have all been evaluated for the prevention or treatment of diarrhoea associated with antibiotic use and found to be safe (Hickson et al., 2007).

[0017] *Example*

[0018] **Use of Probiotics in the treatment *Helicobacter pylori* infections**

[0019] *Helicobacter pylori* (*H. pylori*) is a gram-negative, microaerophilic bacterium that inhabits various areas of the stomach and duodenum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer. Acute infection with the bacterium are usually asymptomatic.

[0020] Once *H. pylori* is detected in patients with a peptic ulcer, the normal procedure is to eradicate it and allow the ulcer to heal. The standard first-line therapy is a one week triple therapy consisting of the antibiotics: amoxicillin and clarithromycin, and a proton pump inhibitor such as omeprazole (Mirbagheri et al., 2006). Variations of the triple therapy have been developed over the years, such as using a different proton pump inhibitor, as with pantoprazole or rabeprazole, or replacing amoxicillin with metronidazole for people who are allergic to penicillin (Malfertheiner et al., 2007). Typically treatment lasts for 7 days with twice daily oral applications.

[0021] Failure rate of triple therapy is 10 to 23 % (Sheu et al., 2006). An increasing number of infected individuals are found to harbour antibiotic-resistant bacteria. This results in initial treatment failure and requires additional rounds of antibiotic therapy or alternative strategies such as a quadruple therapy, which adds a bismuth colloid and uses tetracyclin instead of clarithromycin (Fischbach and Evans, 2007).

[0022] The present invention, time-controlled pharmaceutical composition of probiotic and antibiotic combination treatment described above can help to reduce such problems and in addition side effects which can appear during or after antibiotic treatment.

[0023] Antibiotic-associated gastrointestinal side effects such as diarrhoea, nausea, vomiting, bloating and abdominal pain may represent a serious drawback of anti-*H.pylori* therapies, although they are mild in most cases, usually resulting in discontinue therapy (Bell et al., 1992). These manifestations have been related to quantitative and qualitative changes in the intestinal microflora because of unabsorbed or secreted antibiotics in the intestinal content, with a resulting reduction in normal saprophytic flora and overgrowth by persistence of potentially pathogenic antibiotic resistant indigenous strains (Kabir et al., 1997). Also unabsorbed antibiotics are leading to the prolonged contact with the GI wall, which in it case can lead to irritations or allergies.

[0024] The side effects are a major reason for the only moderate compliance of patients under eradication therapy. As a consequence, attempts have been made to alleviate the side effects of eradication therapy by supplementing the medication with probiotic organisms such as Lactobacillus *spp.*. In a meta-analysis of 14 randomized trials it was found that supplementation with probiotics not only had a positive impact on *H. pylori* therapy-related side effects, but also slightly increased the eradication rates. Most of the studies used Lactobacillus strains, but other bacteria (e.g. *Bifidobacterium longum, Clostridium butyricum*) or a yeast (*Saccaromyces boulardii*) were also used. Probiotics were used as special preparation or in the form of dairy products (Tong et al., 2007).

[0025] Summarizing all said above ANTIPRO concept pharmaceutical

composition of fast acting antibiotic and probiotic can have a positive impact on *H. pylori* treatment. The time-controlled probiotic component of ANTIPRO concept promotes competitive exclusion conditions against pathogens through production of bacteriocins (for example lactic acid), helping to minimize pathogenic bacteria activity between two intakes, thus playing a protective role. Probiotic microorganism within ANTIPRO concept has a therapeutic effect in humans to cure, to mitigate, to treat, to prevent a disease or minimize its side effects.

Brief Description of Drawings

[0026] Fig. 1 illustrates the current treatment of the bacteriological infection where is used the antibiotic treatment,

[0027] Fig.2 illustrates the ANTIPRO concept treatment where is used the pharmaceutical compositions containing time-controlled probiotics and fast acting antibiotics.

Best Mode for Carrying Out the Invention

[0028] The present invention provides method of use of the combination of the antibiotics and probiotics with time-controlled release in single pharmaceutical composition.

[0029] The pharmaceutical composition contains two active substances (the antibiotic and the probiotic) in clearly defined ratio dependant on an infection type.

[0030] ANTIPRO concept brings high concentrations of viable probiotic cells to their destination at the gut mucosa (or other type of microflora) to foster quick restoration of microflora between pharmaco-cinetic cycles of antibiotics. Employing a well-identified timing for release of the probiotic which ensures that antibiotic concentration/effectiveness is below a level that effects viability and multiplication of probiotic may increase beneficial effects compared to current use of probiotic preparations separately outside of single pharmaceutical composition described in the scope of the present invention. The probiotics are released shortly before the end of the pharmaco-cinetic cycle of the antibiotic present in the same pharmaceutical composition according to the present invention.

[0031] In principle, ANTIPRO can be employed to any fast acting antibiotic and to

all the indications these antibiotics are used for.

[0032] Many different pro- and eukaryotic organisms are in use as probiotics, either as monovalent or as multivalent preparation combining different organisms. The most important classes of probiotic organisms include Lactobacilli, bifidobacteria, streptococcus and certain Saccharomyces strains.

