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DEVELOPMENT OF AN APPROACH TO PREDICTING THE BIOAVAILABILITY OF ENTERAL NUTRITION PRODUCTS

Vladimir V. Kondratenko, Evgeniya Yu. Agarkova*
All-Russian Dairy Research Institute, Moscow, Russia

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Abstract
One of the key factors while developing nutritional supplements is their bioavailability. To determine it, expensive and time-consuming clinical studies of developed products are necessary. Using in silico methods may speed up and reduce the costs of such clinical studies. The purpose of this study is to develop an approach to predicting the integral bioavailability of enteral nutrition products (ENPs) based on a comprehensive analysis of the matrices of components and indicators. The includes a comprehensive empirical study based on a comparative statistical analysis of the matrix of studied ENPs components. Available information on the composition and indicators of 52 commercial ENPs was used as a research object. This information was compiled into a matrix of components and indicators, marked according to the intended purposes of the products. The set of products included in the matrix was divided into 2 subsets: ENPs corresponding to a given intended purpose and other ENPs. This made it possible to separate statistically significant components and indicators that define the intended purpose of the product with a given threshold of the maximum error probability for inequality of mean values. Using Harrington's desirability principle in relation to the identified components and indicators made it possible to obtain an integral estimate of desirability for a given intended purpose. A vector characterizing the distance from the integral estimate to the ideal value was introduced as equivalent predicted bioavailability. The upper limit of the optimal range is 0.37, the upper limit of the acceptable range is 0.63. The predicted bioavailability vector scale is the inverse of the integral desirability scale. In contrast to Harrington scaling, the lower the predicted bioavailability value, the more preferable it is. Analysis of the introduced indicator allowed us to establish significant variability in commercial ENPs with respect to predicted bioavailability for diabetes mellitus and thermal injury. Based on the proposed predicted bioavailability vector, a principle has been developed for the evolutionary development of a statistical approach to predicting bioavailability when designing ENPs. This principle is a universal addition to the principle of food combinatorics while developing meat, dairy and plant-based ENPs.

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Introduction

One of the main characteristics of food products is their nutritional value, i. e. the content of proteins, carbohydrates, fats, vitamins and mineral elements [1,2,3]. However, eating nutrient-rich foods does not guarantee that the body will absorb and use them optimally. All other factors being equal, the absorption during digestion of two products with similar nutritional value may vary greatly [4,5]. This depends on the form of nutrients, food processing methods [6], individual physiological characteristics of the body, etc. [7]. Therefore, nutritional value cannot act as a comprehensive characteristic of a product as a factor of nutrient supply [8,9]. In this regard, the issue of nutritional value should be considered more deeply, i. e. from the perspective of the digestibility of the product's nutrients. In this case, the bioavailability of nutrients inevitably acts as a corrective factor that determines the nutritional properties of food products [10,11]. This term refers to the total proportion of nutrients in the food matrix absorbed by the human body during metabolism [12]. All other factors being equal, the higher the indicator value, the better [13]. High bioavailability of food products for healthy people is certainly important for ensuring the normal functioning of the body [14,15]. However, in the case of functional products, especially enteral nutrition (EN), bioavailability is critical [16,17]. In nutritional supplementation, ENPs are a priori nutrient-compensating products providing the person with a particular pathology with the required amount of energy and essential components [18,19]. The bioavailability indicator is very informative, but the procedure for determining it involves expensive *in vitro* [20,21] and *in vivo* testing, as well as clinical studies [22]. This indicator is determined based on the analysis of final and intermediate products of metabolism [23]. As a result, a number of objective consequences inevitably arise:

- bioavailability analysis is carried out *post factum*, which means the need to obtain a set of preliminary and basic preclinical and clinical studies [24]. Moreover, the product itself must have already been produced in some quantity and consumed by laboratory animals and focus-group patients [13,23];
- the bioavailability indicator is discrete, which is inextricably linked with the previous consequence and is characterized by a strict link to the composition and form factor of the product without the possibility of considering the dynamics of mass fractions for one or another component in the composition;
- high resource consumption because preliminary and basic clinical studies are quite expensive and time-consuming and may last for up to a year or more [25,26];
- not applicable to ENPs due to the need for a dynamic design approach. This is due to the fact that the core of any design algorithm is combinatorics [27,28]. For its successful implementation, it is necessary to be able to dynamically change the mass fractions of individual components within certain limits. The process itself must occur before the physical production of the designed product with the identification of a certain set of solutions that satisfy the basic set of criteria [29,30,31].

