Application of micro/nano-fluidics for encapsulation of food bioactive compounds - principles, applications, and challenges

Running title: Micro/nano-fluidics for encapsulation of bioactives

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Abstract

Background

Microfluidics (MFs) and nanofluidics (NFs) techniques are emerging novel technologies gaining more attention in recent years to encapsulate bioactive compounds (bioactives) in the food, drug, and biomedical industries.

Scope and approach

Bioactives, such as fish oil, ascorbic acid, anthocyanins, and essential oils, positively impact human health; they are often poorly absorbed and thermally unstable. In this regard, using MFs/NFs has several benefits for bioactives, e.g. improving the biostability or bioavailability and solubility by the increasing of surface area, uniform size, shape, and controlled release of them, along with their protection against degradation conditions associated with food processing and storage, as well as to ensure safe delivery to the target sites in our body. Additionally, the controlled release approach is an effective tool for delivering bioactives.

Key findings and conclusions

Application of MFs/NFs in food processing and encapsulation of bioactives, nutraceuticals, and food additives is limited. More studies are required to establish the potential efficacy of MFs/NFs in this field. Therefore, the present review highlights various MFs techniques, including modern devices, advantages and disadvantages, the possibility of scaling up the technology, and future indications for encapsulating bioactives.

***Keywords*:** Delivery systems; bioactive compounds; food applications; emulsions; nanocarriers.

1. Introduction

The science of developing, manufacturing, and using processes and devices with nano and micro or small amounts of fluid in a laminar environment is known as the nanofluidics (NFs) and microfluidics (MFs) techniques (Feng, Liu, & Lee, 2021). In the early 1990s, MFs were first applied in different fields, including chemical detection and blood rheology. A decade later, MFs applications spread to various industries, such as chemistry, biology, medicine, agriculture, and food science. The MF technique might improve food safety and quality globally, which has already evolved and revolutionised the agrifood business (Chung et al., 2017). From food safety to developing new goods and components, nanotechnology significantly influences the food science (Pathakoti, Manubolu, & Hwang, 2017). It is projected that nanotechnology would enable the adoption of genetically engineered crops, livestock and fishery production inputs, chemical pesticides, and precision agriculture procedures.

The stability and bioavailability of labile food bioactives/nutraceuticals have been improved using several micro/nano-carriers (Caddeo et al., 2019). Because food-grade delivery vehicles are renewable, biodegradable, and biocompatible, they have been recognised as a viable platform for delivering sensitive bioactives (Rehman et al., 2020). Several delivery systems are developed for food applications, including Pickering or single/double emulsions, surfactant nano-vectors, SLNs (solid lipid nanoparticles), dendrimers, and magnetic nanoparticles (NPs). By increasing diffusion through the gastrointestinal epithelia, food delivery devices may preserve bioactives from degradation and improve their absorption (Araiza-Calahorra & Sarkar, 2019). Additionally, the load of bioactives may be modified by altering the surface properties, configuration, and surrounding environment to obtain a controlled release and biodistribution. Controlling the rate of bioactive distribution, preserving the bioactives for a long time, and delivering bioactives to specific locations may all be accomplished

using bioactive carriers *in vitro* and *in vivo* (Chew, Tan, & Nyam, 2018). Physiological or different environmental factors (e.g., pH, temperature, light, ionic strength, and electrical potential) are responsible for releasing bioactives, in this case, (Ahmad et al., 2019).

Many dietary bioactives, e.g. insoluble vitamins, phenolic compounds, carotenoid pigments, essential oils, and vital fatty acids, tend to be hydrophobic and poorly soluble. Poor bioavailability and stability are key roadblocks to their usage in the nutraceutical and food industries (Rezaei, Fathi, & Jafari, 2019). For a long time, scientists have researched the incorporation of beneficial bioactives into food. Nanoemulsions and nanocomposites are now being developed for this purpose (Hamad, Han, Kim, & Rather, 2018). Nanoencapsulation is a promising strategy to preserve and protect bioactives from harmful environmental conditions and increase their bioavailability and stability due to their effective management of liquid components and reduction of particle size, increasing the surface-to-volume proportion, rendering them greater functionality. In addition, it can reduce volatility, improve chemical and thermal stability, mask flavour and odour, promote controlled release, increase the solubility of lipophilic compounds in aqueous media, and even allow for the development of active packaging materials with antimicrobial and antioxidant properties (Pisoschi et al., 2018). Several recent studies have looked into producing nanocarriers such as nanoemulsions and nanoliposomes/phytosomes, biopolymeric NPs and micelles made of proteins, polysaccharides, or their complexes or conjugates (Jafari, 2017). Because there are so many different types of carriers, bioactives may be nanoencapsulated in several ways. In this regard, equipment such as MF devices, electro-spinning, and electro-spraying are required for nanoencapsulation methods (Jafari, 2017).

The pharmaceutical industry uses delivery systems to improve bioavailability, manage release kinetics, reduce side effects, and mask the unpleasant taste of medicinal chemicals administered (Pathakoti et al., 2017). Each of the several nanoencapsulation technologies has its benefits and

downsides. Emulsification, coacervation, inclusion complexation, nanoprecipitation, solvent evaporation, and supercritical fluid technology are some methods for nanoencapsulation of bioactives. Encapsulation of helpful microorganisms, such as probiotics, allows for their precise and site-specific delivery to the gastrointestinal tract. It is possible to use these encapsulated bacterial formulations in vaccines and immune response enhancement (de Oca-Ávalos, Candal, & Herrera, 2017). In addition, nanoemulsions have been shown to boost curcumin's health benefits (Honarvar, Hadian, & Mashayekh, 2016). A few bioactive-loaded nanocarriers have shown considerable inhibitory effects against certain illnesses, and the bioavailability of most of them has been excellent.

There is still a need for more significant investigation into the possible threats that NPs may pose to human health (Kuswandi, 2017). The direct interaction of NPs employed as food additives, and nutritional/functional components with humans may offer health risks (Karimi, Sadeghi, & Kokini, 2018). One of the primary toxicological processes causing cellular damage and death is generating reactive oxidative species (ROS) (He, Deng, & Hwang, 2019). ROS overproduction can cause neurone damage, autophagy, and severe DNA damage as well as carcinogenesis, mutagenesis, and ageing-related illnesses in humans (de Oliveira Mallia et al., 2022; Khan et al., 2012; Long et al., 2007; Singh et al., 2009). Several researches have focused on *in vitro* toxicity of NPs, but there is very little evidence of *in vivo* toxicity, much alone chronic effects of the nanomaterials (Duncan, 2011; He et al., 2019). However, it is expected that national organisations will increase efforts to regulate, administrate, and assist in adequately creating nano-sized food products while rules are still being established.

