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Mini Review

Characterization of Traditional Chinese Medicine (TCM) Extract: Chemical Compositions, Solution Environment and its Implication in Membrane Process

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ABSTRACT

Membrane technology has been widely employed in beverages processing for clarification, water removal, and aroma recovery. Its application in pharmaceutical processing has been reported in some case studies of TCM manufacturing. Membrane technology has shown superior advantages on retaining active compounds with integrity in TCM extracts. Comprehensive studies revealed that the compositions in TCM extracts could influence the physiochemical properties and solution environment, potentially causing undesirable effects on downstream processing. This review introduced modern analytical methods to the quantification of herbal and TCM extracts, including chromatography and spectroscopy for the quantification of composition and total composition comparison by fingerprints. The performance of membrane technology is largely dependent on the solution environment and the interactions between compounds whereas the characterization approaches currently available for membrane processing are insufficient. The review also underlined recent attempts *via* the aid of modern analytical approaches on the characterization of the solution environment, correlating compositions, physiochemical properties with membrane performance, facilitating qualitative and quantitative description tools for process optimization.

Keywords: Traditional Chinese medicine extract; Characterization; Membrane processing; Solution environment

INTRODUCTION

Modern analytical approaches have aided the identification of compounds in food system, as well as the measurement of physiochemical properties of the system. Processing of food can be optimized by monitoring the concentration of specific compounds, and physiochemical properties including the change in rheology and Total Soluble Solids (TSS) [1-4]. Though analytical chemical approaches have advanced to the extent that characterization of food system empowers process design and optimization, the characterization of TCM extracts has other aspects to address.

Most TCM extracts are generally viewed as complex systems where the combination of compositions act integratively as effective drug [5]. It is generally believed that TCM extract consists of various compounds, acting towards multiple targets in different combinations [6]. The most apparent challenge for TCM processing remains as the characterization of total compositions, which is essential to map the composition-target relationship for drug discovery and development.

Processing of the TCM extracts including extraction, purification, concentration and drying processes is a critical parameter on the effectiveness of the final products. Due to the multi-target properties of TCM extract, it is predominant to retain all active components in the TCM extracts during downstream processing where extreme processing parameters can result in the removal of active compounds further affecting the final drug efficacy adversely. Researchers have shed lights on the implementation of membrane technology in TCM manufacturing for its ability to process the extract at mild conditions. The concentration of Yi Mu Cao extract the dried roots from *Leonurus japonicus* Houtt was achieved by membrane

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distillation [7]. The concentration of Yu-Ping-Feng-San-Decoction [8], and Si-Jun-Zi-Decoction were achieved in reverse osmosis units [9]. Refinement of Qing-Luo-Tong-Bi-Decoction was achieved in an ultrafiltration unit [10].

Purification and concentration by membrane technologies are largely dependent on the compounds to be retained or transported, as well as the total solution environment. Microporous membranes act as a filter by size whereas the mass transfer is governed by the synergistic effects of size, special orientation, and affinity with membrane materials for both ultrafiltration and nanofiltration. It has been observed that compounds with smaller molecular weight than the cut-off weight of the membranes were rejected, resulting in reduced concentration of the active compounds in the final product of TCM [11].

The characterization on the total compositions of the TCM extracts has been a challenge as abovementioned for the evaluation of process design, where compositions of the TCM extracts pose significant impact on the physiochemical properties of the solution *via* microscopic interactions. The lack of characterization approaches of the solution micro-environment suggested the existence of a gap between the analytical methods available and the approaches can be applied to communicate TCM extracts with downstream processing (i.e. membrane technology).

This review aims on outlining the characterization approaches currently applied in TCM processing and methods to visualize the micro-environment of the herbal extracts solution. Novel attempts on bridging the gap between modern analytical chemistry and visualization of solution micro-environment were also discussed, to communicate the complex solution environment with membrane processes.

LITERATURE REVIEW

Membrane technology in food and pharmaceutical processing

Outside of its conventional application in wastewater treatment, membrane technology has been widely employed in many food processing scenarios. The implementation of membrane technologies mostly covers the concentration and flavor reservation in beverages and fruit juice processing. The fractionation of phytosterols and proteins in the fruit juice was realized *via* ultrafiltration membrane processing [12]. Forward osmosis processes have been implemented in many water removal processes [13,14], such as fruit juice [15], and tea extract concentration [16]. Extracts treated by membranes exhibited higher retention on key compounds such as thermo-sensitive compounds (i.e. catechins). The production of non-alcoholic wine is generally produced by the integrated membrane processes of nanofiltration for dealcoholization [17], and pervaporation for aroma recovery [18].

