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Application of probability based multi: Objective optimization in the preparation of drug encapsulation with a designed experiment

Применение многокритериальной оптимизации, основанной на вероятности, при подготовке инкапсуляции лекарственных средств с помощью спроектированного эксперимента

Примена вишкритеријумске оптимизације на базивероватноће у припреми енкапсулације лекова помоћу дизајнираног експеримента

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ABSTRACT:

Introduction/purpose: In this paper, probability based multi – objective optimization (PMOO) is employed to objectively study the optimization problems of the drug encapsulation of water-soluble chitosan (WSC) / poly – gamma – glutamic acid (γ-PGA) – tanshinone IIA (TA) with a response surface design and glycosome – triptolide with an orthogonal experimental design

Methods: In PMOO, a concept of preferable probability has been introduced to describe a preference degree of the performance utility. Each beneficial and unbeneficial utility index contributes a partial preferable probability in a linear manner, positively and negatively, respectively and all the performance utility indicators are simultaneously and equally treated. The total preferable probability of a candidate is the product of all partial preferable probabilities, which thus transfers a multi-objective problem into a single-objective one.

Results: 1. The optimal encapsulation of WSC / γ-PGA – TA is for WSC of 5.755 mg·ml⁻¹, TA of 1.0275 mg·ml⁻¹, when the ratio of TA to the carrier material is 1: 4.9, and the reaction time is 1.302h. 2. The optimal preparation conditions of glycosomes – triptolide are a glycerol concentration of 20%, the phospholipid to cholesterol mass ratio of 30:1 and the phospholipid to triptolide mass ratio of 5:1.

Conclusion: The results show the applicability of PMOO in the optimization of encapsulation composites with designed tests.

KEYWORDS: probability theory, multi-objective optimization, preferable probability, test design, drug encapsulation.

Р е з ю м е :

Введение/цель: В данной статье представлена многокритериальная оптимизация, основанная на вероятности (probability based multi – objective optimization (PMOO)), с целью объективного изучения проблем оптимизации инкапсуляции лекарственных средств из водорастворимого хитозана (WSC) / поли – гама – глутаминовой кислоты ((γ-PGA) – таншинуна IIА (ТА) с дизайном поверхности отклика и глицеросомы – триптолида с помощью ортогональной экспериментальной конструкции.

AUTHOR NOTES

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Методы: В многокритериальной оптимизации, основанной на вероятности, было введено понятие предпочтительной вероятности для описания степени полезности производительности. Каждый полезный или бесполезный индекс производительности линейно влияет на частичную предпочтительную вероятность в положительном или отрицательном смысле, а все показатели полезности одновременно рассматриваются в одинаковом порядке. Общая предпочтительная вероятность кандидата является произведением всех отдельных предпочтительных вероятностей, что переводит многокритериальную проблему в однокритериальную.

Результаты: 1. Оптимальная WSC / γ -PGA-TA составляет для WSC 5,755 мг·мл⁻¹, TA 1.0275 мг·мл⁻¹, когда соотношение TA к материалу-носителю составляет 1: 4,9, а время реакции – 1,302 ч. 2. Оптимальные условия приготовления глицеросомы – триптолида при концентрации глицерина 20%, при массовом отношении фосфолипида к холестерину 30:1 и массовом соотношении фосфолипидов к триптолидам 5:1.

Выводы: Результаты показывают применимость многокритериальной оптимизации, основанной на вероятности, в оптимизации герметизирующих композитов с помощью разработанных тестов.

К л ю ч е в ы е с л о в а : теория вероятностей, многокритериальная оптимизация, предпочтительная вероятность, разработка тестов, инкапсуляция лекарственных средств.

ABSTRACT:

Увод/циљ: У раду је представљена вишекритеријумска оптимизација заснована на вероватноћи (probability based multi objective optimization –PMOO) за објективно проучавање проблема оптимизације енкапсулације лекова помоћу хитозана растворљивог у води (water-soluble chitosan - WSC)/гама полиглутаминске киселине (γ -PGA) – таншинона ПА (TA) помоћу дизајна површине одговора и глицерозома - триптолида помоћу ортогоналног дизајна експеримента.