2. Bioactive compounds and their delivery systems: an overview

Secondary metabolites are the most common bioactives generated by plants, and they are not involved in the plant's circadian functioning but protect them from adverse environmental

conditions (Böttger, Vothknecht, Bolle, & Wolf, 2018; Hooper & Cassidy, 2006). *In vitro*, preclinical, clinical, and epidemiological research have been conducted to determine the chemical properties of bioactives and their use in foods and health benefits (D'Andrea, 2015). In addition to bioactives, functional foods can deliver health advantages because these compounds target systems involved in managing, preventing, and treating illness (Kuswandi, 2017). Among the many bioactives, plant growth factors, alkaloids, pigments, antibiotics, flavonoids, and phenolic acids are the most diverse (Hooper & Cassidy, 2006). They have a wide range of chemical structures, including hydrophilic and lipophilic, and their chemical structures are highly heterogeneous (D'Andrea, 2015).

Table 1 demonstrates the common bioactives in many dietary materials, including grains, fruits, and vegetables. Several bioactives are essential in food and pharmaceutical applications, such as camptothecin, diosgenin, hypericin, paclitaxel, podophyllotoxin, and vinblastine, have been commercially produced by different endophytic fungi present in respective plants (Melo et al., 2020). Thymol, carvacrol, and tocopherol are some of the most common bioactives that exhibit antioxidant properties (Janiszewska-Turak et al., 2017; Yashin, Yashin, Xia, & Nemzer, 2017). In humans, contemporary research on plant bioactives has primarily focused on their targeted application in preventing certain illnesses, e.g. cancer, stomach ulcers, or various chronic diseases and diabetes (Swer, Chauhan, Mukhim, Bashir, & Kumar, 2019; Q. Yao, Lin, Zhu, Xu, & Zhao, 2018). However, the bioaccessibility of bioactives is determined by the initial concentration and content of the food matrix, as well as the solubility, stability, permeability, and metabolic interconversions of bioactives (Błazińska & Sykuła, 2018).

The stability of the desired bioactives is a key consideration to be effectively incorporated into the food systems (Liu et al., 2021). Encapsulation may help preserve bioactives against harmful influences such as light, oxygen, heat, pH, shear, and other deteriorative incidents (Salva, Rocca, Niemeyer, & Delamarche, 2021). Several bioactives have been successfully encapsulated, as shown in **Table 2**. Electro-spinning enables the manufacture of foods with prolonged release behaviour and

a high encapsulation efficiency (EE) of bioactive ingredients such as anthocyanins, essential oils, curcumin, gallic acid, omega-3, probiotics, and vitamins (Mehta et al., 2022). However, the parameters governing the EE and release behaviour of bioactives still need to be clarified, and existing electro-spinning methods rely on single-needle, resulting in low productivity (Huang, Yuan, & Baojun, 2021). Further study is required to improve electro-spinning techniques like multi-needle and optimise operating conditions. The volatile flavours have been encapsulated by using extrusion encapsulation. The fundamental benefit of this procedure is the highly extended shelf life given to flavour components that are often susceptible to oxidation. For example, citrus oils' shelf life is extended up to 5 years through encapsulation by an extrusion process, compared to the normal shelf life of a few months for citrus oils that are not encapsulated (Poshadri & Aparna, 2010). Additionally, fluidised bed coating is used with solvent-based coatings such as gums, starches, and maltodextrin or hot-melt coatings like fatty acids, stearines, emulsifiers, and waxes. Also, freeze-drying, spray-drying, and supercritical fluids techniques are used for encapsulations of bioactives such as anthocyanins, curcumin, essential oils, and vitamins (Mehta et al., 2022; Ozkan, Franco, De Marco, Xiao, & Capanoglu, 2019).

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Table 1 Common bioactive compounds present in foods.

Group	Examples of bioactives	Sources	Health benefits	Applications	References
Flavonols	Myricetin, quercetin	Onion, broccoli, lettuce, beans (green, yellow)	-Antitumor activity -Antioxidant property -Anti-inflammatory -Anti-microbial capacity -Anticancer -Anti-obesity	-Functional food -Nutraceuticals	(Barreca et al., 2021; D'Andrea, 2015; Hooper & Cassidy, 2006)
Flavones	Apigenin, luteolin	Olives, celery	-Anticarcinogenic -Anti-inflammatory -Anticancer	-Pharmaceutical -Cosmetic -Food industries	(Hooper & Cassidy, 2006; Jang et al., 2018; Peng et al., 2021)
Flavan-3-ol	Epicatechin, catechin	Tea, red wine, apple	-Anti-inflammatory activities -Antioxidant properties -Control human blood pressure	-Functional food -Wine industry	(Hooper & Cassidy, 2006; Melo et al., 2020)
Carotenoids	α-, β-, γ-, δ-carontene, lycopene, β-cryptoxanthin, zeaxanthin, lutein	Carrot, tomatoes, mango, banana, tamarillo	-Reduce myocardial infarction -Lower the blook pressure -Protect low-density lipoprotein (LDL) cholesterol oxidation -Anticancer	-Functional additives in the food industry -Fabrication of muffins -As coloring ingredient -Improved sensory properties yogurts	(Janiszewska-Turak et al., 2017; Przybylska, 2020; Zimmer, Mendonça, & Zambiazi, 2022)
Isoflavones	Daidzein, genistein	Soy	-Prevent cardiovascular diseases -Reduce hypertension -Lower the risk of diadetes -Anticancers -Prevent neurological disorders -Prevent osteoporosis	-Medicinal chemistry -Funtional food -Self-medication	(Grynkiewicz, 2020; Hooper & Cassidy, 2006; Hsiao, Ho, & Pan, 2020)
Flavonoids	Luteolin, isorhamnetin, apigenin, quercetin, eriodictyol, naringenin	Parsley, Mexican oregano, celery seeds	-Anti-cancer -Prevent neurological diseases -Reduce cardiovascular diseases -Lower the risk of liver diseases	-Nutraceuticals -Food industry	(Q. Yao et al., 2018; Yashin et al., 2017)
Anthocyanidins	Petunidin, delphinidin, cyanidin, malvidin	Grapes, cherries	-Neuroprotective activities -Anti-inflammatory	-Improve food color -Intelligent food packaging -Chemotherapeutic	(Hooper & Cassidy, 2006; Swer et al., 2019)
Anthocyanins	-	Barberry extract	-Neuroprotective activities -Anticancer -Anti-obesity	-Chemotherapeutic -Intelligent food packaging	(Mahdavi, Jafari, Assadpoor, & Dehnad, 2016; Swer et al., 2019)
Chalcones, Dihydro-chalcones	-	Apple juice, cider, heavily hopped beer, tomatoes	-Anti-cancer -Anti-inflmmatory -Anti-diabeti activity -Neuroprotective activity -Cardioprotective activity -Anti-aging activity -Anti-infective property	-Pharmaceutical -Food industries	(Hooper & Cassidy, 2006; Kar Mahapatra, Asati, & Bharti, 2019)
Flavanones	Hesperidin, naringenin	Citrus fruits	-Hepatoprotective activities -Antioxidant capacity	-Food sectors -Pharmaceutical area	(Błazińska & Sykuła, 2018; Hooper & Cassidy, 2006)

Coenzyme Q_{10}	-	Cereals, meat, nuts, poultry, soybeans, fish	-Antioxidant activity -Enhance the immune system -Free radical scavenger -Useful in treating parkinson's disease	-Pharmaceutical -Food industries	(Jana, Gandhi, & Jana, 2017)
γ-aminobutyric acid	-	Tomato, mulberry leaves, tea leaves, lactic acid bacteria	-Antidepressant -Antihypertensive -Immune system enhancer -Antidiabetic	-Functional food -Nutraceuticals	(Sahab, Subroto, Balia, & Utama, 2020)

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Table 2 Commonly available encapsulation methods for bioactive compounds.