Thus, each subsequent consequence accumulates all the previous ones. In this regard, there is a need to develop flexible approaches to *in silico* predicting the bioavailability for an arbitrary matrix of food products even at the design stage.

The work of many scientific groups from leading research centers in the world based on more or less significant samples of food product sets with clearly established bioavailability values has determined that for individual nutrients this kind of predicting may be very successful. Currently, such models for predicting bioavailability exist as Hallberg and Hulthén model [31] for iron cations, as well as Miller, Krebs and Hambidge model [32] for zinc cations. These models make it possible to predict the bioavailability, taking into account the possible synergistic, antagonistic or additive influence of associated components in the food matrix (macro- and micronutrients of organic and mineral nature).

Unfortunately, for most nutrients, such models have not yet been developed, despite the fact that the demand of food science in this regard is continuously increasing (especially in the field of therapeutic nutrition). Thus, the main approach to predicting the bioavailability of nutrients is *in silico* simulation, which should be based on the existing understanding of the kinetics of metabolic processes in the human body. However, this approach requires operating with adequate databases [33]. Similarly, modern methods for simulation of digestibility processes operate with pharmacokinetics, i. e. the metabolism of individual pharmacological components. This fundamentally distinguishes this approach from ideas about the bioavailability of nutrients from multicomponent food matrices, where simultaneous multiple-vector metabolism occurs. In addition, this approach raises a number of questions: Peters and Dolgos [34] point out the problems of non-identifiability of pharmacokinetic model parameters, and Le Feunteun, Mackie and Dupont [35] put in question the possibility for detailed simulation of nutrient absorption due to the limited understanding of the metabolic process. Cacace et al. [36] propose moving from a physiological pharmacokinetics model to an intestinal physiology model. The necessity and promising outlook of developing fundamentally new approaches to simulation of bioavailability are also stated by Pompa et al. [37] and Sugano [38]. The authors [39] agree with them, emphasizing that existing *in silico* models are not able to provide a comprehensive understanding for the kinetics of human metabolic system interaction with the nutrients in the food matrix of the product.

Thus, there is an objective need to develop an integral empirical approach to predict bioavailability.

The purpose of the study is to develop an approach to indirectly predicting the integral bioavailability of ENPs, including meat and dairy ENPs, based on a comprehensive analysis of their components and indicators through a synthetic parameter, i. e. a vector.

Objects and methods

A set of open access data on the composition, nutritional value, glycemic index, osmolality and appropriateness of ENPs for certain pathologies was used as initial data. We analyzed 52 foreign and domestic commercial ENPs currently present on the Russian market:

- manufactured by Fresenius Kabi Deutschland GmbH (Germany): DIBEN® (1), Fresubin® VB Energy (2), Fresubin® Original (3), Reconvan® (4), Supportan® (5), Fresubin® Energy dietary fiber (6) and Intestamin® (7);
- manufactured by Nestlé S. A. (Switzerland): Impact® Enteral (8), Peptamen® AF (9), Resource® Diabet Plus (10);
- manufactured by Nutricia (Netherlands): Nutrison® 1.0 (11), Nutrison® Advanced Diason (12), Nutridrink Nutrison® Advanced (13), Nutrison® Advanced Cubison (14), Nutrison® Protein Intense (15), Nutrison® Protein Advance (16), Nutrison® Energy (17), Nutrison® Energy Multi Fibre (18), Nutrison® Advanced Peptisorb (19), Nutrison® Diason Energy HP (20), Nutrison® Multi Fibre (21), Nutridrink® (22), Nutridrink® Compact Protein (23), Nutridrink® Compact Fibre (24), Renilon® (25), Forticare® (26), Nutrilis® Powder (27), Nutrilis® Clear (28);
- manufactured by B. Braun SE (Germany): Nutricomp® Hepa Liquid (29), Nutricomp® Diabet Liquid neutral (30), Nutricomp® Energy Fiber Liquid (31), Nutricomp® Peptid Liquid (32), Nutricomp® Intensive Liquid (33), Nutricomp® Standard Liquid (34), Nutricomp® Fiber Liquid (35), Nutricomp® Energy Liquid (36), Nutricomp® Drink Plus (37), Nutricomp® Drink Plus Fiber (38), Nutricomp® Chicken Soup (39), Nutricomp® Vegetable Soup (40), Nutricomp® Drink Renal (41), Nutricomp® Immun Liquid (42), Nutricomp® Enbrace Active (43);

- manufactured by InfaPrim (Russia): Nutrien® standard (44), Nutrien® standard fiber (45), Nutrien® energy (46), Nutrien® diabet (47), Nutrien® hepa (48), Nutrien® nephro (49), Nutrien® pulmo (50), Nutrien® fort (51), Nutrien® elemental (52).