Метод: У вишекритеријумској оптимизацији, заснованој на вероватноћи, уведен је концепт пожељне вероватноће како би се описао степен пожељности корисности неке перформансе. Сваки корисни или некорисни индекс корисности линеарно доприноси делимичној пожељној вероватноћи у позитивном, односно у негативном смислу, а сви показатељи корисности перформанси третирају се подједнако и једновременно. Укупна пожељна вероватноћа кандидата производ је свих парцијалних пожељних вероватноћа, чиме се вишекритеријумски проблем преводи у једнокритеријумски.

Резултати: 1. До оптималне енкапсулације WSC / γ -PGA-TA долази када је WSC 5.755 mg·ml⁻¹, TA 1.0275 mg·ml⁻¹, однос TA и носећег материјала 1:4.9, а време реакције 1.302h. 2. Оптимални услови припреме глицерозома – триптолида су при концентрацији глицерина од 20%, масеном односу фосфолипида и холестерола 30:1 и масеном односу фосфолипида и триптолида 5:1.

Закључак: Резултати показују применљивост вишекритеријумске оптимизације засноване на вероватноћи у оптимизацији енкапсулације композита помоћу дизајнираних тестова.

KEYWORDS: теорија вероватноће, вишекритеријумска оптимизација, пожељна вероватноћа, дизајн теста, енкапсулација лекова.

INTRODUCTION

Currently, probability based multi-objective optimization (PMOO) has been proposed from the viewpoint of probability theory (Zheng et al, 2021). A concept of preferable probability has been introduced to describe a preference degree of the performance utility where each beneficial and unbeneficial utility index contributes a partial preferable probability in a linear manner, positively and negatively, respectively. All the performance utility indicators are simultaneously and equally treated and the total preferable probability of a candidate is the product of all partial preferable probabilities, which thus transfers a multi-objective problem into a single-objective one. PMOO attempts to solve the intrinsic problems of artificial factors in other previous multi-objective optimizations. The new multi-objective optimization method was successfully extended to material selection applications with the multi-objective orthogonal test design method (OTDM), the response surface methodology (RSM) and the uniform test design method (UTDM) as well (Zheng et al, 2021; Zheng et al, 2022a; Zheng et al, 2022b).

Most actual optimality problems in the medical field are multi-objective optimization problems (MOOP). The main feature of multi-objective optimal problems is the contradiction and non-commutability between attributes, but they need to be optimized simultaneously (Mandal et al, 2018; Mirjalili & Dong, 2020; Mankowski & Moshkov, 2021). Besides, there is no uniform metric between theses

attributes in general; therefore, they cannot be compared directly. The previous approaches give a set of optimal solutions, called the non-inferior solution set, such as the commonly used Pareto solution set. Take the preparation of a drug encapsulation composite with biopolymer as an example - it is necessary to consider the encapsulation efficiency and the drug loading efficiency to be optimal objectives at the same time (Yu et al, 2020). On the other hand, in the research of Chinese herbal compound drugs, the dose-effect relationship of Chinese herbal compound has non-linear characteristics - there may be differences in the efficacy of different doses of prescriptions, and the efficacy of Chinese herbal medicines has multiple paths, points, and multiple targets. The selection of different efficacy indicators and index weights, the ratio of the components of the compound and the interaction mechanism between the components are also different. Therefore, it is necessary to seek a proper combination of drugs that can improve the efficacy of the compound and maximize the dose of multiple efficacy indicators (Chen et al, 2021; Wu et al, 2013; Song et al, 1992).

Since probability based multi - objective optimization (PMOO) was proposed from the viewpoint of probability theory, which has the advantages of excluding inherent problems of artificial factors in other multi - objective optimizations, it has had successful applications in many practical examples. In this paper, PMOO is used to objectively perform the overall optimal preparation of the drug encapsulation of water-soluble chitosan/poly - gama - glutamic acid - tanshinone IIA with a response surface design and glycosome - triptolide with an orthogonal experimental design, so as to open a new application field.