Bioactive compounds	Encapsulation method	Principle	Advantages	Disadvantages	References
Anthocyanin, essential oils, curcumin, gallic acid, omega-3, probiotics, vitamins,	Electro-spinning	-The introduction of a high voltage (1-30 kV) direct or alternate current electric field via a cell solution or dispersion constitutes the electrospinning and electro spraying process. -Dry fibre particles are produced by atomising this with a blunt-ended stainless steel needle, capillary, or by spinning it in the direction of the collector.	-These techniques are straightforward, inexpensive, and easily adjustable. -They also retain microbial cells.	- Rely on single-needle - Low productivity	(Mehta et al., 2022)
Kenaf oil extract, phycocyanin, ascorbic acid, phenolic compounds, pobiotics	Extrusion	-Forcing a core material in a mass of molten wall material through a set of dies (on a smaller scale for the lab) or a single die with the necessary cross section into a desiccant liquid bath. -When the coating material comes into touch with liquids, it hardens and entraps the active ingredients.	-The substance is completely encircled by the wall material; any remaining core is rinsed from the outside; and it is a comparatively low-temperature entrapping technique.	-Particle sizes are larger -Slow production rate	(Poshadri & Aparna, 2010; Sultana, Chan, Pushpamalar, & Choo, 2022)
Choline bitartrate benthol, carotenoids	Fluidized bed coating	-This method depends on hot-air nozzle spraying the coating material into a fluidised bed of core material.	It permits a particular distribution of capsule sizes and low porosities in the final product.at low-cost procedure.	-Direct exposure to high temperature -Cluster formation of fabricated particles	(Poshadri & Aparna, 2010; Reddy, Agarwal, Shah, & Suriya, 2022)
Acerola pulp and residue, anthocyanins, ascorbic acid, curcumin, carotenoids, phenolic compounds, limonene, vitamin E	Freeze-drying	Lyophilization of an emulsion solution containing a core material and a coating material causes the trapping to happen.	-The main benefit of freeze drying is that it is a straightforward procedure carried out at low working temperatures without the presence of air, resulting in products that are prolonged and of higher quality by preventing deterioration brought on by oxidation or chemical change. -The best technique for dehydrating nearly all heat-sensitive materials, including natural oils, colours, fragrances, medicines, and water-soluble components, is freeze drying.	-Open porous structure in the developed product -High cost -High time consumption	(Z. Fang & Bhandari, 2012; Kandasamy & Naveen, 2022; Ozkan et al., 2019; Suganya & Anuradha, 2017)
Curcumin, tamarillo juice, betalains, anthocyanins, probiotics, saffron extract, phenolic compounds, lycopene, astaxanthin	Spray drying	-Core material is dispersed in an entrapment material before being atomized and sprayed into a chamber using a hot air desiccant.	-The encapsulates produced by the spray drying process have very good solubility and reconstitution properties, low water activity, and are simpler to carry and store.	-Not suitable for highly viscous components -Clog the nozzle at high temperature	(Mehta et al., 2022; Mudalip, Khatiman, Hashim, Man, & Arshad, 2021)
Carotenoids, essential oils, omega-3, red palm oil, polyphenol compounds, pink pepper extract	Supercritical fluids	-Rapid Expansion of supercritical solutions, a supercritical fluid derived method in which active compound and polymer solutes are dissolved in a supercritical fluid, and then the solution is expanded through a tiny nozzle into a lower pressure area. As a result of the dramatically reduced solvent power of supercritical fluids, solutes precipitate.	-The effective management of particle size and shape, high yield and bioavailability of heat-labile active components, improved encapsulation efficiency, simpler solvent removal, and obtaining solvent-free droplets.	-Complications in extracting polar compound -Inefficiency in cleaning up	(Mehta et al., 2022)

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3. Nano/micro-fluidic devices, types, and operating principles

Using current NFs/MFs, various industrial procedures have been transformed for the controlled synthesis of multicomponent carrier systems with complex architectures and a wide range of functionalities. MFs involving two or more wholly or partly incompatible fluids are known as multiphase MFs. They has been widely used to improve mixing, promote mass transfer across phase barriers, and minimise dispersion. Because MF systems can handle reagents in the pico- to micro-litre range, they have unique properties, e.g. nanoseconds of mixing, reaction, and self-assembled structures, real-time monitoring/imaging, and direct scale-out. As a result of these features, it is possible to produce relatively low-cost and high-throughput micro/nanocarriers at relatively low cost and high throughput, e.g. polymeric NPs, liposomes, and hybrid NPs (Ran et al., 2017).

3.1 Types of microfluidics

It is possible to manage the flow behaviour of a small fluid volume by using MF technology, which integrates diverse fluids into microchannels (tens to hundreds of micrometres in diameter). MF techniques have been applied in bioengineering and food safety engineering (Liu et al., 2021). Different MF types produce various droplet production processes according to the designed channel shape. In microchannel-based devices, there are four typical structures: The microchannels include terrace-like, T-junction, Y-junction, and flow-focusing microchannel devices (FFD) (Chiesa et al., 2018), as shown in **Fig. 1**. Some microchannels distribute the scattered phase at the top and on both sides of the main channel, where the continuous phase flows, in a terrace-like microchannel device, droplets develop when the dispersed phase thread descends into a deeper well from the flat surface onto which the compressed dispersed phase has been applied.

T-junction devices use a microchannel perpendicular to the main channel where the continuous phase flows to distribute the scattered stage. After a thread is broken, droplets are formed

near the microchannel junction or farther downstream. Continuous phase flow drags away droplets that develop perpendicular to the main channel. In contrast to T-junction devices, Y-junction microchannel devices modify that design. The continuous phase flows parallel to the dispersion phase via a perpendicular microchannel. The merger of these two channels forms the primary channel. First, the dispersion phase has a contact angle of 90° with the continuous phase; this angle decreases to roughly 120° when the disperse phase merges with the main channel. Hydrodynamic focusing is the foundation of FFDs. Continuous and dispersed phases are given via separate channels in a microchannel. The dispersed phase is mixed with the continuous phase at the limiting point, and a droplet is formed. As a result, the mixing occurs in a relatively small area with laminar flow conditions (Chiesa et al., 2018; Gyimah, Scheler, Rang, & Pardy, 2022; Yu et al., 2019).

