

ORGANIC SOLVENT NANOFILTRATION FOR HERBAL EXTRACT PURIFICATION AND SOLVENT RECOVERY IN VIETNAM: A SHORT REVIEW

NGUYEN TRAN DUY BAO

Faculty of Applied Science and Technology (FAST),
Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam
Khoa Khoa học Ứng dụng và Công nghệ,
Đại học Nguyễn Tất Thành, TP.Hồ Chí Minh, Vietnam
Email: ntddbao@ntt.edu.vn

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Abstract:

The separation and purification of herbal extracts often involve thermal distillation, which may degrade heat-sensitive bioactive compounds. Conventional methods, including distillation and chromatography, can also require substantial energy and large volumes of organic solvents. Organic solvent nanofiltration (OSN) offers a potential alternative by enabling separation at relatively low temperatures and facilitating solvent recovery. As research and industrial activity in herbal extraction expands in Vietnam, OSN may support more efficient and continuous processing. This short review examines OSN membranes and their potential applications in purifying herbal extracts and recovering solvents in Vietnam, while outlining the challenges and opportunities associated with their wider adoption.

Keywords: Organic solvent nanofiltration, OSN membrane, thermolabile APIs, non-thermal concentration, solvent recovery

Ứng dụng công nghệ màng lọc nano trong dung môi hữu cơ để tinh sạch dịch chiết dược liệu và thu hồi dung môi tại Việt Nam: Bài tổng quan ngắn

Tóm tắt:

Quá trình phân tách và tinh sạch dịch chiết dược liệu thường sử dụng phương pháp chưng cất bằng nhiệt, có thể làm phân hủy các hợp chất có hoạt tính sinh học nhạy cảm với nhiệt. Các phương pháp truyền thống, bao gồm chưng cất và sắc ký, cũng có thể tiêu tốn nhiều năng lượng và lượng lớn dung môi hữu cơ. Công nghệ màng lọc nano trong dung môi hữu cơ (OSN) là một giải pháp tiềm năng, cho phép phân tách ở nhiệt độ tương đối thấp và hỗ trợ thu hồi dung môi. Trong bối cảnh hoạt động nghiên cứu và sản xuất liên quan đến chiết xuất dược liệu tại Việt Nam ngày càng mở rộng, OSN có thể góp phần nâng cao hiệu quả và hỗ trợ quá trình xử lý liên tục. Nghiên cứu này xem xét màng OSN và tiềm năng ứng dụng trong tinh sạch dịch chiết dược liệu, thu hồi dung môi tại Việt Nam, đồng thời chỉ ra những thách thức và cơ hội đối với việc áp dụng công nghệ này trên phạm vi rộng hơn.

Từ khóa: lọc nano dung môi hữu cơ, màng lọc OSN, API kém bền nhiệt, cô đặc không dùng nhiệt, thu hồi dung môi.

1. Introduction

Separation and purification are essential for producing high-quality products across the chemical, pharmaceutical, and food industries (Sholl & Lively, 2016). However, these processes traditionally rely on energy-heavy distillation, which alone consumes 10–15% of global energy (Lively & Sholl, 2017). While membrane technologies like reverse osmosis have successfully reduced the energy consumption of water-based separations, there is still a massive need for efficient, low-energy separations in organic solvents (Szekely, Jimenez-Solomon, Marchetti, Kim, & Livingston, 2014). The pharmaceutical and botanical industries use large volumes of these solvents to extract valuable compounds, and recovering both the solvent and the final product is a major challenge (Constable, Jimenez-Gonzalez, & Henderson, 2007). This is especially true in Vietnam, home to highly sought-after medicinal plants like Ngoc Linh ginseng (yielding Saponin MR2), Madagascar periwinkle (Vinca alkaloids), and sweet wormwood (Artemisinin) (Hien, 1994; Linh et al., 2019; Pham, Vuong, Bowyer, & Scarlett, 2020). Because these complex molecules are highly sensitive to heat, traditional extraction methods like steam distillation or vacuum evaporation are far from ideal (Chemat et al., 2020). They demand huge amounts of energy and expose delicate plant materials to high temperatures, which often permanently damages the bioactive compounds and significantly lowers the final product yield (Abubakar & Haque, 2020).