PRINCIPLE AND METHOD OF PROBABILITY BASED MULTI - OBJECTIVE OPTIMIZATION (PMOO)

In PMOO (Zheng et al, 2021), all indices of the performance utility of candidates are divided into both beneficial or unbeneficial types according to the practical requirement or preference preliminarily; a beneficial utility index contributes a partial preferable probability in a linear manner positively, i.e.,

$$P_{ij} = \gamma_j U_{ij}, i = 1, 2, \dots, n; j = 1, 2, \dots, m. \quad (1)$$

In Eq. (1), U_{ij} is the j^{th} performance utility index of the i^{th} candidate scheme; P_{ij} represents the partial preferable probability of the beneficial performance utility indicator U_{ij} ; n is the total number of candidate schemes in the scheme group involved; m is the total number of performance utility indicators of each candidate scheme in the group; and γ_j is the normalized factor of the j^{th} performance indicator.

Furthermore, according to the general principle in probability theory (Zheng et al, 2021), the normalization of partial preferable probability P_{ij} for the index i in the j^{th} performance indicator leads to the following result naturally

$$\gamma_j = \frac{1}{n \bar{U}_j}, \quad (2)$$

$\bar{U}_j$ is the arithmetic mean value of the j^{th} performance indicator in the scheme group involved.

Similarly, an unbeneficial utility index contributes a partial preferable probability in a linear manner negatively, i.e.,

$$P_{ij} = \eta_j (U_{j\max} + U_{j\min} - U_{ij}), i = 1, 2, \dots, n; j = 1, 2, \dots, m. \quad (3)$$

In Eq. (3), $U_{j\max}$ and $U_{j\min}$ represent the maximum and minimum values of the performance utility index U_j in the j^{th} group, respectively. Furthermore, the normalized factor η_j of the j^{th} group of performance indicator is

$$\eta_j = \frac{1}{[n(U_{j\min} + U_{j\max}) - n\bar{U}_j]}. \quad (4)$$

Moreover, according to probability theory (Zheng et al, 2021), the total / comprehensive preferable probability of the i^{th} candidate scheme is the product of its partial preferable probability P_{ij} of each performance utility indicator in the optimization, i.e.,

$$P_i = P_{i1} \cdot P_{i2} \cdots P_{im} = \prod_{j=1}^m P_{ij}. \quad (5)$$

Thus, by using the total preferable probability of a candidate alternative being the product of all partial preferable probabilities, it naturally transfers a multi-objective problem into a single-objective one.

The total preferable probability P_i of a candidate is the unique decisive index in the competitive optimization process. The main characteristic of PMOO is that the treatment for both the beneficial performance utility index and the unbeneficial performance utility index is equal without any artificial or subjective scaling factors and the requirements of simultaneous optimization for multi - objectives are met from the viewpoint of probability theory.

APPLICATIONS IN DRUG ENCAPSULATION WITH A DESIGNED EXPERIMENT

Optimal preparation of drug encapsulation has been one of important issues in recent years. In this paper, the optimization problems of water-soluble chitosan / poly – gama - glutamic acid - tanshinone IIA with a response surface design and glycosome - triptolide with an orthogonal experimental design are restudied by employing PMOO objectively.

1) Application of PMOO in the optimal preparation of the encapsulation composite of water-soluble chitosan / poly - gama - glutamic acid - tanshinone IIA with a response surface design

Yu et al (2020) conducted the optimal preparation of the encapsulation composite of water-soluble chitosan/poly-gama-glutamic acid - tanshinone IIA with a response surface design, based on the traditional treatment of a response surface design with the "additive" algorithm multi - attribute utility theory. As it was pointed in (Zheng et al, 2021), there exist intrinsic problems of artificial and subjective factors in the "additive" algorithm of the previous multi-attribute utility theory (Zheng et al, 2021). Here, the optimal preparation of the encapsulation composite of water-soluble chitosan / poly – gama - glutamic acid - tanshinone IIA with a response surface design is reanalyzed by PMOO once more.

