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(54) **Titre : COMPOSITIONS PHARMACEUTIQUES ET METHODES POUR ERADICATION BACTERIENNE AMELIOREE**
(54) **Title: PHARMACEUTICAL COMPOSITIONS AND METHODS FOR IMPROVED BACTERIAL ERADICATION**

(57) **Abrégé/Abstract:**
Disclosed are once-a-day penicillin-type antibiotic products, comprising at least one modified release dosage form comprising penicillin-type antibiotics and pharmaceutically acceptable carriers, that are administered once-a-day in a dosage and for a number of days that provide a Total T>MIC that is sufficient to achieve at least the minimum amount of bacterial eradication for treatment of a bacterial infection. In one embodiment the products provide a $T>MIC_{90}$ in the serum for at least 5 hours (preferably for at least five consecutive hours), within a 24-hour dosing interval, for a given bacterial pathogen's MIC_{90}, while providing a total dosage of the penicillin-type antibiotic for a 24-hour dosing interval.

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(57) Abstract: Disclosed are once-a-day penicillin-type antibiotic products, comprising at least one modified release dosage form comprising penicillin-type antibiotics and pharmaceutically acceptable carriers, that are administered once-a-day in a dosage and for a number of days that provide a Total T>MIC that is sufficient to achieve at least the minimum amount of bacterial eradication for treatment of a bacterial infection. In one embodiment the products provide a $T>MIC_{90}$ in the serum for at least 5 hours (preferably for at least five consecutive hours), within a 24-hour dosing interval, for a given bacterial pathogen's MIC_{90}, while providing a total dosage of the penicillin-type antibiotic for a 24-hour dosing interval.

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PHARMACEUTICAL COMPOSITIONS AND METHODS FOR IMPROVED BACTERIAL ERADICATION

By: Henry H. Flanner, M.S.; Robert J. Guttendorf, Ph.D.; Susan P. Clausen, Ph.D.; Donald Treacy, Ph.D. and Beth A. Burnside, Ph.D.

This invention is directed to compositions and methods for improving the efficacy of *time-dependent* antibiotics when used in the treatment of humans or animals having bacterial infections. As used herein the term "time-dependent antibiotic" shall denote those *antimicrobial* compounds in general, and *antibiotics* in particular, having an efficacy that is believed to be *more* dependent on the daily *time* that the compound's concentration is above the minimum inhibitory concentration (MIC) rather than the number of *multiples* of that MIC achieved. Non-limiting examples of such *time-dependent antibiotics* shall include the penicillins, the beta-lactams, the cephalosporins, and the carbapenams. This invention is particularly directed to compositions and methods for improving the efficacy of *beta-lactam* antibiotics when used in the treatment of humans or animals having bacterial infections. This invention is more particularly directed to compositions and methods for improving the efficacy of *amoxicillin* and *cephalexin* when either is used in the treatment of humans or animals having bacterial infections.

In the bacterial infection treating discipline it has been widely accepted that the efficacy of any given dosing regimen utilizing a time-dependent antibiotic is founded upon achieving and / or maintaining a minimum inhibitory concentration (MIC) of the time-dependent antibiotic (not bound to serum proteins) for a certain minimum percentage of time in a day (i.e. a Daily T>MIC). (*See* Auckenthaler R, *Pharmacokinetic and pharmacodynamics of oral beta-lactam antibiotics as a two-dimensional approach to their efficacy*; J Antimicrob Chemother. 2002 Jul; 50 Suppl:13-7). (*See also* Vanderkooi O, Low D, *Antimicrobial Resistance and the Pneumococcus,* Infectious Diseases and Microbiology Rounds, May 2004, Vol. 3, Issue 5).

The instant invention provides both *new* and *improved* therapeutic paradigms and products for use with a given time-dependent antibiotic against a given bacterial pathogen having a known, or determinable, MIC for the given (or predictably similar acting) time-dependent antibiotic, which paradigms and products are derived from Applicants' development of a unique model parameter.

This model parameter may serve as a more accurate barometer for predicting the efficacy of a given dosing regimen than has the prior art's heretofore and enduring focus on daily T>MIC.

In accordance with an aspect of the present invention, there is provided a product and treatment regimen for use of a time-dependent antibiotic for treating a bacterial infection, in which the treatment is based on achieving a Total T>MIC to achieve a desired result, generally a percent eradication (or clinical outcome) of the bacterial pathogen that causes the infection.

The course of treatment may be determined for a specified dosage of antibiotic and for the MIC of the bacteria being treated by such antibiotic.

Based on PK data for the antibiotic of interest (or a closely related antibiotic) and the specified dosage, the daily time over MIC is determined.

In addition, based on actual treatment data (e.g., clinical trial data) for such antibiotic (or closely related antibiotic) there is determined the percent eradication (or clinical cure rate) of the bacteria over the specified course of treatment at a specified dosage.

By using (1) the daily time over MIC (Daily T>MIC) determined from the PK data and (2) the percent eradication (or clinical cure rate) over the course of treatment reported in the actual treatment, the total time over MIC (Total T>MIC) that achieved the bacterial eradication (or clinical cure rate) can be determined.

Such data is then plotted and art-recognized techniques may be used to establish an equation based on the data.

By way of mathematical and statistical modeling Applicants calculated the *actual* pharmacokinetic (PK) curves from the data from their own failed amoxicillin Phase III Trial against *Streptococcus pyogenes*, and from the data of published studies. Those published studies used various dosing regimens of penicillin VK *also* against *Streptococcus pyogenes*. This modeling led to Applicants' novel finding that *duration* of the dosing regimen is a statistically important factor in the bacterial eradication rate.

From those *actual* pharmacokinetic curves Applicants have developed their model parameter that takes dosing regimen *duration* into account as a determinant of bacterial eradication, while providing an excellent fit to the (PK) data of Applicants own failed amoxicillin Phase III Trial and to the (PK) data of the literature Applicants surveyed. Applicants have termed this novel treatment duration-encompassing model parameter as "Total T>MIC," which they define by the general equation:

$$\text{Total T>MIC} = \text{Daily T>MIC} \times \text{Duration of Dosing Regimen}$$

Thus, the Total T>MIC parameter includes both Daily T>MIC and Duration in a single parameter that provides a better model and explanation of the eradication rate of various regimens than either Daily T>MIC or Duration alone.

In accordance with one aspect of the *method* of the instant invention actual pharmacokinetic (PK) data is used to determine the concentration in serum of a drug at a given dosage, so as to further determine the Daily T>MIC provided by the drug at that given dosage. Studies reported in the literature are then consulted to determine the number of days that the drug was used at that given dosage to obtain a percent eradication. Based on the number of days of duration and the PK data, Applicants have found that they can then calculate the Total T>MIC that provides that percent eradication.

In another aspect this invention relates to an antibiotic product, to its formulation, and to its use in treating bacterial infections. Particularly, this invention relates to an antibiotic product that contains a *penicillin-type* antibiotic, as well as to the product's formulation and to its use in treating bacterial infections, wherein the infecting pathogen has an $MIC_{90} \geq 0.06$ μg/mL. for the penicillin-type antibiotic used. More particularly, this invention relates to such an antibiotic product that contains a *beta-lactam* antibiotic, as well as to the product's formulation and to its use in treating bacterial infections. Still more particularly, this invention relates to such a product that contains *amoxicillin*, to the product's formulation, and to the product's use in treating bacterial infections.

In accordance with an aspect of the invention there is provided a once-a-day penicillin-type antibiotic product for treating a bacterial infection in a patient or subject, comprising a penicillin-type antibiotic *composition*.

In accordance with a further aspect of the invention the penicillin-type antibiotic *composition* comprises at least one dosage form, which dosage form comprises at least one penicillin-type antibiotic and a pharmaceutically acceptable carrier. The dosage form(s) is / are formulated such that when the penicillin-type antibiotic composition is administered to a patient or subject in need thereof, the composition provides (or maintains) a concentration of the given penicillin-type antibiotic in the serum at or above the MIC_{90} for an infecting bacterial pathogen for at least 5 hours within a 24-hour dosing interval. The dosage form(s) is / are further formulated such that the penicillin-type antibiotic composition *provides* (and preferably *maintains*) a serum concentration of the given penicillin-type antibiotic that is $\geq$ 0.06 μg/mL., and such that the penicillin-type antibiotic composition contains the total dosage of the given penicillin-type antibiotic for a 24-hour dosing interval.

In a further aspect, the once-a-day pharmaceutical formulation providing a daily dosage of penicillin-type antibiotic such as to provide (or *maintain*) a serum concentration of penicillin-type antibiotic in a patient or subject at or above a bacterial pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) of a 24-hour dosing interval, comprises a modified release dosage form(s) or an immediate release dosage form(s) in combination with a modified release dosage form(s), with such modified release dosage form(s) being: a delayed release dosage form(s), a sustained (or extended) release dosage form(s), and / or combinations of the forgoing. Such sustained (or extended) release dosage forms may be formulated so that initiation of release of the penicillin-type antibiotic therefrom is not substantially delayed after administration of the penicillin-type antibiotic composition or it may be formulated so that initiation of release of the penicillin-type antibiotic therefrom is substantially delayed after administration of the penicillin-type antibiotic composition.

In accordance with a still further aspect of the invention the penicillin-type antibiotic composition may be labeled for use. Such labeling for use may comprise directives conveyed in any tangible or verbal medium of expression to administer the composition once-a-day to a patient or subject in need thereof, to treat an indication known, or suspected, to be caused by a bacterial pathogen, known, or suspected, to have an $MIC_{90} \geq$ 0.06 μg/mL. for the penicillin-type antibiotic used. As non-limiting examples of the forms in which and / or on which the labeling for use of the penicillin-type antibiotic composition may be expressed there may be mentioned: prescriptions;

protocols; labels; packaging; packaging inserts; coatings; embossings; scorings; trademarks and/or trade-dress, or portions thereof, such as by way of marks and/or dress, or portions thereof, denoting *daily*, *once-a-day*, *one-a-day*, *24-hour*, and like marks and/or like dress, or portions thereof; imprinted blister packets; capsule shells; and combinations of the foregoing.

In a preferred embodiment of the once-a-day product the penicillin-type antibiotic composition is formulated so as to *maintain* a concentration of the penicillin-type antibiotic in the serum of the patient or subject at or above the MIC_{90} of the infecting bacterial pathogen for that penicillin-type antibiotic for at least five *consecutive* hours out of a 24-hour dosing interval.

As referred to herein, and as is known in the art, the term "MIC_{90}" refers to the minimum concentration of a specific antibiotic that is required to inhibit the growth of ninety percent (90%) of the strains of a specific microoganism (bacterial pathogen) species.

As referred to herein, and as is known in the art, the term "penicillin-type antibiotic" generally and broadly refers to an antibiotic from the penicillin class of antibiotics, and shall include beta-lactams, such as amoxicillin.

According to one aspect of the present invention, there is provided a once-a-day amoxicillin antibiotic product comprising; first, second, and third amoxicillin antibiotic dosage forms, each of said amoxicillin antibiotic dosage forms comprising at least one amoxicillin antibiotic and a pharmaceutically acceptable carrier, said first amoxicillin antibiotic dosage form being, an immediate release dosage form, said second and third amoxicillin antibiotic dosage forms being delayed release dosage forms, wherein said second amoxicillin antibiotic dosage form comprises amoxicillin coated with a methacrylic acid copolymer dispersion, wherein the methacrylic acid copolymer dispersion comprises Eudragit® L30D-55, and said third amoxicillin antibiotic dosage form comprises amoxicillin coated with a first layer of the methacrylic acid copolymer dispersion and a second layer of AQ0AT AS-HF, and wherein each of said first, second, and third amoxicillin antibiotic dosage forms is for initiation of release at different times and Cmax of the total amoxicillin antibiotic for release from said amoxicillin antibiotic product is for achievment in less that 12 hours from administration; wherein said product contains the total dosage of amoxicillin, for

a 24-hour dosing interval.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical representation showing four different model fits of data, a portion of which is shown in Table 1, wherein percentage of bacterial eradication is expressed as functions of Total T>MIC.

Figure 2 is a graphical representation showing plots of fractional daily T>MIC plotted against the duration of treatment, wherein the various plots are the plots at different percentages of bacterial eradication.

Figure 3 is a flow chart illustrating the general procedure to make a multiparticulate tablet.

DETAILED DESCRIPTION OF THE INVENTION

In the treatment of bacterial infections, penicillin-type antibiotics, such as *beta-lactams*, are generally dosed in formulations that require multiple administrations over the course of any given 24-hour period. As is known in the art, such dosing regimens may be twice-a-day (b.i.d.), whereby the composition is administered every 12 hours; three times daily (t.i.d.), whereby the composition is administered every 8 hours; four times daily (q.i.d.), whereby the composition is administered every 6 hours; or such dosing regimens may even conceive of dosing the composition in excess of four administrations per day. Repeated administrations of a drug throughout a 24-hour period may be disruptive to meals or sleep, thereby presenting a significant inconvenience for patients. In the treatment of elderly or incapacitated patients multiple administration regimens can result in poor compliance, and hence an ineffective treatment of the infection. Existing immediate release and modified release *amoxicillin* formulations are designed and intended to be administered at least twice-a-day or more, to thereby prolong delivery of the drug throughout the duration of a 24-hour period. Some of these formulations contain relatively high doses of amoxicillin that can exacerbate untoward gastrointestinal side effects, including nausea and diarrhea.

Accordingly, there is a need in the art for effective once-a-day compositions and regimens, that would allow for less frequent dosing, but would neither compromise the effectiveness of the given antibiotic, nor require such a high dosage thereof as would exacerbate side effects or multiply production costs.

General Description of the Total T>MIC Aspects of the Invention

The data necessary for a determination of this modeling parameter such as drug, regimen, Days Tx, and Eradication are culled from the studies published in the literature, or otherwise known to the formulation artisan from clinical trials or similar sources. Table 1 is a compilation of a portion of the data from the various penicillin VK / *Streptococcus pyogenes* studies that the Applicants utilized to calculate the *actual* pharmacokinetic curve and to develop the Total T>MIC model parameter.

Table 1.