To overcome the drawbacks of heat-based processing, organic solvent nanofiltration (OSN) has emerged as a gentle, energy-efficient alternative. Instead of boiling liquids, OSN uses simple pressure at mild or room temperatures to separate molecules, typically those between 200 and 1000 Da, without phase changing (Buonomenna & Bae, 2015; Marchetti, Jimenez Solomon, Szekely, & Livingston, 2014). By avoiding the need to vaporize large amounts of solvent, OSN protects the delicate structure of heat-sensitive active pharmaceutical ingredients (APIs) while dramatically cutting down the energy consumption compared to traditional distillation method (Buonomenna & Bae, 2015).

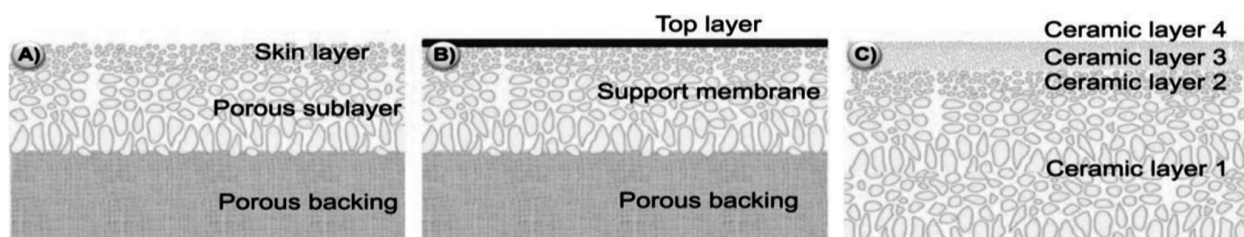
The true potential of OSN goes well beyond simply concentrating extracts at low temperatures. Botanical and pharmaceutical manufacturing is heavily dependent on solvents, often generating massive amounts of organic waste (Buonomenna & Bae, 2015). However, by setting up OSN in a continuous, closed-loop system, it becomes possible to concentrate the target APIs while simultaneously recovering and recycling the solvent in a single step. Additionally, OSN serves as an excellent purification tool. The extraction process can sometimes introduce hazardous impurities, reactive reagents, or natural toxins, which pose severe health risks even at trace levels (Buonomenna & Bae, 2015). The OSN membrane acts as a precise molecular filter, allowing these smaller, harmful impurities to wash away into the permeate while safely retaining the larger, valuable API molecules. This makes it much easier for manufacturers to meet strict safety and toxicological regulations (Buonomenna & Bae, 2015). Ultimately, this short review aims to introduce OSN as a practical, transformative platform for Vietnamese scientists and engineers working to modernize the nation's botanical extraction and refinement processes.

2. Overview and separation mechanisms of organic solvent nanofiltration

The fundamental of OSN membrane separation relies on the selective permeation of molecules across a semi-permeable barrier under an applied hydraulic pressure gradient (Baker & Baker, 2012). Unlike aqueous nanofiltration, where electrostatic interactions often dominate, the separation mechanism in OSN is governed by a complex interplay of size exclusion (steric hindrance) and the solution-diffusion model. Consequently, the separation efficacy is highly dependent on solute-solvent-membrane thermodynamic interactions (Nguyen Thi et al., 2022). For practical implementation in botanical extraction and API refinement, the core prerequisite for any OSN membrane is exceptional chemical, thermal, and mechanical stability. Any structural degradation, such as excessive swelling or compaction in aggressive extraction solvents (such as ethanol, methanol, or ethyl acetate), can lead to critical functional failure (Buonomenna

& Bae, 2015). Based on their material composition and structural architecture, current OSN membranes are broadly classified into three main categories: polymeric, inorganic, and mixed matrix membranes (MMMs) (Baker & Baker, 2012).

