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VECTOR THEORY AND OPTIMAL CHOICE OF ANTIMICROBIAL DRUG FOR LOCAL WOUND TREATMENT

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Introduction

Introduction and practical use of mathematical methods in various fields of human activity makes it possible to move from chaotic empirical facts to purposefully build relationship between facts, phenomena or objects, predicting properties and behavior of factors in different conditions that are interesting for people, search of optimal solutions in practical problems.

Historically, mathematical methods follow physics step by step, only by the end of XIX century mathematics started to be used in chemistry and by the middle of XX century, in biology, medicine, psychology, sociology and other sciences.

At the moment, it leads to breakthrough results, for example, in biology, genetic cod has been determined with physical and chemical methods of analysis; structure and activity of complex macromolecules is predicted; in pharmacology, pharmacological properties of synthetic drugs are predicted; in medicine, it has made it possible to visualize data that improve dramatically diagnosis accuracy and decrease invasiveness of diagnostic procedures, etc.

Another important problem in medicine and pharmacy is optimal choice among several alternatives. For example, in medicine, it is a choice of the drug for treatment among analogs; in pharmaceutical technology, it is selection of excipients among analogs for development of the drug form with optimal pharmacological, technological and economical parameters etc [1].

The **aim** of this paper is to show the possibility of vector theory use for choice of optimal antimicrobial drug for local wound treatment among analogs taking into account several parameters all at the same time.

Materials and methods

For the study we have chosen the following drugs:

1. Decasan solution, Yuria-pharm, Ukraine, No. 120312, expiration date 03 / 2015, 200 ml/bottle, content per 1 ml: decamethoxine – 0.2 mg.
2. Ioddicerin solution, PJSC Farmak, Kiev, Ukraine, No. 31212, expiration date 01/2016, 25 ml/bottle, content per 1 g: iodine - 5 mg, dimethyl sulfoxide – 300 mg, glycerin – 695 mg.
3. Laevomecol ointment, PJSC Viola Pharmaceutical plant, Zaporizhzhia, Ukraine, No. 580814, expiration date 08/2016, 40 g/pack, content per 1 g: chloramphenicol – 7.5 mg, methyluracil – 40 mg;
4. Laevosinum ointment, JSC Nizhpharm, the Russian Federation, Nizhniy Novgorod, No. 350414, expiration date 05/2016, 40 g/pack, content per 1 g: chloramphenicol – 10 mg, sulfodimetoxin – 40 mg , methyluracil – 40 mg, trymecain – 30 mg;
5. Methyluracilum cum Myramistino ointment, PLC Darnitsa Pharmaceutical company, Kiev, Ukraine, No. ML 41013, expiration date 11/2015, 15 g/pack, content per 1 g: methyluracil—50 mg, myramistin—5 mg;
6. Myramistinum-Darnitsa ointment, PLC Darnitsa Pharmaceutical company, Kiev, Ukraine, No. MR 10514, expiration date 06/2016, 15 g/pack, content per 1 g: myramistin 5 mg;
7. Calendula tincture, (1:10) with 70 % ethanol, public enterprise "Lugansk regional "Pharmacy" pharmaceutical factory, Lugansk, Ukraine, No. 51212, expiry date 01/2017;
8. Sophora japonicum tincture, (1:2) with 48 % ethanol, CJSC "Pharmaceutical factory "Viola", Zaporozhe, Ukraine, batch No. 040213, expiry date 02/2015;
9. Povidone-Iodine liniment, PJSC SIC Borshchahivskiy CPP, Kiev, Ukraine, No. 030714, expiration date 08/2016, 30 g/pack, content per 1 g: povidone-iodine – 100 mg;
10. Ranostop ointment 10%, PJSC Phytopharm, Artemivsk, Ukraine, No. 10714, expiration date 07/2016, 40 g/pack, content per 1 g: povidone-iodine – 100 mg.