[0033] In the preferred embodiment the number of the probiotics is between 10^4 to 10^{17} CFU per single dose of the pharmaceutical composition.

[0034] In addition the probiotics used in the pharmaceutical composition shall not be resistant to the antibiotic within in the same pharmaceutical composition.

[0035] Clinical studies are available on the effects of probiotics on the gastrointestinal side effects, most of them showing a beneficial effect.

[0036] Combining an effective probiotic with an antibiotic in a single pharmaceutical composition may reduce side effect burden on patients, increase compliance and to improve the effectiveness and/or efficacy of antibiotic therapy.

[0037] Examples

[0038] In current invention ANTIPRO concept has been described for a fixed combination product of clarithromycin and a probiotic for *H. pylori* eradication triple therapy as an example. However, clarithromycin is used in many other types of infections. As an example, Clarithromycin 500 mg Modified Release Tablets from *Abbott Laboratories* are indicated for treatment of infections caused by susceptible organisms, including lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia as well as upper respiratory tract infections for example, sinusitis and pharyngitis. Thus ANTIPRO concept can be applied in various disease treatments.

[0039] **Conceivable types of pharmaceutical dosage forms of ANTIPRO:**

- Press-coated tablets (multi-layer tablets):

[0040] Brief concept description: The probiotic component is formulated with excipients as the tablet core and then protected by a coating or lacquer with time-controlled release characteristics.

[0041] A mixture of the antibiotic ingredient and excipients is then press-coated as a layer “around” the probiotic tablet core and may be also lacquered with a time controlling lacquer or coat for controlled immediate dissolution.

- Capsules:

[0042] ANTIPRO concept delivered in capsules with appropriate probiotic or mixture of the probiotic with a carrier (e.g. fish oil) in the core of the capsule. This mixture is coated with the reliable/time-controlled layer which is resistant to the antibiotics use in the capsule.

- Another concept idea could be the development of a divided doseformulation (e.g. pellets or microcapsules) with different coating systems, where the antibiotic component is lacquered to have immediate release characteristics and the probiotic ingredient is coated or lacquered with a gastric resistant lacquer or coat. The differently lacquered or coated probiotic and antibiotic divided dose formulations are then filled into hard gelatin capsules of the desired capsule size.

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[0043]

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Claims

1. Method of use antibiotic and probiotic combination in a time-controlled manner in single pharmaceutical composition, wherein in use of the pharmaceutical composition at first step of the pharmaco-cinetic cycle the antibiotic deploys its effect against infection achieving the maximum level followed by time-controlled release of the probiotics.
2. Method of use according to the claim 1, wherein after achieving the maximum level, shortly before the end of the pharmaco-cinetic cycle of the single dose the probiotic population is released.
3. Method of use according to claim 1, wherein the time of releasing the probiotic depends on the antibiotic/probiotic ratio, which enables rapid multiplication of the probiotics to suppress further pathogenic activity between two pharmaco-cinetic cycle.
4. Method of use according to claim 3, wherein the multiplication of the probiotics act to further to suppress pathogenic activity until next use of the pharmaceutical composition containing the antibiotic and probiotic combination.
5. Method of use according to claim 4, wherein probiotic used in the pharmaceutical composition is not resistant to the antibiotic within in the same pharmaceutical composition.
6. Method of use according to any of preceding claims, wherein the antibiotic within in the pharmaceutical composition is preferably fast acting antibiotic.
7. Method of use according to any of preceding claims, wherein the number of the probiotics is between 10^4 to 10^{17} CFU per single dose of the pharmaceutical composition.
8. A single pharmaceutical composition comprising the antibiotic and probiotic, whereas the probiotics have time-controlled release.
9. A pharmaceutical composition according to the claim 8, wherein the probiotic population is released shortly prior the end of the pharmaco-cinetic cycle of the single dose.