Figure 1: Schematic illustration the cross-section structure of different types of membranes: (a) integrally skinned asymmetric (ISA); (b) thin film composite (TFC); and (c) ceramic membrane; Reproduced with permission from the article (Cseri et al., 2017)



2.1. Polymeric membranes

Polymeric materials currently dominate both academic research and industrial OSN applications due to their high flexibility, tunable physicochemical properties, and cost-effective scalability (Baker & Baker, 2012). However, their intrinsic vulnerability to swelling, aging, and compaction in polar aprotic solvents remains a significant operational hurdle. Because these membranes are initially fabricated by dissolving parent polymers in strong solvents, they risk re-dissolution during prolonged operation. To mitigate this, intensive post-treatment cross-linking, via chemical agents, thermal annealing, or UV irradiation is mandatory (Buonomenna & Bae, 2015).

Structurally, these polymeric membranes are synthesized in two primary architectures: integrally skinned asymmetric (ISA) membranes and thin-film composite (TFC) membranes (Figure 1). Fabricated predominantly via the Loeb-Sourirajan phase inversion technique, ISA membranes consist of a dense, selective skin layer seamlessly integrated over a highly porous sublayer of the same polymer (e.g., polyimide, polyether ether ketone [PEEK], or polyvinylidene fluoride [PVDF]) (Loeb & Sourirajan, 1963). This monolithic structure renders them highly resistant to delamination under harsh hydrodynamic shear, making them robust candidates for processing viscous botanical extracts. Conversely, TFC architectures decouple the active layer from the structural support. In this configuration, an ultrathin active layer (50–500 nm, commonly polydimethylsiloxane [PDMS] or polyamide) is synthesized via interfacial polymerization or dip-coating over a distinct, solvent-resistant porous support, such as cross-linked polyimide or polyacrylonitrile (PAN) (Solomon, Bhole, & Livingston, 2012; White & Nitsch, 2000). This decoupling provides a distinct engineering advantage, allowing researchers to precisely tailor the molecular weight cut-off (MWCO) of the top layer while independently maximizing the solvent permeance and mechanical strength of the underlying sublayer (Solomon et al., 2012).

2.2. Inorganic Membranes

Inorganic membranes, primarily fabricated from ceramics (such as Al_2O_3 , SiO_2 , TiO_2 , and ZrO_2), offer a robust alternative, boasting superior mechanical resilience, thermal stability, and absolute immunity to solvent-induced swelling (Marchetti et al., 2014) (Figure 1). Despite these advantages, their translation to large-scale botanical processing is hindered by inherent material brittleness and the high capital cost of manufacturing. Furthermore, native ceramic surfaces are dominated by hydroxyl groups, rendering them highly hydrophilic. This restricts the flux of non-polar or moderately polar solvents frequently used in phytochemistry (Marchetti et al., 2014). To circumvent this, contemporary research focuses on surface functionalization, such as grafting hydrophobic Grignard reagents, or depositing active nanoporous layers of zeolites or silica, successfully driving the MWCO of ceramics down to the highly selective 200–350 Da range (Baker & Baker, 2012).

2.3. *Mixed matrix membranes (MMMs)*

Acting as a technological bridge, mixed matrix membranes (MMMs, or nanocomposites) combine the easy manufacturing of polymers with the structural strength of inorganic materials. By blending inorganic nanofiller particles, such as zeolites, metal-organic frameworks (MOFs), silica, or carbon nanotubes, directly into the polymer base. These blended membranes become highly resistant to harsh solvents, less prone to clogging, and much better at maintaining the structure under high pressure (Marchetti et al., 2014). However, a major research in developing MMMs is getting these nanoparticles to spread out evenly. The particles may clump together or fail to bond properly with the surrounding polymer, it can create microscopic gaps and defects that ultimately ruin the membrane's ability to filter accurately (Marchetti et al., 2014).

3. Implementing OSN in Vietnamese herbal processing

3.1. *Non-thermal concentration of thermolabile APIs*

Extracting complex, heat-sensitive botanical compounds require separation technologies that avoid aggressive thermal loads. This intense heat can permanently damage the plant's natural structure and destroy highly valuable compounds (Geens, De Witte, & Van der Bruggen, 2007; Székely, Bandarra, Heggie, Sellergren, & Ferreira, 2011). For valuable Vietnamese plants, like those producing Saponin MR2, Vinca alkaloids, and Artemisinin, this heat stress lowers both the medical quality and the commercial value of the final medicines (APIs).