The development is based on a comprehensive empirical study based on a comparative statistical analysis of component matrix of the studied ENPs.

Mathematical processing was carried out using Microsoft Excel 2010 spreadsheet processor (Microsoft Ink.) with the "Solution Search" add-on installed. The search for a solution was carried out using the simplex method, as the most universal method, with automatic scaling and accuracy limitation of 10^{-8}.

Results and discussion

Systematization of commercial ENPs

Commercial ENPs of foreign and domestic production presented on the Russian market are of great variability both in manufacturing companies, ingredients and composition, quality indicators and intended purpose. Hereinafter, the term "ingredients" refers to the elements of the formulation and the term "components" refers to the micronutrients and macronutrients. Intended purpose refers to a pathology for which the manufacturer formally declares the applicability of a specific ENP. As a result of systematization of the source data set, ENP applicability matrix by intended purpose (Table 1) and components/indicators matrix (supplemental file) were generated.

Analysis of the applicability matrix showed that, in terms of occurrence, the intended purposes of the studied commercial ENPs significantly differ (Table 2). In the studied set, no more than six products were noted to be used for hypercatabolism or cardiovascular diseases. At the same time, 38 products have been identified as being used for oncological diseases.

For example, in the ENP set, the occurrence of intended purposes belonging to the first quartile is more than four times higher than that for the fourth quartile. This distribution is presumably related to the current distribution of nutrient supply demand regarding ENPs. At the same time, there is some probability of mistake in this assumption due to the initial limitation of the sample. The use of quartiles I and IV for comparison was assumed due to the fact that the extreme quartiles of almost any data set that includes different numerical values are poles in the range, i. e. they have the maximum possible differences.

Determining the maximum error probabilities for inequality of mean values

The design of ENPs within the framework of formal criteria for meeting a certain intended purpose involves the resulting set of formulations. However, the multiplicity of results underlying the combinatorial approach *a priori* implies some variability. It concerns both the composition

Table 1. ENP applicability matrix by intended purpose

Intended purpose	ENP codes *
Diabetes mellitus	1, 10, 12, 20, 22, 30, 47
Preparing for surgery	2 to 4, 6 to 8, 11 to 13, 16, 17, 20 to 23, 26, 28 to 30, 33, 34, 37 to 40, 43, 51
Postoperative period	2 to 4, 6 to 14, 16 to 17, 19 to 23, 26 to 30, 32 to 40, 42, 43, 51, 52
Thermal injury	2, 4, 6, 7, 9, 11, 12, 14 to 21, 23, 30, 31, 33, 35, 37, 42, 44 to 47, 50
Sepsis	2, 6, 8, 9, 11, 12, 15 to 21, 30, 33, 35, 37, 42
Multiple injuries	4, 6 to 12, 14 to 21, 23, 31, 34 to 36, 42
Gastrointestinal diseases	3, 6, 7, 9, 11 to 24, 32, 34 to 40, 43 to 45, 47, 52
Eating disorders, dysphagia	4, 6, 9, 11 to 14, 16 to 23, 27, 28, 30, 33 to 35, 37 to 40, 43, 52
Oncological diseases	2, 3, 5, 6, 8, 11 to 13, 15 to 24, 26 to 28, 30 to 40, 43 to 47, 51, 52
Cardiovascular diseases	2, 6, 8, 9, 11, 13, 18 to 20
Cardiopulmonary diseases	2, 6, 17, 18, 21, 33, 50
Mental illness	9, 11 to 14, 17 to 23, 29, 30, 34 to 40, 43, 44
Neurological disorders	3, 5, 6, 12 to 24, 28, 30, 31, 34 to 40, 43
Geriatrics	34, 35, 37, 44
Cystic fibrosis	2, 13, 20, 23, 44 to 47
Liver diseases	2, 8, 9, 11, 13, 17 to 23, 29, 30, 34, 35, 41, 48
Kidney failure	26, 41, 49
Coma	3, 6, 31, 34 to 36, 50
AIDS **	2, 5, 11 to 13, 17 to 23, 31, 36 to 40, 42
Cachexia	2, 3, 5, 6, 8, 9, 11, 16 to 18, 20, 29 to 31, 34 to 38, 41 to 43, 51
Multiple organ failure	6 to 9, 16, 18, 36, 42
Palliative conditions	44 to 47, 50
Critical conditions	44 to 47
Covid-19	22, 33, 50

* Product codes are determined in "Objects and methods" section.