Receptors fixed on a particular surface and analytes flowing near these immobilised receptors are required for several applications in MFs (Salva et al., 2021). Developing a biofunctional and biocompatible surface in MFs is critical in making the MFs/NFs channel suitable for biological applications. It is possible to immobilise biomolecules on the channel surface using a biofunctional channel. These biomolecules include proteins, antibodies, cells, DNA, and enzymes. Using a reliable immobilisation strategy in NFs/MFs-based biosensors, for example, may increase the efficacy of the bioreceptors in selectively collecting the sample analyte, resulting in higher signals and lower limits of detection (Luka et al., 2015).

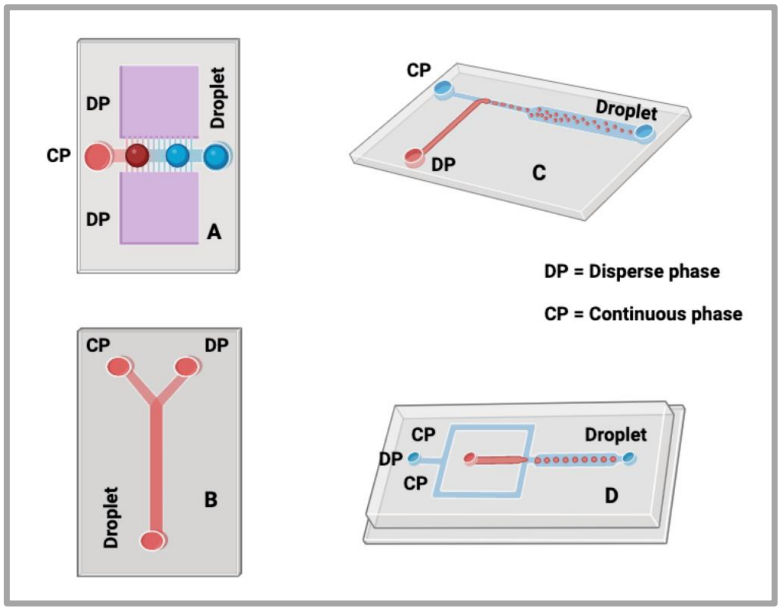


Fig. 1. Microchannel-based microfluidic devices: (A) Terrace-like device; (B) Y-junction device; (C) T-junction device; and (D) Flow-focusing microchannel device (FFD).

3.2 Operating principles

The foundational ideas of MF technology, built on blending procedures and regulations in a constrained area, are illustrated in **Fig. 2**. This method's ability to transform bulk techniques into a microchannel with a width of around 100 μm is a key component. Compounds are combined in this channel by pumping for synthesis and separation analysis. Contrary to popular belief, MF devices are not merely scaled-down replicas of their macroscale equivalents when mixing. Physical characteristics and diffusion-based mass transport cannot be linearly scaled from large to small scales. The main characteristic of MFs is the laminar flow, which cannot be accomplished in macroscale devices. Viscous forces have a key role in this phenomenon, which cannot be disregarded. A MF mixer should also be designed to take advantage of the physical characteristics of mass and fluid motion in a micro-confined environment, as it is not simply a scaled-down replica of an existing macroscale mixing device. The most fluid motion may be classified as either turbulent or laminar. A vortex forms in turbulent flow, whereas laminar flow is defined by fluid moving in parallel layers with no flow current running perpendicular to the flow direction (Chiesa et al., 2018).

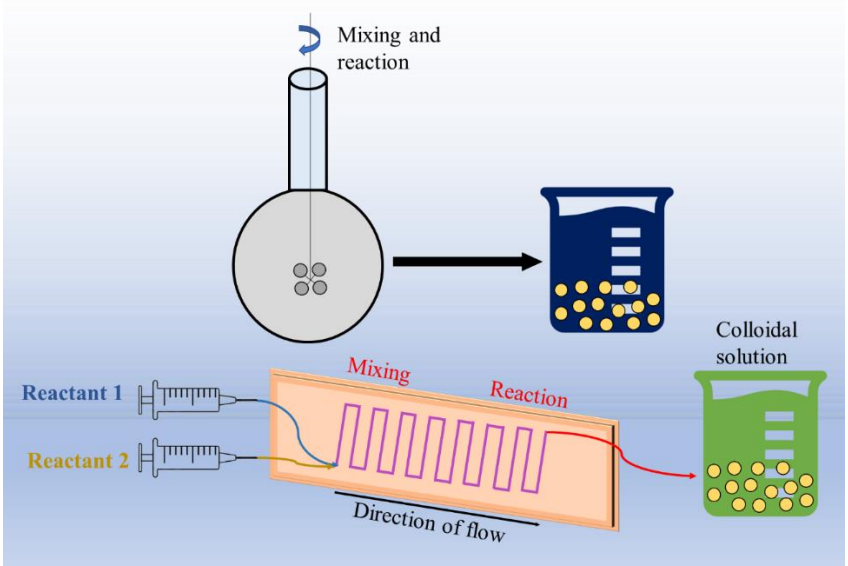


Fig. 2. Basic principles of the microfluidic technique

3.3 Materials of microfluidic devices

Various substrates have been biofunctionalised and utilised in MF devices, including glass slides and polymeric materials. Individual physical and chemical qualities like optical transparency, flexibility, mechanical strength, and chemical resistance may be achieved by combining each of these substrates. For the development of diverse biological applications, choosing the most appropriate approach for functionalising each substrate is essential.

The silanol groups in silicon made it an ideal material for MF devices since they could be readily changed. Fluorescence detection is challenging to combine with silicon since it is an infrared-transparent (Xing et al., 2020). Making Si-glass devices is costly, but they have great pressure and chemical resistance. Wet or dry etching methods often restrict MF channel design to open 2D configurations in the Si-glass devices (Berlanda, Breitfeld, Dietsche, & Dittrich, 2020). Glass is the most often utilised medium for MF chip production and surface functionalisation. In addition to its chemical stability, high-pressure resistance, hydrophilicity, and adaptability to several surface biofunctionalisation processes, glass offers many other benefits (Vong et al., 2011). Glass has a low

autofluorescence, is durable, chemically homogenous, and is stable (Salva et al., 2021). It is transparent and may be made in enormous quantities with a smooth surface. As a result, it is feasible to modify the characteristics of glass, such as its polarity and wettability, by applying different coatings and surface functionalisation processes to its surface. As an obstacle, amorphous glass is difficult to prepare to produce high aspect ratio anisotropic structures (Hou et al., 2017). Liquid glass can be made using a photocurable amorphous silica nanocomposite (Kotz et al., 2016). Using this technology, MF systems based on glass may be prototyped and fabricated at minimal cost, with excellent fidelity, and without the requirement for clean-room equipment or dangerous chemicals.

