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Novel Theory and Methods for Chemomic Multi-component Release/Dissolution Kinetics of Traditional Chinese Medicine

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[**ABSTRACT**] **AIM:** To establish a novel theory for the release/dissolution kinetics of the traditional Chinese medicines (TCMs) with the aim of the multi-component chemome. **METHODS:** The theory and method for the release/dissolution kinetics of the TCMs were established on the basis of the overall spectrum of the chemome of the TCMs. The released chemomic levels of TCMs were processed by Kalman filter method with stochastic simulation data as an illustration of the methodology feasibility. **RESULTS:** Methodology study indicated that Kalman filter method was validated with good linearity, reproducibility, stability in calculation of the chemomic concentrations for the evaluation of the multi-component TCM release profile. **CONCLUSION:** Kalman filter method is feasible for the evaluation of chemomic multi-component release/dissolution kinetics of TCMs, which is in line with the holistic theories of traditional Chinese medicine with illustrative visualization to simplify the massive results. The new theory shows methodological significance in optimal design of multi-component drug delivery systems of TCMs. A further study may be required to clarify the significance of the new method to pharmacokinetics and pharmacodynamics of TCM .

[**KEY WORDS**] Traditional Chinese medicine; Chemome; Chemomic concentration; Multi-component; Kalman filter method; Release; Dissolution

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Traditional Chinese medicines (TCMs), usually administered as compound preparations of herbals and minerals, are lack of methodology in quality control of release kinetics for the complexity of the multi-component of the TCMs. It has currently been a major barrier to the modernization of TCM formulations and hence TCM internationalization. At present, most research for the release characteristics of the TCM preparations focus on the release profile of a single component or a small number of components [1-15] and the correlation of *in vitro* release and *in vivo* absorption kinetics of a specific component representing the kinetic characteristics of the multi-component TCM [16-19], while the component efficacy relationship was not well demonstrated. It is obvious that the kinds of researches did not consider TCM and the compound formulation as a holistic approach. Meanwhile, the development of systems-biology-based pharmacoinformatics provides new opportunities and methodologies in harmony with the traditional theory and philosophy of TCM to identify the multi-component factors of TCM efficacy [20-21].

The dosage forms of TCMs, mainly pills, powders, and other solid dosage forms, are usually made of powders from the herbals and minerals. In addition to the dosage form factors, there are marked slow release characteristics from the efflux of the components diffusing out of the cell structure of the herbal powders to the media. Solid dosage forms prepared with the viscous extract of TCMs, namely, large Honey Pill, Honey Pill, tablets, usually disintegrate slowly with a release manner as a sustained release profile, but it is rare to see the established Chinese quality control criteria of TCM Pills and other traditional forms to have a release/dissolution control. For example, Chinese Pharmacopoeia (2005 edition) contains resumption of 223 pills without a quality standard of the release/dissolution. It is simply a disintegration test by the appendix of the same Pharmacopoeia in pills as an indirect control [22].

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Therefore, in order to quantify the traditional dosage form with new features and technological content, it is essential to establish a release/dissolution kinetics theory and method in agreement with the current international practice of quality control for the DDS for the multi-component release of TCMs, which is in line with the tradition TCM theory and practice as a compound formulation with multi-component characteristics. For the evaluation of the multi-component characteristics of the TCMs, namely, chemome, the suitable new theories and new methods should be targeted on the overall components in the TCMs, so as to establish a modernized module for the research and development of the multi-component TCM dosage forms and develop the TCMs into pharmacokinetically significant DDS with quantitative features of the release kinetics.

1 Principles

The dissolved of the TCMs are a group of components, chemome, which are usually all the detectable components found in the release/dissolution media during the release profile and believed to include at least the efficacy materials of the TCM. During the *in vitro* and/or *in vivo* release profiles of the TCMs, the composition and relative contents of all the compounds within the chemome are the primary kinetic characteristics of TCM formulations, it means that the emphasis should be put on the release/dissolution kinetics of the components in TCMs as a chemomic release/dissolution process.

1.1 *TCM chemome and its related concepts*

Chemome: The pools of all the compounds contained in a TCM herb or a TCM dosage form, and usually being regarded as all the detectable components released from the TCM into the medium.