** AIDS, acquired immunodeficiency syndrome.

Table 2. Occurrence of intended purposes in the set of studied ENPs*

Intended purpose	Occurrence	
	Frequency	Quartile
Oncological diseases	38	I
Postoperative period	37	
Thermal injury	29	
Eating disorders, dysphagia	28	
Neurological disorders	26	II
Preparing for surgery	26	
Gastrointestinal diseases	23	
Multiple injuries	22	
Cachexia	22	
AIDS	19	III
Sepsis	18	
Liver diseases	16	
Mental illness	16	
Cystic fibrosis	9	
Diabetes mellitus	7	IV
Coma	7	
Cardiopulmonary diseases	7	
Hypercatabolism	6	
Cardiovascular diseases	6	

* The table does not include intended purposes with an occurrence of 4 or less.

itself and its potential effect on the human body with pathology corresponding to the intended purpose of ENP. Existing methods for assessing this effect determine the nutrient bioavailability of the product. Due to their *a posteriori* nature, such methods are effective as a final control, but not in the process of actively generating many optimal formulations. To increase the efficiency of searching for an optimal set of solutions, let us postulate that the functional ENPs on the market have fairly high bioavailability. Let us also postulate that, other factors being equal, the bioavailability of an ENP specialized in relation to pathology is determined by the key components in its composition, which have statistical differentiation from the general set of other ENPs. Consequently, at the product design stage, there is a possibility of predictive assessment of its bioavailability. At the same time, taking into account the above postulates, to determine the predicted bioavailability, let us use a comparative statistical analysis of data from the matrix of components and main indicators of commercial ENPs. As an example, let us consider the determination of the predicted bioavailability of commercial ENPs for intended purposes, related to quartiles I and IV in Table 2. Let us take diabetes mellitus and thermal injury as such intended purposes.

For each intended purpose, from the considered set of products D, we will generate two non-overlapping subsets D_1 and D_0 (Figure 1).

Subset D_1 will include the set of all ENPs for the given intended purpose. Subset D_0 will include all the other products of set D that are not intended for the given intended purpose. In this case, the main condition for the existence of set D and subsets D_1 and D_0 is the following:

$$D_1 \subset D \wedge D_0 \subset D \wedge D_1 \cup D_0 = D \wedge D_1 \cap D_0 = \varnothing. \quad (1)$$

Furthermore, within set D and subsets D_1 и D_0, we will leave only those components and indicators whose number of numerical values both within subset D_1 and subset D_0 is at least two. Thus, both for subsets D_1 and D_0 and for set D, the value of z will be the same. As a result, each of the remaining components and indicators a_j will correspond to a certain number of numerical values both within subset D_1 and subset D_0. Thus, within each of the subsets, statistical processing [40] may be carried out in relation to each of these components and indicators to find the mean value ($\overline{du}_j$ and $\overline{eu}_j$, respectively) and the value of the variation interval ($d\Delta_j$ and $e\Delta_j$, respectively):

- for subset D_1

$$\overline{du}_j = \frac{\sum_{i=1}^{dk_j} du_{ij}}{dk_j}, \quad (2)$$

$$\pm d\Delta_j = t_{(d\alpha,\, dk_j - 1)} \cdot \frac{SD_j}{\sqrt{dk_j}}, \quad (3)$$

- for subset D_0

$$\overline{eu}_j = \frac{\sum_{i=1}^{ek_j} eu_{ij}}{ek_j}, \quad (4)$$

$$\pm e\Delta_j = t_{(e\alpha,\, ek_j - 1)} \cdot \frac{SD_j}{\sqrt{ek_j}}, \quad (5)$$

where du_{ij} and eu_{ij} are i-th numerical value of j-th component or indicator of subsets D_1 and D_0, respectively; SD is standard deviation; t is Student's test; dk_j and ek_j are the number of numerical values of j-th component or indicator of subsets D_1 and D_0, respectively; $d\alpha$ and $e\alpha$ are error probability value for subsets D_1 and D_0, respectively.