OSN technology solves this bottleneck by functioning as a robust, non-thermal concentration platform. These OSN systems work perfectly at room temperature, separating the desired molecules without conducting phase transition (Geens et al., 2007). In a typical OSN setup, the membrane acts like a very fine sieve. It rejects the larger, valuable API molecules in the main flow while letting the smaller solvent liquids pass freely through (Geens et al., 2007; Székely et al., 2011) (Figure 2). Because this process relies on simple pressure instead of heat, the delicate structure of the medicines remains completely safe and intact (Geens et al., 2007). For large-scale manufacturing, multi-stage membrane cascades can achieve exceptionally high yields even further, ensuring very little of the valuable API compound is lost while creating highly concentrated extracts (Székely et al., 2011).

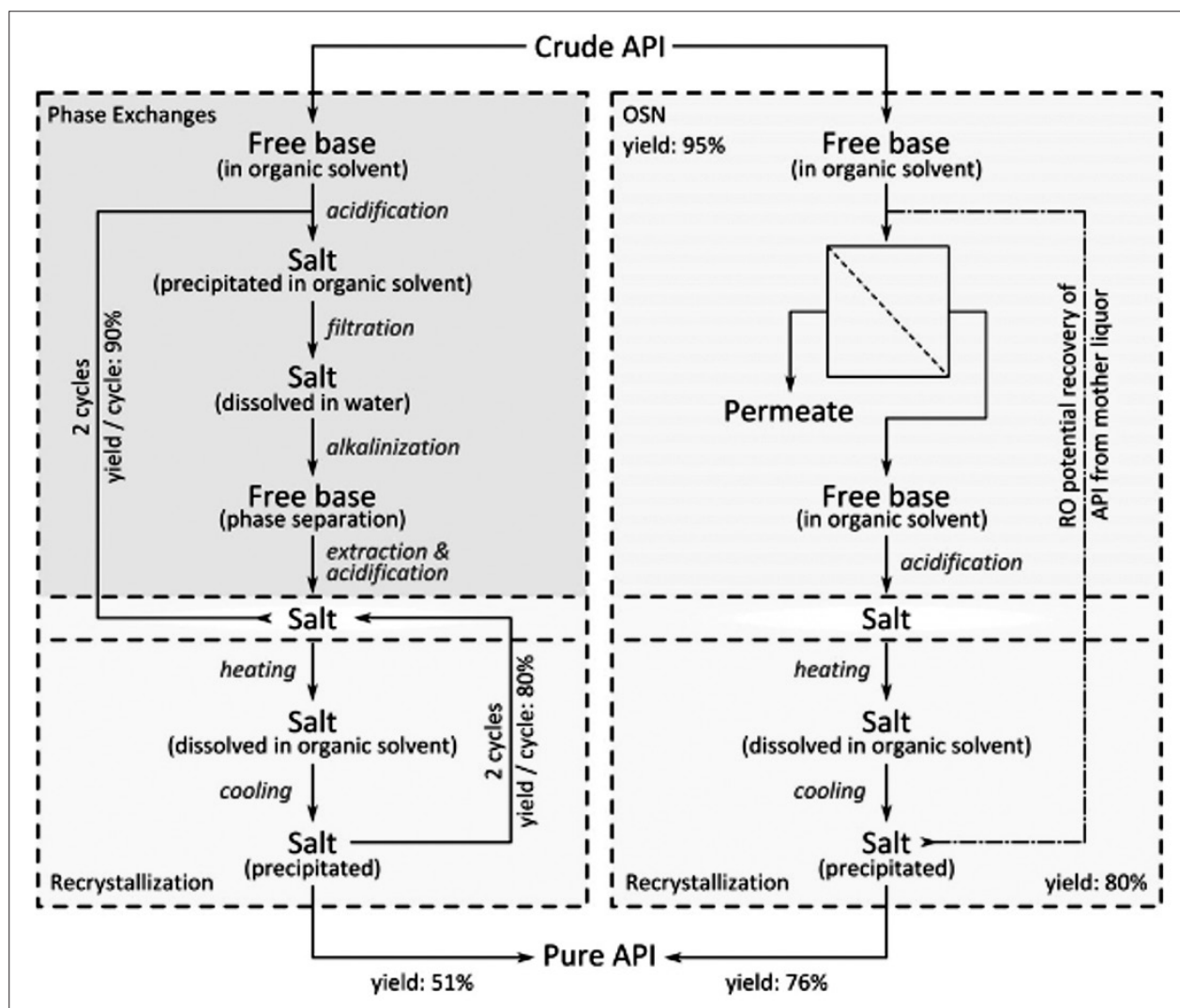
Research data proves just how well this heat-free approach protects delicate plants. For instance, processing at room temperature can save over 95% of the antioxidants in fragile extracts (Saykova, Trayanov, Bojkova, Stoilova, & Funeva-Peycheva, 2020). This completely avoids the 30% to 50% losses usually seen with traditional distillation (Baker & Baker, 2012; Buonomenna & Bae, 2015). Similarly, using membranes to concentrate plant extracts effectively captures valuable APIs without the intense heat that normally causes unwanted chemical reactions. By entirely eliminating heat-intensive distillation, OSN prevents the breakdown of heat-sensitive molecules (Marchetti et al., 2014; Székely et al., 2014). Ultimately, using OSN in Vietnamese herbal processing does more than just produce a larger amount of extract. This heat-free method delivers high-grade pure medicines, significantly raising the overall quality of Vietnam's botanical manufacturing.