Antimicrobial activity of drugs was studied by agar well diffusion method, on the following test-strain microorganisms: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, and *Candida albicans* ATCC 885-653.

Well diameter was 10 mm, the volume of drug in the well was 0.27±0.02 ml, microbial burden of agar upper layer was 10^7 CFU/ml, and total layer height in Petri dish was 4.0±0.5 mm.

For optimal choice, we used the following criteria:

Antimicrobial activity (in the form of integral index of drug's antimicrobial activity), *A*;
Price of the drug, *B*;
Pharmacological and technological index, *C*;
Drug's spectrum of antimicrobial activity on test-strain microorganisms in the form squared correlation coefficient (r^2), *E*.

Integral index of drug's antimicrobial activity, *A*, was calculated by formula [2]:

$$A = \sqrt{\left(\frac{a_1 \cdot D_1}{25}\right)^2 + \ldots + \left(\frac{a_n \cdot D_n}{25}\right)^2} \qquad (1)$$

Where:

A is integral index of drug's antimicrobial activity, it is gradation and non-dimensional value, if we

use the diameter of inhibition growth zone, the ranges of index value are: 1.0-1.5 for low level of drug's antimicrobial activity, 1.5-2.5 for intermediate level of drug's antimicrobial activity, and over 2.5 for high level of drug's antimicrobial activity. These values are obtained by calculation using limit values of inhibition zone diameter (10, 15, 25 mm) in formula (1);

a_1, ... a_n are relative and normative weighting coefficient of test-strain microorganisms' significance in diseases against which the drug is used. It is a proportion of people affected by this type of pathogenic microorganism. The coefficient value is within the range of 0 to 1. In our calculations we took these coefficients as 1, as we supposed that all test-strains of microorganisms used are very important in the study.

D_1 ... D_n is the mean value of the diameter of inhibition growth zone of test-strain used, mm.

25 is a norming quantity that makes it possible to calculate of abovementioned gradation limits of integral index of drug's antimicrobial activity (*A*).

Correlation coefficient (*r*) between vectors (drugs) was calculated by the following formula:

$$r = \frac{\sum\left[a_i^X \cdot D_i^X \cdot a_i^{St} \cdot D_i^{St}\right]}{\sqrt{\sum\left[a_i^X \cdot D_i^X\right]^2} \cdot \sqrt{\sum\left[a_i^{St} \cdot D_i^{St}\right]^2}} \quad (2)$$

where

a_i^X, ... a_i^{St} are relative and norming weighting coefficients of test-strains' significance, which are denoted as *X* for the test drug and *St* for the standard (in our calculation as 1).

D_i^X ... D_i^{St} is the mean of inhibition zone diameter of the test-strain, *X* for the drug studied and *St* for the standard, in mm.

Pharmacological and technological index was calculated by the following formula:

$$C = \sqrt{\frac{\sum\left(\frac{ci}{c_i^{\max}}\right)^2}{n}} = \sqrt{\frac{\left(\frac{c1.1}{1}\right)^2 + \left(\frac{c1.2}{1}\right)^2 + \left(\frac{c1.3}{1}\right)^2 + \left(\frac{c2.1}{1}\right)^2 + \left(\frac{c2.2}{1}\right)^2 + \left(\frac{c3.1}{1}\right)^2}{6}} \quad (3)$$

Where

C is integral pharmacological and technological index (non-dimensional value), $C \leq 1$;

ci is pharmacological, technological, costumer-oriented parameter, which equals 1 in case of positive effect of the drug, and 0 in case of negative effect of the drug (see table 1);

c_i^{max} is maximal value of parameter that equals 1;

n is total number of parameters.

This index is an integral and non-dimensional value, which, in authors' opinion, combines the following important characteristics of the drug for local treatment: pharmacological (hyperosmosis, presence of additional pharmacological properties, and presence of an irritative effect), technological (ease of manufacture, expenditures due to special containers), and costumer-oriented (usability).