Let us assume that the values of $d\alpha$ and $e\alpha$ are equal. Due to the physical meaning of Student's test, the smaller the values of $d\alpha$ and $e\alpha$, the greater the values of $d\Delta_j$ and $e\Delta_j$, and vice versa. Therefore, when $\overline{du}_j \neq \overline{eu}_j$, there inevitably exists a value of $d\alpha$ and $e\alpha$ (let us denote it as α_m), at which the following condition will be true

$$\begin{cases} \dfrac{\overline{du}_j - d\Delta_j}{\overline{eu}_j + e\Delta_j} = 1, \overline{du}_j > \overline{eu}_j \\ \dfrac{\overline{du}_j + d\Delta_j}{\overline{eu}_j - e\Delta_j} = 1, \overline{du}_j < \overline{eu}_j \end{cases}. \quad (6)$$

When α_m is exceeded (if $\alpha_m < 1$), the variation intervals formed by the mean values of similar components or indicators of two subsets D_1 and D_0 and by the corresponding variation intervals do not overlap. In other words, α_m represents the maximum error probability for inequality of mean values. Due to the limited nature of the general set of ENPs under consideration, let us assume a value of α_m within 0.2 as a factor for the statistical acceptability of differences in mean values.

Components/ indicators	Products			
	1	2	…	k
a_1	u_{11}	u_{12}	…	u_{1k}
a_2	u_{21}	u_{22}	…	u_{2k}
a_3	u_{31}	u_{32}	…	u_{3k}
…	…	…	…	…
a_z	u_{z1}	u_{z2}	…	u_{zk}

set D

=

Components/ indicators	Products		
	d_1	…	d_k
a_1	du_{11}	…	du_{1dk}
a_2	du_{21}	…	du_{2dk}
a_3	du_{31}	…	du_{3dk}
…	…	…	…
a_z	du_{z1}	…	du_{zdk}

subset D_1

+

Components/ indicators	Products		
	e_1	…	e_k
a_1	eu_{11}	…	eu_{1ek}
a_2	eu_{21}	…	eu_{2ek}
a_3	eu_{31}	…	eu_{3ek}
…	…	…	…
a_z	eu_{z1}	…	eu_{zek}

subset D_0

Figure 1. Generation of subsets D_1 and D_0 from set D

Table 3. Maximum error probability matrix for inequality of α_m mean values

Diabetes mellitus		Thermal injury	
components/indicators	α_m	components/indicators	α_m
components		*components*	
saturated fatty acids	0.01449*	taurine	0.15066
monounsaturated fatty acid	0.03319	medium-chain triglycerides	0.05634
carbohydrates	0.11769	docosahexaenoic acid	0.05385
pantothenic acid B5	0.19965	carbohydrates	0.13299
pyridoxine B6	0.15404	sugars	0.12888
biotin	0.04297	lactose	0.19027
indicators		biotin	0.04294
glycemic index	0.02698	*indicators*	
		dietary fibers	0.16446
		caloric value	0.14725
		osmolarity	0.14228

* Highlighted values are within $\alpha \le 0.05$

Carrying out statistical processing for each similar component and indicator of both subsets made it possible to identify those for which ENPs with given intended purpose are statistically acceptable different from the rest. The results of α_m determination for diabetes mellitus and thermal injury are presented in Table 3. The values of α_m were calculated by numerical methods in the environment of Microsoft Excel 2010 spreadsheet processor (Microsoft Ink.), using the method of searching for solutions to problems by the simplex method with automatic scaling and accuracy limitation of 10^{-8}.

The calculation results made it possible to identify six components and one indicator as acceptable in the case of diabetes mellitus. In the case of thermal injury, there are already seven components and three indicators. It is worth noting that, due to their nature, acceptable indicators for differentiating subsets indirectly include a set of components not included in the final tables and do not increase their dimensions.

It is particularly remarkable that for individual components and indicators, the value of the maximum error probability for inequality of mean values is in the range of 0.05 to 0.06. Among the components, both for diabetes mellitus and for thermal injury, these include fatty acids or triglycerides, and biotin.