Organic materials are often sturdy and economical. Additionally, they offer more rapid and straightforward production techniques than inorganic materials. Polymeric materials are organic molecules with long chain lengths, such as elastomers and thermoplastics (Xing, Esser, & Dittrich, 2016). Organic materials such as polydimethylsiloxane (PDMS), polycarbonate (PC), polymethyl methacrylate (PMMA), polystyrene (PS), cyclic olefin copolymer (COC), Thermoset Polyester (TPE), polyurethane methacrylate (PUMA), and Norland Adhesive 81 (NOA81) are frequently used in the fabrication of MF devices for research and large-scale applications (Salva et al., 2021). These polymers are protein-coated, optically transparent, simple to prototype or manufacture in large quantities, do not need cleanroom facilities, and are cost-effective to create. Due to cost-effectiveness and ability to provide visual control of the process, PDMS is the most often utilised material in manufacturing MF devices. Compared to other materials, polymers are inexpensive and facilitate the manufacturing of MF equipment. Additionally, no toxic etching chemicals are required during the manufacturing process (Jurinjak Tušek et al., 2021).

Many studies have been conducted on the NFs phenomena. Advances in micro/nanofabrication technology have enabled these advancements (Kan, Zhang, Malar, & Maarel,

2012). For instance, recent research used soft lithography to merge nanochannels 800 nm in length and 400 nm in height into microchannels. Based on droplet formation with a regulated size of up to 51 nm, the NF device was investigated for water in oil emulsions. Additionally, these nanoemulsions were employed as a template for the formation of 60 nm protein nano gels from three distinct proteins, namely β -lactoglobulin, lysozyme, and fibroin, hence explaining the charge and electric double layer overlap seen in nanochannels (Xu, 2018), as shown in **Fig. 3**. At nanoscales, hitherto unobserved physical processes and mechanisms develop and take control, allowing for the exploration of new scientific discoveries and applications of fluids. The representative phenomena and effects revealed thus far include nonlinear transport (such as concentration polarisation and ion-current rectification) and altered liquid properties of water (such as a lower dielectric constant, increased viscosity, and increased proton mobility) due to the ultrahigh surface-to-volume ratios.

In NFs, interfacial contact between core and wall fluids is fundamental. To assist in generating spherical droplets and delay the release of bioactives, it is necessary to use this ingredient. In addition, it aids in developing nano-droplets of the same size and shape [154]. It comprises a base-fabricated collection of components, including a moulded set of channels. As these channels are connected in all directions, fluid flows through them. Hydrostatic pressure is used to inject gas and liquid from a syringe. MFs/NFs emulsion devices of four varieties, including single-, double-, multi-, and flow-focused devices. Nanoemulsions, nanoliposomes, and NPs may all be made using this technology (Noore, Rastogi, O'Donnell, & Tiwari, 2021). The first NF devices were made of silicon. Si etching is a delicate procedure that must be handled with care. There have been a few successes in making nanochannels with two critical dimensions < 100 nm threshold (Mannion, Reccius, Cross, & Craighead, 2006). Other organisations have explored other means of creating NF chips because of the complex processing necessary to manufacture SiO_2 NF lab-on-chip devices.

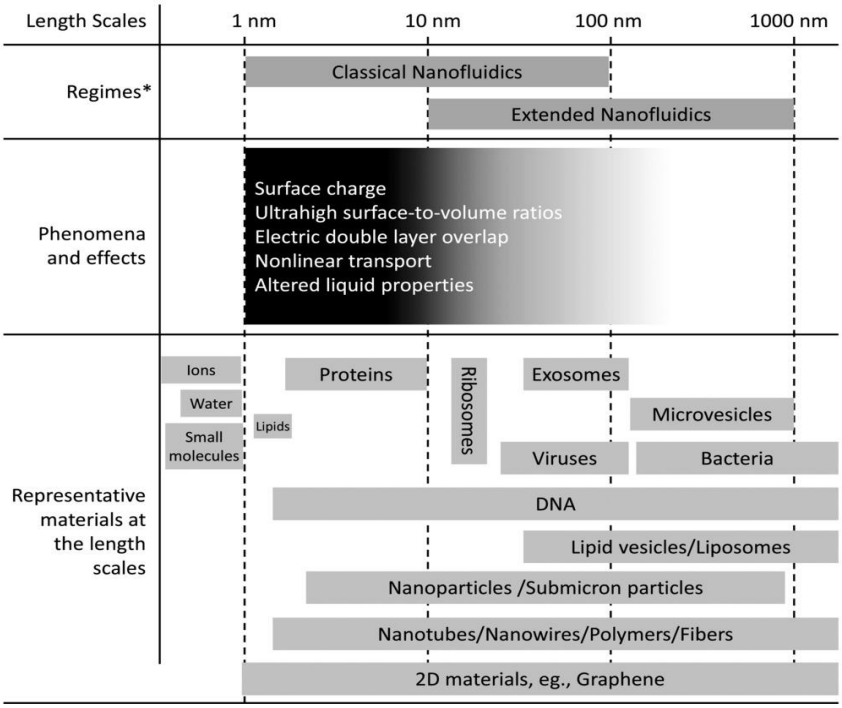


Fig. 3. At the same length scales as nanofluidics, representative materials and nanometric objects exhibit remarkable transport processes, and effects occur (Xu, 2018).

Glass substrates (often fused-silica glass) have been utilised to fabricate nanochannels in recent years. For NF devices, glass became a prominent substrate material because of its exceptional qualities suitable for chemical and biological investigations and applications. Thermal stability, chemical/biological inertness (i.e., non-reactive), mechanical strength, and hydrophilicity are only a few of these qualities' many advantages for handling liquids. As well as having a high initial investment in both the glass substrate and the nanofabrication technology used to create the nanochannels, the delicate, sophisticated, and time-consuming processes required in high-end clean rooms make the process of creating glass nanochannels prohibitively expensive (Xu et al., 2012). The development of glass NF devices has been constrained to a few research organisations due to the high cost and tight requirements that must be met.

Polymer-based MF devices in biological applications have become a more significant (Lei, Ahsan, Budraa, Li, & Mai, 2004). In terms of price and processing flexibility, polymer-based products

311 are a viable option (Uba, Hu, Weerakoon-Ratnayake, Oliver-Calixte, & Soper, 2015). Polymeric NPs
312 are often designed to distribute functional chemicals in a regulated and targeted manner (Paredes,
313 Asensio, Llabot, Allemandi, & Palma, 2016). Particles having sizes of < 100 nm are known as
314 biopolymeric NPs. Using aggregative (net attraction) or segregative (net repulsion) interactions, for
315 example, these NPs may be created by stimulating self-association or aggregation of single
316 biopolymers or causing phase separation in mixed biopolymer systems. Despite its widespread use in
317 the creation of MF devices, the fabrication of nanochannels in soft materials such as PDMS has
318 encountered several difficulties. Due to the low rigidity of normal PDMS (low Young's modulus),
319 dimensional instability and roof collapse of channel systems after bonding pose a substantial
320 difficulty. Hence, it may consider using the hard-PDMS (h-PDMS) (Xu, 2018). Wang, Yan, Geng,
321 Gan, & Fang (2019) explored the effect of PDMS weight ratio on nanochannel size. According to the
322 experimental findings, PDMS weight ratios were altered by nanochannel diameters during the second
323 transfer phase due to the thermal expansion of the polycarbonate sheet. Finally, connecting a PDMS
324 nanochannel chip to a PDMS microchannel chip made it possible to create MF/NF devices with three
325 distinct nanochannel diameters.

