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CLARITHROMYCIN SYNERGISM WITH ESSENTIAL AND TRACE ELEMENTS

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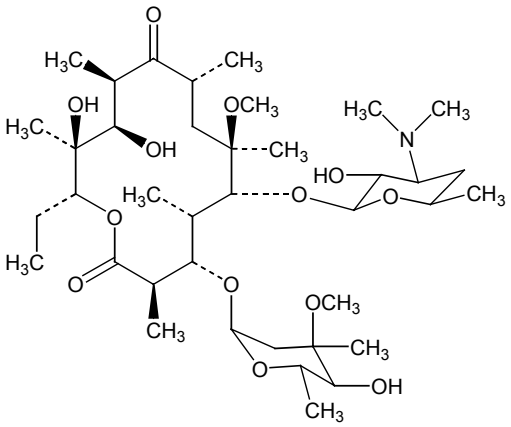
ABSTRACT

In order to ascertain the role of various essential and trace element complexation on the antibacterial activity of various macrolide antibiotics, the synergistic or antagonistic behavior of clarithromycin metal complexes has been studied and compared with the parent drug. Metal complexes of clarithromycin with magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc and cadmium has been investigated for their antibacterial activity and compared with clarithromycin by observing the changes in minimum inhibitory concentration (*MIC*) and by measuring the zone of inhibition. of complexes against both gram negative and gram positive microorganisms. Various microorganisms used were *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris, Shigella dysentary, Kelebcilla pneumoni and Staphylococcus epidermidis.* For *MIC* observation, serial dilution method was employed and zone sizes were determined by diffusion disk method.

Our investigations divulge that formation of clarithromycin complexes results in synergistic effect i.e., antimicrobial activity of complexes of clarithromycin increases with respect to parent clarithromycin drug and *MIC* of drug metal complexes decreased.

INTRODUCTION

Clarithromycin (6-O-Methyl-erythromycin A) is (2R,3S,4S,5R,6R,8R,10R,11R,12S,13R)-3-(2,6-Dideoxy-3-C,3-o-dimethyl-α-L-ribo-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2, 4, 6, 8,10,12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-D-xylo-hexopyranosyloxy) penta decan-13-olide (Florey 1996; Jame and Reynold 1996; Dollery 1999) is marketed under various trade names Biaxin (USA), Klaricid Switzerland and Klaricid (UK). It has a molecular formula $C_{38}H_{69}NO_{13}$, molecular weight 747.96 and has the following structure.



Clarithromycin

Clarithromycin is a new semi-synthetic 14-membered macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactone ring. Chemically clarithromycin is 6-O-methyl erythromycin A (Physician's Desk Reference 1995; British Pharmacopoeia 1998; Kalaricid Insert, 1998; Florey 1996). It has *in vitro* activity against many Gram positive and Gram negative aerobic and anaerobic organisms with increased tissue or cellular penetration (United States Pharmacopeia 1999). The minimum inhibitory concentrations of clarithromycin are generally two to four fold lower than those of erythromycin against gram-positive bacteria. Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible organisms and by inhibiting protein synthesis through translocation of amino acyl transfer-RNA (Florey 1996; Petska and Weissbach 1977).

The site of action of clarithromycin is same as that of erythromycin. The more potent anti-inflammatory effects exhibited by clarithromycin may enhance its clinical efficacy. It has been demonstrated that clarithromycin inhibits the production of interleukin-1 (IL-1) by murine peritoneal macrophages, lymophocyte proliferation and lymphocyte transformation of murine spleen cells at low concentrations (Dautzenberg *et al.,* 1993) and is 2 to 10 times more active than erythromycin in several experimental animal infection models (Loza *et al.*, 1992). Clarithromycin is effective in sinusitis and otitis media (Karma *et al.,* 1991; Marchi 1990; Aspin *et al.,* 1994; Gooch *et al.,* 1999), lung lesions (Hajime *et al.,* 1994), ventricular dysrhythmias and other chest infections (Kundu *et al.,* 1997; Aldons 1991; Neu & Chick 1993; Anderson *et al.*, 1991; Chien *et al.,* 1993; Bradbury 1993; de Wilde *et al.,* 1985; Hamedani *et al.*, 1991; Still 1993).