Drug	Regimen	MIC-90	Daily T>MIC	Days Tx	%Erad	Total T>MIC	Ref
Pen VK	500 TID	0.015	48.10%	0	7	0	Zwart et al, BMJ 2000
Pen VK	500 TID	0.015	48.10%	3	41	1.443	Zwart et al, BMJ 2000
Pen VK	500 TID	0.015	48.10%	7	72	3.367	Zwart et al, BMJ 2000
Pen VK	500 TID	0.015	48.10%	10	89	4.81	Ketek SBA; Norrby et al, Scand J Infect Dis 2001
Pen VK	600 TID	0.015	49.80%	10	86	4.98	Carbon et al, J Antimicrob Chemother 1995
Pen VK	250 QID	0.015	55.30%	10	100	5.53	McCarty 1993
Pen VK	250 QID	0.016	55.30%	10	85.5	5.53	Muller 1992
Pen VK	250 QID	0.03*	46.40%	10	82	4.64	Omnicef label; Tack et al, AAC 1998
Pen VK	250 TID	0.015	39.29%	10	96	3.929	Gerber et al, AJDC 1987
Pen VK	250 TID	0.015	39.29%	5	92	1.9645	Gerber et al, AJDC 1987
Pen VK	800 BID	0.015	35.00%	10	94	3.5	Stromberg et al, Scand J Infect Dis 1988
Pen VK	800 BID	0.015	35.00%	5	73	1.75	Stromberg et al, Scand J Infect Dis 1988
Pen VK	750 QD	0.015	17.30%	10	82	1.73	Gerber et al, AJDC 1989

- "Zwart et al, BMJ 2000" is Zwart S, Sachs AP, Ruijs GJ, Gubbels JW, Hoes AW, de Melker RA; Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults; BMJ; 2000 Jan 15; 320(7228):150-4.

- "Norrby et al, Scan J Infect Dis 2001" is Norrby SR, Rabie WJ, Bacart P, Mueller O, Leroy B, Rangaraju M, Butticaz-Iroudayassamy E; Efficacy of short-course therapy with the ketolide telithromycin compared with 10 days of penicillin V for the treatment of pharyngitis/tonsillitis; Scand J Infect Dis; 2001; 33:883–890.

- "Carbon et al, J Antimicrob Chemother 1995" is Carbon C, Chatelin A, Bingen E, Zuck P, Rio Y, Guetat F, Orvain J, A double-blind randomized trial comparing the efficacy and safety of a 5-day course of cefotiam hexetil with that of a 10-day course of penicillin V in adult patients with pharyngitis caused by group A beta-haemolytic streptococci; J Antimicrob Chemother; 1995 Jun; 35(6):843-54.

- "McCarty 1993" is McCarty JM; Comparative efficacy and safety of cefprozil versus penicillin, cefaclor and erthyromycin in the treatment of streptococcal pharyngitis and tonsillitis; Eur J Clin Microbiol Infect Dis; 1994 Oct; 13(10):846-50.

- "Muller 1992" is Müller O, Spirer Z, Wettich K.; Loracarbef versus penicillin V in the treatment of streptococcal pharyngitis and tonsillitis; Infection; 1992 Sep-Oct; 20(5):301-8.

- "Tack et al, AAC 1998" is Tack KJ, Henry DC, Gooch WM, Brink DN, Keyserling CH, and The Cefdinir Pharyngitis Study Group; Five-Day Cefdinir Treatment for Streptococcal Pharyngitis; Antimicrob. Agents Chemother; May 1998; 42:1073-1075.

- "Gerber et al, AJDC 1987" is Gerber MA, Randolph MF, Chanatry J, Wright LL, De Meo K, Kaplan EL; Five vs ten days of penicillin V therapy for streptococcal pharyngitis; Am J Dis Child; 1987 Feb; 141(2):224-7.

- "Stromberg et al, Scand J Infect Dis 1988" is Strömberg A, Schwan A, Cars O; Five versus ten days treatment of group A streptococcal pharyngotonsillitis: a randomized controlled clinical trial with phenoxymethylpenicillin and cefadroxil; Scand J Infect Dis; 1988; 20(1):37-46.

- "Gerber et al, AJDC 1989" is Gerber MA, Randolph MF, DeMeo K, Feder HM Jr., Kaplan EL; Failure of once-daily penicillin V therapy for streptococcal pharyngitis; Am J Dis Child; 1989 Feb; 143(2):153-5.

Fig. 1 shows four different model fits of data a portion of which is shown in Table 1 wherein % bacterial eradication is expressed as functions of Total T>MIC. Fig. 1 also graphically illustrates how the model may be used to select regimens having adequate doses (which relate to the Daily T>MIC) and sufficient Durations (more importantly), so as to achieve desired eradication of *Streptococcus pyogenes*, or desired eradication of *other* infectious microbial species that have been similarly studied in *existing* literature and / or clinical trials, or that may be similarly studied in *future* literature and / or clinical trials.

It should be understood that in accordance with the invention, the model parameter, Total T>MIC, can be accurately related to the observed eradication of various regimens through *various* mathematical equations and functions. For the data presented in Figure 1 either a simple Emax model or a sigmoid Emax model can provide an adequate fit. However, in accordance with the invention there are *manifold* mathematical models and relationships that can be used to provide an adequate relationship of Total T>MIC to % Eradication, as is demonstrated by the four *different* model fits shown in Figure 1. One of ordinary skill in the art of PK / PD modeling will select which model is appropriate for the given data set depending on his experience, the type and origin of the data, and a variety of statistical measures such as akaike information criterion, root mean square error, r^2, residual analysis, and others. The artisan of ordinary skill in PK / PD modeling will appreciate that very often more than one mathematical model form can provide an adequate fit.

Example 1

Total T>MIC in a Simple Emax Model or Sigmoid Emax Model

Determination of the Total T>MIC parameter requires two separate terms, Duration and Daily T>MIC. Both of these are derived from the dosing regimen or clinical trial studied and / or

reported in the literature. For example, some of the data in Figure 1 is presented in tabular form in Table 1 above.

The information in Table 1 was collected from several studies published in the literature. Information such as drug, regimen, Days Tx and Eradication can be taken directly from the literature articles. Information such as the MIC will often have been determined as part of the study and may be reported in the article, but in many cases it may not have been determined or reported. In those cases wherein the MIC was not determined and reported Applicants assumed that the MIC was equal to 0.015μg/mL, the MIC determined in the Phase III Clinical Trial conducted by Applicants.

The Daily T>MIC must also be calculated for each different regimen, and at the *relevant* MIC. This information was not presented in any of the articles and so it was calculated by Applicants. The Daily T>MIC is calculated for each regimen by creating a plasma profile from pharmacokinetic data published in the literature. Prior to creating the plasma profile a pharmacokinetic model is developed from plasma profiles from one or more doses reported in the literature. The PK model is first checked for accuracy against the profiles used in the derivation of the model and then the PK profile of regimens for which *actual* plasma data do not exist are *simulated* so that the Daily T>MIC may be calculated. The models are industry standard compartmental models, generated with WinNonlin, a common program used in the pharmaceutical industry for pharmacokinetic analysis and modeling.

Once the Daily T>MIC for each regimen has been calculated, the Total T>MIC is calculated by multiplying the Daily T>MIC by the Duration of Therapy (Days Tx in the table). Thus a composite parameter, Total T>MIC, is constructed that includes *both* factors relevant to eradication of *Streptococcus pyogenes* by a given regimen. The equation can then be used to determine the Total T>MIC required to achieve eradication rates ≥ 85% (or any other desired eradication rate).

Penicillin and amoxicillin are both beta-lactam antibiotics and have the same mechanism of action against *Streptococcus pyogenes*. Therefore, the pen VK Total T>MIC model can be applied to assist in the prediction or selection of the appropriate dosing regimen of amoxicillin Pulsys™. The Pulsys™ technology is illustrated in U.S. Patent 6,544,555.

Applicants found that when the Daily T>MIC of

Applicants' once-daily 775 mg tablets and the clinical trial's 7 day dosing Duration were plugged

into the Total T>MIC model the predicted eradiation rate was 87%. The actual eradication rate was 77% thus the prediction is within the error of the model.

In order to determine the *optimum* dose and duration of amoxicillin Pulsys™ the Daily T>MIC of amoxicillin was obtained from pharmacokinetic studies conducted by Applicants on various amoxicillin Pulsys™ formulations. Bearing in mind that it is desirable from therapy compliance, convenience, and marketing perspectives to keep the duration of a dosing regimen to 10 days or less, Applicants selected a formulation that provided a Daily T>MIC that when multiplied by 10 days of Duration exceeded the Total T>MIC corresponding to an 85% (actually 90% was used to provide a margin of error) eradication rate.

Emax is a typical model used to describe pharmacodymic relationships between a parameter of interest and a pharmacodynamic effect. Illustrating an aspect of the instant invention a simple Emax model provides an excellent relationship between the Total T>MIC parameter and the eradication rate.

In accordance with an aspect of one embodiment of the instant invention a simple Emax model takes the following mathematical form:

$$E = E0 + (Emax - E0)*(TotalT>MIC/(Total\ T>MIC + Total\ T>MIC50)$$

wherein,

E is the % eradication, these values are taken from the reference data set;
E0 is the % eradication at Total T>MIC of 0, i.e. spontaneous eradication or placebo effect;
Emax is the maximimum eradication, set to a constant 100% in the model;
Total T>MIC is the parameter calculated by multiplying daily T>MIC times the number of days the product was administered; and
Total T>MIC50 is a fitted parameter that corresponds to Total T>MIC where E=50%.

In development of the above equation for a given set of reference literature data, a computer

program such as WinNonlin, Statgraphics, SigmaPlot, SAS, JMP, Excel or other modeling software is employed to fit the parameters E0 and Total T>MIC50. For the data in Figure 1 the fitted Emax model was determined to be:

$$\%\text{Eradication} = 5.75 + 94.3*\text{Total T>MIC}/(\text{Total T>MIC} + 0.74)$$

This equation can now be utilized to solve for the *optimum* duration to achieve a given eradication rate. This is especially useful for developing novel products, because once the daily time above MIC of the novel product is determined, the number of studies required to determine an effective dosing regimen can be greatly reduced, thus saving valuable time to market and clinical study costs. It is to be understood that the constants of the hereinabove equation will vary depending on the drug formulation that is used.

Example 2

General Linear Modeling Methodology

As earlier noted, alternative modeling methodologies may also be employed in practicing the instant invention. One such method is termed general linear modeling (GLM) and is a common method for developing models that include multiple variables. The advantage of GLM is that each of the important variables, Duration and Daily T>MIC, are modeled *independently* and do not have to be combined into a *single* composite factor. In application of the GLM with 2 variables (Duration and Daily T>MIC) the data are handled in 3 dimensions, instead of 2 as for the Total T>MIC case. This can lead to a greater understanding of the relationship between Duration and Daily T>MIC, and detection of possible synergistic effects *not* detected in the single variable model. To illustrate this two dosing regimens may be considered, wherein Formulation A provides 100% Daily T>MIC and is administered for 5 days thereby providing a Total T>MIC of 5 days; and wherein Formulation B provides 50% Daily T>MIC and is administered for 10 days thereby providing a Total T>MIC of 5 days. There is no guarantee that the eradication rate from both regimens would be equivalent, but the Total T>MIC model would predict them to be equivalent. The GLM model would have two different points on a 3 dimensional surface for the two regimens in question, thus the GLM model is able account for effects not detectable in the single parameter Total T>MIC model. In fact, the synergy term in the GLM is actually the Total T>MIC parameter. A contour plot of the response surface from the GLM approach for the data shown in Figure 1 is provided below in Figure 2.

Succinctly, GLM is a statistical modeling approach based on the determination of significant factors in a data set, and finding coefficients to those factors that fit the data. A benefit of this type of approach when used for the data in Figure 1 is that it breaks the Total T>MIC into its component parts, daily T>MIC and Duration, and weights each according to the data. Total T>MIC may also be included in the model as an interaction term if it is determined be a significant factor. In this approach there is no specific model form as there is with the Emax model: the model form is based on the analysis of data and can take many forms such as a simple linear or complex polynomial form. Typically a statistical software package, such as Statgraphics, SAS, JMP, Statistica, or Minitab is used to develop a GLM. For the data in Figure 1 a general linear model approach yielded the following equation:

$$\% \text{ Eradication} = 6.81 * \text{Duration} + 0.48 * \text{Daily T>MIC}$$

wherein,

% Eradication is the eradication rate;

Duration is the number of days the dose is administered; and

Daily T>MIC is the percent T>MIC per day provided by the dose regimen.

The GLM equation may now be solved as the Emax model above to derive the *optimum* duration given a T>MIC or the required daily T>MIC for a known duration. This model approach provides an improved ability to fit effects that are dependent upon more than one factor. The Total T>MIC is such a parameter because it is actually made up of two factors, duration and daily T>MIC. The GLM provides a means to generate different eradication rates in the case where two regimens provide the same Total T>MIC, such as when a product with 50% daily T>MIC is administered for 10 days versus a product with a 100% daily T>MIC administered for 5 days.

Figure 2 illustrates the strong effect of Duration on % eradication. Relative changes in Duration increase % eradication more than the same magnitude of change in Daily T>MIC. To Applicants' knowledge this effect has never been disclosed previously and is the basis for changing the amoxicillin Pulsys™ regimen from 7 days to 10 days.

Example 3

Modified Multiple Parameter Emax

One potential limitation of the GLM approach is that in the case of lower order models there is a potential for the predicted effect to go above the maximum allowable effect, e.g. 100% eradication. In order to overcome this limitation, the inventors have modified the simple Emax model to be able to incorporate more than just the Total T>MIC term. This improved equation provides the ability to model each important term in the data set, Duration, Daily T>MIC and Total T>MIC, thus best fitting each data point in the appropriate factor space, but adding the maximum effect limitation, e.g. 100% eradication. The equation has the same form as the simple Emax model, except that the Total T>MIC50 term is changed to a term that incorporates the Duration and the Daily T>MIC, as shown below:

$$E = E0 + (Emax-E0)*(\text{Total T>MIC})/(\text{Total T>MIC} + (a + b*\text{Duration} + c*\text{Daily T>MIC}))$$

wherein,

E = Eradication rate, expressed here as a fraction not as percent in this model;
E0 is the fraction eradicated at a Total T>MIC of 0, i.e. spontaneous eradication or placebo effect;
Emax is the maximum eradication, set to a constant of 1.0 (representing 100% in this model);
Total T>MIC is the parameter calculated by multiplying daily T>MIC times the number of days the product was administered;
Duration is the number of days the dose is administered;
Daily T>MIC is the fraction T>MIC per day provided by the dose regimen; and
a, b, and c are coefficients determined during the fitting of the reference data.