326 **4. Encapsulation of bioactive compounds by microfluidics technique**

327 The encapsulation of bioactives through modern MFs methods is discussed in the following sections
328 and a summary is presented in **Table 3**.

329 **4.1 Chlorophyll**

330 Chlorophyll is a great naturally produced pigment from plants and algae, which is widely used
331 in food, pharmaceutical, and cosmetic industries due to its novel attributes, e.g. non-toxicity or low
332 toxicity and an excellent capacity to hinder the occurrence of cancer (Boon, McClements, Weiss, &
333 Decker, 2010; Karg et al., 2021; Ye, Fan, Keen, & Han, 2019). However, using chlorophyll has

drawbacks, such as its pigment composition is not precisely understood, and it tends to become unstable when added to foods with varying pH levels (Agarry, Wang, Cai, Kan, & Chen, 2022; Hosikian, Lim, Halim, & Danquah, 2010). To increase its stability as a food colouring ingredient, the copper ion must be substituted for the magnesium centre, which makes it more costly than artificial colourings. The copper complex is considered harmless and allowed to be used in most countries as a food additive since it is not absorbed by the body and is entirely eliminated as an excretion product. Nevertheless, current laws require that the concentration of free ionisable copper in the colouring be kept < 200 ppm (Mohd Amin, Karim, Yusof, & Muhammad, 2023).

In addition, for the application of chlorophyll as a food colourant additive, several factors such as oxygen, high temperature, acid, and illumination are the main culprits for the quality degradation of chlorophyll that render colour changes (Tena, Lobo-Prieto, Aparicio, & García-González, 2019). To extend the shelf-life of chlorophyll, some methods such as glycerin, alkalinising agents, blanching, copper complexations, and storage at low temperatures have been used, but existing methods are not suitable for the commercialisation of products with desirable storage periods (Ngamwonglumlert, Devahastin, & Chiewchan, 2017; Ozkan et al., 2019). In this regard, C.-J. Hsiao et al. (2020) reported that using chlorophyll-encapsulated polycaprolactone (Chl-PCL) with droplet MFs chip techniques exhibited the highest chlorophyll stability in storage periods. In addition, the MF method had the potential for the uniform distribution of particle size; thus, the size of Chl-PCL was controllable during the production stage, which is more convenient for transportation and longtime storage due to its capacity to scatter UV light.

4.2 Fish oils

Fish oils are rich in polyunsaturated fatty acids, especially docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), that are usually used in the human diet due to their anti-arrhythmic and

anti-inflammatory features (Binsi et al., 2017). Both the EPA and DHA are more susceptible to harmful oxidation when in contact with light, oxygen, and heat, which makes a difficult situation during the handling and application of fish-based oil in the food industry (Talita A Comunian & Favaro-Trindade, 2016). Furthermore, a strong odour is produced by the degradation of fish oil, one of the most prominent causes of consumers' rejection of fish oil-based food products. Even though several encapsulation techniques such as spray drying, spray chilling, SLNs, liposomes, and complex coacervation have been used for fish oil to minimise its unpleasant odour, uniform particle size production is challenging, which influence the behaviour and texture of microcapsules that create unstable condition during application in food products (Martins, Poncelet, & Renard, 2017; Mohammed, Tan, Abd Manap, Alhelli, & Hussin, 2017). To overcome these problems, some experts suggest using glass MF devices with single, double, and multi-compartment emulsions to produce identical particle sizes (Duncanson et al., 2012). Talita A Comunian, Ravanfar, Selig, & Abbaspourrad (2018) described fish oils encapsulated using glass MF devices; a combination of different proteins such as casein, whey protein, and gelatin as emulsions showed better fish oil stability due to the reduction of oxidation rate. In addition, Ravanfar, Comunian, Dando, & Abbaspourrad (2018) reported glass MF devices and homogenisation techniques using microgel from whey protein, $CaCl_2$, and laccase as cross-linking agents, and pectin as barrier materials for fish oil encapsulation, and found MFs methods are physicochemical stable than homogeniser.

4.3 Echium oil

Echium oil obtained from echium seed (*Echium plantagineum* L.) is rich in EPA and DHA and commonly used in food products due to its health benefits components (Ghorbanzade, Jafari, Akhavan, & Hadavi, 2017). In recent years, the oxidation rate of echium oil has been reduced through the application of phenolic compounds and encapsulation techniques, which is preventing the

formation of malonaldehyde during the storage periods. Accordingly, MFs techniques are gaining popularity due to sound control systems, higher efficiency, and ease of releasing bioactive compounds. Talita A Comunian et al. (2017) demonstrated the encapsulation of echium oil with phenolic compounds using glass MF devices and the double emulsion method and found that echium oil encapsulated with phenolic compounds exhibited more stability than non-encapsulated oil in 30 days of storage at 40°C.

4.4 Anthocyanins

Anthocyanins and norbixin are standard natural pigments used in the food industry due to their potential health benefits, such as anti-allergenic components, antioxidant activity, antimicrobial capacity, and mediating cytotoxicity (Mikulic-Petkovsek, Ivancic, Schmitzer, Veberic, & Stampar, 2016; Sigurdson, Tang, & Giusti, 2017). Anthocyanins are extracted from different types of vegetables and fruits, and norbixin is collected from the seasonal fruit *Bixa orellana* (Sathiya Mala, Prabhakara Rao, Prabhavathy, & Satyanarayana, 2015; Yousuf, Gul, Wani, & Singh, 2016). Both natural pigments are unstable under unfavourable conditions such as temperature, light, and low and high pH; thus, application in food products is challenging (Cortez, Luna-Vital, Margulis, & Gonzalez de Mejia, 2017). In this regard, MF methods have attracted the scientific community's attention globally due to their capacity to produce microcapsules with a desirable form with excellent functionality (Datta et al., 2014). For example, T. A. Comunian, Ravanfar, Alcaine, & Abbaspourrad (2018) used an MF-based encapsulation technique to protect anthocyanins and norbixin; in an MF device, palm oil was used as a barrier in W/O/W emulsion, and encapsulated pigments showed more excellent stability with desirable particle size and suitable morphology in storage condition that would be potential candidates for the application in food products.