Table 1 cited the analysis results of utility in the optimal preparation of the encapsulation composite of water-soluble chitosan (WSC) / poly-gama-glutamic acid (γ -PGA) - tanshinone IIA (TA) with a response surface design (Yu et al, 2020). The input variables include x_1 , x_2 , x_3 and x_4 , in which x_1 is the WSC concentration ($\text{mg} \cdot \text{ml}^{-1}$), x_2 represents the TA concentration ($\text{mg} \cdot \text{ml}^{-1}$), x_3 is the ratio of TA to the carrier material (in weight), and x_4 indicates the reaction time (h). The encapsulation efficiency Y_e and the drug loading efficiency Y_c are the optimal objectives, which belong to the beneficial type index. Table 2 shows the evaluation results for the preferable probability in the spirit of a response surface design.

Table 2 indicates that experiments 2 and 25 are the appropriate schemes with the highest total partial probability for the preparation of the encapsulation composite of water-soluble chitosan / poly-gama-glutamic acid - tanshinone IIA with a response surface design comparatively.

Furthermore, the regression of the data in Table 2 can be used to conduct profound optimization. Eq. (6) is the regressed formula of the total preferable probability P_t vs the input variables, x_1 , x_2 , x_3 and x_4 .

$$P_t \times 10^3 = 1.9644 - 0.1787x_1 + 0.0254x_2 - 7.2 \times 10^{-5}x_3 + 0.1717x_4 - 0.4411x_1^2 - 0.7445x_2^2 - 0.5602x_3^2 - 0.1494x_4^2 + 0.3381x_1x_3 - 0.0329x_1x_4 - 0.0172x_2x_3 + 0.0913x_2x_4 + 0.0443x_3x_4$$

$$R^2 = 0.8620.$$

(6)

TABLE 1
Details of the BoxBehnken test design and the results

Test No.	x_1	x_2	x_3	x_4	Encapsulation efficiency Y_e (%)	Drug loading efficiency Y_c (%)
1	1	0	1	1	79.31	5.25
2	0	0	0	0	93.25	11.22
3	0	0	0	0	94.31	9.92
4	0	0	-1	1	85.22	6.38
5	0	1	1	0	72.51	4.38
6	0	0	-1	-1	75.87	5.18
7	1	0	0	-1	84.56	6.97
8	0	0	0	0	90.34	10.09
9	0	-1	0	1	85.69	6.38
10	1	1	0	0	79.84	6.39
11	0	0	1	1	87.21	7.89
12	-1	0	0	-1	92.80	8.73
13	1	0	0	1	89.96	6.34
14	0	0	1	-1	79.65	6.05
15	0	-1	0	-1	80.79	5.08
16	-1	1	0	0	66.73	3.96
17	0	1	0	-1	78.62	4.26
18	-1	0	1	0	76.97	6.32
19	-1	0	0	1	90.73	9.58
20	0	-1	1	0	78.22	4.73
21	1	0	-1	0	78.34	6.21
22	1	0	0	0	84.97	5.07
23	-1	-1	0	0	84.46	6.01
24	0	-1	0	0	83.36	6.32
25	0	0	0	1	95.02	11.03
26	0	-1	-1	0	80.33	4.98
27	0	1	-1	0	70.67	5.38
28	0	0	0	0	92.73	9.89
29	-1	0	-1	0	80.39	6.54

Таблица 1 – Подробная информация о конструкции теста Бокса-Бенкена и результатах
Табела 1 – Детали теста Бокс-Бенкен дизајна и његови резултати

TABLE 2
Evaluation results of the preferable probability of utility in the preparation of the
encapsulation composite of WSC gama-PGA-TA in the spirit of a response surface design

Test No.	x_1	x_2	x_3	x_4	Encapsulation efficiency Y_e (%)	Drug loading efficiency Y_c (%)
1	1	0	1	1	79.31	5.25
2	0	0	0	0	93.25	11.22
3	0	0	0	0	94.31	9.92
4	0	0	-1	1	85.22	6.38
5	0	1	1	0	72.51	4.38
6	0	0	-1	-1	75.87	5.18
7	1	0	0	-1	84.56	6.97
8	0	0	0	0	90.34	10.09
9	0	-1	0	1	85.69	6.38
10	1	1	0	0	79.84	6.39
11	0	0	1	1	87.21	7.89
12	-1	0	0	-1	92.80	8.73
13	1	0	0	1	89.96	6.34
14	0	0	1	-1	79.65	6.05
15	0	-1	0	-1	80.79	5.08
16	-1	1	0	0	66.73	3.96
17	0	1	0	-1	78.62	4.26
18	-1	0	1	0	76.97	6.32
19	-1	0	0	1	90.73	9.58
20	0	-1	1	0	78.22	4.73
21	1	0	-1	0	78.34	6.21
22	1	0	0	0	84.97	5.07
23	-1	-1	0	0	84.46	6.01
24	0	-1	0	0	83.36	6.32
25	0	0	0	1	95.02	11.03
26	0	-1	-1	0	80.33	4.98
27	0	1	-1	0	70.67	5.38
28	0	0	0	0	92.73	9.89
29	-1	0	-1	0	80.39	6.54