Pharmaceutical processing on the other hand, has a rather subtle requirement for both the retention and removal rate for specific compounds, hence resulting in limited research and applications of membrane technology in pharmaceutical processing. The most promising application of membrane technology for pharmaceutical purposes has been realized in the Traditional Chinese Medicine (TCM) sector for herbal extract processing.

TCM extract processing by membrane technology

Microfiltration membranes acting like a size sieving filter depending on the pore size and structures, are believed to have the ability to obtain target compounds with minimum loss, where it is generally accepted that the molecular weight of the target compounds are below a few thousand Da in TCM extracts [19]. Previous studies suggested that the characterization of TCM aqueous environment is of great interest for process design and product quality control by membrane process. The physio-chemical properties of the aqueous environment poses significant impact on the membrane performance when processing herbal extracts such as TCM extracts [20]. Hence the characterization and quantification of herbal extracts solution environment is regarded as a pivotal aspect for the design of membrane process.

Conventional characterization approaches in membrane technology includes the characterization of membrane properties, and the characterization of both the feed and permeate. Rejections of the membrane process can be evaluated from the measurement of the conductivity meter as an indication of total dissolved solids (TDS) and total organic compounds (TOC) in the permeate collected, whereas chemical compositions can be characterized by liquid chromatography for specific compounds. The characterization and quantification have always been a challenge in complex herbal extract systems, correlating the process parameters, chemical compositions and drug efficacy. The conventional characterization approaches used in membrane technology is no longer sufficient for pharmaceutical processing of TCM extracts. It remains as a great challenge to quantify the TCM solution characteristics for membrane processing. There have been attempts to characterize and quantify the solution environment, enabling comprehensive research into the interaction between membranes and extract solution.

For instance, Brix is an effective approach to indicate total soluble solids in the aqueous system, measured by a refractometer. Li, et al. characterized the change in physiochemical properties of the aqueous extract environment by the measurement of the refractometer and evaluated the energy consumption of Yu-Ping-Feng-San extracts concentration process by membrane technologies [8]. The existence of certain compounds could also cause severe foaming in the system [9], resulting in reduced water removal efficiency and loss of active ingredients from overflowing.

Apart from the physiochemical properties of the solution environment, the micro-structure, microscopic state and chemical composition of the specific compounds are also critical to the separation efficiency by interacting with the membrane surface and pores [11,21]. We believe the visualization of solution environment of TCM extracts involves the characterization on the compositions, allowing further analysis of molecular interaction between compounds in the micro-environment.

Characterization of chemical compositions in the herbal extract

The characterization of chemical compositions has been a great challenge in food and pharmaceutical processes involving herbal extracts. The conventional characterization for composition analysis with known information and confirmed structures is generally achieved by chromatography (i.e. high performance liquid chromatography HPLC, and gas chromatography GC) and UV-Vis spectrometer. Specific compounds, also known as biomarkers are generally identified and quantified by HPLC and GC approaches, by recognizing the peaks of absorbance at certain retention time [22,23]. Group of compounds with similar functional groups (i.e. total flavonoids) were generally detected using UV-Vis spectrometer [24].

The composition of TCM herbal extracts after membrane processing was verified by measuring the concentration of target compounds by chromatography and UV-Vis spectrometer and evaluate the retention and rejection rate in most reported studies [10,25-29]. It has been used to verify the retention of certain substances in Chinese medicine extract by membrane processes.

Total compositions are generally characterized by fingerprints obtained *via* the means of chromatography and spectrum [30-32]. Particularly, the retentate of concentration process by nanofiltration and reverse osmosis is subjected to HPLC testing to access similarity of compositions before and after the membrane process to evaluate the integrity of the total compositions [9].

The quantification of non-target compounds in the extract system is still regarded as a challenge due to the lack of reference. Mass Spectroscopy (MS) is a common approach to determine the molecular weight for unknown compounds [33] while Nuclear Magnetic Resonance (NMR) spectroscopy is a popular mean to determine the structures of the unknown compounds. Recent studies suggested that key ion filtering and mass defect filtering by liquid chromatography and MS were used to identify non-target compounds [34-36].