4.5 Ascorbic acid

Ascorbic acid (AA) is commonly used as a food additive because of its antioxidant property. However, the acidic nature of AA influences the interaction with other components in food, negatively affecting the sensory quality of AA-fortified foods; consequently, the shelf-life of foods is reduced (Abountiolas & do Nascimento Nunes, 2018). Additionally, AA oxidises when in contact with oxygen, light, temperature, and moisture. Talita A. Comunian, Abbaspourrad, Favaro-Trindade, & Weitz (2014) reported encapsulation of AA by using the MF method to protect AA from the adverse environmental condition and found using palm oil in the oil phase and solution of PVA in the continuous phase in MF device help to produce solid lipid microcapsule that showed greater efficiency to protect AA during storage.

4.6 Proteins and peptides

Proteins and peptides quickly deteriorate under adverse conditions that cause aggregation, denaturation, precipitation and adsorption (Talita Aline Comunian & Jafari, 2019). In addition, using protein as a therapeutic agent has poor bioavailability, and increasing the bioavailability rate is challenging due to unstable non-covalent interactions between secondary, tertiary, and quaternary structures of proteins. In this regard, polymeric microcapsules can show good potentiality in oral protein supply. MF technology exhibits positive attitudes toward preparing microcapsules due to great controlling power in the fabrication process (Natarajan, Krithica, Madhan, & Sehgal, 2011). Furthermore, MF techniques have an excellent capacity to mix immiscible liquids in a unique manner using a 3D flows (Utada et al., 2007). Pessi et al. (2014) observed the efficiency of bovine serum albumin in the encapsulation stage and identified that using MF techniques accelerates the efficiency rate (84%) with the controlled release of therapeutics protein due to its suitable particle size (23-47 μm). Therefore, the MF method allows the application of protein in food and biomedical sectors (Sarabandi, Sadeghi Mahoonak, Hamishekar, Ghorbani, & Jafari, 2018).

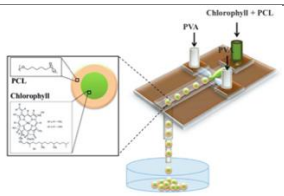
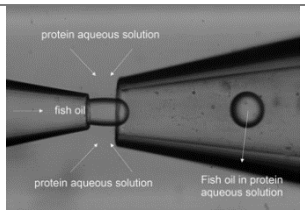
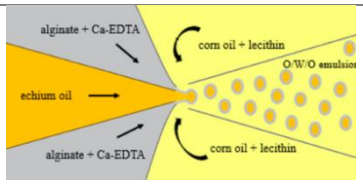
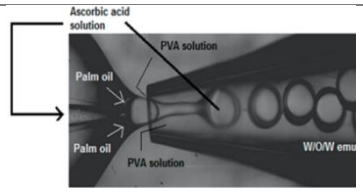
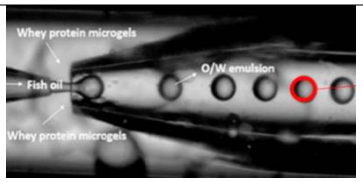
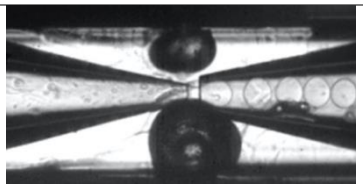
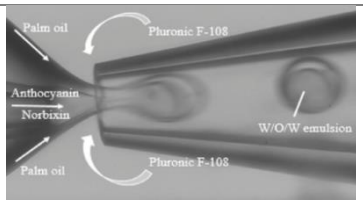
4.7 Caffeine

Caffeine is a hydrophilic bioactive that benefits the central nervous and cardiac systems increases alertness, and relaxes smooth muscles (Noor, Shah, Gani, Gani, & Masoodi, 2018). If caffeine is encapsulated, it can be sustained for a more extended period, delivering a regulated release after consumption and hiding the bitter taste (Fuciños et al., 2017). For pharmaceutical goods, caffeine has already been encapsulated in various colloidal systems. To achieve greater encapsulation effectiveness, improved stability, ensure homogeneity, and enhance physicochemical properties (polydispersity, zeta potential, and mean size) of caffeine, MFs have been employed in recent years (Shepherd, Issadore, & Mitchell, 2021). MFs techniques allowed for a more extended residence period leading to the highest EE (70%) of the caffeine (Fonseca, Santos, Czaikoski, & Cunha, 2022).

4.8 Lutein

An increased risk of age-related eye disorders is associated with inadequate lutein intake (Roberts & Dennison, 2015). However, because of its susceptibility to breakdown and limited bioaccessibility in the gastrointestinal tract, lutein has only been minimally absorbed into diets (Teixé-Roig, Oms-Oliu, Ballesté-Muñoz, Odriozola-Serrano, & Martín-Belloso, 2020). By using the MFs that can regulate fluid flows at the microscale, it can facilitate the effective encapsulation of lutein for commercial applications, e.g. functional foods (Y. Yao et al., 2021). At the same time, curcumin has inhibitory effects on tumour cell growth; however, curcumin's low solubility in water limits its biological activity (J. Fang, Lu, & Holmgren, 2005). In this regard, liposomes are useful carriers of curcumin due to their structural resemblance to cellular membranes. Still, current techniques for dual-loading liposome synthesis are limited to scaled-up applications (Aditya et al., 2015). Several articles reported using a dual-loading method with MF assembly for liposomal encapsulation of medicines or functional bioactives with enhanced bioavailability (Hong et al., 2020).

450 **Table 3** Recent advances in microfluidic technique for the encapsulation of bioactive compounds

Bioactive compound	Formulation/ compounds	Device	System setup	Major findings	References
Chlorophyll	Chl-PCL emulsion Chlorophyll-encapsulated poly-caprolactone (Chl-PCL)	Flow-focusing		-Particle range was 68 to 247 µm -Chlorophyll-loaded PCL showed greater chlorophyll stability -Solid microcapsule was more accessible for transportation, storage and food industry application	(C.-J. Hsiao et al., 2020)
Fish oil	O/W emulsion Gelatin/casein/ whey protein	Flow-focusing		-Zeta potential was -24 to +11 mV at 0 days but -16 to -0.54 mV after 15 days of storage - Particle size was 77 to 97 µm and 79 to 107 µm at 0 days and 15 days respectively -Combination of 1% casein and 0.5% gelatin, and MF techniques showed good protection ability against harmful lipid oxidation and extending product shelf life	(Talita A Comunian et al., 2018)
Echium oil	O/W/O emulsion Quercetin/ sinapic acid	Flow-focusing		-Control sample without addition of phenolic compounds showed high oxidative attitude compared to oil sample treated with quercetin and sinapic acid -Combination of MF and ionic gelation methods would potentially protect the echium oil	(Talita A Comunian et al., 2017)
Ascorbic acid	W/O/W emulsion Palm fat	Flow-focusing		-Encapsulation of ascorbic acid (AA) using palm fat as membrane of capsule and MF method showed good performance during storage -MF technique extend AA shelf life by protecting the sample from organic solvents and temperature	(Talita A. Comunian et al., 2014)
Fish oil	O/W emulsion Whey protein/ beet pectin/ laccase/$CaCl_2$ salt	Flow-focusing		-Microcapsules treated with laccase exhibited outstanding stability compared to control -Cross-linking compounds in microcapsules were more powerful using MFs techniques	(Ravanfar et al., 2018)
Therapeutic proteins	W/O/W emulsion Bovine serum albumin (BSA)	Flow-focusing		-Using MF method, therapeutic proteins successfully developed -The range of particle size was 23 to 27 µm -Encapsulation efficiency with BSA showed highest value (84%)	(Pessi et al., 2014)
Anthocyanins and norbixin	W/O/W double emulsion Palm oil	Flow-focusing		-The particle size and encapsulation efficiency of encapsulated anthocyanins were 187 to 90 µm and 47.8 to 54.87% respectively -In case of norbixin, particle size and efficiency were 164 to 184 µm and 49.18 to 74.73% respectively -Encapsulation of natural pigments using MF technique provided strong protection	(T. A. Comunian et al., 2018)