In development of the above equation for a given set of reference literature data, a computer program such as Statgraphics, SigmaPlot, SAS, JMP, Excel, or other modeling software is employed to fit the parameters E0, a, b, and c. For the data in Figure 1 the fitted model was determined to be:

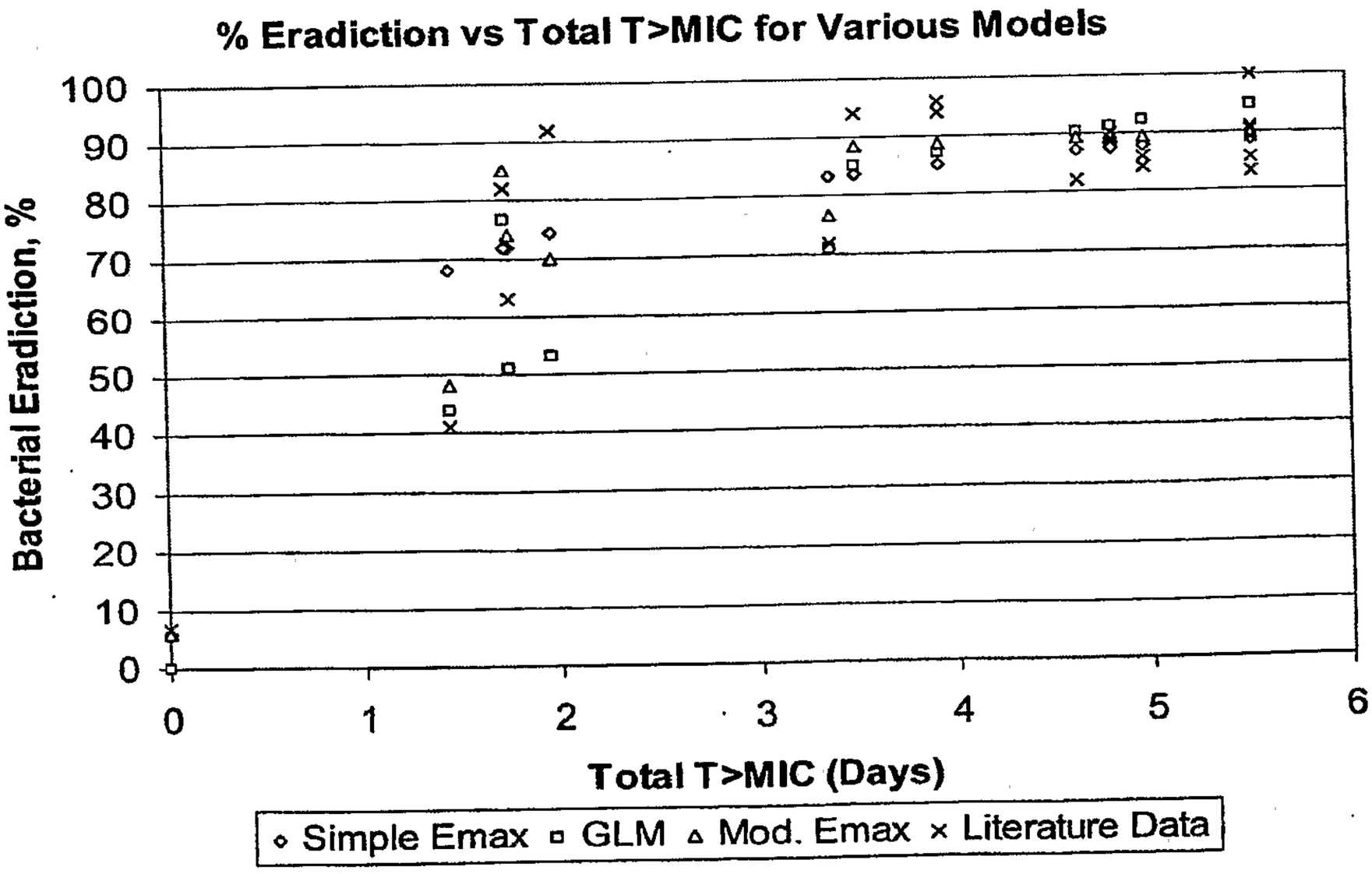
$$\text{Fraction Eradicated} = 0.058 + 0.942*\text{Total T>MIC} /$$

(-2.99 + 0.316*Duration + 10.94*Daily T>MIC)

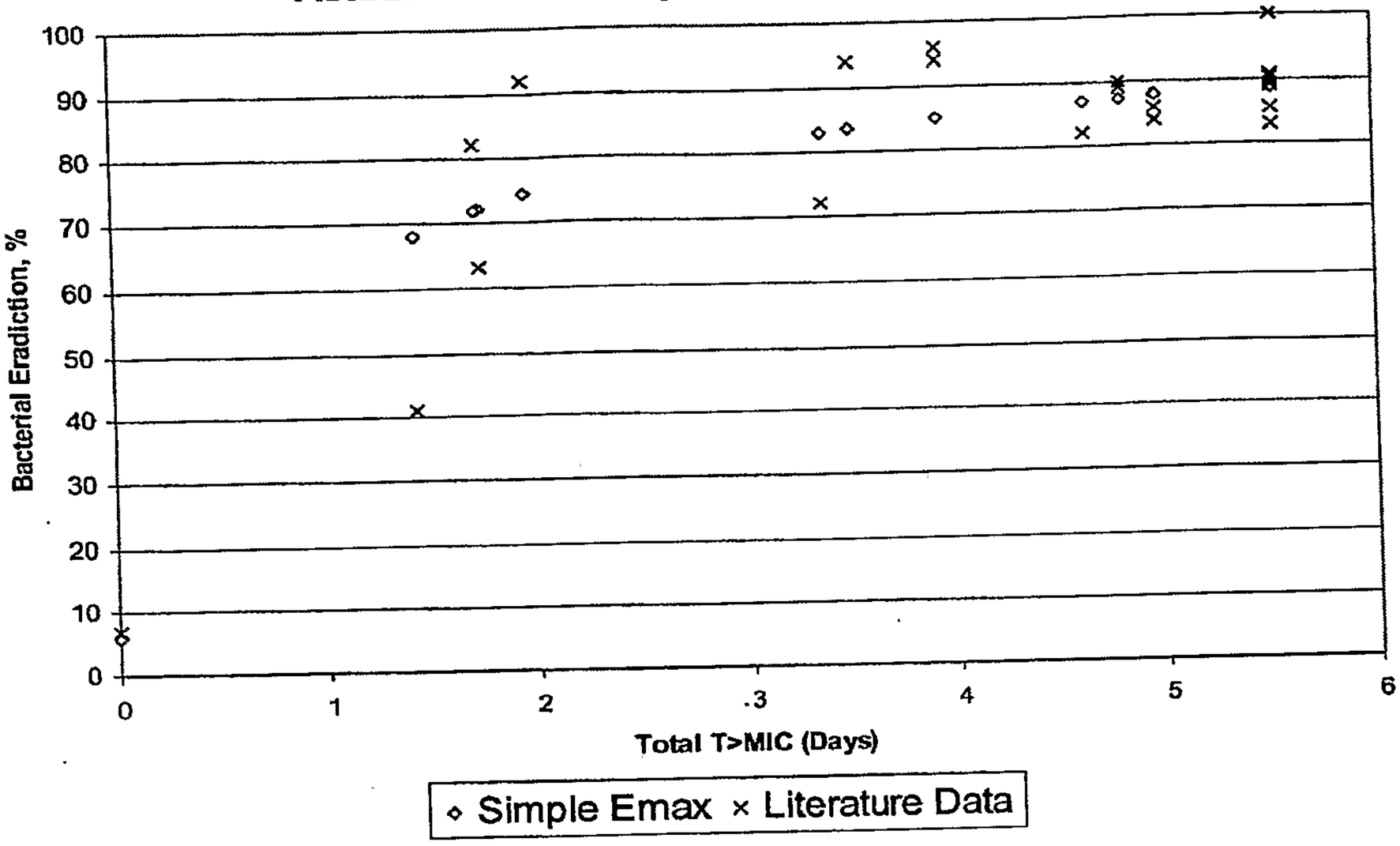
This equation may now be utilized to determine the *optimum* Duration of a novel therapy provided the daily T>MIC is known or vice versa. The equation developed here can maintain the maximum effect below the 100% limit, and, *unlike* the simple Emax model, can fit individual points with a common Total T>MIC *but*, different duration or daily T>MIC, that may lead to different eradication rate because of the response to duration and daily T>MIC, can be different.

Each of the three different approaches above are only example of the types of model fitting that may be conducted in the type of analysis disclosed by the inventors. Depending on the nature of the data set being modeled one of the above forms may be preferred, or perhaps a modification of the above models will be required. One skilled in the art will be able to develop alternative models by rearranging model terms or using different model forms, and, these modifications are within the scope of the present invention.

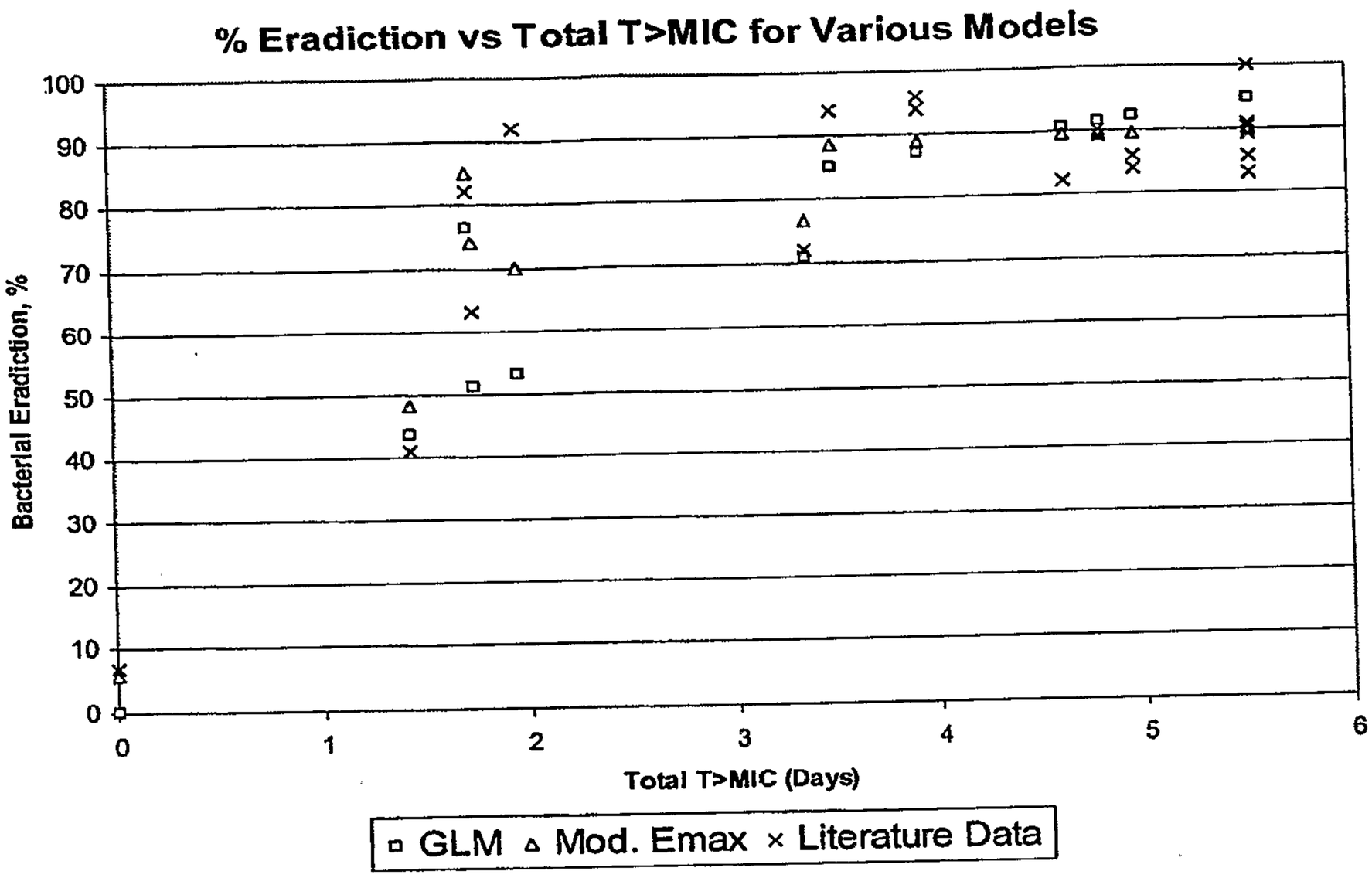
For further illustration, below is a plot of the fitted data from all models vs the actual literature data.



For further illustration, below is a plot of the actual data vs. the Simple Emax fitted data.



For further illustration, below is a plot of the actual literature data vs the GLM and modified Emax models.



In preferred embodiments of the product the desired percentage of eradication of the known bacterial pathogen is one that achieves clinical efficacy in the host for a condition caused by, or suspected to be caused by, the bacterial pathogen.

In a preferred embodiment of the product the antibiotic is a beta-lactam antibiotic. In a more preferred embodiment of the product the antibiotic is a penicillin antibiotic. In a particularly preferred embodiment of the product the antibiotic is amoxicillin.

In preferred embodiments of the method the desired percentage of eradication of the known bacterial pathogen is one that achieves clinical efficacy in the host for a condition caused by, or suspected to be caused by, the bacterial pathogen.

In a preferred embodiment of the method the antibiotic is a beta-lactam antibiotic. In a more preferred embodiment of the method the antibiotic is a penicillin antibiotic. In a particularly preferred embodiment of the method the antibiotic is amoxicillin.