Data in Table 1 below demonstrate a simple variant for coding of pharmacological, technological and costumer-oriented parameters.

For ease of calculations, we used binary variant of quantitative evaluation of different parameters (*ci*: pharmacological, technological, and costumer-oriented), wherein a positive side of parameter we assigned as 1, and negative side of parameter as 0.

Table 1. Simplified variant for coding of pharmacological, technological and costumer-oriented parameters

Pharmacological parameters, c1	1. Presence of hyperosmosis properties, c1.1	Yes	1
		No	0
	2. Presence of additional pharmacological properties, c1.2	Yes	1
		No	0
	3. Presence of an irritative effect, c1.3	Yes	0
		No	1
Technological parameters, c2	4. Ease of manufacture, c2.1	Yes	1
		No	0
	5. Expenditures due to special containers, c2.2	Yes	0
		No	1
Costumer-oriented parameters, c3	6. Usability for patients, c.3.1	Yes	1
		No	0

In order to integrate various qualitative and quantitative parameters into one index (vector object in multidimensional factors' space) we should modify these parameters to non-dimensional normalized values.

For this purpose we may use a desirability theory; the questions related to design of desirability function are presented in other works [3, 4] in more detail.

The scale of desirability values are ranged from 0 to 1. We symbolized partial desirability functions in parameters selected as A_1, B_1, C_1 … Z_1.

It should be noted that value A_1=0 is associated with absolutely unacceptable level of this factor (a very poor quality), and A_1=1 corresponds to the best level of this factor (a very good quality), moreover, its further improvement is impossible or unreasonable.

Desirability levels and respective numerical values are presented in Table 2.

Table 2. Basic values of desirability scale

Desirability value of response	Quantitative values for scale of desirability
Very good	0.80-1.00
Good	0.63-0.80
Satisfactory	0.37-0.63
Poor	0.20-0.37
Very poor	0.00-0.20

Transfer from original values of parameters *A*, *B*, *C*, …, *Z* to non-dimensional normalized values, particular desirability functions A_1, B_1, C_1, …, Z_1, are well defined in graphic form, but it is better to approximate by analytical functions, for example:

$$A_1 = \exp\left[-\exp(-(k_0 + k_1 \cdot A))\right] \quad (4)$$

$$B_1 = \exp\left(-\left|\frac{2 \cdot B - (B_{\max} - B_{\min})}{B_{\max} - B_{\min}}\right|^n\right) \quad (5)$$

Where
A_1, B_1 are particular functions of desirability, $0 \le (A_1; B_1) \le 1$;
A, *B* are integral indexes of drug's antimicrobial activity and its price, respectively;
B_{max} is an extreme maximum value of drug's price, accepted as 30 grn;
B_{min} is an extreme minimum value of drug's price, accepted as 5 grn;
k_0, k_1 are constants equal to «-2.23» and «1.49», respectively;
n is positive number, accepted as 2 ($0 < n < \infty$).

Formula (4) is used for the case, when parameter values are limited only from one side, e.g. for integral index of drug's antimicrobial activity: $A_{min} \le A$ or $A \le A_{max}$.

Formula (5) is used for the case, when parameter values are limited from two sides, e.g. for price of drug $B_{min} \le B \le B_{max}$.

If the researcher has normalized partial desirability functions with respect to parameters of interest, it is possible to combine them in *n*-dimensional space to one overall desirability function.

Overall desirability function can be calculated as arithmetic or geometric mean value of desirability function of these parameters [3, 4].

However, as it has been noted above, overall desirability function can be calculated as vector into *n*-dimensional space of normalized desirability function based on individual parameters typical for the drug:

$$\alpha_1 = \sqrt{(a_1 \cdot A_1)^2 + \ldots + (a_Z \cdot Z_1)^2} \quad (6)$$

Where
α_1 is integrated index of overall desirability function;
a_1 ... a_Z are relative and normalized weighting coefficient of partial desirability functions with respect to individual parameters;
A_1 ... Z_1 are normalized partial desirability functions with respect to individual parameters typical for the drug.