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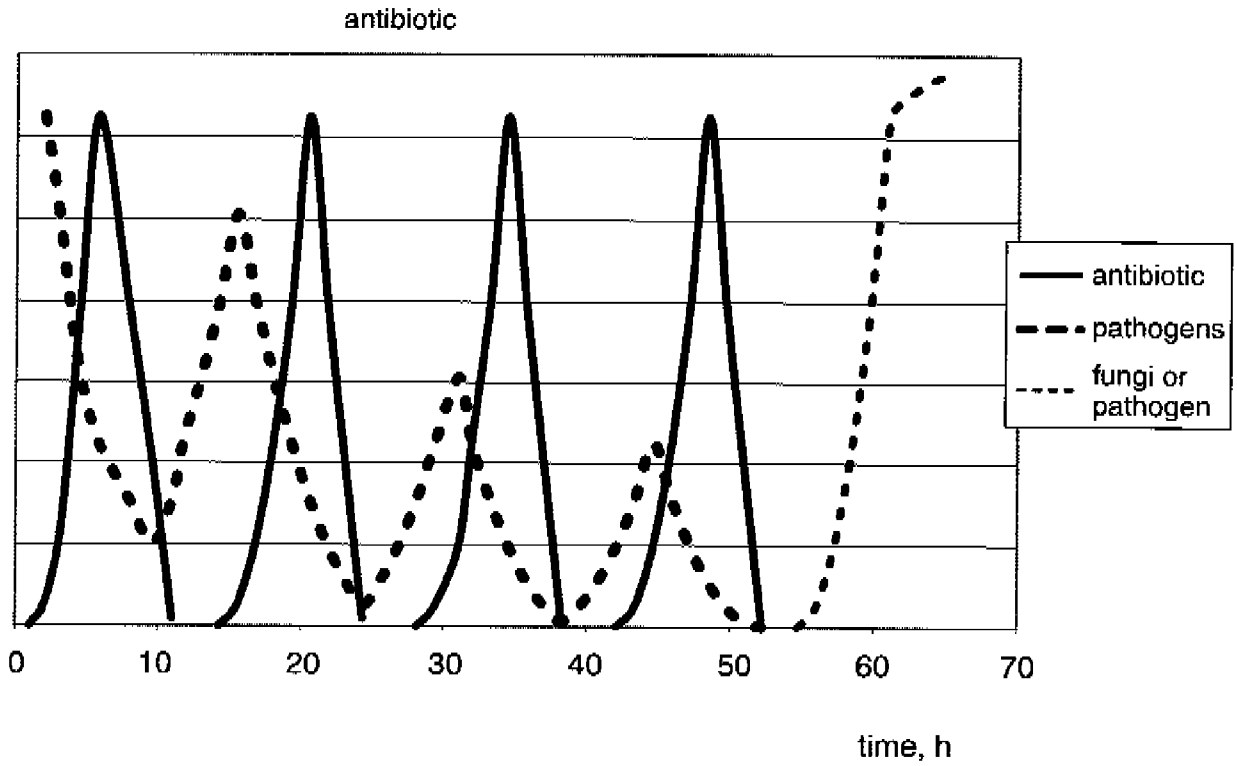
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FIG 1

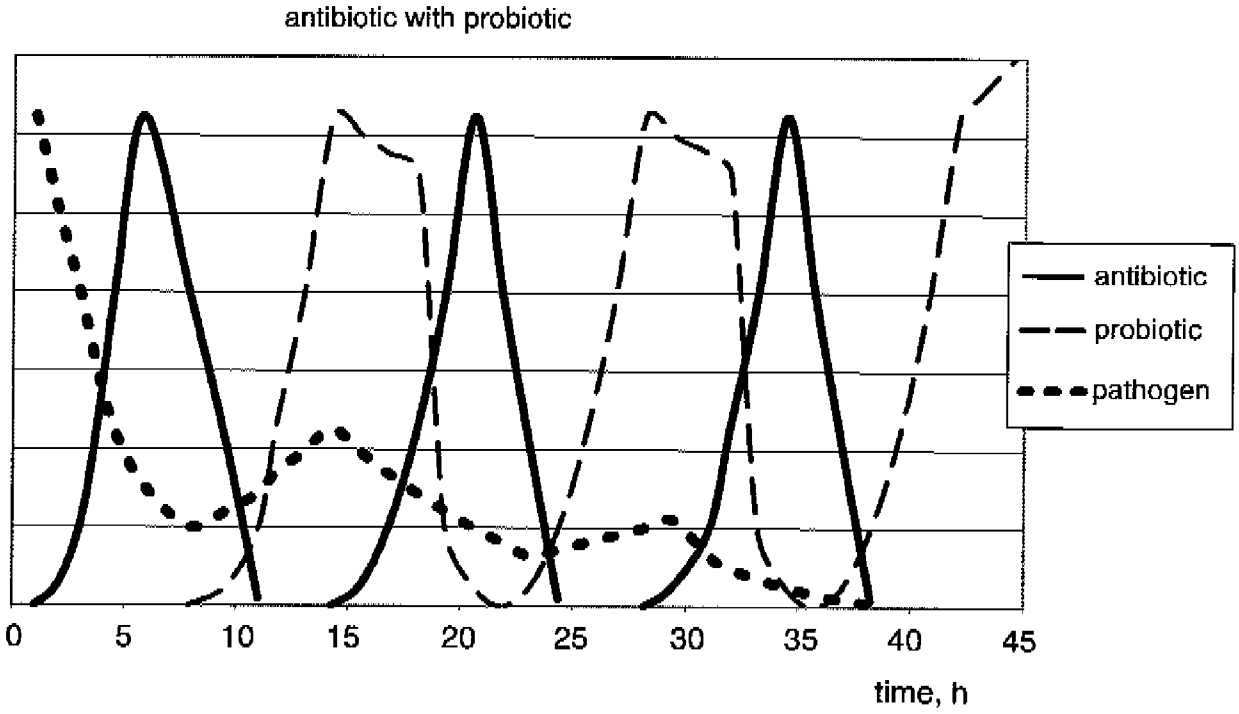
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FIG 2