In another embodiment of the invention, there is provided a once-a-day antibiotic *product* comprised of at least one modified release antibiotic dosage form. The modified release antibiotic dosage form comprises at least one antibiotic and a pharmaceutically acceptable carrier. The modified release antibiotic dosage form is formulated such that it contains the *proper dose* of antibiotic as a single unit for repeated once-daily administration in a treatment regimen of *specified duration*, whereby a plurality of once-daily administrations of the units ultimately achieves a desired "Total T>MIC" in the patient's blood.

In another embodiment of the invention, there is provided a *method* of therapeutically effectively treating a patient in need of treatment for bacterial infection, comprising administering a once-a-day antibiotic product comprised of at least one modified release antibiotic dosage form. The modified release antibiotic dosage form comprises at least one antibiotic and a pharmaceutically acceptable carrier. The modified release antibiotic dosage form is formulated such that it contains the *proper dose* of antibiotic as a single unit for repeated once-daily administration in a treatment regimen of *specified duration*, whereby a plurality of once-daily administrations of the units ultimately achieves a desired "Total T>MIC" in the patient's blood.

In another embodiment of the invention, there is provided a once-a-day antibiotic *product* comprised of at least one modified release antibiotic dosage form. The modified release antibiotic dosage form comprises at least one antibiotic and a pharmaceutically acceptable carrier. The modified release antibiotic dosage form is administered such that it provides the *proper duration* of antibiotic therapy as a single unit for repeated once-daily administration in a treatment regimen of *specified daily dosage*, whereby a plurality of once-daily administrations of the units ultimately achieves a desired "Total T>MIC" in the patient's blood.

In another embodiment of the invention, there is provided a *method* of therapeutically effectively treating a patient in need of treatment for bacterial infection, comprising administering a once-a-day antibiotic product comprised of at least one modified release antibiotic dosage form. The modified release antibiotic dosage form comprises at least one antibiotic and a pharmaceutically acceptable carrier. The modified release antibiotic dosage form is administered such that it provides the *proper duration* of antibiotic therapy as a single unit for repeated once-daily administration in a treatment regimen of *specified daily dosage*, whereby a plurality of once-daily administrations of the

units ultimately achieves a desired "Total T>MIC" in the patient's blood. It is to be understood that the embodiment of the invention with respect to total time over MIC_{90} may or may not incorporate a formulation that provides for the herein described daily time over MIC; however, such a formulation is preferred.

Although embodiments of the instant invention allow for a Daily T>MIC that is less than that generally believed to be required in the art, in preferred embodiments the Daily T>MIC is generally not less than about 20%.

In one preferred embodiment the invention is directed to an antibiotic product that contains a *beta-lactam* antibiotic, as well as to the product's formulation and to its use in treating bacterial infections, wherein the infecting pathogen has an $MIC_{90} \geq 0.015$ µg/mL. for the *beta-lactam* antibiotic used. In a more preferred embodiment, the invention is directed to such an antibiotic product that contains a *beta-lactam* antibiotic, as well as to the product's formulation and to its use in treating bacterial infections, wherein the infecting pathogen has an $MIC_{90} \geq 0.015$ µg/mL. for the *beta-lactam* antibiotic used. In a particularly preferred embodiment, the invention is directed to such an antibiotic product that contains *amoxicillin*, as well as to the product's formulation and to its use in treating bacterial infections, wherein the infecting pathogen has an $MIC_{90} \geq 0.015$ µg/mL. for *amoxicillin*.

Daily T>MIC Embodiments

In one aspect the present invention provides for a once-a-day pharmaceutical formulation providing a *daily dosage* of penicillin-type antibiotic, such as to provide a serum concentration of penicillin-type antibiotic in a patient or subject at or above an infecting bacterial pathogen's drug-specific MIC_{90} for at least five hours within the 24-hour period following administration.

In a preferred aspect the present invention provides for a once-a-day pharmaceutical formulation providing a *daily dosage* of penicillin-type antibiotic, such as to *maintain* a serum concentration of penicillin-type antibiotic in a patient or subject at or above an infecting bacterial pathogen's drug-specific MIC_{90} for at least five *consecutive* hours within the 24-hour period following administration.

More specifically, in accordance with one aspect of the invention there is provided a once-a-day penicillin-type antibiotic composition comprising at least one dosage form that contains a penicillin-type antibiotic and a pharmaceutically acceptable carrier. In a further aspect of the invention the once-a-day penicillin-type antibiotic composition is formulated so that when administered to a patient, or to subject, it *provides* a $T>MIC_{90}$ in the serum for at least 5 hours within the 24-hour period following administration. In a still further aspect of the invention the serum concentration that is *provided* for at least 5 hours is one that is ≥ 0.06 μg/mL. In a yet still further aspect of the invention the once-a-day penicillin-type antibiotic composition contains the total dosage of the penicillin-type antibiotic for a twenty-four hour dosing interval.

Preferably, in one aspect of the invention there is provided a once-a-day penicillin-type antibiotic composition comprising at least one dosage form that contains a penicillin-type antibiotic and a pharmaceutically acceptable carrier. In a further preferred aspect of the invention the once-a-day penicillin-type antibiotic composition is formulated so that when administered to a patient, or to a subject, it *maintains* a $T>MIC_{90}$ in the serum for at least 5 *consecutive* hours within the 24-hour period following administration. In a still further preferred aspect of the invention the serum concentration that is *maintained* for at least 5 *consecutive* hours is one that is ≥ 0.06 μg/mL. In a yet still further preferred aspect of the invention the once-a-day penicillin-type antibiotic composition contains the total dosage of the penicillin-type antibiotic for a twenty-four dosing interval.

In one once-a-day embodiment, the composition *provides* a serum concentration of penicillin-type antibiotic in a patient or subject that is at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen causing the infection in the patient or subject, for at least five hours within the 24-hour period following administration.

In another once-a-day embodiment, the composition *maintains* a serum concentration of penicillin-type antibiotic in a patient or subject that is at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen causing the infection in the patient or subject, for at least five *consecutive* hours within the 24-hour period following administration.

In one embodiment the composition *provides* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's drug-specific MIC_{90} for at

least five hours within the 24-hour period following administration. In another embodiment the composition *provides* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for at least six hours within the 24-hour period following administration. In another embodiment the composition *provides* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for at least eight hours within the 24-hour period following administration. In another embodiment the composition *provides* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for at least nine hours within the 24-hour period following administration. Generally, the composition does not *provide* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for more than nine hours within the 24-hour period following administration.

In one embodiment the composition *maintains* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's drug-specific MIC_{90} for at least five *consecutive* hours within the 24-hour period following administration. In another embodiment the composition *maintains* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for at least six *consecutive* hours within the 24-hour period following administration. In another embodiment the composition *maintains* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for at least eight *consecutive* hours within the 24-hour period following administration. In another embodiment the composition *maintains* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for at least nine *consecutive* hours within the 24-hour period following administration. Generally, the composition does not *maintain* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's MIC_{90} for more than nine *consecutive* hours within the 24-hour period following administration.

In particularly preferred embodiments the penicillin-type antibiotic is amoxicillin.

Generally, the daily dosage of penicillin-type antibiotic will depend on various factors such as the bacterial pathogen to be targeted, the known resistance or susceptibility of the bacterial pathogen to the given penicillin-type antibiotic, and the known MIC_{90} of the given bacterial pathogen for the given penicillin-type antibiotic.

Generally, the daily dosage of amoxicillin used in the invention comprises from about 250 to about 3000 mg. Preferably the daily dosage of amoxicillin used in the invention comprises from about 500 to about 2500 mg. More preferably the daily dosage of amoxicillin used in the invention comprises from about 775 to about 1550 mg.

In an embodiment the daily dosage of amoxicillin is 775 mg.

In a further aspect, the present invention provides a method of treating infection in a patient or subject caused by bacterial pathogens, comprising administering to the patient or subject once-a-day the herein-above described and herein-below described penicillin-type antibiotic compositions so as to maintain a serum concentration of penicillin-type antibiotic in a patient or subject at or above a given bacterial pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) of a 24-hour dosing interval. As non-limiting examples of the infectious bacterial pathogens against which the herein-above described and herein-below described penicillin-type antibiotic compositions may be used there may be mentioned Aerobic Gram-positive microorganisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococci* (Groups C, F, G), and *Viridans* group streptococci; Aerobic Gram-negative microorganisms such as *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Bordetella pertussi*, *Legionalla pneumophila*, *Pasteurella multocida* and *Klebsiella pneumoniae*; Anaerobic Gram-positive microorganisms such as *Clostridium perfringens*, *Peptococcus niger*, and *Propionibacterium acnes*; Anaerobic Gram-negative microorganisms such as *Prevetolla melaninogenica* (formerly *Bacterocides melaninogenicus*); *Mycoplasma pneumoniae*; *Chlamydia pneumoniae*; *Mycobacterium avium complex* (MAC) consisting of *Mycobacterium avium* and / or *Mycobacterium intracellulare*; *Helicobacter pylori*; *Bacterocides fragilis*; *Fusobacterium nucleatum*; *Peptostreptococcus magnus*; *Peptostreptococcus micros*; and *Escherichia coli*.

In a further aspect, the once-a-day pharmaceutical formulation providing a daily dosage of penicillin-type antibiotic such as to provide (or *maintain*) a serum concentration of penicillin-type antibiotic in a patient or subject at or above a bacterial pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) of a 24-hour dosing interval, may comprise a modified release dosage form(s) or an immediate release dosage form(s) in combination with a

modified release dosage form(s), with such modified release dosage form(s) being: a delayed release dosage form(s), a sustained (or extended) release dosage form(s), and / or combinations of the forgoing. The formulating of such dosage forms will be apparent to those of skill in the art in view of the disclosures herein further guided by the disclosures of U.S. Patent Application Serial Numbers 10/894,787; 10/894,786; 10/894,994; 10/917,059; 10/922,412; and 10/940,265; and by the disclosures of U.S. Patents 6,544,555; 6,623,757; and 6,669,948.

In one preferred embodiment the once-a-day pharmaceutical formulation providing a daily dosage of penicillin-type antibiotic, such as to provide (or *maintain*) a serum concentration of penicillin-type antibiotic in a patient or subject at or above a bacterial pathogen's drug-specific MIC_{90} for at least five hours, (preferably for at least five *consecutive* hours) of a 24-hour dosing interval, comprises a sustained (or extended) release dosage form(s). In this embodiment the sustained (or extended) release dosage form(s) is designed and intended to release the penicillin-type antibiotic slowly over time, such as to *maintain* a serum concentration of penicillin-type antibiotic in a patient or subject at or above a bacterial pathogen's drug-specific MIC_{90} for at least five *consecutive* hours.

In a preferred embodiment, the penicillin-type antibiotic composition is a once a day composition, whereby after administration of the penicillin-type antibiotic composition, no further composition is administered during the day; i.e., the preferred regimen is that the composition is administered only once over a twenty-four hour period. Thus, in accordance with the present invention, there is a single administration of a penicillin-type antibiotic composition formulated so as to provide (or *maintain*) a serum concentration of penicillin-type antibiotic in a patient or subject at or above a bacterial pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) within the 24-hour period following administration. The term single administration means that the total penicillin-type antibiotic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or capsule or two or more thereof, provided that they are administered at essentially the same time.

In an embodiment of the invention the penicillin-type antibiotic composition comprising at least one modified release dosage form formulated so as to provide (or maintain) a concentration of the given penicillin-type antibiotic in the serum at or above the MIC_{90} for an infecting bacterial

pathogen for at least 5 hours within a 24-hour dosing interval, is further formulated so as to achieve Cmax in the serum for the total penicillin-type antibiotic released from the composition in less than about 12 hours following administration of the penicillin-type antibiotic composition, or following initial release of penicillin-type antibiotic from the penicillin-type antibiotic composition. In this embodiment (as in all embodiments) the dosage form(s) is / are further formulated such that the penicillin-type antibiotic composition provides (and preferably maintains) a serum concentration of the given penicillin-type antibiotic that is ≥ 0.06 μg/mL., and such that the penicillin-type antibiotic composition contains the total dosage of the given penicillin-type antibiotic for a 24-hour dosing interval.

In another embodiment of the present invention there is provided a penicillin-type antibiotic pharmaceutical composition which is comprised of at least two, preferably at least three, penicillin-type antibiotic dosage forms (at least one of which is a modified release dosage form). Such dosage forms are formulated so that each of the dosage forms has a different release profile and so that the composition provides (and preferably maintains) a penicillin-type antibiotic concentration in the patient's serum that equals or exceeds the pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) within the 24-hour period following administration.

In another embodiment of the invention there are at least two, preferably at least three dosage forms (at least one of which is a modified release dosage form), each of which has a different release profile, the release profile of each of the dosage forms being such that the dosage forms each start release of the penicillin-type antibiotic contained therein at different times after administration of the penicillin-type antibiotic composition, and the composition provides (and preferably maintains) a penicillin-type antibiotic concentration in the patient's serum that equals or exceeds the pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) within the 24-hour period following administration.

Thus, in accordance with this embodiment of the present invention, there is provided a single or unitary antibiotic composition that has contained therein at least two, preferably at least three penicillin-type antibiotic dosage forms (at least one of which is a modified release dosage form), each of which has a different release profile, whereby the penicillin-type antibiotic contained in each of such dosage forms is released at different times, and the penicillin-type antibiotic composition provides a daily dosage of penicillin-type antibiotic, such as to provide (or *maintain*) a serum

concentration of penicillin-type antibiotic in a patient or subject at or above a bacterial pathogen's drug-specific MIC_{90} for at least five hours (preferably at for least five *consecutive* hours) within the 24-hour period following administration.

In accordance with another embodiment of the invention, the antibiotic composition may be comprised of at least four different dosage forms, each of which starts to release the penicillin-type antibiotic contained therein at different times after administration of the penicillin-type antibiotic composition, and the composition provides (or *maintains*) a penicillin-type antibiotic concentration in the patient's serum that equals or exceeds the pathogen's drug-specific MIC_{90} for at least five hours (preferably for at least five *consecutive* hours) within the 24-hour period following administration.

The penicillin-type antibiotic composition generally does not include more than five dosage forms with different release times.

In accordance with another embodiment, the penicillin-type antibiotic composition has an overall release profile such that when administered the maximum serum concentration of the total antibiotic released from the composition is reached in less than twelve hours, preferably in less than eleven hours, and that maximum serum concentration is at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen.