3.2. *Membrane-based purification of APIs*

The extraction of valuable medicines (APIs) from plants often accidentally pull-out unwanted chemicals. A major worry in pharmaceutical manufacturing is the presence of genotoxic impurities (GTIs), dangerous little compounds that can cause genetic damage or cancer, even in tiny amounts. Because of this, health regulators have very strict safety limits, meaning manufacturers need highly reliable ways to clean up their final products (Guideline, 2006).

OSN technology offers a great, non-thermal way to clear out these dangerous impurities. It works by taking advantage of the physical and chemical differences between the valuable API and the hazardous waste (Orehek, Teslic, & Likozar, 2021). Generally, engineers use three different strategies for OSN

Figure 2: Schematic comparison of API purification between conventional separation and the OSN membrane process; reproduced with permission from (Székely et al., 2011)

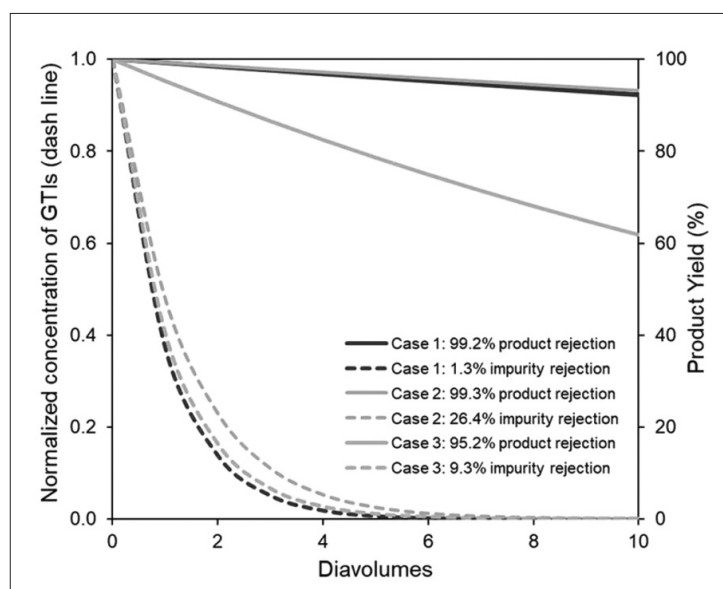


purification, depending on the sizes of the molecules they are trying to separate (Orehek et al., 2021). Depending on the size of the molecules, purification falls into three types: impurities GTIs that are smaller, larger, or almost the exact same size as the target APIs.

In the first and most common scenario, the GTIs are much smaller than the APIs, typically weighing in at just 55 to 225 Da (Székely et al., 2011) (case 1 in Figure 3). For large, complex molecules like Saponin MR2, OSN is operated in the continuous diafiltration mode. The membrane's active layer securely retains the large API in the retentate, while fresh solvent is continuously added to physically wash the smaller GTIs and residual low-molecular-weight contaminants through the membrane into the permeate. This constant-volume diafiltration can effectively purge trace impurities down to ppm levels, ensuring strict compliance with threshold of toxicological concern limits without subjecting the API to degradative heat (Székely et al., 2011).

