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An approach to optimize the batch mixing process for improving the quality consistency of the products made from traditional Chinese medicines*

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Abstract: The efficacy of traditional Chinese medicine (TCM) is based on the combined effects of its constituents. Variation in chemical composition between batches of TCM has always been the deterring factor in achieving consistency in efficacy. The batch mixing process can significantly reduce the batch-to-batch quality variation in TCM extracts by mixing them in a well-designed proportion. However, reducing the quality variation without sacrificing too much of the production efficiency is one of the challenges. Accordingly, an innovative and practical batch mixing method aimed at providing acceptable efficiency for industrial production of TCM products is proposed in this work, which uses a minimum number of batches of extracts to meet the content limits. The important factors affecting the utilization ratio of the extracts (URE) were studied by simulations. The results have shown that URE was affected by the correlation between the contents of constituents, and URE decreased with the increase in the number of targets and the relative standard deviations of the contents. URE could be increased by increasing the number of storage tanks. The results have provided a reference for designing the batch mixing process. The proposed method has possible application value in reducing the quality variation in TCM and providing acceptable production efficiency simultaneously.

Key words: Batch-to-batch quality consistency, Batch mixing, Production efficiency, Traditional Chinese medicine
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1 Introduction

Traditional Chinese medicine (TCM) offers a plethora of treatment options for complex diseases (Zhang *et al.*, 2009; Wang *et al.*, 2010; Efferth and Koch, 2011). Because the efficacy of TCM is based on the combined effects of its constituents, variation in chemical composition between batches of TCM has always been the deterring factor in achieving consistency in efficacy (Gao *et al.*, 2010). The concept "It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design." was stated in the quality by design initiative (ICH, 2009) and widely accepted in the pharmaceutical manufacturing industry (García-Muñoz *et al.*, 2010; Huang *et al.*, 2010; Prpich *et al.*, 2010; Michaels *et al.*, 2011; Yacoub *et al.*, 2011). Despite previous efforts in evaluating the batch-to-batch consistency of TCM after the production process (Fan *et al.*, 2006; Xie *et al.*, 2008; Tistaert *et al.*, 2011; Wang *et al.*, 2011), there is a greater need to improve the quality consistency of TCM during the manufacturing processes (Huang and Qu, 2011).

One main source of quality variation in TCM comes from raw herbal materials that differ by region,

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climate, and time of harvest, and another source is the fluctuation of operations in the production processes. Batch mixing, a method also used in other industries like wine-making and metallurgy (Kumral, 2005; 2006), can reduce the impact of variations in raw materials and the fluctuation in operations on the quality of the final drug product. In the batch mixing process of TCM, different batches of herbal extracts are mixed in a well-designed proportion to get a mixture in which the contents of the important constituents are closer to the reference standard. Consequently, the batch-to-batch quality difference in the mixtures is significantly smaller when compared with the original extracts.

Previous studies (Liu *et al.*, 2006; Qu *et al.*, 2006; Luo *et al.*, 2007; Yang H.H. *et al.*, 2007; Yang M. *et al.*, 2009) have proposed methods to determine the optimal mixing ratio based on the quality of existing extracts. These methods maximize the similarity in content between the mixture and the reference standard using optimal searching algorithms and usually mixing many batches of extracts. However, using fewer batches of extracts is preferred in industrial production for easier operation and trace-back according to the 'Good Manufacturing Practice' guidelines in case of product defects. In addition, when applied several times, these methods generate too many batches of residual extracts that have to be discarded due to limited storage time and number of storage tanks, leading to a low utilization ratio of the extracts (URE), i.e., the ratio of the total amount of mixtures to the total amount of extracts. Therefore, the applicability of these methods is limited in industrial production.

To achieve an acceptable URE, it is desirable to use up some batches of extracts in one mixing to reduce the number of residual batches. This study proposes a new method that mixes the minimum number of batches of extracts to simplify the mixing operation and reduce the number of residual batches. To verify the feasibility of this method, simulation studies of the batch mixing process were conducted. The impacts of some important factors on URE were studied, which provide a reference for the designing of the batch mixing process. The results have shown that the proposed method has possible application value in reducing the quality variation in the mixtures and simultaneously providing an acceptable URE.