At the same time, the region of integrated index of overall desirability function with optimal values automatically shows the most reasonable variants of drug choice for treatment.

However, it is possible that none of the drugs is located within this optimal region; in this case we may select the drug with nearest value to the optimal zone.

For calculation of the distance between coordinates of optimal zone and test drug we used the following formula:

$$\Delta_{\alpha\min} = \sqrt{[a_1 \cdot (A_1 - A_{onm})]^2 + \ldots + [a_Z \cdot (Z_1 - Z_{onm})]^2} \quad (7)$$

Results and their discussions

Antimicrobial activity of drugs determined by agar well diffusion method is presented in Table 3.

Table 3. Antimicrobial activity of drugs by agar well diffusion method

No.	Drug's name	Growth inhibition zone diameter of test microorganisms, mm; *n*=6, *P*=0.95					
		S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. vulgaris ATCC 4636*	*P. aeruginosa* ATCC 27853	*B. subtilis* ATCC 6633	*C. albicans* ATCC 885-653
1	Decasan water solution 0.02%	20.3±0.6	14.7±0.6	14.0±1.0	13.7±0.6	25.0±1.0	21.7±1.6
2	Ioddicerin glycerin solution 0.5 %	21.1±0.8	20.0±0.6	17.4±0.6	15.1±0.8	20.3±0.5	15.6±0.5
3	Laevomecol ointment	27.7±0.6	28.2±0.8	27.1±0.4	28.6±0.6	30.8±0.5	Growth
4	Laevosinum ointment	28.3±0.5	26.1±0.6	27.6±0.4	28.0±0.9	24.7±0.7	Growth
5	Methyluracilum cum Myramistino ointment	27.7±0.4	28.8±0.7	23.6±0.6	23.2±0.5	25.4±0.9	Growth
6	Myramistinum-Darnitsa ointment	17.6±0.7	16.3±0.4	15.4±0.5	14.7±0.6	17.8±0.7	20.3±0.5
7	Calendula tincture	12.7±0.4	13.3±0.5	13.7±0.6	12.7±0.5	13.0±0.9	13.7±0.5
8	Sophora japonicum tincture	26.7±0.5	24.3±0.4	15.7±0.8	14.3±0.6	25.7±0.7	14.3±0.6
9	Povidone-Iodine liniment	17.0±0.6	16.7±0.9	23.1±0.8	19.8±0.7	20.3±0.5	20.1±0.4
10	Ranostop ointment 10%	18.4±0.4	15.2±0.7	14.9±0.4	14.7±0.9	20.3±0.6	17.6±0.7

Table 4 demonstrates data on the following main parameters: integral index of drug's antimicrobial activity (*A*), square of correlation coefficient ($E=r^2$) calculated by formulas (1) and (2), and price of the drug obtained from the site's data as of March 05, 2016 [5], for individual antimicrobials that may be used for local wound treatment.

Table 4. Pharmacological and economical parameters of antimicrobials for local wound treatment tested.

No.	Drug's name	Integral index of drug's antimicrobial activity, *A*	Price of the drug, grn. *B*	Square of correlation coefficient (r^2), *E*
1	Decasan water solution 0.02%	1.84	54.96	0.95
2	Ioddicerin glycerin solution 0.5 %	1.80	15.81	0.98
3	Laevomecol ointment	2.55	9.92	0.83
4	Laevosinum ointment	2.41	29.43	0.83
5	Methyluracilum cum Myramistino ointment	2.31	28.77	0.83

6	Myramistinum-Darnitsa ointment	1.68	31.99	0.98
7	Calendula tincture	1.29	6.30	0.99
8	Sophora japonicum tincture	2.05	7.87	0.93
9	Povidone-Iodine liniment	1.92	24.03	0.98
10	Ranostop ointment 10%	1.66	28.74	0.99

The values of integral pharmacological and technological index for antibacterial drugs tested are presented in Table 5.