On the other side, the GTIs are bigger than the APIs (case 2 in Figure 3). In raw herbal extracts, this usually means getting rid of heavy, clunky materials like plant waxes or sticky resins. In this setup, engineers choose a membrane that lets the small, valuable medicine molecules and the liquid solvent slip right through, while completely blocking the bulky plant waste so it still remains.

Figure 3: Evaluation of GTI removal from APIs using constant volume diafiltration across three separation scenarios. Case 1 shows optimal separation. Case 2 maintains high API rejection but requires more solvent cycles due to elevated GTI rejection. Case 3 demonstrates sub-optimal API rejection, leading to high product loss during purification; Reproduced with permission from article (Székely et al., 2011)



3.3. Recovery of organic solvents

In pharmaceutical manufacturing, producing APIs requires large amounts of organic solvents. Life cycle analyses show that these solvents make up over 95% of the total raw materials and consume about 60% of the overall energy used in API production (Buonomenna & Bae, 2015; Marchetti et al., 2014). Currently, most of this waste solvent is simply burned on-site or sent away for disposal. However, as environmental rules get stricter and fresh solvents become more expensive, finding sustainable ways to recover them is essential. OSN technology has emerged as a top-tier technology for APIs extraction process because it is highly energy-efficient, affordable to run, and easily integrates into existing manufacturing systems (Ott et al., 2014).

A major application for OSN is recovering solvents from early-stage of the liquid mixtures, which often contain highly diluted APIs alongside various impurities. the OSN membrane is successfully recovering both the expensive solvent and the valuable medicine significantly boosts the overall efficiency of production (Buonomenna & Bae, 2015). Some studies using commercial membranes (like Starmem™ and PuraMem™) have shown that OSN can efficiently recover up to 80% of the solvent on its own. When combined with traditional distillation to process the remaining fraction, this hybrid approach consumes nine times less energy than relying on distillation alone (Xiao, Feng, Goundry, & Karlsson, 2024).

OSN solvent recovery is particularly effective when coupled with continuous diafiltration. In an advanced closed-loop configuration, a primary membrane unit purifies the API solution, while a secondary unit recovers the permeating solvent and recycles it directly in situ back to the feed tank (Rundquist, Pink, & Livingston, 2012) (Figure X). This continuous OSN cycle improves the sustainability of the process. Comparative life cycle assessments reveal that OSN-based solvent recovery can reduce the

The trickiest scenario is the GTIs and the APIs are almost exactly the same size (case 3 in Figure 3). Because they are so similar, a simple physical sieve won't work. For these challenging separations, OSN has to rely on more subtle chemical behaviors instead of just size. By carefully choosing a membrane material that reacts differently to the specific shape, electrical charge, or bonding style of the molecules, engineers can coax the impurity to pass through the filter while keeping the medicine safely behind.

By using these smart filtration strategies, OSN gives botanical manufacturers a highly effective way to remove dangerous contaminants on a large scale. This ensures that high-value Vietnamese botanical extracts keep their natural healing power while easily meeting the strict safety and purity standards required by the global pharmaceutical market (Buonomenna & Bae, 2015).

carbon footprint by up to 95% compared to conventional distillation and adsorption, mainly by eliminating solvent incineration and high-heat vaporization (Buonomenna & Bae, 2015). Furthermore, integrating solvent recovery into diafiltration yields over 70% for the mass intensity credit and 73% for solvent intensity credit reductions (Kim, Székely, Valtcheva, & Livingston, 2013). Economically, this closed-loop OSN system can reduce overall processing costs by up to 92%, by providing massive financial incentives, especially when handling high-value APIs (Kim et al., 2013).