2 Methods

2.1 Symbols

The following symbols are used in the batch mixing optimization model:

t, the number of targets, i.e., the number of the constituents with controlled contents in the mixture;

s, the number of storage tanks, i.e., the maximum number of batches of extracts that can be stored;

$\boldsymbol{x}=[x_1, x_2, \ldots, x_s]$, the amounts of each stored batch of extract used for mixing;

$\boldsymbol{u}=[u_1, u_2, \cdots, u_s]$, the amounts of each batch of extract stored;

$\max\boldsymbol{l}=[\max l_1, \max l_2, \ldots, \max l_t]$, the maximum content limits for the constituents in the mixtures;

$\min\boldsymbol{l}=[\min l_1, \min l_2, \ldots, \min l_t]$, the minimum content limits for the constituents in the mixtures;

$\boldsymbol{a}_k=[a_{1k}, a_{2k}, \ldots, a_{tk}]^{\mathrm{T}}$, the contents of the constituents in the kth batch of extract stored. For unidentified constituents, test values obtained by certain analytical methods can be used, for example peak areas on the chromatographic fingerprint;

$\boldsymbol{A}=[\boldsymbol{a}_1, \boldsymbol{a}_2, \ldots, \boldsymbol{a}_s]$, the matrix ($t\times s$) consists of the contents of the constituents in the batches of extracts stored;

b, the amount of mixture needed in each batch.

2.2 Optimization model for batch mixing

To get a mixture with the contents of the important constituents in the range of content limits, different batches of herbal extracts were mixed in a certain proportion. Therefore, the following constraints must be satisfied in the batch mixing:

$$\sum_{i=1}^{s} x_i = b, \tag{1}$$

$$\min\boldsymbol{l}^{\mathrm{T}} \le \frac{\boldsymbol{A}\cdot\boldsymbol{x}^{\mathrm{T}}}{b} \le \max\boldsymbol{l}^{\mathrm{T}}, \tag{2}$$

$$\boldsymbol{0} \le \boldsymbol{x}^{\mathrm{T}} \le \boldsymbol{u}^{\mathrm{T}}, \tag{3}$$

where Eq. (1) determines the amount of mixture needed for the follow-up process. The contents of the constituents in the mixture are assumed to be the weighted average of the contents in the extracts, where the weights are the amounts of each batch used for mixing; Eq. (2) ensures that the contents are in the range of their limits; and, Eq. (3) is the maximum amount of each batch that can be used for mixing.

To address the practical problem, this study improves the methods described previously (Liu *et al.*, 2006; Qu *et al.*, 2006; Luo *et al.*, 2007; Yang H.H *et al.*, 2007; Yang M. *et al.*, 2009) to determine the optimal mixing ratio. A new method for batch mixing is proposed, which mixes a minimum number of batches of extracts and tries to use up some batches of extracts to reduce the number of residual batches. The new objective function is

$$\max \sum_{i=1}^{s} x_i^2, \tag{4}$$

which maximizes the sum of squares of the used amounts of each batch. Therefore, the optimization model in this study is to maximize the value of Eq. (4) when constraints of Eqs. (1)–(3) are satisfied.

As the sum of the amounts of the extracts used is a constant (Eq. (1)), the more batches used, the smaller the objective function value would be. For example, if one batch of extract without mixing can meet the constraints of Eqs. (1)–(3), then the optimization result would be just using that batch to get the maximum objective function value b^2. Therefore, the optimization result tends to end up with fewer batches used and a lower number of residual batches.

The optimization model can be solved by quadratic programming (QP) algorithm, which is faster in calculation than sequential QP algorithm (Qu *et al.*, 2006) and genetic algorithm (Yang *et al.*, 2009). To solve the QP problem, the "quadprog" function in the optimization toolbox of MATLAB 7.9 software (the Mathworks, USA) was used and the medium-scale quadprog algorithm was applied.