Drug interactions of clarithromycin are circumstantial to its oral absorption as well as with the concomitant use of other drugs (Hassan *et al.,* 1999). The potentially hazardous interactions are likely to be similar to erythromycin (Neu 1991; Joel *et al.,* 1996). A number of drug interactions of clarithromycin with several drugs have been reported (Kundu *et al.,* 1997; Gracey *et al.,* 1999; Hill *et al.,* 1996). Clarithromycin has shown potentially useful interactions with omeprazole in *Helicobacter pylori* infection and in combination therapy in *Mycobacterium avium* infection (Dollery 1999; Lauby 1996). However, there have been no clarithromycin-metal interactions reported in the literature although the interactions of erythromycin with antacids containing di- and trivalent metal cat ions have been reported (Arayne & Sultana 1993).

Present studies comprise of antibacterial studies of metal complexes of clarithromycin with magnesium, calcium, chromium, manganese, ferric, cobalt, nickel, copper, zinc and cadmium and changes in microbiological activity of the parent clarithromycin after complexation has been studied. These studies were carried out by observing the minimum inhibitory concentration (*MIC*) and by measuring the zone of inhibition of the complexes and compared with the parent clarithromycin against both Gram negative and Gram positive microorganism.

Various microorganisms used were *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus Vulgaris, Shigella dysentary, Kelebcilla pneumoni and Staphylococcus epidermidis*. For *MIC* observation, serial dilution method was employed and zone sizes were determined by diffusion disk method.

EXPERIMENTAL

Materials

Clarithromycin metal complexes (table 1) used for antibacterial studies were synthesized in Lab-9 of the department of chemistry, University of Karachi. The synthesis and characterization of these complexes are reported elsewhere.

The organisms used in the antimicrobial studies of clarithromycin metal complexes were *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris, Shigella dysentary, Kelebcilla pneumoni* and *Staphylococcus epidermidis.* Media was Muller-Hinton agar and broth. Routine laboratory chemicals like barium chloride, sulfuric acid, sodium carbonate, mercuric chloride, sodium citrate and hydrochloric acid, organic polar and non-polar solvents, de-ionized water and pH 2 buffer solution were used in these experiments.

Table 1
Clarithromycin metal complexes

S. No	Sample code	Complex	M.P. °C
1	190	Clarithromycin	206
2	191	Clarithromycin magnesium	202
3	192	Clarithromycin calcium	196
4	193	Clarithromycin chromium	182
5	194	Clarithromycin manganese	172
6	195	Clarithromycin ferric	192
7	196	Clarithromycin cobalt	300
8	197	Clarithromycin nickel	198
9	198	Clarithromycin copper	120
10	199	Clarithromycin zinc	192
11	200	Clarithromycin cadmium	184

Methods

1 *Preparation of pH 2 buffer solution*

Citrate buffer of pH 2 was prepared by mixing 300 ml of 0.1M sodium citrate solution and 150 ml of 0.1M hydrochloric acid solution in a liter beaker and the final pH was adjusted by either of the two solutions. This buffer was sterilized by autoclaving at 121 °C and at 15 psi pressure for 15 minutes.

2 *Preparation of solutions of drug*

The stock solution of clarithromycin was prepared by dissolving 0.025 gram of drug in distilled ethanol in a 25 ml volumetric flask and the final volume was made up with the same solvent. Aliquots were diluted between 0.25 μg/ml to 1 μg /ml to give the required concentrations of 0.5, 1, 2, 4, 8, 16, 32, 64 and 128 μg/ml.

For subsequent dilutions of drug highest concentration was taken first i.e., 128 μg/ml was made by diluting 6.4 ml of stock solution in a 50ml volumetric flask up to the mark with the buffer of pH 2. Aliquots of 64, 32, 16, 8, 4, 2, 1 and 0.5 μg/ml concentrations were prepared by serially diluting the later solution in the same solvent.

3 *Preparation of solutions of metals*

The stock and primary standard solutions of metal salts were prepared exactly in the same manner as those prepared for the antibiotics in the required concentrations (128, 64, 32, 16, 8, 4, 2, 1 and 0.5 μg/ml). The stock and primary standard solutions of clarithromycin metal

complexes (as given in table 1) were also prepared in the same manner as those for clarithromycin in the same concentrations.

4 Preparation of Mueller–Hinton agar (MHA), Mueller-Hinton broth (MHB), preparation of inoculums, controlling inoculum's density, MacFarland turbidity standards and agar dilution susceptibility tests were carried out according to standard procedures reported elsewhere (Sultana *et al.,* 2001).