In all embodiments of the invention as herein-above and herein-below described the penicillin-type antibiotic is formulated so as to provide (or maintain) a penicillin-type antibiotic concentration in the patient's serum that equals or exceeds the pathogen's drug-specific MIC, for at least five hours (preferably for at least five consecutive hours) within a 24-hour period when administered once-a-day.

In all embodiments of the invention the composition is designed and intended to provide a serum concentration of $\geq$ 0.06 μg/mL. of penicillin-type antibiotic for at least 5 hours.

In preferred embodiments of the invention the composition is designed and intended to provide a serum concentration of $\geq$ 0.06 μg/mL. of penicillin-type antibiotic for at least 5 *consecutive* hours.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the composition may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary antibiotic composition. Thus, as a non-limiting example, a three dosage form antibiotic composition may include a first dosage form in the form of a tablet that is an immediate release tablet, and may also include two or more additional tablets, each of which provides for a delayed release or a sustained release of the penicillin-type antibiotic, as hereinabove described, to provide (and preferably maintain) a serum concentration of the penicillin-type antibiotic at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen for at least five (preferably for at least five *consecutive* hours) hours within a 24-hour dosing interval.

After administration to a subject, the concentration of antibiotic may be measured in whole blood or plasma obtained from the subject. As known in the art, such measured antibiotic concentration includes antibiotic bound to serum proteins. As known in the art, unbound antibiotic concentration may be determined by use of a correction factor based on known or measured binding of the antibiotic to serum proteins.

Further Description of the Invention

In accordance with an aspect of the invention there is provided a once-a-day beta-lactam antibiotic product for treating a bacterial infection in a patient or subject, comprising a beta-lactam antibiotic *composition*.

In particularly preferred embodiments the beta-lactam antibiotic is amoxicillin.

As herein-above discussed and herein-below discussed, the daily dosage of beta-lactam antibiotic will depend on various factors such as the bacterial pathogen to be targeted, the known resistance or susceptibility of the bacterial pathogen to the given beta-lactam antibiotic, and the known MIC_{90} of the given bacterial pathogen for the given beta-lactam antibiotic.

Generally, the daily dosage of amoxicillin used in the invention comprises from about 250 to about 3000 mg. Preferably the daily dosage of amoxicillin used in the invention comprises from about 500 to about 2500 mg. More preferably the daily dosage of amoxicillin used in the invention

comprises from about 775 to about 1550 mg.

In an embodiment the daily dosage of amoxicillin is 775 mg. and the optimal duration of therapy taking into account therapy, compliance, convenience, and marketing concerns, is 10 days.

In an embodiment the daily dosage of amoxicillin is 775 mg. and the optimal duration of therapy taking into account only efficacy concerns, is 10 days.

In a further aspect, the present invention provides a method of treating various indications in a patient, or in a subject, caused by bacterial pathogens, which treating comprises administering to the patient, or to the subject, once-a-day the herein-above described and herein-below described beta-lactam antibiotic compositions. As non-limiting examples of the indications for which the herein-above described and herein-below described beta-lactam antibiotic compositions may be used to treat a patient there may be mentioned: pharyngitis, tonsillitis, sinusitis, bronchitis, pneumoniae, ear infection (otitis media), uncomplicated skin and skin structure infections, and uncomplicated urinary infections.

As non-limiting examples of the infectious bacterial pathogens against which the herein-above described and herein-below described beta-lactam antibiotic compositions may be used there may be mentioned Aerobic Gram-positive microorganisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococci* (Groups C, F, G), and *Viridans* group streptococci; Aerobic Gram-negative microorganisms such as *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Bordetella pertussi*, *Legionalla pneumophila*, *Pasteurella multocida* and *Klebsiella pneumoniae*; Anaerobic Gram-positive microorganisms such as *Clostridium perfringens*, *Peptococcus niger*, and *Propionibacterium acnes*; Anaerobic Gram-negative microorganisms such as *Prevetolla melaninogenica* (formerly *Bacterocides melaninogenicus*); *Mycoplasma pneumoniae*; *Chlamydia pneumoniae*; *Mycobacterium avium complex* (MAC) consisting of *Mycobacterium avium* and / or *Mycobacterium intracellulare*; *Helicobacter pylori*; *Bacterocides fragilis*; *Fusobacterium nucleatum*; *Peptostreptococcus magnus*; *Peptostreptococcus micros*; and *Escherichia coli*.

In a preferred embodiment the composition is formulated to specifically target the bacterial pathogen *Streptococcus pyogenes*.

It will be appreciated by those of ordinary skill in the art that the methods and formulations hereinabove described and hereinbelow described for the beta-lactam antibiotic amoxicillin, or for other beta-lactam antibiotics, are also applicable to amoxicillin, or to other beta-lactam antibiotics, in combination with clavulanate, or in combination with other beta-lactamase inhibitors, particularly for treating infections where beta-lactamase producing pathogens are implicated.

While the hereinabove described and hereinbelow described compositions and methods may be used to improve the efficacy of any beta-lactam antibiotic, they are particularly useful for improving the efficacy of antibiotics that include a beta-lactam ring or a portion thereof, as non-limiting examples of such antibiotics there may be mentioned penicillin derivatives, such as penicillin V, penicillin G, penicillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, piperacillin, nafcillin, cloxacillin, dicloxacillin, monobactams such as aztreonam, and carbapenems such as imipenem.

In accordance with another embodiment, the beta-lactam antibiotic composition has an overall release profile such that when administered the maximum serum concentration of the total antibiotic released from the composition is reached in less than twelve hours, preferably in less than eleven hours, and that maximum serum concentration is at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen.

In accordance with one embodiment of the invention, there are at least three dosage forms (at least one of which is a modified release dosage form). One of the at least three dosage forms is an immediate release dosage form whereby initiation of release of the beta-lactam antibiotic therefrom is not substantially delayed after administration of the beta-lactam antibiotic composition. The second and third of the at least three dosage forms are delayed release dosage forms (each of which may be a pH sensitive or a non-pH sensitive delayed dosage form, depending on the type of beta-lactam antibiotic composition), whereby the beta-lactam antibiotic released therefrom is delayed until after initiation of release of the beta-lactam antibiotic from the immediate release dosage form. More particularly, the beta-lactam antibiotic released from the second of the at least two dosage forms achieves a Cmax (maximum serum concentration in the serum) at a time after the beta-lactam antibiotic released from the first of the at least three dosage forms achieves a Cmax in the serum, and the beta-lactam antibiotic released from the third dosage form achieves a Cmax in the serum

after the Cmax of beta-lactam antibiotic released from the second dosage form and the overall Cmax is at least equivalent to the drug-specific MIC_{90} of the baterial pathogen.

In one embodiment, the second of the at least two dosage forms initiates release of the beta-lactam antibiotic contained therein at least one hour after the first dosage form, with the initiation of the release therefrom generally occurring no more than six hours after initiation of release of beta-lactam antibiotic from the first dosage form of the at least three dosage forms.

As hereinabove indicated, some embodiments of the beta-lactam antibiotic composition may contain three, four, or more different dosage forms (provided that at least one is a modified release dosage form).

In one three-dosage form embodiment, the beta-lactam antibiotic released from the third dosage form reaches a Cmax at a time later than the Cmax is achieved for the beta-lactam antibiotic released from each of the first and second dosage forms. In a preferred embodiment, release of beta-lactam antibiotic from the third dosage form is started after initiation of release of beta-lactam antibiotic from both the first dosage form and the second dosage form. In one embodiment, Cmax for beta-lactam antibiotic released from the third dosage form is achieved within eight hours.

In another three-dosage form embodiment the release of beta-lactam antibiotic from the second dosage form may be contemporaneous with initiation of release of beta-lactam antibiotic from the first dosage form.

In another three-dosage form embodiment the release of beta-lactam antibiotic from the third dosage form may be contemporaneous with initiation of release of beta-lactam antibiotic from the second dosage form.

In another embodiment, the beta-lactam antibiotic composition may contain four dosage forms (at least one of which is a modified release dosage form), with each of the four dosage forms having different release profiles, whereby the beta-lactam antibiotic released from each of the four different dosage forms achieves a Cmax at a different time.

As hereinabove indicated, in an embodiment, irrespective of whether the antibiotic contains

at least two or at least three or at least four different dosage forms each with a different release profile, Cmax for all the beta-lactam antibiotic released from the beta-lactam antibiotic composition is achieved in less than twelve hours, and more generally is achieved in less than eleven hours and is at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen.

In a preferred embodiment, the beta-lactam antibiotic composition is a once a day composition, whereby after administration of the beta-lactam antibiotic composition, no further composition is administered during the day; i.e., the preferred regimen is that the composition is administered only once over a twenty-four hour period. Thus, in accordance with this preferred embodiment, there is a single administration of an beta-lactam antibiotic composition with the beta-lactam antibiotic being released in a manner such that overall beta-lactam antibiotic release is effected with different release profiles in a manner such that the overall Cmax for the beta-lactam antibiotic composition is reached in less than twelve hours and is at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen. The term single administration means that the total beta-lactam antibiotic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or capsule or two or more thereof, provided that they are administered at essentially the same time.

In general, each of the dosage forms in the beta-lactam antibiotic compositions may have one or more beta-lactam antibiotics, and each of the dosage forms may have the same beta-lactam antibiotic or different beta-lactam antibiotics.

It is to be understood that when it is disclosed herein that a dosage form initiates release after another dosage form, such terminology means that the dosage form is designed and is intended to produce such later initiated release. It is known in the art, however, notwithstanding such design and intent, some "leakage" of antibiotic may occur. Such "leakage" is not "release" as used herein.

In one four-dosage form embodiment, the fourth dosage form may be a sustained release dosage form or a delayed release dosage form. If the fourth dosage form is a sustained release dosage form, even though Cmax of the fourth dosage form is reached after the Cmax of each of the other dosage forms is reached, beta-lactam antibiotic release from such fourth dosage form may be initiated prior to or after release from the second or third dosage form.

The beta-lactam antibiotic composition of the present invention, as hereinabove described, may be formulated for administration by a variety of routes of administration. For example, the beta-lactam antibiotic composition may be formulated in a way that is suitable for topical administration; administration in the eye or the ear; rectal or vaginal administration; as a nasal preparation; by inhalation; as an injectable; or for oral administration. In a preferred embodiment, the beta-lactam antibiotic composition is formulated in a manner such that it is suitable for oral administration.

For example, in formulating the beta-lactam antibiotic composition for topical administration, such as by application to the skin, the dosage forms, each of which contains a beta-lactam antibiotic, may be formulated for topical administration by including such dosage forms in an oil-in-water emulsion, or a water-in-oil emulsion. In such a formulation, an immediate release dosage form may be in the continuous phase, and a delayed release dosage form may be in a discontinuous phase. The formulation may also be produced in a manner for delivery of three dosage forms as hereinabove described. For example, there may be provided an oil-in-water-in-oil emulsion, with oil being a continuous phase that contains the immediate release component, water dispersed in the oil containing a first delayed release dosage form, and oil dispersed in the water containing a third delayed release dosage form.

It is also within the scope of the invention to provide a beta-lactam antibiotic composition in the form of a patch, which includes beta-lactam antibiotic dosage forms having different release profiles, as hereinabove described.

In addition, the beta-lactam antibiotic composition may be formulated for use in the eye or ear or nose, for example, as a liquid emulsion. For example, the dosage form may be coated with a hydrophobic polymer whereby a dosage form is in the oil phase of the emulsion, and a dosage form may be coated with hydrophilic polymer, whereby a dosage form is in the water phase of the emulsion.

Furthermore, the beta-lactam antibiotic composition having at least one modified release dosage form (whether or not combined with additional dosage forms to provide a plurality of different release profiles) may be formulated for rectal or vaginal administration, as known in the art. This may take the form of a cream, an emulsion, a suppository, or other dissolvable dosage

form similar to those used for topical administration.

In a preferred embodiment, the beta-lactam antibiotic composition is formulated in a manner suitable for oral administration. Thus, for example, for oral administration, each of the dosage forms may be used as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical composition, for example, in a capsule, or embedded in a tablet, or suspended in a liquid for oral administration.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the composition may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary antibiotic composition. Thus, as a non-limiting example, a three dosage form antibiotic composition may include a first dosage form in the form of a tablet that is an immediate release tablet, and may also include two or more additional tablets, each of which provides for a delayed release or a sustained release of the beta-lactam antibiotic, as hereinabove described, to provide (and preferably maintain) a serum concentration of the beta-lactam antibiotic at least equivalent to the drug-specific MIC_{90} of the bacterial pathogen.

The formulation of a beta-lactam antibiotic composition including at least three dosage forms with different release profiles for different routes of administration is deemed to be within the skill of the art from the teachings herein. As known in the art, with respect to delayed release, the time of release can be controlled by a variety of mechanisms such as pH, coating thickness, choice of polymer, and combinations of the foregoing.

In formulating a beta-lactam antibiotic composition in accordance with one embodiment of the invention, an immediate release dosage form of the composition generally provides from about 20% to about 50% of the total dosage of beta-lactam antibiotic to be delivered by the composition, with such immediate release dosage form generally providing at least 25% of the total dosage of the beta-lactam antibiotic to be delivered by the composition. In many cases, an immediate release dosage form provides from about 20% to about 30% of the total dosage of beta-lactam antibiotic to be delivered by the composition; however, in some cases it may be desirable to have an immediate release dosage form provide for about 45% to about 50% of the total dosage of beta-lactam antibiotic to be delivered by the composition.

The remaining dosage forms deliver the remainder of the beta-lactam antibiotic. If more than one modified release dosage form is used each of the modified release dosage forms may provide about equal amounts of beta-lactam antibiotic; however, they may also be formulated so as to provide different amounts.

In accordance with the present invention, each of the dosage forms contains the same beta-lactam antibiotic; however, each of the dosage forms may contain more than one beta-lactam antibiotic.

In one embodiment, where the composition contains one immediate release component and two modified release components, the immediate release component provides from 20% to 35% (preferably 20% to 30%), by weight, of the total beta-lactam antibiotic; where there are three modified release components, the immediate release component provides from 15% to 30%, by weight, of the total beta-lactam antibiotic; and where there are four modified release components, the immediate release component provides from 10% to 25%, by weight, of the total beta-lactam antibiotic.