A simple case is presented to illustrate the advantages of the optimization model. Suppose that 100 kg of extract is needed, and the contents of two constituents must be in the range of content limits shown in Table 1. Three batches of extracts are available and each batch is 75 kg. The contents of the constituents in the extracts are shown in Table 1 and none of the extracts meet the content limits. Therefore, batch mixing is required. Three solutions that meet the content limits are listed in Table 2, and Solution 3 is the optimum solution obtained from the optimization model proposed. Solution 1 needs three batches of extracts, whereas Solutions 2 and 3 need two batches. A comparison between the objective function values of Solutions 1 and 2 shows that when the objective function is optimized, the number of batches needed is reduced. Solution 3 can use up the whole batch of Extract 3 to avoid its residual. A comparison between the objective function values of Solutions 2 and 3 shows that when the objective function is optimized, the amounts of extracts used are more concentrated in some batches, which helps to reduce the number of residual batches.

Table 1 Content limits and the contents of the constituents in three batches of extracts

Constituent	Content limit	Extract 1	Extract 2	Extract 3
1	19–21	20	17	23
2	38–42	45	40	30

Table 2 Contents of the constituents in the mixtures and the objective function values of three batch mixing solutions

Solution	x_1 (kg)	x_2 (kg)	x_3 (kg)	Content of constituent 1	Content of constituent 2	Objective function value
1	40	30	30	20	39	3400
2	70	0	30	20.9	40.5	5800
3	75	0	25	20.75	41.25	6250

2.3 Batch mixing process

In TCM manufacturing, batch mixing can be conducted with the extracts obtained from previous processes like decoction, concentration, and purification. The extracts created are first stored in the storage tanks. Batch mixing ratios are calculated according to the optimization model and mixtures are created for the follow-up process. The batch mixing process (Fig. 1) is composed of the following two steps:

(1) When a new batch of extract is created, check whether there is an empty tank. If yes, the new extract is stored and the data of the extracts in storage are updated. Otherwise, the oldest batch of extract is purged to make an empty tank for storing the new extract.

(2) Solve the optimization model to check whether a mixture that meets the content limits can be created. If so, create the mixture and update the data of the extracts in storage. Then the batch mixing calculation can be conducted again. When no satisfactory mixture can be created, the process is paused until a new batch of extract is created in the next production cycle.

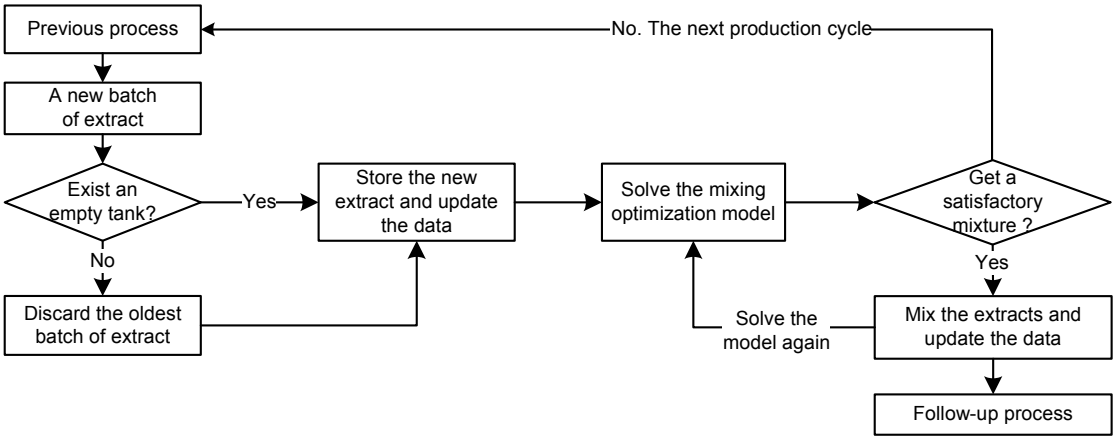

Fig. 1 Batch mixing process

In the production, extracts with compositions deviating too much from the control ranges may be obtained. Since it is difficult to mix these extracts with other batches of extracts to get a satisfactory mixture, they may be discarded. There are two reasons for discarding the oldest batch of extract: (1) one batch of extract not used up for a long time is the batch with excessively large quality deviation and difficult to mix with other batches; (2) the extracts are vulnerable to contamination and chemical degradation in long-time storage.

According to the description of the batch mixing process, the factors affecting URE are mainly: (1) the number of targets, t; (2) the production level of the previous processes, which is reflected in the batch-to-batch relative standard deviations (RSDs) of the contents of the constituents in the extracts; (3) the content limits; and, (4) the number of storage tanks, s. In the design stage, s should be determined according to the production level and the expected URE.