Chemomic standard compositional spectrum: If the number of components in a TCM dosage form is ***m***, after the release profile has been terminated, the chemomic moiety released from a unit dosage is mathematically recorded as:

$$M_i = \left| M_1 \quad M_2 \quad M_3 \quad \cdots \quad M_{m-1} \quad M_m \right| \tag{1}$$

The maximum release moieties of all the components of the dosage form constitute the elementary composition characteristics of the TCM, thereafter, the maximum release moieties for the components of the standard dosage represent the composition of the TCM and form a quantitative standard spectrum of the TCM.

Chemomic concentration standard spectrum: The chemomic concentration is the pools of the concentrations of all the compounds released from the TCM dosage form, which is named as *G* as a concentration of a group of components to distinguish from the conventional terminology of concentration of a single compound:

$$G_S = \frac{M_i}{V} = \left| C_1 \quad C_2 \quad C_3 \quad \cdots \quad C_{m-1} \quad C_m \right| \tag{2}$$

Where *C* is the concentration of each component, *V* is the volume of the release media.

Chemomic concentration: This paper defines the chemomic concentration as a relative measurement value through comparing the chemome in the release medium to the standard chemomic spectrum to reflect the chemomic level as an overall concentration feature, which is a contribution from all the concentrations of all the components within the release medium, but is neither simply a sum of all the component addition nor an average of the concentrations of the components. In another words, chemomic concentration is a chemomic concentration parameter in reference to the standard chemomic spectrum.

1.2 *Chemomic release/dissolution*

1.2.1 *Determination of the released chemome*

The number for tested dosage forms is ***x*** (it is usually 6, the corresponding subscript is ***p***), the number of compounds in the TCM chemome is ***m*** (the corresponding subscript is ***i***), the release/dissolution sampling points is ***n*** (the corresponding subscript is ***j***), the release medium volume is ***V*** mL, and the sample size is ***v*** mL. After each sampling, the same volume of fresh medium was added.

Samples are taken at time points of $\boldsymbol{T}$= [$\boldsymbol{T_1}$, $\boldsymbol{T_2}$, $\boldsymbol{T_3}$, …, $\boldsymbol{T_j}$, $\boldsymbol{T_{j+1}}$, …,$\boldsymbol{T_{n-1}}$, $\boldsymbol{T_n}$]. For example, the concentrations of the components in $\boldsymbol{p}^{\text{th}}$ dosage form are determined as:

$$C_{p,i,j} = \begin{vmatrix} C_{p,1,1} & C_{p,1,2} & C_{p,1,3} & \cdots & C_{p,1,n-1} & C_{p,1,n} \\ C_{p,2,1} & C_{p,2,2} & C_{p,2,3} & \cdots & C_{p,2,n-1} & C_{p,2,n} \\ C_{p,3,1} & C_{p,3,2} & C_{p,3,3} & \cdots & C_{p,3,n-1} & C_{p,3,n} \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ C_{p,m-1,1} & C_{p,m-1,2} & C_{p,m-1,3} & \cdots & C_{p,m-1,n-1} & C_{p,m-1,n} \\ C_{p,m,1} & C_{p,m,2} & C_{p,m,3} & \cdots & C_{p,m,n-1} & C_{p,m,n} \end{vmatrix} \tag{3}$$

The chemomic concentration of dosage form ***p*** at time point $\boldsymbol{t_j}$ ($\boldsymbol{G_{p,j}}$) is obtained by comparing the concentrations of the components within the chemome with the concentration standard chemomic spectrum. Therefore, the chemomic concentration of the TCM dosage form released in the medium is:

$$G = \left| G_{p,1} \quad G_{p,2} \quad G_{p,3} \quad \cdots \quad G_{p,n-1} \quad G_{p,n} \right| \tag{4}$$

Obviously, the accumulative chemomic release material moiety ($\boldsymbol{Q_{p,j}}$) of the dosage form ***p*** at the time point $\boldsymbol{t_j}$ is:

$$Q_{p,j} = G_{p,j}V + v\sum_{k=1}^{j-1} G_{p,k} \tag{5}$$

1.2.2 *Chemomic release/dissolution*

The chemomic concentration is calculated and obtained based upon the chemomic concentration standard spectrum, it means that the chemomic concentration is equivalent to 1 when the chemome is fully released, because the concentration of all the components are theoretically equal to that of the chemomic standard concentration spectrum. Thus, the chemomic release/dissolution of the dosage form ***p*** is:

$$\begin{aligned} R_{p,j} &= \frac{Q_{p,j}}{V \times 1} \times 100\% \\ &= \left(G_{p,j} + \frac{v}{V}\sum_{k=1}^{j-1} G_{p,k} \right) \times 100\% \end{aligned} \tag{6}$$