With respect to the modified release components, where there are two modified release components, the first modified release component (the one released earlier in time) provides from 30% to 60%, by weight, of the total beta-lactam antibiotic provided by the two modified release components with the second modified release component providing the remainder of the beta-lactam antibiotic.

Where there are three modified release components, the earliest released component provides 20% to 35% by weight of the total beta-lactam antibiotic provided by the three modified release components, the next in time modified release component provides from 20% to 40%, by weight, of the beta-lactam antibiotic provided by the three modified release components and the last in time providing the remainder of the beta-lactam antibiotic provided by the three modified release components.

When there are four modified release components, the earliest modified release component provides from 15% to 30%, by weight, the next in time modified release component provides from 15% to 30%, the next in time modified release component provides from 20% to 35%, by weight,

and the last in time modified release component provides from 20% to 35%, by weight, in each case of the total beta-lactam antibiotic provided by the four modified release components.

The Immediate Release Component

The immediate release portion of this system can be a mixture of ingredients that breaks down quickly after administration to release the beta-lactam antibiotic. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other three components.

The materials to be added to the beta-lactam antibiotics for the immediate release component can be, but are not limited to, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylatedchitosan, cross-linked chitosan, cross-linked hydroxymethyl chitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives (Carbopol, Eudragit, etc.), polyethylene glycols, such a low molecular weight PEGs (PEG2000-10000) and high molecular weight PEGs (Polyox) with molecular weights above 20,000 daltons.

It may be useful to have these materials present in the range of 1.0 to 60% (W/W).

In addition, it may be useful to have other ingredients in this system to aid in the dissolution of the drug, or the breakdown of the component after ingestion or administration. These ingredients can be surfactants, such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, one of the non-ionic surfactants such as the Pluronic line of surfactants, or any other material with surface active properties, or any combination of the above.

These materials may be present in the range of 0.05-15% (W/W).

The non-pH Sensitive Delayed Release Component

The components in this composition are the same as the immediate release unit, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

Several methods to affect a delayed release with non-pH dependent polymers are known to those skilled in the art. These include soluble or erodible barrier systems, enzymatically degraded barrier systems, rupturable coating systems, and plugged capsule systems among others. These systems have been thoroughly described in the literature (see "A Review of Pulsatile Drug Delivery" by Bussemer and Bodmeier in the Winter 2001 issue of American Pharmaceutical Review) and formulations and methods for their manufacture are hereby incorporated by reference.

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax™, Polyox™), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit™), propylene glycol, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component.

The pH Sensitive (Enteric) Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate pthalate, Eudragit L, Eudragit S, Eudragit FS, and other pthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W).

Sustained Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, ethylcellulose; hydroxypropylmethylcellulose; hydroxypropylcellulose; hydroxyethylcellulose; carboxymethylcellulose; methylcellulose; nitrocellulose; Eudragit R; Eudragit RS; and Eudragit RL; Carbopol; or polyethylene glycols with molecular weights in excess of 8,000 daltons.

These materials can be present in concentrations from 4-20% (W/W).

When it is desired to delay inititiation of release of the sustained release dosage form, an appropriate coating may be used to delay inititiation of the sustained release, such as a pH sensitive or a non-pH sensitive coating.

The non-pH Sensitive Coating for Sustained Release Dosage Form

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit RS), cellulose acetate, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component. Preferably the materials are present in an amount just enough to provide the desired *in vivo* lag time and T_{max}.

The pH Sensitive Coating for Sustained Release Dosage Form

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate pthalate, Eudragit L, Eudragit S, Eudragit FS, and other pthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W) or more. Preferably the materials are present in an amount just enough to provide the desired *in vivo* lag time and T_{max}.

As hereinabove indicated, the units comprising the beta-lactam antibiotic composition of the

present invention can be in the form of discrete pellets or particles contained in the capsule, or particles embedded in a tablet or suspended in a liquid suspension.

The beta-lactam antibiotic composition of the present invention may be administered, for example, by any of the following routes of administration: sublingual, transmucosal, transdermal, parenteral, etc., and preferably is administered orally. The composition includes a therapeutically effective amount of the beta-lactam antibiotic, which amount will vary with the beta-lactam antibiotic to be used, the disease or infection to be treated, and the number of times that the composition is to be delivered in a day. The composition is administered to a patient or subject in an amount effective for treating a bacterial infection.

This system will be especially useful in extending the practical therapeutic activity for antibiotics with elimination half lives of less than 20 hours and more particularly with elimination half-lives of less than 12 hours, and will be particularly useful for those drugs with half-lives of 2-10 hours. The following are examples of some antibiotics with half-lives of about 1 to 12 hours: imipenem, ertapenem, (carbapenems) penicillin V, peniciliin salts, and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium (and other salts of carbenicillin) mezlocillin, piperacillin, piperacillin and taxobactam, ticarcillin, ticarcillin and clavulanate potassium, (penicillins).

The beta-lactam antibiotic composition should be administered for a sufficient amount of time to treat the infection. In one embodiment the beta-lactam antibiotic composition is administered for 10 days.

The invention will be further described with respect to the following examples; however, the scope of the invention is not limited thereby. All percentages in this specification, unless otherwise specified, are by weight.

The following examples detail the general procedures for making immediate release, delayed release (both pH sensitive and non-pH sensitive types), sustained release, and delayed sustained release components for the dosage form of the present invention. Any combination of the

components that results in the desired time above MIC would be included as part of this disclosure. Specific examples of combinations of the components are given, but are not limited to the ones described herein. Additionally, there is an example of a multi-unit dosage form specific to amoxicillin type tablets, but any appropriate therapeutic agent could be substituted.

Additional Examples

I. Immediate Release Component

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into a capsule or sachet with a suitable filler.

Ingredient	Conc. (% W/W)
Example 1:	
Amoxicillin	65% (W/W)
Microcrystalline cellulose	20
Povidone	10
Croscarmellose sodium	5
Example 2:	
Amoxicillin	55% (W/W)
Microcrystalline cellulose	25
Povidone	10
Croscarmellose sodium	10

Example 3:

Amoxicillin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 4:

Amoxicillin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 5:

Amoxicillin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 6:

Clarithromycin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 7:

Clarithromycin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 8:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 9:

Clarithromycin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 10:

Ciprofloxacin	65% (W/W)

Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 11:

Ciprofloxacin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 12:

Ciprofloxacin	75% (W/W)
Polyethylene glycol 4000	10
Polytheylene glycol 2000	10
Hydroxypropylcellulose	5

Example 13:

Cirpofloxacin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 14:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 15:

Ceftibuten	75% (W/W)
Polyethylene Glycol 4000	20
Polyvinylpyrrolidone	5

II. non-pH Sensitive Delayed Release Component

Any of the methods described in "A Review of Pulsatile Drug Delivery" by Bussemer and Bodmeier in the Winter 2001 issue of American Pharmaceutical Review may be utilized to make the pH independent delayed release component described. Examples 16 and 17 utilize an organic acid layer underneath a layer of Eudragit RS to result in a rapid increase in the permeability of the Eudragit film after a set amount of time depending on the permeability and thickness of the film thus allowing the inner core to release through the Eudragit membrane. Example 18 utilizes a core with a highly swellable polymer that ruptures the insoluble coating membrane after a certain amount of time determined by the permeability, plasticity and thickness of the external cellulose acetate membrane. The coatings are applied to the core via methods such as wurster column coating in a fluid bed processor as known to those skilled in the art.

Additionally, this component may be formed as in example 19. In this example the component is prepared by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven.

After the component is allowed to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into a capsule with a suitable encapsulator.

Ingredient	Conc. (% W/W)
Example 16:	
Core from Example 4	65% (W/W)
Citric Acid	10
Eudragit RS Polymer	20
Talc	4
TEC	1
Example 17:	
Core from Example 9	75% (W/W)
Citric Acid	10

Eudragit RS Polymer	10
Talc	4
TEC	1

Example 18:

Core from Example 1	93% (W/W)
Cellulose Acetate	6.75
PEG 400	0.25

Example 19:

Ciprofloxacin	70% (W/W)
Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

III. Enteric Release Component

Examples 20-27 utilize film coating techniques commonly known to those skilled in the art to create the enteric release component by layering of such enteric polymers onto an active core. In general the steps involve first making a coating dispersion or solution in organic or aqueous solvent. Second, the coating is applied at the proper conditions to produce an acceptably uniform film. This is done in a suitable coating apparatus such as a pan coater or a fluid bed wurster column coater. Optionally the product may be further cured if necessary.

To create a matrix type enteric component, formulate the ingredients of examples 28-32 by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool.

The product produced by either manner may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into capsules using a suitable capsule filler such as a MG2 Futura.

Ingredient	Conc. (% W/W)

Example 20:

Core from Example 1	65% (W/W)
Cellulose Acetate Pthalate	30
TEC	5

Example 21:

Core from Example 5	75% (W/W)
Cellulose Acetate Pthalate	20
Triacetin	5

Example 22:

Core from Example 1	65% (W/W)
Eudragil L	25
Talc	8
TEC	2

Example 23:

Core from Example 1	65% (W/W)
Eudragit FS	28
Talc	5
TEC	2

Example 24:

Core from Example 1	65% (W/W)
Eudragit S	28
Talc	5
TEC	2

Example 25:

Core from Example 7	75% (W/W)
Eudragit L	20
Talc	3.5
TEC	1.5

Example 26:

Core from Example 11	60% (W/W)
Eudragit L	35
Talc	4
TEC	1

Example 27:

Core from Example 15	65% (W/W)
Cellulose Acetate Pthalate	32.5
TEC	2.5

Example 28:

Amoxicillin	75% (W/W)

Microcrystalline Cellulose	5
Hydroxypropylcellulose pthalate	20

Example 29:

Amoxicillin	60% (W/W)
Lactose	10
Eudgragit L 30D	30

Example 30:

Ciprofloxacin	70% (W/W)
Polyethylene glycol 4000	10
Cellulose acetate pthalate	20

Example 31:

Clarithromycin	60% (W/W)
Polyethylene glycol 2000	10
Lactose	20
Eudragit L 30D	10

Example 32:

Ceftibuten	70% (W/W)
Microcrystalline cellulose	20
Cellulose acetate pthalate	10

IV. Sustained Release Component

Examples 33-38 utilize film coating techniques commonly known to those skilled in the art to create the sustained release component by layering of such sustained release polymers onto an active core. In general the steps involve first making a coating dispersion or solution in organic or aqueous solvent. Second, the coating is applied at the proper conditions to produce an acceptably uniform film. This is done in a suitable coating apparatus such as a pan coater or a fluid bed wurster column coater. Optionally the product may be further cured if necessary. Curing studies are recommended with sustained release membranes.

To create a matrix type sustained release component, formulate the ingredients of example 39-42 by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool.

The product produced by either manner may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into capsules using a suitable capsule filler such as a MG2 Futura.

	Ingredient	Conc. (% W/W)
Example 33:		
	Core from Example 1	75% (W/W)
	Ethylcellulose	20
	HPC	5
Example 34:		
	Core from Example 5	80% (W/W)
	Eudragit RS	10
	Eudragit RL	5
	Talc	3
	TEC	2

Example 35:

Core from Example 5	90% (W/W)
Ethylcellulose	9
Triacetin	1

Example 36:

Core from Example 7	90% (W/W)
Surelease	10

Example 37:

Core from Example 11	85% (W/W)
Kollicoat SR	10
TBC	5

Example 38:

Core from Example 15	80% (W/W)
Polyethylene glycol 8000	5
Eudgragit RS 30D	15

Example 39:

Amoxicillin	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

Example 40:

Ciprofloxacin	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

Example 41:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10
Hydroxypropylcellulose	5

Example 42:

Ceftibuten	75% (W/W)
Lactose	15
Polyethylene glycol 4000	5
Polyvinylpyrrolidone	5

III. Sustained Release Dosage Form With Coating To Delay Initiation of Sustained Release:

Delaying the initiation of the sustained release of antibiotic in the present invention is achieved by either coating the immediate release component bead with a sustained release coating

and then subsequently applying an enteric coating or non pH sensitive delayed release coating to that coated bead, or alternatively the sustained release matrix component bead may be coated with an enteric coating or non pH sensitive delayed release coating.

Coatings can be applied to either the sustained release coated beads or the sustained release matrix beads to form a product which pulses the therapeutical agent in a desired environment or location of the GI tract.

III A. The following examples describe the detailed preparation of the sustained-release coating materials to be applied to the immediate release beads from section I of the examples, resulting in a sustained release component of the invention.

Example 43. Eudragit RS example – organic coating

Component	Percentage (%)
Part A	
Eudragit RS-100	6.0
Triethyl Citrate	1.0
Talc	0.5
Acetone	92.5

Step 1. Dissolve Eudragit in Acetone.

Step 2. Mix TEC and talc in a separate container with some Acetone.

Step 3. Add step 2 to Step 1, and allow to mix for 20 minutes before spraying.

Example 44. SureleaseTM example- aqueous coating

Component	Percentage (%)
Part A	
Surelease	90
Purified Water	10.0

Step 1. Mix surelease and water for 30 minutes before spraying.

Directions for application of the sustained release coating to the beads:

Charge a wurster column equipped fluid bed with the beads to be coated. Spray the coating onto the beads at a rate and temperature known to those skilled in the art of bead coating so as to efficiently coat the beads to give a weight gain of between 4 and 20 %. Dry the beads to the specified level of coating solvent for optimum handling and stability. Cure the beads for additional congealing of the sustained release film if required.

III B. The following are examples of the pH sensitive, or enteric release, coating that can be used to optionally delay the onset of action of any or all of the second, third, or additional dosage forms.

The composition of the aqueous Eudragit L30D-55 dispersion to be applied to the immediate release components that have been treated with the above-described sustained release coatings, or to the sustained-matrix pellets is provided below in Example 45.

Example 45. Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

Step1 Suspend triethyl citrate and talc in deionized water.

Step 2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

Step 3 Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

Step 4 Allow the coating dispersion to stir for one hour prior to application onto the matrix pellets.

Example 46. Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the matrix pellets is provided below:

Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0

Solid Content	20.0
Polymer Content	12.0

Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part I:

(i) Dispense Eudragit® S 100 powder in deionized water with stirring.

(ii) Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

(iii) Allow the partially neutralized dispersion to stir for 60 minutes.