2.4 Simulations

Simulations were conducted to study the batch mixing process proposed in this work. To simplify the simulation, the amounts of each batch of extract and b, the amount of mixture needed in each batch, were all set to 100. Two assumptions were made as follows.

Assumption 1 The content of the mth constituent of the kth extract stored, a_{mk}, conforms to

$$a_{mk} \sim \mathrm{N}(\overline{a_m}, \sigma_m), \tag{5}$$

$$\sigma_m = \mathrm{RSD}_m \cdot \overline{a_m}, \tag{6}$$

where a_{mk} is a normally distributed random data with the mean $\overline{a_m}$ and the SD σ_m, and RSD_m is the batch-to-batch RSD of the content of the mth constituent. In the simulations, RSDs of different constituents were set to the same for simplicity. Then Eq. (7) is obtained from Eqs. (5) and (6):

$$\frac{a_{mk} - \overline{a_m}}{\overline{a_m}} \sim \mathrm{N}(0, \mathrm{RSD}_m). \tag{7}$$

Assumption 2 $\max l_m$ and $\min l_m$ conform to

$$\max l_m = \overline{a_m} \cdot (1 + c), \tag{8}$$

$$\min l_m = \overline{a_m} \cdot (1 - c). \tag{9}$$

When c=0.05, the control range is 95%–105%, which was used throughout the simulation. Then, the constraint of Eq. (2) can be transformed to

$$-c \le \frac{\boldsymbol{T} \cdot \boldsymbol{x}}{b} \le c, \tag{10}$$

where $\boldsymbol{T}$ is a matrix converted from $\boldsymbol{A}$ and its element is calculated as

$$a_{mk}^{\mathrm{new}} = \frac{a_{mk} - \overline{a_m}}{\overline{a_m}}. \tag{11}$$

Based on the above assumptions, $\overline{a_m}$ has no effect on the optimization result. Therefore, normally distributed random data were generated according to Eq. (7) to constitute $\boldsymbol{T}$ and Eq. (2) in the model was

replaced by Eq. (10). Then the simulations can be conducted according to Fig. 1.

Two simulation studies were conducted according to whether a correlation existed between the contents of the constituents. In simulation study 1, the contents were uncorrelated. In simulation study 2, the contents were correlated and this situation is often shown in TCM extracts, especially when the constituents for content control originate from one herb. In this study, the correlation coefficients between the contents were set to the same value of r for simplicity.

The process of simulation was as follows: The matrix $\boldsymbol{D}$ ($t\times K$) formed by the contents of the constituents of K batches of extracts was created. In every production cycle, one column of $\boldsymbol{D}$ was taken as the contents of the newly created extract batch. $\boldsymbol{T}$ and $\boldsymbol{u}$ were updated according to Fig. 1. Then batch mixing was conducted and $\boldsymbol{T}$ and $\boldsymbol{u}$ were updated again. When K batches of data had been used up, URE was calculated. The above procedures were repeated six times to get the average URE. The simulations were conducted in MATLAB 7.9.

3 Results and discussion

3.1 Simulation 1: contents uncorrelated

3.1.1 Determination of the number of total batches for simulation

Firstly, the number of total batches K should be determined for the subsequent simulations. When t=3, s=10, and RSD=30%, different K values were used for simulation and the UREs and their SDs are shown in Fig. 2. When K>200, URE was close to a constant and the SDs were small enough. Hence, K was set to 300 in the subsequent simulations.

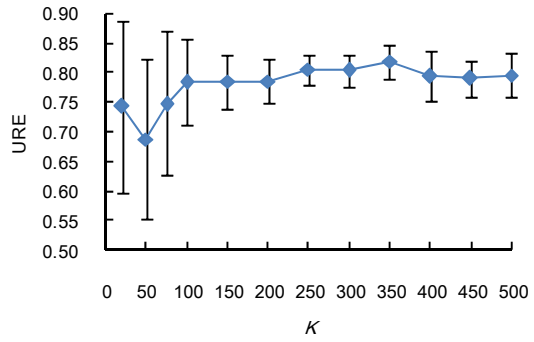

Fig. 2 UREs in simulations using different values of total batches K (data are expressed as mean±SD)