Таблица 2 – Результаты оценки предпочтительной вероятности полезности при приготовлении герметизирующего композита WSC / gama-PGA-TA в духе конструкции поверхности отклика

Табела 2 – Резултати евалуације пожељне вероватноће корисности у припреми композита WSC / gama-PGA-TA за енкапсулацију у складу са дизајном површине одговора

The total preferable probability P_t gets its maximum $P_{tmax} \times 10^3 = 2.0394$ at $x_1 = 5.755 \text{ mg} \cdot \text{ml}^{-1}$, $x_2 = 1.0275 \text{ mg} \cdot \text{ml}^{-1}$, $x_3 = 1:4.9$, and $x_4 = 1.302 \text{ h}$.

Simultaneously, the encapsulation efficiency Y_e (%) and the drug loading efficiency Y_c (%) of the preparation can be fitted, and are given as follows

$$Y_e = 92.4514 - 0.8660x_1 - 2.6375x_2 + 0.1389x_3 + 2.2449x_4 - 4.8949x_1^2 - 10.3491x_2^2 - 8.7025x_3^2 - 0.1760x_4^2 + 6.1970x_1x_3 + 0.7516x_1x_4 + 0.9875x_2x_3 - 0.6621x_2x_4 - 0.6855x_3x_4 \quad (7)$$

Y_e gets its optimal $Y_{eopt} = 93.43\%$ at $x_1 = 5.755 \text{ mg} \cdot \text{ml}^{-1}$, $x_2 = 1.0275 \text{ mg} \cdot \text{ml}^{-1}$, $x_3 = 1:4.9$, and $x_4 = 1.302 \text{ h}$.

$$Y_c (\%) = 10.0612 - 0.8559x_1 + 0.2232x_2 - 0.0247x_3 + 0.7516x_4 - 1.9370x_1^2 - 3.3194x_2^2 - 2.3077x_3^2 - 0.7432x_4^2 + 1.5714x_1x_3 - 0.2467x_1x_4 - 0.1875x_2x_3 + 0.4711x_2x_4 + 0.2385x_3x_4 \quad (8)$$

Y_c gets its optimal $Y_{opt} = 10.40\%$ at $x_1 = 5.755 \text{ mg} \cdot \text{ml}^{-1}$, $x_2 = 1.0275 \text{ mg} \cdot \text{ml}^{-1}$, $x_3 = 1:4.9$, and $x_4 = 1.302 \text{ h}$.

The predicted values for Y_e and Y_c are close to the averaged encapsulation efficiency and the drug loading average, so their values of the tested encapsulated composite were 91.89% and 10.29%, respectively (Yu et al, 2020). This indicates that this is a reasonable method for the optimal conditions of an encapsulation composite with a response surface design.

2) Application of PMOO in the optimal preparation of the encapsulation composite of glycosomes – triptolide with an orthogonal experimental design

Zhu et al (2022) conducted optimizing glycosome formulations via an orthogonal experimental design to enhance transdermal triptolide delivery. The entrapment efficiency (EE) of the nanocarriers and the drug loading (DL) are taken as evaluated attribute indexes. The glycerol concentration (A, %), the phospholipid to cholesterol mass ratio (B, m/m) and the phospholipid to triptolide mass ratio (C, m/m) were set as independent variables with three levels of A (10, 20, 30 %), B (10:1, 20:1, 30:1 m/m) and C (5:1, 15:1, 30:1 m/m). Thereafter, the three-level orthogonal table $[L_9(3^4)]$ was employed in the study.