The concept of 'material basis-Q-markers' was proposed to facilitate an efficient approach to reflect the effects of the compositions and manufacturing process on the TCM products. The approach involves the chemometrics characterization with the aid of modern algorithm from data science coupled with the conventional chromatography [37], where pattern recognition is implemented for correlating the drug properties with efficacy in a complex extract system. Particularly, chemical fingerprints and metabolic fingerprints (i.e. pharmacodynamics, and network pharmacology) were integrated to identify the Q-markers *Alisma orientale* (Sam). Juzep. [38]. The concept of material basis-Q-markers will help the research and implementation of membrane technology for TCM processing to evaluate the effectiveness of the process.

Visualization of the solution environment

Advanced techniques are applied to aid the visualization of microscopic interactions in the complex solution environment. Fluorescence quenching was applied in the aqueous system of the tea extracts to estimate the binding ability between polyphenols and β-casein as proteins by measuring the fluorescence intensity [39]. Change in surface hydrophobicity of the specific molecules in the solution environment can also be estimated *via* the measurement of fluorescence intensity [40]. These approaches could be applied to aid the quantification of interaction between compounds in complex extract system and membrane surface, further elucidating the mass transfer mechanism in membrane processing.

Furthermore, the microscopic interactions could also pose substantial impact on its physiochemical properties. Investigation on foaming behavior in natural surfactants system of saponins has involved analytical methods [41-44], such as the measurement of surface tension, interfacial rheology, surface elasticity and the microscopic morphologies of the bubbles. This could provide innovative perspectives into correlating the physiochemical with chemical compositions in complex systems of herbal extracts, translating to parameters recognized in the mass transfer model in separation processes.

Novel approaches are introduced to visualize the effect of micro-environment on membrane performances. In line near-infrared spectroscopy as an emerging Process Analytical Technology (PAT), has been employed in food processing to replace off-line HPLC for indication of concentrations [45]. Near-infrared spectroscopy was implemented to indicate protein concentration with proper calibration [46]. With real-time knowledge in concentration change, it is possible to study the instant transport mechanism of membrane process in a complex system.

Membrane processes are also largely dependent on the physiochemical properties of the solution environment. Visualization on the rheological and microstructural properties in skim milk processing in an ultrafiltration unit was attempted, to evaluate the Bulk Nanobubbles (BNB) on fouling propensity [47]. Tan, et al. proposed that the foaming in Si-Jun-Zi Decoction can be characterized *via* the macroscopic observation of foam properties and the measurement of physiochemical properties (surface tension, zeta potential etc.) [9]. The quantification of foaming in TCM solution environment was correlated to the physiochemical properties and transport mechanism of RO process.

DISCUSSION

The characterization of the TCM extracts has always been a challenge. Specific compounds in the extract solution can be easily quantified by analytical approaches, while the identification and quantification of the compounds hardly reflect the total solution environment. The compounds present in the solution interacts at microscopic scale (molecular adsorption, hydrophobic interaction etc.). TCM extract is a complex system consists of thousands of chemical compounds where the combinations of various compounds act integratively towards multiple targets, showing total drug efficacy. This could further influence the physiochemical properties of the total solution environment at macroscopic aspect and the retainment rate of the bioactive compounds, eventually the total drug efficacy is compromised.

Separation technologies implemented in TCM pharmaceutical processing are largely reliant on the compound properties (size, interactions etc.), as well as the physiochemical of the solution environment. For example, the concentration of TCM extracts requires constant removal of water and changing the physiochemical properties of the solution, posing significant effect on the water removal rate in membrane distillation [25]. The characterization of the change in physiochemical can help research in quantifying the effects of physiochemical properties in the TCM solution on the transport mechanism of membrane. Attempts have been demonstrated to characterize the solution environment to aid the visualization of total compounds in terms of microscopic interactions, physiochemical properties, and to quantify their effects on the mass transfer in separation technologies. With knowledge available on the rejection and retention of specific compounds or group compounds during membrane processes, design of the membrane and process can be achieved to acquire comprehensive active compounds in the TCM extracts showing total drug efficacy. Undesirable phenomena in the TCM extracts such as foaming can be mitigated and improvement of mass transfer can be anticipated in membrane processing [9].

CONCLUSION

Processing of herbal extracts for food purposes and TCM extracts share a great number of similarities while the major difference between these two lies on the characterization and evaluation of the final products. While the characterization of total composition still remains as a great challenge to identify the correlation of drug efficacy and the compound compositions for TCM extracts, fingerprints analysis of the extracts by modern analytical has facilitated the evaluation of the TCM products *via* various processing conditions, particularly including membrane separation technologies. The implementation of modern analytical techniques for solution environment characterization might be able to translate the properties of TCM extracts to the transport parameters of membrane processes.

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