3.1.2 Effect of batch mixing

The simulation result at K=300 is used here as an example to demonstrate the effect of batch mixing. In total, 1 445 batches of mixtures were created from 1 800 batches of extracts (URE=0.803). On average, one batch of mixture was mixed using 3.6 batches of extracts. The RSDs of the contents of the constituents before mixing were 29.7%, 30.7%, and 30.0%, respectively, and only 5 batches of extracts had contents all in the control ranges. However, after mixing, the RSDs were 4.41%, 4.42%, and 4.44%, respectively (Fig. 3), and all the mixtures had contents in the control ranges. Although about 20% of the extracts could not be used, the batch-to-batch difference decreased significantly.

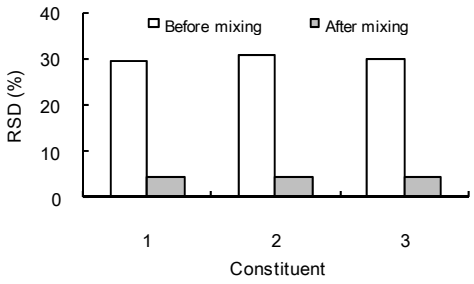

Fig. 3 RSDs of the contents of the constituents before and after batch mixing

3.1.3 Impact of the number of targets on URE

To study the impact of the number of targets on URE, different t values were used for simulation at s=10 and RSD=30%. The result shows URE decreased with the increase in t (Fig. 4). This is because the more targets used, the more content limit constraints were put on the mixture and the harder it was to get satisfactory mixtures.

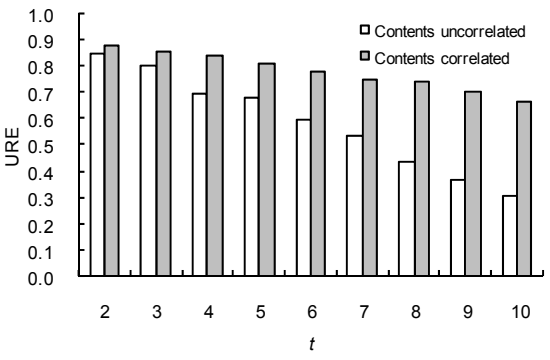

Fig. 4 UREs in simulations using different numbers of targets t under the situations of the contents uncorrelated or correlated (r=0.8)

3.1.4 Impacts of the number of storage tanks and RSD on URE

In the design stage of the batch mixing process, URE should be estimated beforehand and the number of storage tanks, s, should be determined according to the production level and the expected URE. Therefore, simulations were conducted at t=3 to study the impacts of s and RSD on URE. In Fig. 5, when s was small, URE increased evidently with the increase in s. However, when s was large enough, URE could not be increased observably with the increase in s and URE was largely determined by RSD. The required s to reach the expected URE can be determined from the results in Fig. 5. For example, to make URE>0.75, the required s under different production levels (reflected by RSD) is shown in Fig. 6 with white bars. A larger s was required for a larger RSD (i.e., lower production level).

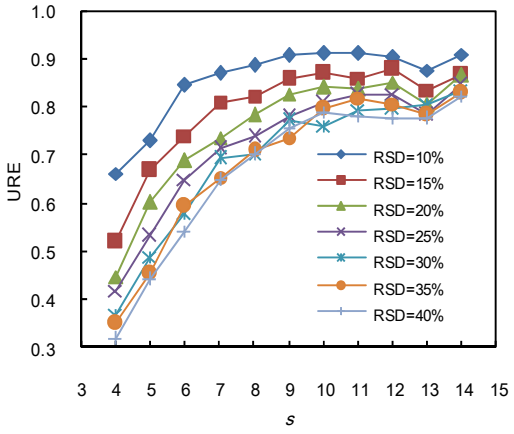

Fig. 5 UREs in simulations using different numbers of storage tanks s and RSD values under the situation of the contents uncorrelated