5 *Preparation, inoculation and incubation of antimicrobial plates*

The agar medium prepared in conical flask was allowed to cool to 50°C on a water bath. Petri dishes were sterilized by placing them in an oven at 150°C for one and a half hour and labeled according to their concentrations (0.5 µg/ml to 128 µg/ml). Various dilutions of clarithromycin and clarithromycin metal complexes were prepared according to the procedures described above. These were added to the melted and cooled medium in a ratio of 1 part dilution to 9 part medium (2 ml of dilution of each to 18ml of agar for each petri dish). The medium was mixed by gently shaking the flask several times and the contents were poured into appropriate number of petri dishes marked, set aside on a flat horizontal surface and allowed to harden undisturbed till the contents solidified (Bertina, 1987).

An inoculum (1 - 2 ml) of each organism was applied to the surface of each antimicrobial petri dish with the help of a sterilized wire loop. The inoculum was applied as a spot that made a circle (Bertina 1987; National Committee For Clinical Laboratory Standards 1990). The inoculated petri dishes were not disturbed until the spot of inoculum was absorbed completely, after which they were then inverted and incubated at 37 °C for 24 hours to obtain the growth of the test organism. Incubation under increased CO_2 atmosphere was avoided because of the resulting increase in surface pH, which might adversely affect some antimicrobial agents. The petri dishes were then examined for the presence or absence of growth. The lowest concentration of each antimicrobial that inhibited growth was considered the MIC (single colony or haze growth was ignored) (American Public Health Association 1987).

RESULTS AND DISCUSSION

Selection of an antibiotic for therapy of bacterial infection often depends on knowledge of the susceptibility of the infecting organism (Gennaro, 1985). Usually, it is possible to determine susceptibility by *in vitro* tests. When they are properly standardized, the result obtained correlate well with the response to therapy observed in clinical practice (Weissbach, 1977). Like the rest of the macrolide group, clarithromycin exerts its bacteriostatic antibacterial action (Florey, 1996; Joel, 1996; Weissbach, 1977). Some *Staphylococci* are sensitive to erythromycin, the range of *MIC* is very high for *Staphylococcus epidermidis*, 8 to > 32 µg/ml, and for *Staphylococcus aureus*, 0.12 to > 128 µg/ml. Erythromycin resistant strains of *Staphylococcus aureus* are also resistant to clarithromycin.

Reference standard of clarithromycin during present *in vitro* studies verified that clarithromycin is active against both gram positive and gram negative strains of organisms. Table 2 indicate that *Staphylococcus aureus* was susceptible at higher *MIC* value which was found at 128, 64, 32, 16 and 8 µg/ml concentration while resistant at lower *MIC* value at 4, 2, 1, 0.5 µg/ml concentration. *Streptococcus faecalis*, *Escherichia coli*, *Salmonella Typhii*, *Proteus vulgaris*, *Shigella dysentery*, were susceptible at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentration, while on the other hand *Kelebcilla pneumoni* and *Staphylococcus epidermidis* were resistant at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin magnesium complex

Antibacterial activity of clarithromycin magnesium complex as shown in table 3 reveal that *Staphylococcus aureus,* was resistant at 8, 4, 2, 1, 0.5 µg/ml concentration while susceptible at higher *MIC* values 128, 64, 32, 16 µg/ml concentration where as *Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris* and *Shigella dysentary* were found susceptible at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentration while *Kelebcilla pneumoni* and *Staphylococcus epidermidis* were resistant at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin calcium complex

Antibacterial activity of clarithromycin calcium complex as shown in table 4 reveal that *Staphylococcus aureus,* was resistant at 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentration while susceptible at higher *MIC* values 128, 64 µg/ml concentration. *Streptococcus faecalis,* was susceptible at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations. *Escherichia coli* was susceptible at 128, 64, 32 16, 8, 4, 2 µg/ml concentrations, while resistant at lower concentrations. On the other hand *Salmonella typhi* was susceptible at 128, 64, 32 16, 8, 4, 2, 1 µg/ml concentrations where as resistant at lower *MIC* value at 0.5 µg/ml concentration. *Proteus vulgaris* and *Shigella dysentary* were found susceptible at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations while *Kelebcilla pneumoni* and *Staphylococcus epidermidis* were found resistant at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin chromium complex

Clarithromycin chromium complex as shown in table 5 was susceptible against *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris* and *Shigella dysentery* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations while resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin manganese complex