Here, the optimal preparation of the encapsulation composite of glycosomes – triptolide with an orthogonal experimental design is restudied by PMOO again. Table 3 cited the experimental arrangement and the results based on the $L_9(3^4)$ orthogonal design (Zhu et al, 2022).

The encapsulation efficiency and the drug loading efficiency belong to the beneficial type index. Table 4 shows the evaluation results of the preferable probability of the experimental data; Table 5 represents the evaluation results of the range analysis for total preferable probability.

From Table 5, the optimal composite is $C1A2B3$, which is the same as the first glanced rank 1 of test No. 6 in Table 4 luckily.

TABLE 3
Experimental arrangement and the results based on the $L_9(3^4)$ orthogonal design

Test No.	A	B	C	EE (%)	DL (%)
1	1	1	1	65.67	15.41
2	1	2	2	61.87	5.97
3	1	3	3	55.79	3.12
4	2	1	2	65.56	5.71
5	2	2	3	54.64	3.07
6	2	3	1	77.40	16.19
7	3	1	3	43.25	2.93
8	3	2	1	67.37	15.97
9	3	3	2	54.85	6.06

Таблица 3 – Экспериментальная схема и результаты, основанные на ортогональной конструкции $L_9(3^4)$

Табела 3 – Уређеност експеримента и резултати засновани на ортогоналном дизајну $L_9(3^4)$

TABLE 4
Evaluation results of the preferable probability of the experimental data

Test No.	Partial preferable probability		Total preferable probability and rank	
	EE	DL	$P_t \times 10^2$	Rank
1	0.1202	0.2070	2.4883	3
2	0.1132	0.0802	0.9082	5
3	0.1021	0.0419	0.4280	7
4	0.1200	0.0767	0.9205	4
5	0.1000	0.0412	0.4125	8
6	0.1417	0.2175	3.0813	1
7	0.0792	0.0394	0.3116	9
8	0.1233	0.2146	2.6455	2
9	0.1004	0.0814	0.8173	6

Таблица 4 – Результаты оценки предпочтительной вероятности экспериментальных данных
Табела 4 – Результати евалуације пожељне вероватноће експерименталних података

TABLE 5
Evaluation results of the range analysis for total preferable probability

Level	A	B	C
1	1.2749	1.2401	2.7384
2	1.4714	1.3221	0.8820
3	1.2581	1.4422	0.3840
Range	0.2133	0.2021	2.3544
Order	2	3	1

Таблица 5 – Результаты оценки анализа диапазона предпочтительной вероятности
Табела 5 – Результати евалуације анализе рангирања за пожељну вероватноћу

DISCUSSION

Since many problems involved in drug research are multi-objective optimization ones such as encapsulation efficiency and drug loading efficiency being optimal objectives in the preparation of drug encapsulation composites with biopolymer, it is necessary to reach the optimal status at the same time. In the investigation of Chinese herbal compound drugs, the dose-effect relationship of Chinese herbal compounds has non-linear characteristics, and there may be differences in the efficacy of different doses of prescriptions. Furthermore, the efficacy of Chinese herbal medicines has multiple paths, points, and multiple targets. The PMOO method attempted to deal with the problem of simultaneous optimization of multiple objectives and to exclude the intrinsic problems of previous optimization methods due to subjective factors, so it might be an appropriate assessment for drug research.

The above results indicate that probability based multi-objective optimization is applicable in the preparation of encapsulation composites with a designed test.

CONCLUSION

The newly developed probability based multi-objective optimization method has been successfully applied for the appropriate optimal preparation of the drug encapsulation composite with a designed test, which includes the water-soluble chitosan / poly - gama - glutamic acid - tanshinone IIA with a response surface design and glycosome - triptolide with an orthogonal experimental design. The main features of the new probability theory are: the treatment for both the beneficial performance utility index and the unbeneficial performance utility index being equal and simultaneous; no artificial or subjective scaling factors involved in the assessment process; and fulfilling the requirements of simultaneous optimization for a multi – objective problem from the viewpoint of probability theory. The potential future direction for the application of the probability theory based multi-objective optimization method is to explore more cases with complexity.

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