3.4. OSN membrane limitations

Even with the huge benefits of saving energy and recycling solvents, using OSN technology on a large scale comes with a few physical and chemical challenges. The most immediate hurdle when filtering thick plant extracts is a traffic jam effect called concentration polarization (Baker & Baker, 2012). As the membrane blocks heavy molecules, like plant waxes, sticky resins, and the valuable medicines (APIs), these large particles pile up thickly right against the filter's surface. This dense layer acts like a physical wall, pushing back against the pressure of the system and making it much harder for liquid to pass through. Because of this, the flow rate drops rapidly, meaning operators must carefully adjust fluid speeds or clean the membrane often to keep the process running smoothly (Marchetti et al., 2014).

Beyond these physical blockages, the strong organic solvents used to extract plant compounds can also threaten the membrane itself (Marchetti et al., 2014). Most OSN membranes are made of flexible plastics (polymers) because they are cost-effective, but they can act a bit like a sponge structure. When constantly soaked in harsh solvents, the polymer material absorbs the liquid and swells up. This swelling physically stretches the tiny, carefully designed pathways inside the membrane. Once these internal pathways become too wide, the filter loses its precision, which can allow valuable medicine molecules to accidentally leak out or let unwanted impurities slip through (Marchetti et al., 2014; Nguyen Thi et al., 2022).

The biggest threat to a membrane's lifespan, however, is permanent chemical damage caused by the solvents changing over time. A well-known example happens with common extraction solvents like tetrahydrofuran (THF). When exposed to normal air and light in a factory, THF naturally breaks down to form highly aggressive molecules called peroxides (Szekely et al., 2014). When this damaged solvent is forced through the OSN system, these dangerous peroxides act like microscopic scissors that attack and snap the chemical bonds holding the plastic membrane together. This chemical damage slowly destroys the filter's structure, causing it to lose its mechanical strength and eventually dissolve entirely into the liquid stream (Szekely et al., 2014). This kind of chemical breakdown completely ruins the membrane's ability. To prevent this, factories set up strict safety rules, such as adding special chemicals to neutralize the peroxides, keeping oxygen out of the processing tanks, and constantly testing the solvent's quality (Szekely et al., 2014). Ultimately, these stability issues highlight exactly why scientists are working so hard to develop tougher materials, like mixed-matrix and ceramic membranes, that can easily survive the harsh conditions of large-scale botanical manufacturing (Szekely et al., 2014). Moreover, the scale-up ability of the membrane filtration system is also a challenge, the membrane for pharmaceutical application has to achieve a strictly regulation for GMP standards.

4. Conclusion and perspectives

Modernizing botanical extraction means moving away from harsh, heat-heavy processing. Organic solvent nanofiltration OSN technology has proven to be a highly effective technology for refining complex plant extract. By operating entirely refining process at room temperature, and eliminates the risk of heat damage. This ensures that valuable, heat-sensitive API compounds, like Saponin MR2, Vinca alkaloids, and Artemisinin, keep their natural structure and healing properties completely intact.

Beyond just keeping the product pure, OSN completely changes the cost and environmental impact of pharmaceutical manufacturing. By setting up a closed-loop membrane system, factories can concentrate their valuable APIs and recover the liquid solvents at the exact same time. This continuous recycling setup can cut solvent use by up to 59%, massively reducing the total amount of materials needed for botanical refinement. In an industry where organic solvents make up the vast majority of processing waste, saving this much chemical material is a major breakthrough (Szekely et al., 2014).

For Vietnam, the potential for scaling up OSN technology in pharmaceutical production is promising. Moreover, Vietnam is well-known for a rich variety of medicinal plants, yet the local extraction industry still often relies on distillation methods that waste energy and solvents. This technological gap significantly limits the global export value of Vietnamese botanicals. To stay competitive and meet strict international safety standards, it is crucial for Vietnam to bring OSN into its manufacturing systems. Adopting this advanced technology will empower local factories to extract medicines more efficiently, boost the medical quality of their products, and realize massive financial savings by dramatically reducing chemical consumption and hazardous waste disposal costs.

Looking forward, reaching this full industrial potential will require focused research to overcome current technical barriers. Future work needs to prioritize creating next-generation membranes that can handle harsh organic solvents without swelling up, getting clogged, or chemically breaking down. Finally, the OSN membrane technology is a transformative technology that can perfectly bridge the gap between Vietnam's abundant herbal resources and the strict demands of modern, eco-friendly pharmaceutical manufacturing ■

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