Table 5. Values of integral pharmacological and technological index for antibacterial drugs for wound treatment tested

No.	Drug's name	Individual pharmacological and technological index						Integral pharmacological and technological index, *C*
		c1.1	c1.2	c1.3	c2.1	c.2.2	c3.1	
1	Decasan water solution 0.02%	0	0	1	0	0	0	0.41
2	Ioddicerin glycerin solution 0.5 %	0	0	1	1	1	0	0.71
3	Laevomecol ointment	1	1	1	0	1	1	0.91
4	Laevosinum ointment	1	1	1	0	1	1	0.91
5	Methyluracilum cum Myramistino ointment	1	1	1	0	1	1	0.91
6	Myramistinum-Darnitsa ointment	1	0	1	0	1	1	0.82
7	Calendula tincture	0	1	0	0	1	0	0.58
8	Sophora japonicum tincture	0	1	0	0	1	0	0.58
9	Povidone-Iodine liniment	0	0	1	0	1	1	0.71
10	Ranostop ointment 10%	0	0	1	0	1	1	0.71

For conversion from original values of parameters *A*, *B* to partial normalized desirability functions A_1, B_1, we used formulas (4) and (5), respectively.

We used direct conversion of square values of original parameters *C*, *E* to partial normalized desirability functions C_1, E_1 ($C_1=C^2$ and $E_1=E=r^2$), according to data indicated in Table 2.

Table 6 presents data on values of partial normalized desirability functions for test drugs and overall desirability function calculated by formula (6) with weight coefficient that equals 1, and distance between optimal value of virtual drug with all indexes of partial normalized desirability functions for them equal 1 and drugs tested.

Table 6. Values of partial normalized desirability functions for test drugs, overall desirability function and distance between optimal value of virtual drug and drugs tested

Drug's name	The values of desirability function, A_i	The values of desirability function, B_i	The values of desirability function, C_i	The values of desirability function, E_i	The values of overall desirability function, α_i	The distance from optimal value, Δ_i
1. Laevomecol ointment	0.812	0.958	0.828	0.83	1.72	0.31
2. Ioddicerin glycerin solution 0.5 %	0.529	0.932	0.504	0.98	1.54	0.69
3. Sophora japonicum tincture	0.645	0.872	0.336	0.93	1.47	0.77
4. Povidone-Iodine liniment	0.587	0.427	0.504	0.98	1.32	0.86
5. Methyluracilum cum Myramistino ointment	0.743	0.184	0.828	0.83	1.40	0.89
6. Laevosinum ointment	0.774	0.160	0.828	0.83	1.41	0.90
7. Calendula tincture	0.256	0.782	0.336	0.99	1.33	1.02
8. Ranostop ointment 10%	0.457	0.184	0.504	0.99	1.22	1.10
9. Myramistinum-Darnitsa ointment	0.467	0.088	0.672	0.98	1.28	1.11
10. Decasan water solution 0.02%	0.549	0.000001	0.168	0.95	1.11	1.38
11. Virtual drug	1	1	1	1	2	0

As it can be seen from Table 6, the top five probable candidates for choice are as follows: Laevomecol ointment, Ioddicerin solution, Sophora japonicum tincture, Povidone-Iodine liniment, and Methyluracilum cum Myramistino ointment.

It is interesting to note nearly equal values of overall desirability function and distance between optimal value of virtual drug and Methyluracilum cum Myramistino ointment and Laevosinum ointment.

Of course, these results do not take into account some other important drug's parameters. Moreover, these results can be significantly changed, if we use other criteria and their limits. However, it is important to authors to get across the idea and calculation procedure of parameters and overall desirability function that can be of interest to specialists.