Determination of the predicted bioavailability vector

Due to natural statistical variability, all values of each of z components and indicators within subset D_1 are in the interval between a certain minimum $du_{j(\min)}$ and maximum $du_{j(\max)}$. Consequently, in contrast to the arithmetic mean, the most typical value will correspond to the median $du_{j(\text{med})}$. Thus, the general condition for the existence of a statistically acceptable component or indicator a_j of ENP with given intended purpose is as follows:

$$\forall a_j\Big|_{\alpha_m \le 0.2} : \quad a_j\left[du_{j(\min)}; du_{j(\max)}; du_{j(med)}\right]. \quad (7)$$

Therefore, the closer the numerical value of a component or indicator is to $du_{j(\text{med})}$, the more typical it will be for the given intended purpose. Whereas extreme values will be on the border of acceptability. In this case, for an impersonal assessment of the optimality of the component or indicator value, we can use Harrington's two-way desirability function [40,41]:

$$d_j = \exp\left(-\left|q_j\right|^{n_j}\right), \quad (8)$$

where d_j is a particular value of the desirability function;

$q_j = \dfrac{2 \cdot du_j - \left(du_{j(\max)} + du_{j(\min)}\right)}{du_{j(\max)} - du_{j(\min)}}$ is an argument of the desirability function;

n_j is exponent.

Due to the specific feature of this type of Harrington desirability function, extreme values are *a priori* assumed to be equal to $1/e$ (approximately 0.37), where e is the base of the natural logarithm. Intermediate may be assigned a value of 0.63 or 0.8 [41,42]. Since, in this case, we postulated that the median value of each partial sample obtained was close to the ideal bioavailability value for the selected product range, we chose a value of 0.8. Then, in accordance with the methodology for finding the parameter n_j of Harrington's two-way desirability function, we compare the reference value of desirability $q_{j(\text{mid})}$ equal to 0.8 to intermediate (in our case, median $du_{j(\text{med})}$) values of the argument. Then, in accordance with [41], we can determine n_j using the formula:

$$n_j = \frac{\ln\left\{-\ln\left[d_{j(mid)}\right]\right\}}{\ln\left[q_{j(mid)}\right]}. \quad (9)$$

The calculation results are presented in Table 4.

As the table data shows, the values of n_j vary within fairly wide limits. However, it is not possible to give an unambiguous analytical assessment of these circumstances due to the highly empirical nature of the indicator.

Specific feature of Harrington's particular desirability functions is the possibility of involving their arbitrary population in the integral estimate of the desirability indicator in relation to the object being studied. The integral value of

Table 4. Matrix of exponents n_j

Diabetes mellitus		Thermal injury	
components/indicators	n_j	components/indicators	n_j
components		*components*	
saturated fatty acids	0.9320	taurine	18.7392
monounsaturated fatty acid	0.9320	medium-chain triglycerides	4.4578
carbohydrates	1.3653	docosahexaenoic acid	1.2726
pantothenic acid B5	1.0820	carbohydrates	0.6133
pyridoxine B6	1.3653	sugars	9.9676
biotin	0.3257	lactose	12.1716
indicators		biotin	3.7753
glycemic index	0.9927	*indicators*	
		dietary fibers	1.7703
		caloric value	0.9922
		osmolarity	1.5434

Table 5. Predicted bioavailability vectors of ENPs for diabetes mellitus

Item No.	Product ID	d	$\vec{v}_{BA}$
1	10	0.649872	0.350128*
2	30	0.592027	0.407973
3	47	0.569146	0.430854
4	20	0.507267	0.492733
5	1	0.494916	0.505084
6	12	0.474662	0.525338
7	22	0.388335	0.611665

* Treatments with high predicted bioavailability ($\vec{v}_{BA} \le 0.37$)

Table 6. Predicted bioavailability vectors of ENPs for thermal injury

Item No.	Product ID	d	$\vec{v}_{BA}$	Item No.	Product ID	d	$\vec{v}_{BA}$
1	18	0.719421	0.280579*	16	47	0.557450	0.442550
2	20	0.680163	0.319837*	17	15	0.556581	0.443419
3	17	0.653087	0.346913*	18	2	0.548933	0.451067
4	42	0.641100	0.358900*	19	45	0.545660	0.454340
5	16	0.617214	0.382786	20	9	0.538522	0.461478
6	14	0.610536	0.389464	21	11	0.533331	0.466669
7	19	0.608547	0.391453	22	12	0.526965	0.473035
8	31	0.604305	0.395695	23	50	0.482528	0.517472
9	36	0.601881	0.398119	24	30	0.477161	0.522839
10	46	0.600013	0.399987	25	44	0.473995	0.526005
11	37	0.590680	0.409320	26	34	0.472923	0.527077
12	33	0.585353	0.414647	27	6	0.469957	0.530043
13	21	0.579623	0.420377	28	7	0.389956	0.610044
14	35	0.575514	0.424486	29	23	0.367879	0.632121
15	4	0.565899	0.434101				