(iv) Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part II:

(i) Disperse talc in the required amount of water

(ii) Homogenize the dispersion using a PowerGen 700D high shear mixer.

(iii) Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used to coat matrix pellets with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

(i) Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

(ii) Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

III. C. The following examples describe the detailed preparation of the non pH sensitive coating

materials to be used to optionally delay the onset of action of any or all of the second, third, or additional dosage forms.

Example 47. Rupturable Film

Component	Percentage (%)
Part A	
Cellulose Acetate 398-10	6.0
PEG 400	1.5
Acetone	92.5

Step 1. Dissolve cellulose acetate in Acetone.

Step 2. Add TEC to Step 1, and allow to mix for 20 minutes.

Directions for application of the sustained release coating to the beads:

Charge a wurster column equipped fluid bed with the beads to be coated. The beads must contain a component which will swell rapidly upon exposure to moisture. Beads containing croscarmellose sodium in Section I are good candidates as are beads with swellable hydrophilic polymers from Section II. Spray the coating onto the beads at a rate and temperature known to those skilled in the art of bead coating so as to efficiently coat the beads to give a weight gain of between 4 and 20 %. Dry the beads to the specified level of coating solvent for optimum handling and stability.

Coating Conditions for the application of the rupturable film coating.

The following coating parameters were used to coat matrix mini tablets from a previous example with the rupturable film coating. A 2.5% weight gain provided the desired lag time.

Coating Equipment	Vector LDCS Coating System with 1.3L pan
Spray nozzle diameter	0.8 mm
Material Charge	800 grams
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	18 to 23 °C
Atomization Air Pressure	25 psi
Pump Rate	6 grams per minute

The enteric coatings and non-pH sensitive coatings as described above can be applied to either a sustained release matrix bead as in examples 16-25, or to the immediate release component beads that have been previously treated with a sustained release coating, to thereby provide a sustained release bead with a delayed onset of action. In addition, the enteric coating or non-pH sensitive coating can be applied to the immediate release component bead directly to provide delayed onset of action.

IV. Example Final Compositions

After one or all of the desired individual components are manufactured, the final dosage form is assembled and may take the shape of a tablet, capsule or sachet. Preferably the final dosage form takes the shape of a capsule or tablet. Most preferably the final dosage form is a tablet.

One or more of the individual components can be used to achieve the desired Daily T>MIC. If one were to include three components in one's dosage form then preferably the first, second, and third dosage forms provide 20-70%, 10-70% and 10-70% of the total dosage form, respectively. More preferably the ratio of first, second and third dosage forms are in the range of 25-66%, 15-60% and 15-60% of the total dosage form respectively. Most preferably the ratio of the first, second and third dosage forms are in the range of 33-60%, 25-50%, and 25-50% respectively. One can also utilize one, two, three, or four or more components, and balance the ratio of the components in such a way to meet the Daily T>MIC criteria.

V. Example of three component Amoxicillin Tablet and Sprinkle dosage forms.

V-1. Description of the Dosage Form

API content can range for example from 10 to 80 % therapeutic compound, and in the case the therapeutic compound is amoxicillin, it most preferably would contain 775 mg amoxicillin. The tablet can be of any desired shape, with a target gross weight of approximately 1500 mg. The tablet can optionally be coated with a film, and/or imprinted.

The following specific example is written for components that contain amoxicillin, however other therapeutic agents can be substituted with proper proportion adjustments known to one skilled in the art of oral dosage form development.

The tablet of this invention is a rapidly disintegrating formulation containing three active intermediate compositions, an immediate-release granulation (Amoxicillin Granules) and two functionally coated delayed-release pellets (Amoxicillin Pulse 2 Pellets and Amoxicillin Pulse 3 Pellets). Non-functional, color and clear film coats are optionally applied to the outer surface and/or the coated tablets are imprinted.

Figure 3 is a flowchart describing the General Procedure to Make a Multiparticulate Tablet.

Table 2 provides the qualitative and quantitative composition of three example amoxicillin tablet formulations on a weight to weight (w/w%) basis of individual ingredients. For formulation B, an example set of procedures and component compositions for making this type of tablet is expanded. Table 3 provides the qualitative and quantitative composition of an example amoxicillin Tablet formulation on the basis of the tablet core, coatings, and its active intermediate compositions. Tables 4, 5, 6, and 7 provide the qualitative and quantitative composition of the Amoxicillin Granules, Amoxicillin Core Pellets, Amoxicillin Pulse 2 Pellets, and Amoxicillin Pulse 3 Pellets, respectively. An optional coating can be applied and optional tablet imprinting can be used to complete the product presentation.

Table 2 Example Quantitative Compositions of Example Amoxicillin Tablets.

Component	A (w/w%)	B (w/w%)	C (w/w%)
Amoxicillin, USP	78.476	59.524	62.821
Silicified Microcrystalline Cellulose	0.000	20.676	21.900
Crospovidone, NF	0.000	3.892	4.100
Methacrylic Acid Copolymer Dispersion, NF	4.272	2.926	2.879
Opadry® Blue[1]	0.000	2.415	0.000
Talc, USP	3.617	2.036	1.804
Hydroxypropyl Methylcellulose Acetate Succinate [1]	4.107	1.939	1.229
Microcrystalline Cellulose, NF	4.276	1.787	1.545
Povidone, USP	1.716	1.546	1.691
Opadry® Clear [1]	0.000	0.966	0.000
Magnesium Stearate, NF	0.000	0.966	1.000
Triethyl Citrate, NF	1.806	0.939	0.694
Polyoxyl 35 Castor Oil, NF	0.843	0.345	0.299
Sodium Lauryl Sulfate, NF	0.129	0.0152	0.039
Opadry II White, 33G28523	0.761	0.000	0.000
Opacode® Black [1]	0.000	Trace Amount	0.0
Purified Water, USP[1]	*	*	*
Total	100.0	100.0	100.0

[1]Water removed during processing

Table 3 Composition of an Example Amoxicillin Tablet by component.

Core Tablet	**w/w%**
Amoxicillin Granules	28.6
Amoxicillin Pulse 2 Pellets	24.1
Amoxicillin Pulse 3 Pellets	20.9
Silicified Microcrystalline Cellulose	21.4
Crospovidone	4.0
Magnesium Stearate	1.0
Core Tablet Weight	**100**

V-2 Amoxicillin Granules

Table 4 Qualitative and Quantitative Composition of Amoxicillin Granules

Component	**w/w%**
Amoxicillin	97.0
Povidone	3.0
Purified Water[1]	N/A
Total Amoxicillin Granules	**100**

[1]Water removed during processing

General Procedure for Manufacturing Amoxicillin Granules:

A standard wet granulation process known to one skilled in the art is used for preparation of the Amoxicillin Granules. The wet granules are discharged and fed into a Dome Extrusion Granulator. The wet extruded granules are then dried for a fixed period of time or until the LOD (loss on drying) of the granules is suitable for the formulation, typically less than 15%. The dried granules are then sized in a Rotating Impeller Screening Mill. The milled material is collected into drums.

V-3 Amoxicillin Core Pellets

The Core Pellets are used as the starting material for the later preparation of the Pulse 2 Pellets and the Pulse 3 Pellets used in the tablet preparation. They also serve as the core pellet for the immediate release pellet in the sprinkle dosage form. The core pellets are prepared using the unit operations of wet granulating, extruding, spheronizing, fluid bed drying and sizing. The composition of the core pellets is listed in Table 5.

Table 5 Composition of Amoxicillin Core Pellets

Amoxicillin Trihydrate (92%) Pellet	
Component	**w/w%**
Amoxicillin Trihydrate, Powder Grade, USP	92.0
Microcrystalline Cellulose, NF	5.0
Povidone K30, USP	2.0
Polyoxyl 35 Castor Oil, NF	1.0
Total	**100**

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V-4 Amoxicillin Pulse 2 Pellets

Table 6 lists the composition of the example Amoxicillin Pulse 2 Pellets.

Table 6 Composition of Amoxicillin Pulse 2 Pellets

Component	w/w%
Amoxicillin	76.6
Microcrystalline Cellulose (Avicel® PH-101)	4.19
Povidone (Kollidon™ 30)	1.69
Polyoxyl 35 Castor Oil (Cremophor EL)™	0.80
Methacrylic Acid Copolymer Dispersion (Eudragit® L30D-55)[1]	10.41
Talc	5.19
Triethyl Citrate	1.00
Purified Water[2]	N/A
Total Amoxicillin Pulse 2 Pellets	**100.0**

[1] Amount per tablet of the solids content
[2]Water removed during processing

The Amoxicillin Pulse 2 Pellets are prepared by coating the previously prepared Amoxicillin Core Pellets with a functional film coat of methacrylic acid copolymer dispersion, 20% w/w. Prior to the coating process, a dispersion of the methacrylic acid copolymer is made according to the manufacturer's instructions. The dispersion is applied to the Amoxicillin Core pellets using a Fluid Bed Bottom Spray Coater, equipped with appropriate spray nozzles and a fixed column gap distance.

The pellets are then appropriately sized. The Amoxicillin Pulse 2 Pellets may be held in ambient warehouse conditions until further processing.

V-5 Amoxicillin Pulse 3 Pellets

The amoxicillin pulse 3 pellets are prepared by coating the previously prepared Amoxicillin Core Pellets with a 5% w/w subcoat of methacrylic acid copolymer, followed by a

20 % w/w functional film coat of hypromellose acetate succinate.

Table 7 lists the composition of the example amoxicillin Pulse 3 pellets

Table 7. Composition of Amoxicillin Pulse 3 Pellets

Component	Amount/Tablet (mg)
Amoxicillin	222.6
Microcrystalline Cellulose (Avicel® PH-101)	12.1
Povidone (Kollidon 30)	4.8
Polyoxyl 35 Castor Oil (Cremophor EL)	2.4
Methacrylic Acid Copolymer Dispersion (Eudragit® L30D-55) [1]	7.6
Hypromellose Acetate Succinate (AQOAT AS-HF)	29.0
Talc	12.4
Triethyl Citrate	10.6
Sodium Lauryl Sulfate	0.9
Purified Water[2]	N/A
Total Amoxicillin Pulse 3 Pellets	**302.4**

[1] Amount per tablet of the solids content

[2] Water removed during processing

Prior to the subcoating process, a dispersion of the methacrylic acid copolymer is made according to the manufacturer's instructions. The second coating material, the hypromellose acetate succinate dispersion is prepared according to the manufacturer's instructions. The subcoat layer, is then applied to the Amoxicillin Core Pellets using the same Fluid Bed Bottom Spray Coater as used for preparation of the Pulse 2 Pellets.

The hypromellose acetate succinate coating dispersion is then immediately applied to the sub-coated pellets still in the Fluid Bed Bottom Spray Coater. The atomization air used for the second coating process is set at the same pressure as used for the sub coating process. The coating process is complete when all of the dispersion has been applied. Following a drying

period the final coated pellets are cooled.

The coated, dried and cooled Amoxicillin Pulse 3 Pellets are collected into lined drums The coated Pulse 3 Pellets are then sized. The Amoxicillin Pulse 3 Pellets may be held in ambient warehouse conditions until further processing.

V-6 Tabletting

The amoxicillin granules, pulse 2 pellets and pulse 3 pellets can be combined at the desired ratio and compressed on a rotary or other type of tablet press with suitable tooling installed for the desired size tablet. Ratios of Pulses or pellets can vary depending on the absorption characteristics of the desired drug. Ratios can range from front loaded (middle loaded or back loaded as per discussion in the specs section. The percent of each component can range from 10 – 90 % for each of the at least 3 components in this example. For example, but not in anyway limiting, pulse 1 can be 10%, pulse 2 can be 80 % and pulse 3 can be 10 %. Or, as an alternate non-limiting example, pulse 1 can be 30%, pulse 2 can be 50 % and pulse 3 can be 20 %. In a preferred embodiment the tablet is manufactured by combining the immediate-release granulation (Pulse 1, 45%) with two functionally coated delayed-release pellets (Pulse 2, 30% and Pulse 3, 25%).

V-7 Optional Coatings

An additional optional coating can be applied to the tablet, or directly to the core, pulse 2 and pulse 3 pellets according to the manufacturer's recommendation for the coating process conditions and procedures.

An optional printing on the tablets can be done using a formula as supplied by the manufacturer or as modified to suit the tablet characteristics. Additional optional ingredients are Microcrystalline Cellulose and Colloidal Silicon Dioxide. These can be added to prevent tacking and sticking if necessary. These two materials can be optionally obtained as the composition Prosolv SMCC® 90 (FMC).

V-8 Sprinkle dosage form

These coated or uncoated pellets can be filled to give the desired dose into an appropriate

dosing device at the desired ratios as described above either separately or all together, such as a sachet, capsule, or other means of delivering the material to the consumer.

For example the core pellets may be coated with a non-functional immediate release film coating to produce Pulse 1 pellets. The Pulse 1 pellets as well as Pulse 2 and Pulse 3 pellets may be used as a sprinkle product by placing the Pulse 1, Pulse 2 and Pulse 3 pellets in a sachet, capsule or other form that can be used for simultaneous delivery of the three pulses in a particulate form. In one embodiment, Pulse 1, Pulse 2 and Pulse 3 are combined to provide 45%, 30% and 25% of Pulse 1, Pulse 2, and Pulse 3, respectively.

Such combination of Pulses 1, 2 and 3 may be formulated into a sprinkle product; e.g., a twice-a-day product that contains 475 mg or 775 mg of amoxicillin. In another embodiment, Pulse 1, 2 and 3 may be combined into a once-a-day sprinlde product that contains 775 mg or 1250 mg or 1550 mg of amoxicillin. The sprinkle product may be sprinkled over applesauce, yogurt, or other soft food for administration. The product should not be chewed or crushed.