It should be also noted, that from data in Table 6 we can determine low values of desirability function (weak points) for the drug and, if needed, work upon them.

For example, if we develop a drug in the form of glycerin solution of the extract from *Calendulae flos* in easy to use package, it will change the drug rating significantly.

It leads to increased integral index of drug's antimicrobial activity, decreased ethanol content in the drug, decreased irritation to minimum (c1.3=1, instead of c1.3=0 for tincture), improved costumer-oriented parameters (c3.1=1, instead of c3.1=0 for tincture), increased expenditures due to special container (c2.2=0, instead of c2.2=1 for tincture) and increased price of the drug.

For example, if we take A=1.60; B=10; E=0.99; C=0.71 (c1.1=0; c1.2=1; c1.3=1; c1.4=0; c1.5=0; c1.6=1), we will have values of overall desirability function and distance between optimal value of virtual drug and our drug equal to α_1=1.53, Δ_1=0.76.

It will change of significantly our drug's rating among 10 drugs selected for the study, moving it from the 7-th to the 3-rd position.

As can be seen from the above, use of vector theory together with desirability theory makes it possible to make an optimal choice of the drug with antimicrobial activities for local wound treatment between analogs; in addition it give us a possibility to predict its location when we change values of original parameters.

Conclusions.

In this paper we have shown the possibility of vector theory use for optimal choice of antimicrobial

drugs for wound treatment among analogs by taking into account several criteria at the same time.

This mathematical method together with desirability theory gives us a possibility to determine low values of desirability function (weak points) for the drug and to predict its rating when we change values of original parameters.

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VECTOR THEORY AND OPTIMAL CHOICE OF ANTIMICROBIAL DRUG FOR LOCAL WOUND TREATMENT

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Introduction. One of important problems in the field of medicine and pharmacy is an optimal choice among several alternatives. For example, the choice of drugs for treatment among several analogs, selection of excipients among analogs for development of pharmaceutical forms with optimal pharmacological, technological and economical parameters, etc.The **aim** of the work is to show the possibility of vector theory use for optimal choice of antimicrobial drugs for local wound treatment among analogs taking into account several criteria at the same time. **Materials and methods.** For our investigation we have chosen ten drugs with antimicrobial properties for local wound treatment in different pharmaceutical forms (ointment, liniment, water and glycerin solution, tincture). We have determined antibacterial activity of drugs by agar well diffusion method on six test-stain microorganisms: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillus subtilis* ATCC 6633, and *Candida albicans* ATCC 885-653. Well diameter was 10 mm, the volume of drug in the well was 0.27±0.02 ml, microbial burden of agar upper layer was 10^7 CFU/ml, and total layer height in Petri dish was 4.0±0.5 mm. In order to integrate various qualitative and quantitative parameters into one index (vector object in multidimensional factors' space) we modify these parameters to non-dimensional normalized values. For this purpose we use a desirability theory. We have chosen the following criteria for optimal choice of the drug: antimicrobial activity (integrated index of drug's antimicrobial activity), drug's price, pharmacological and technological index, spectrum of drug's action on test strains of microorganisms studied. **Results and their discussions.** Using vector and desirability theory, we have obtained the following range of drugs in decreasing order: Laevomecol ointment, Ioddicerinum, Tincture of Sophora japonica, Povidone-Iodine liniment, Methyluracilum cum Myramistino ointment, Laevosinum ointment, Tincture of calendula, Ranostop ointment 10%, Myramistinum-Darnitsa ointment, and Decasanum water solution 0.02 %. **Conclusions.** In this paper we have shown the possibility of vector theory use for optimal choice of antimicrobial drugs for wound treatment among analogs by taking into account several criteria at the same time. This mathematical method together with desirability theory gives us a possibility to determine low values of desirability function (weak points) for the drug and to predict its rating when we change values of original parameters.

Key words: vector theory, optimal choice of wound treatment drug.