* Treatments with high predicted bioavailability ($\vec{v}_{BA} \le 0.37$)

desirability (d) may be defined as the geometric mean for the values of particular desirability functions for components and indicators within each analyzed product [41,42]:

$$d = \sqrt[z]{\prod_{j=1}^{z} d_j}\ , \qquad (10)$$

Ideally, the integral desirability values should tend to be equal to 1. However, due to the orientation of the scale, direct use of the integral desirability value to indirectly assess predicted bioavailability is quite inconvenient. In this regard, we introduce a synthetic indicator, predicted bioavailability vector, which is equal to the distance in the metric of integral desirability values to the value of one:

$$\vec{v}_{BA} = 1 - d, \qquad (11)$$

In other words, the lower the value of $\vec{v}_{BA}$, the higher the predicted bioavailability, and vice versa. In this case, the upper limit of the optimal value of the predicted bioavailability vector is 0.37, and the upper limit of the acceptable value is 0.63. Then the maximum predicted bioavailability will correspond to the predicted bioavailability vector value equal to zero.

The results of $\vec{v}_{BA}$ determination for the studied ENPs according to their intended purpose are presented in Tables 5 and 6. The data were ranked in order of predicted bioavailability decreasing.

Analysis of the data obtained showed that ENPs specialized for their intended purpose form a fairly wide range of potential bioavailability. Moreover, among the ENPs specialized for diabetes mellitus, only one corresponded to the optimum area of predicted bioavailability. Among products specialized for thermal injury, there were already four of such nearly optimal ones. At the same time, in the subsets of both intended purposes, there were ENPs for which the predicted bioavailability vector was in the upper limit of the acceptability area. In the subset of products for diabetes mellitus, there was one such product, and in the subset of products for thermal injury, there were two such

products. Such products are formally in the acceptability area, but in relation to the intended purpose, they need to be adjusted in composition to reduce $\vec{v}_{BA}$.

The use of the predicted bioavailability vector in enteral nutrition products based on a comparative statistical analysis of the components/indicators matrix for commercial products allows us to neutralize the entire series of consequences arising from the nature of the currently used bioavailability indicator. At the same time, the need for clinical studies of developed products is not completely eliminated. But these studies move into the category of validation of a new product within the target significance. They are not involved in the design process. Instead, this function falls on the predicted bioavailability vector.

Moreover, with the practical application of the predicted bioavailability vector, the potential for its evolutionary development arises, the principle of which is presented in Figure 2.

This principle assumes that during each application of the predicted bioavailability vector, components and indicators of the designed new ENP are included in the components/indicators matrix after its clinical validation. At the same time, due to the increase in the number of products in the matrix and in the subset of products with the given intended purpose, a statistical refinement of intervals, medians and the maximum error probabilities for inequality of mean values will inevitably occur. This in turn will lead to clarification of exponents and, as a consequence, the values of the predicted bioavailability vector. As a result, the development of each new product will become the next iteration of evolutionary development. In this case, the statistics will work according to the "black box" principle, gradually improving the result without the need for a large-scale simulation of individual component influence on the bioavailability, taking into account the disturbing influence of associated components.

Conclusion

In contrast to direct simulation of the bioavailability for individual nutrients, a comparative statistical analysis of the existing commercial ENPs preliminary differentiated by intended purpose may be a significant tool for predicting bioavailability. Dividing a set of products included in the original matrix into a subset corresponding to a given intended purpose and a subset of the remaining ENPs made it possible to isolate statistically significant components and indicators that identify the products with the intended purpose for a given threshold of the maximum error probability for inequality of mean values. The use of Harrington's desirability principle in relation to the identified components and indicators made it possible to obtain an integral estimate of desirability for a given intended purpose. A vector that characterizes the distance from the integral estimate to the ideal value was introduced fs the equivalent predicted bioavailability (1). The smaller the vector values, the higher the predicted bioavailability. The upper limit of the optimal range is 0.37, and the upper limit of the acceptable range is 0.63. This indicator allowed us to establish significant variability in commercial ENPs with respect to predicted bioavailability for diabetes mellitus and thermal injury. Based on the proposed predicted bioavailability vector, a principle has been developed for the evolutionary development of a statistical approach to determining predicted bioavailability when designing ENPs. This principle is a universal addition to the principle of food combinatorics when developing meat, dairy and plant-based ENPs.