The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole. The present invention also extends to formulations which are bioequivalent to the pharmaceutical formulations of the present invention, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the so-called "Orange Book" (Approved Drug Compositions with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

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CLAIMS:

1. A once-a-day amoxicillin antibiotic product comprising;

first, second, and third amoxicillin antibiotic dosage forms, each of said amoxicillin antibiotic dosage forms comprising at least one amoxicillin antibiotic and a pharmaceutically acceptable carrier, said first amoxicillin antibiotic dosage form being, an immediate release dosage form, said second and third amoxicillin antibiotic dosage forms being delayed release dosage forms, wherein said second amoxicillin antibiotic dosage form comprises amoxicillin coated with a methacrylic acid copolymer dispersion, wherein the methacrylic acid copolymer dispersion comprises Eudragit® L30D-55, and said third amoxicillin antibiotic dosage form comprises amoxicillin coated with a first layer of the methacrylic acid copolymer dispersion and a second layer of AQOAT AS-HF, and wherein each of said first, second, and third amoxicillin antibiotic dosage forms is for initiation of release at different times and Cmax of the total amoxicillin antibiotic for release from said amoxicillin antibiotic product is for achievment in less than 12 hours from administration; wherein said product contains the total dosage of amoxicillin, for a 24-hour dosing interval.

2. The product of claim 1, wherein said total dosage of amoxicillin is from about 775 mg to about 1550 mg.

3. The product of claim 1 or 2, wherein said first amoxicillin antibiotic dosage form comprises 10-90% of the product, wherein said second amoxicillin antibiotic dosage form comprises 10-90% of the product, and wherein said third amoxicillin antibiotic dosage form comprises 10-90% of the product.

4. The product of claim 1 or 2, wherein said first amoxicillin antibiotic dosage form comprises 45% of the product, wherein said, second amoxicillin antibiotic dosage form comprises 30% of the product, and wherein said third amoxicillin antibiotic dosage form comprises 25% of the product.

5. The product of any one of claims 1 to 3, wherein when the product is for administration to a patient or subject in need thereof, the product provides a concentration of

amoxicillin in the serum at or above the MIC_{90} for an infecting bacterial pathogen for at least 5 hours within a 24-hour dosing interval.

6. The product of any one of claims 1 to 5, wherein said second and third amoxicillin antibiotic dosage forms further comprise microcrystalline cellulose, povidone, and polyoxyl 35 castor oil.

7. The product of any one of claims 1 to 6, wherein amoxicillin is the only antibiotic present in the first, second, and third amoxicillin antibiotic dosage forms.

8. A use of a once-a-day amoxicillin antibiotic product as defined in any one of claims 1 to 7 for treatment of a bacterial infection with the amoxicillin in a patient or subject in need thereof.

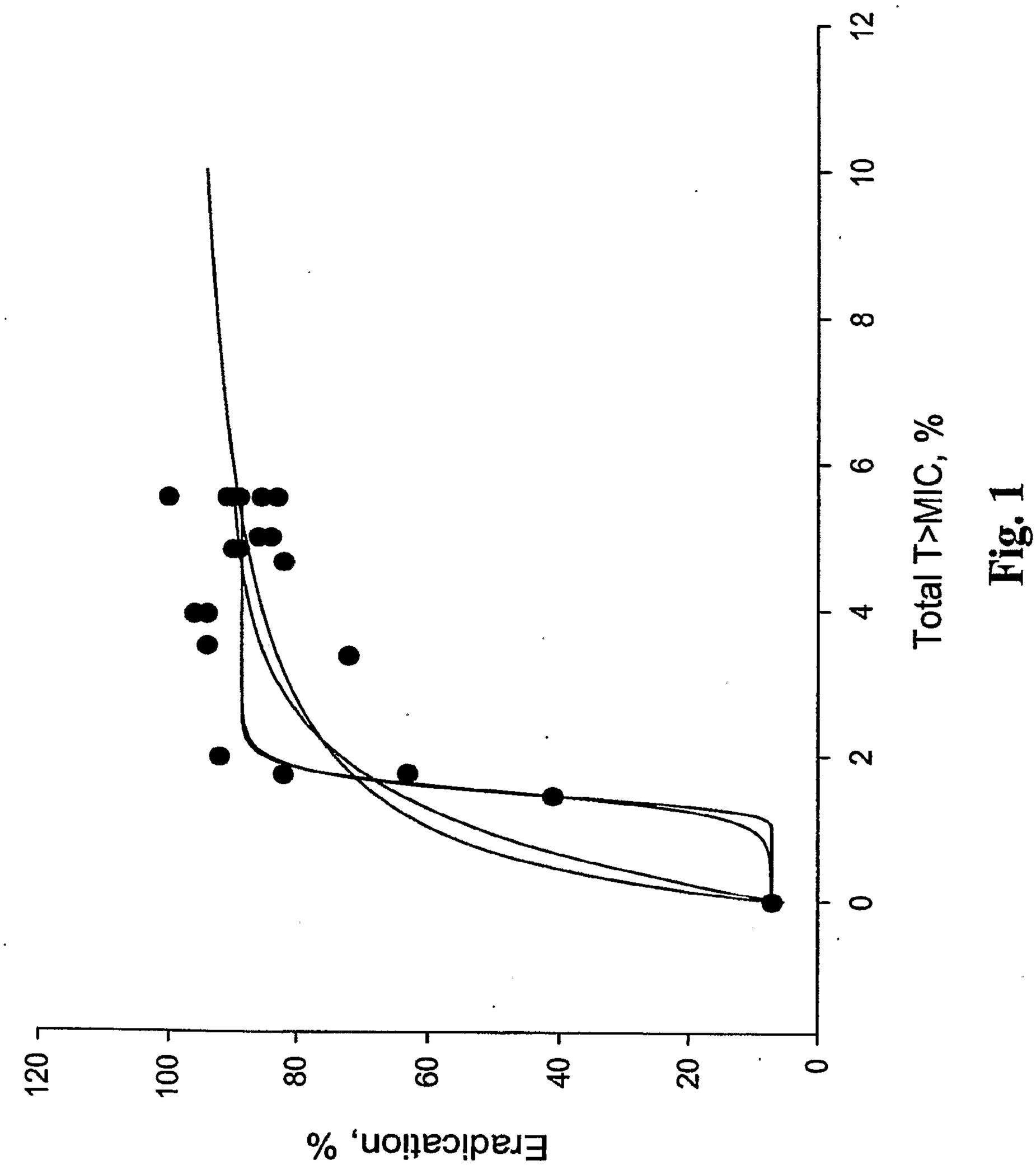
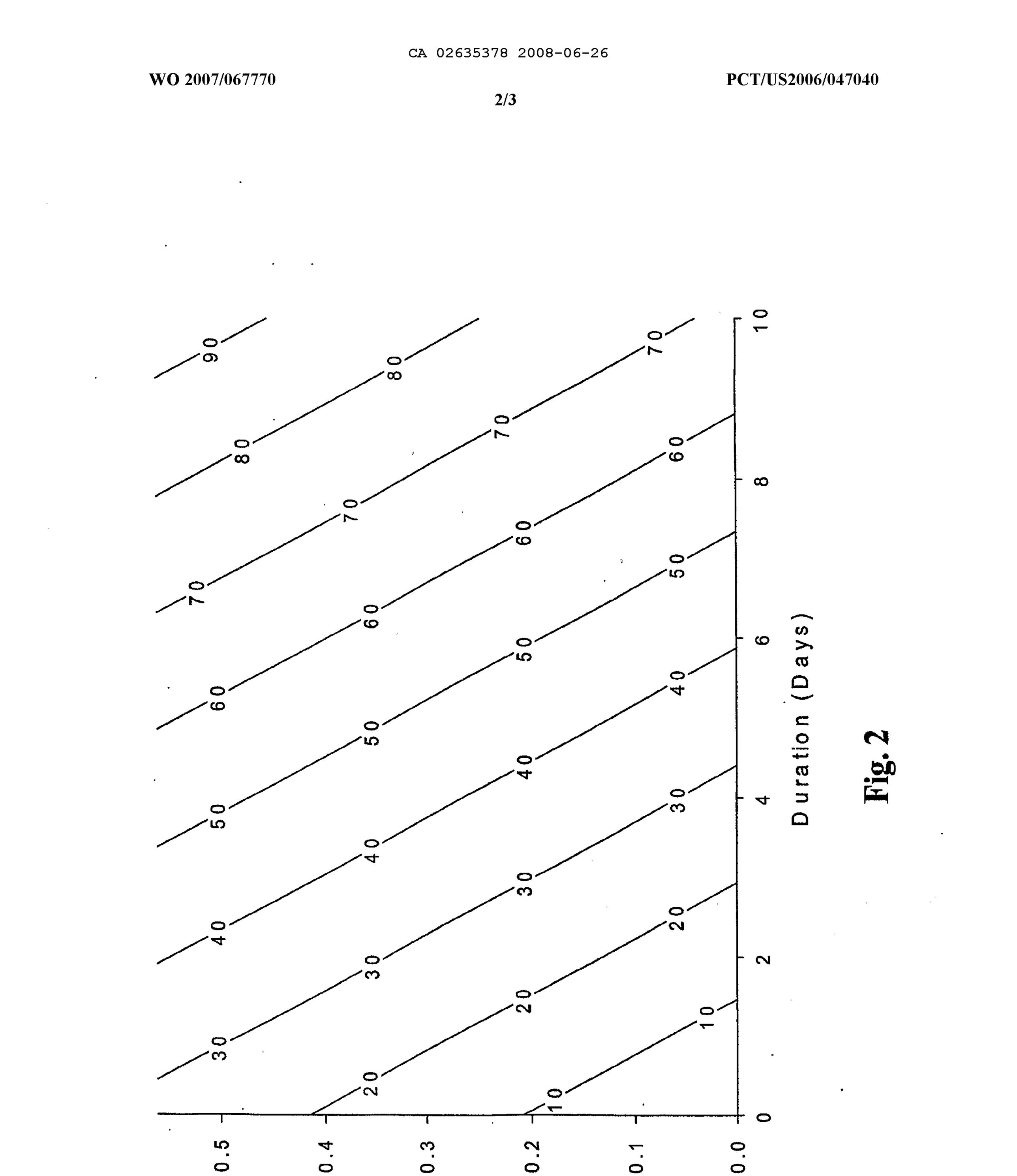


Fig. 1


Fraction Daily T>MIC
0.5
0.4
0.3
0.2
0.1
0.0
Duration (Days)
0
2
4
6
8
10
10
20
30
40
50
60
70
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30
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40
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60

Fig. 2

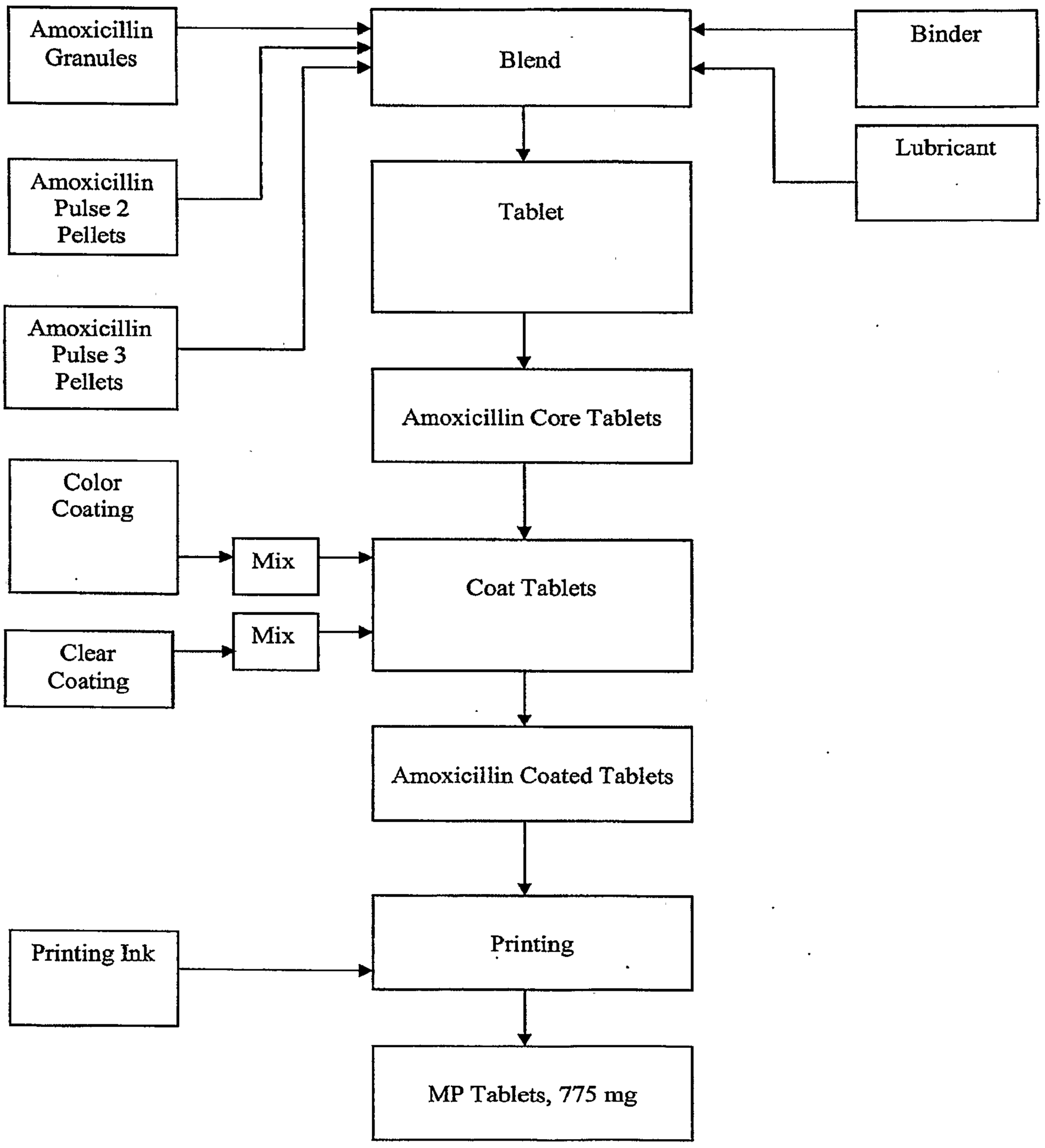
Amoxicillin Granules
Amoxicillin Pulse 2 Pellets
Amoxicillin Pulse 3 Pellets
Blend
Binder
Lubricant
Tablet
Amoxicillin Core Tablets
Color Coating
Clear Coating
Mix
Mix
Coat Tablets
Amoxicillin Coated Tablets
Printing Ink
Printing
MP Tablets, 775 mg

Fig. 3