451

5. Challenges of micro/nano-fluidics technique and different factors affecting their efficiency

MF/NF technologies have potential advantages compared to conventional methods for encapsulating bioactives. Still, some challenges or limitations should be overcome to commercialise these technologies on a large scale. The flow rates applied for the MF/NF devices at 15-20 mL/h make the technology challenging to obtain a suitable sample volume in the industrial scale (Panáček et al., 2006). In this regard, parallel devices can be considered simultaneously during the production of high-volume samples at a commercial level. Another noteworthy point, some devices of MF/NF techniques are non-food grade (Talita Aline Comunian & Jafari, 2019). Chemicals like poly-allylamine hydrochloride (PAH) and poly-acrylic acid (PAA), which are pricy and inedible and interact with bioactives to cause contamination, are utilised in MF/NF procedures (Francisco, Santos, & Cunha, 2022). To overcome these limitations, glass MF equipment would be a suitable option in food sectors due to its lower ability to interact with other materials (Talita A Comunian et al., 2018). Moreover, biocompatible materials such as soy protein, chitosan, alginate, and carrageenan gums as replacements for PAH and PAA may hinder the interactions between bioactives and the MF device which would be employed as a food-grade device (Francisco et al., 2022). The NF may be a smart technique for synthesising nanomaterials; nevertheless, understanding nanomaterials' synthesising process and development need a toxicity evaluation before application in food sectors. (Bazana, Codevilla, & de Menezes, 2019; Khoo, Lin, Huang, & Tseng, 2011; Ropers, 2019; Spina et al., 2016; Xu, 2018). Consequently, the consumer acceptance level would be high and high market penetration of this method will be achieved.

Additionally, knowledge gaps are needed to be addressed, operator training is required, and collaboration between industrial and academic researchers is strongly needed to improve the perception of consumers and industrial sectors in the world. However, the most paramount factors,

such as size, shape, type, pH of the fluid, temperature, and concentration of NPs, have greatly influenced the activity of MF/NF techniques (Ropers, 2019). These factors are responsible for the erosion and clogging of the device channels; thus, further theoretical and experimental research is necessary to identify other factors to characterise the performance level of MF/NF methods (Sezer, Atieh, & Koç, 2019).

There are good possibilities to scale up the MF/NF techniques on an industrial scale due to their high heat transfer ability and thermal conductivity at low concentrations of NPs, lower viscosity, and smaller equipment (Xu, 2018). However, some limitations, e.g. high initial cost, complications in analyte detection, and technical difficulties in fluid control, need to be overcome for use on an industrial scale (Chen et al., 2021; Yamamoto, Ota, & Tanaka, 2020). Nisisako & Torii (2008) used glass MF chips to produce a large volume (320 mL/h) of MFs to scale up the production system and obtained monodisperse droplets (96.4 μm) for industrial use. Similarly, Tetradis-Meris et al. (2009) studied the parallel integration of MF equipment, scaled up 180 suitable MF devices with a bit of coefficient variation, and attained monodisperse W/O emulsion. Furthermore, (Kobayashi, Wada, Uemura, & Nakajima, 2010) developed single emulsions through MF/NF devices by reducing particle size to improve the large-scale parallel process to obtain large-volume samples within a short period. van Dijke, Schroën, van der Padt, & Boom (2010) used the edge-based droplet generation (EDGE) method to produce single (O/W) and double (W/O/W) emulsion for the encapsulation of sunflower oil, skim milk, and whey protein. It is anticipated that encapsulation of bioactives is possible on a large scale by using double emulsions techniques, but additional measure is required during the production of double emulsion, and scaling up the double emulsion is more complex than single emulsion (Maan, Nazir, Khan, Boom, & Schroën, 2015; Romanowsky, Abate, Rotem, Holtze, & Weitz, 2012).

For the successful scale-up of the MF/NF techniques, significant challenges of nanofluids such as high production cost, high viscosity, some anomalous high thermal conductivity, increased pressure drop than base fluid, and low specific heat should be considered. Additionally, for sustainable nanotechnology, both the MF/NF processes need more studies that promote the excellent controlled release of bioactives and help to commercialise these novel methods with potential applications in industrial sectors.

6. Conclusion and future perspective

In recent years, both MF/NF technologies have offered innovative approaches for encapsulating bioactives, solving key problems in the agriculture, food, biosystem, and pharmaceutical industries. Encapsulated bioactives are well-suited as additives in global food sectors. Therefore, the global market is expected to expand the MF/NF technologies due to their significant benefits in different industrial sectors. Even though the MF/NF technologies have demonstrated several advantages, such as improved high oxidative stability of bioactives, extended thermal stability, controlled release of bioactives, and increased bioavailability, market penetration of these technologies will require proper validation. In addition, the optimisation of these technologies is needed from an encapsulation point of view and addressing the research gap in different sectors for their potential applications.

Additionally, due to nanochannels' ultrasmall size and confined nature, clogging and fouling are significant problems that affect practically all NF applications (Xu, 2018). By carefully crafting nanochannel shapes, covering channel walls, and reducing interactions between nanomaterials and channel walls, as well as non-specific biomolecule adsorption, clogging, and fouling, may be reduced. The current MF technologies must be improved since they are either too expensive or complex to be included in a helpfull system. In order to go from the lab into the real world and solve issues facing

the food and pharmaceutical sectors, new tools and equipment must operate at better levels of throughput and precision than conventional macro-scale automated equipment. Also, more studies are needed to characterise the toxicity and safety of materials used in MF/NF technologies. Global regulations should be drafted to promote these technologies, which benefit health. The release of bioactives depends on several environmental factors, such as light, pH, ionic strength, temperature, and electrical potential. Hence, improving current MF/NF technologies that are too sensitive to environmental features or have a high cost to integrate into a functional process is necessary. Consequently, MF/NF technologies can be applied to encapsulate bioactives that play a crucial role in the cosmetic, food and pharmaceutical sectors in the near future.

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