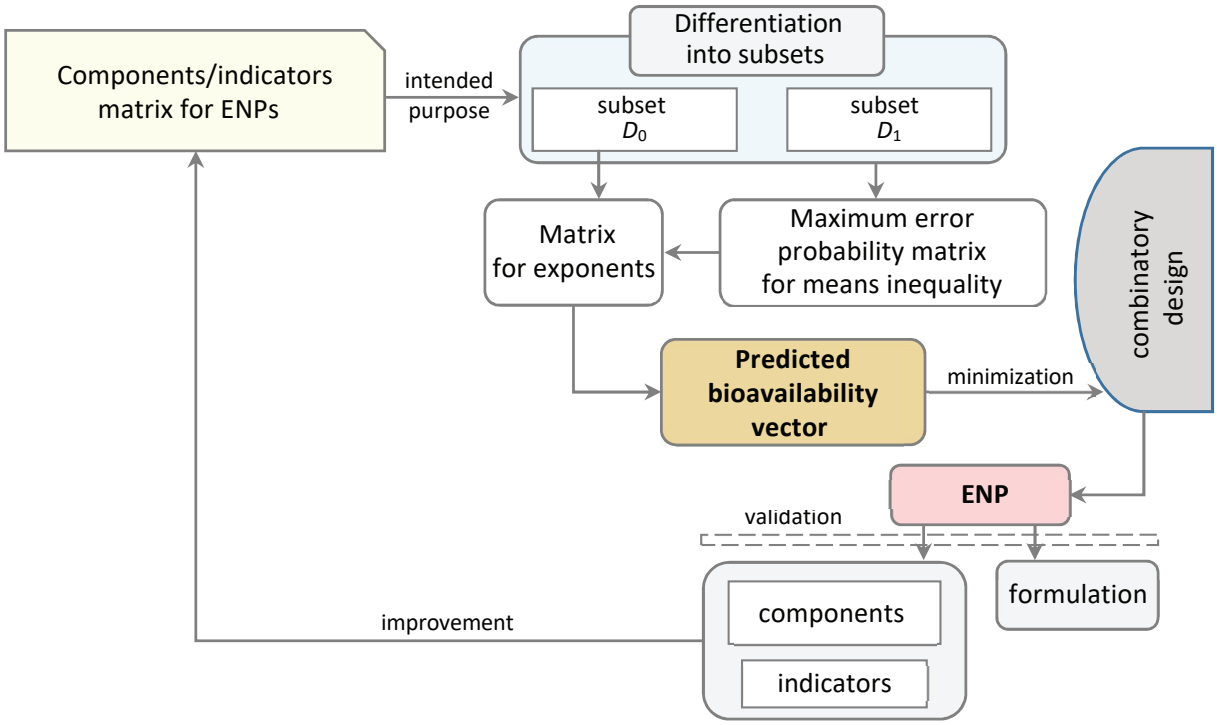

Figure 2. Evolutionary development principle of the statistical approach to determining the predicted bioavailability vector for the design of ENPs

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AUTHOR INFORMATION

Vladimir V. Kondratenko, Candidate of Technical Sciences, Docent, Senior Researcher, Laboratory of Technology of Milk-Protein Concentrates, Food Additives and Production of Products Based on Them, All-Russian Dairy Research Institute. 35/7, Lyusinovskaya str., 115093, Moscow, Russia. Tel.: +7–499–237–04–02, E-mail: v_kondratenko@vnimi.org
ORCID: https://orcid.org/0000-0002-0913-5644

Evgeniya Yu. Agarkova, Candidate of Technical Sciences, Head of the Laboratory, Laboratory of Technology of Milk-Protein Concentrates, Food Additives and Production of Products Based on Them, All-Russian Dairy Research Institute. 35/7, Lyusinovskaya str., 115093, Moscow, Russia. Tel.: +7–499–237–04–02, E-mail: e_agarkova@vnimi.org
ORCID: https://orcid.org/0000-0001-8967-7074
* corresponding author

All authors bear responsibility for the work and presented data.

All authors made an equal contribution to the work.

The authors were equally involved in writing the manuscript and bear the equal responsibility for plagiarism.

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