Antibacterial activity of clarithromycin manganese complex as shown in table 6 reveal that *Staphylococcus aureus,* was resistant at lower *MIC* value at 1, 0.5 µg/ml concentration while susceptible at 128, 64, 32, 16, 8, 4, 2 µg/ml concentration where as *Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris and Shigella dysentary* were susceptible at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentration, while resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin iron complex

Antibacterial activity of clarithromycin iron complex (table 7) reveal that *Staphylococcus aureus,* was resistant at lower *MIC* value at 2, 1, 0.5 µg/ml concentration while susceptible at 128, 64, 32, 16, 8, 4 µg/ml concentration where as *Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris and Shigella dysentary* were found susceptible at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations. This complex was resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 4, 2, 1, 0.5 µg/ml concentrations and. 4, 2, 1, 0.5 µg/ml concentrations respectively where as susceptible at 128, 64, 32, 16, 8 and 128, 64, 32, 16, 8 µg/ml concentrations respectively.

Clarithromycin cobalt complex

Clarithromycin cobalt complex (table 8) was susceptible against *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris* and *Shigella*

dysentery at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations while resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin nickel complex

Antibacterial activity of clarithromycin nickel complex as shown in table 9 reveal that *Staphylococcus aureus,* was resistant at moderate *MIC* values (8, 4, 2, 1, 0.5 µg/ml concentrations), while susceptible at 128, 64, 32, 16 µg/ml concentration where as *Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris and Shigella dysentary* were found susceptible at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations whilst resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin copper complex

Clarithromycin copper complex (table 10) reveal that *Staphylococcus aureus,* was resistant at 16, 8, 4, 2, 1, 0.5 µg/ml concentration while susceptible at higher *MIC* values 128, 64, 32 µg/ml concentration. *Streptococcus faecalis, Escherichia coli, Salmonella typhi. Proteus vulgaris* were susceptible at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations while *Shigella dysentary* was found resistant at 8, 4, 2, 1, 0.5 µg/ml concentrations while susceptible at 128, 64, 32 16 µg/ml concentrations where as *Kelebcilla pneumoni* and *Staphylococcus epidermidis* were found resistant at 128, 64, 32 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin zinc complex

Clarithromycin zinc complex (table 11) was susceptible against *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris* and *Shigella dysentery* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations while resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Clarithromycin cadmium complex

Clarithromycin cadmium complex as shown in table 12 was susceptible against *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhii, Proteus vulgaris* and *Shigella dysentery* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations while resistant against *Kelebcilla pneumoni* and *Staphylococcus epidermidis* at 128, 64, 32, 16, 8, 4, 2, 1, 0.5 µg/ml concentrations.

Table 2

Clarithromycin reference standard

S. No	Organism	Concentration (µg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	R	R	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentery*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 3
Clarithromycin magnesium complex

S. No	Organism	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	R	R	R	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 4
Clarithromycin calcium complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	R	R	R	R	R	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	R	R	S	S	S	S	S	S	S
4	*Salmonella typhii*	R	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 5
Clarithromycin chromium complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	S	S	S	S	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 6
Clarithromycin manganese complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	S	S	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 7
Clarithromycin ferric complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	R	S	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	S	S	S	S	S
8	*Staphylococcus epidermidis*	R	R	R	R	S	S	S	S	S

Table 8
Clarithromycin cobalt complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	S	S	S	S	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 9
Clarithromycin nickel complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	R	R	R	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 10
Clarithromycin copper complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	R	R	R	R	R	R	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	R	R	R	R	R	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 11
Clarithromycin zinc complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	S	S	S	S	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

Table 12
Clarithromycin cadmium complex

S. No	Organisms	Concentration (μg/ml)								
		0.5	1	2	4	8	16	32	64	128
1	*Staphylococcus aureus*	S	S	S	S	S	S	S	S	S
2	*Streptococcus faecalis*	S	S	S	S	S	S	S	S	S
3	*Escherichia coli*	S	S	S	S	S	S	S	S	S
4	*Salmonella typhii*	S	S	S	S	S	S	S	S	S
5	*Proteus Vulgaris*	S	S	S	S	S	S	S	S	S
6	*Shigella dysentary*	S	S	S	S	S	S	S	S	S
7	*Kelepcilla pneumoni*	R	R	R	R	R	R	R	R	R
8	*Staphylococcus epidermidis*	R	R	R	R	R	R	R	R	R

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