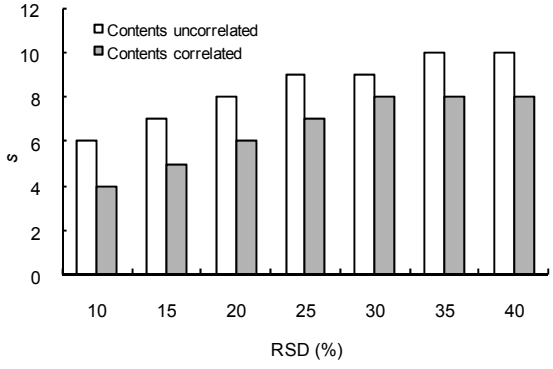

Fig. 6 Required numbers of storage tanks s for different RSDs to make URE>0.75 under the situations of the contents uncorrelated or correlated (r=0.8)

3.2 Simulation 2: contents correlated

3.2.1 Impact of the correlation on URE

In TCM extracts, the contents of some constituents are generally correlated, especially when the constituents originate from one herb. To study the impact of the correlation on URE, random data conforming to multivariate normal distribution with different correlation coefficients were created. The simulations were conducted with other important parameters set as t=3, s=10, and RSD=30%. When r>0.8, URE was obviously higher (Fig. 7). That was because the correlation reduced the randomness of the contents and the contents of different constituents in one extract batch tended to simultaneously deviate high or low, which is favored in batch mixing.

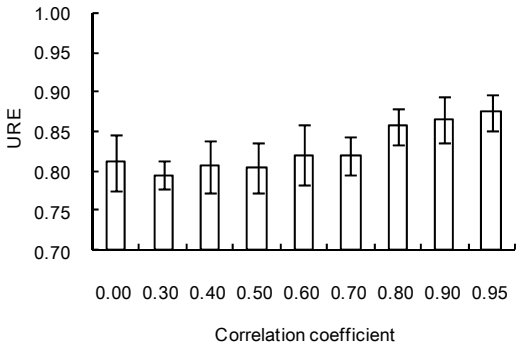

Fig. 7 Impact of the correlation coefficients between the contents of the constituents on URE (data are expressed as mean±SD)

3.2.2 Impact of the number of targets on URE

To study the impact of the number of targets on URE when the contents were correlated, different t values were used for simulation at r=0.8, s=10, and RSD=30%. The result is shown in Fig. 4 with grey bars. URE decreased with the increase in t, similar to the situation when the contents were uncorrelated. However, the degree of the decline was significantly smaller. This was also due to the reduced randomness of the contents caused by the correlation and this impact was more obvious at a high t value.

3.2.3 Impacts of the number of storage tanks and RSD on URE

The impacts of the number of storage tanks and RSD on URE at t=3 and r=0.8 are shown in Fig. 8. The impacts were similar to that in the situation when

the contents were uncorrelated. The grey bars in Fig. 6 show the required s to make URE>0.75 under different RSDs. Compared with the situation when the contents were uncorrelated, the s needed here was smaller, because the URE was higher at the same s.

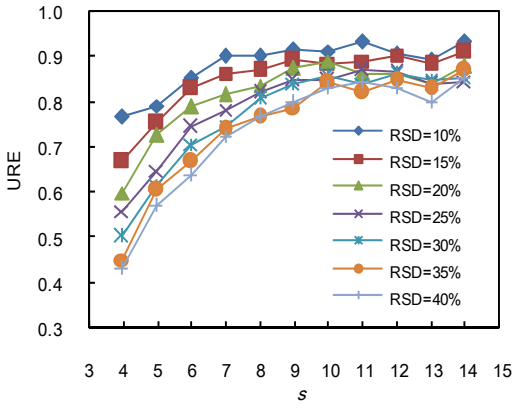

Fig. 8 UREs in simulations using different numbers of storage tanks s and RSD values under the situation when the contents were correlated

4 Conclusions

The batch mixing process can significantly reduce the variation in the quality of TCM extracts among different batches by mixing them in a well-designed proportion. The batch mixing method proposed in this work uses a minimum number of batches of extracts to meet the content limits, which is more practical in industrial production. The impacts of the important factors on URE were studied by simulations, which provide a reference for designing the batch mixing process. The results of the study have demonstrated that batch mixing is a valuable method to improve the batch-to-batch quality consistency of TCM and may contribute to the increase in consistency of the efficacy of TCM. This work may also have reference implications for other industries like food engineering and petrochemical engineering.

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Compliance with ethics guidelines

Bin-jun YAN and Hai-bin QU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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