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ADSORPTIVE BUBBLE SEPARATION METHODS (ABSM): FOAM FRACTION

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ABSTRACT

Foam fractionation is an ecological and economical method belonging to the adsorptive bubble separation techniques. It represents an alternative to traditional methods used for the enrichment and isolation of biomolecules. Separation occurs due to the chemical or physical adsorption of surfactant molecules on the surface of the sprayed air bubble or the carrier gas rising through the liquid sample. This unit operation has the potential to use it as a low-cost industrial method for the enrichment and isolation of pharmaceutical biomolecules, proteins, enzymes, polymers, and secondary metabolites of plants and microorganisms. This review focuses mainly on the separation of biomolecules on a large scale and on parameters that influence the efficiency of the separative method.

Introduction

The demand for purified biochemicals, such as proteins, alkaloids, phenolic substances, polymers, and another variety of organic substances has markedly increased in the last few decades (Albijanic, Ozdemir, Nguyen, & Bradshaw, 2010; M. Backleh, Ekici, Leupold, Coelhan, & Parlar, 2004; M. Backleh, Ekici, Leupold, & Parlar, 2003; Y. C. Chen & H. Parlar, 2013; Zheng, 2014). The separation of biologically active natural products from useful aromatics plants or medicinal herbs is of great importance to the pharmaceutical and food industries (Karaogul, Parlar, Parlar, & Alma, 2016). Therefore, there is an interest in economic methods that can isolate and enrich

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biochemical products (Y. C. Chen & H. Parlar, 2013).

The methods like ultrafiltration, sedimentation, reverse osmosis, zone melting, thermal diffusion, multi-stage processes, electrophoresis, chromatography, foam fractionation, flocculation, and solvent extraction methods have been used extensively since ancient times to purify a sample of impurities or to enrich any substance in the sample (Sedwick, Shinn, & Zeitlin, 2006).

With the development of technology in recent years, researchers have begun to re-evaluate many active substances in plant extracts using separation techniques developed with new analytical equipment or so-called new separation techniques. Such techniques include supercritical extraction, solvent extraction, separation of liquid and gaseous membranes, as well as foam fractionation and chromatographic methods, which it is often used for quantitative and qualitative analysis (Thompson, 2004). The purification of many substances is based on traditional enrichment methods which it is usually combined with chromatographic processes, in which substances purification is done by ion exchange hydrophobic interaction and size exclusion chromatography. Traditional methods of enriching biochemical molecules generally involve expensive purifications and lead to expensive end products. For this reason, it is necessary to develop new techniques capable of increasing the purification capacity and decreasing the overall costs (Y. C. Chen & H. Parlar, 2013). With the development of technology in recent years, researchers have begun to re-evaluate many active substances in plant extracts using separation techniques developed with new analytical equipment, such as the foam fraction method or so-called adsorptive bubble chromatography(Datta, Ghosh, Chakraborty, Gangopadhyay, Prabir, & Datta, 2015; Raks, Al-Suod, & Buszewski, 2018; Thompson, 2004).

Adsorptive bubble chromatography represents a promising method for the isolation and enrichment of various substances. It is simple, easily scalable, inexpensive, and environment friendly (Y.-C. Chen & H. Parlar, 2013; Y. C. Chen & H. Parlar, 2013). It does not need to use organic solvents as well as a mobile phase and/or does not need a stationary phase. To increase the selectivity of the process, it is aimed to carry out a selective separation by performing a metal ion-tweezing adsorptive bubble chromatography process (Y.-C. Chen & H. Parlar, 2013; Y. C. Chen & H. Parlar, 2013; X. Liu, Yu, Xie, Li, Chen, & Li, 2010).

1. Classification of Adsorptive Bubble Separation Methods (ABSM)

The adsorptive bubble separation technique has been known since the beginning of the 20. Century (Ekici, Backleh-Sohrt, & Parlar, 2005). A summary table of the classification of adsorptive bubble separation methods is shown below. Knowing this table is of great importance. Because it has been noted in the literature that many terms are confused with each other.

Flotation and foam fraction are sub-classified methods of Foaming Adsorptive Bubble Chromatography. The foam flotation method is widely used in industry. The well-known method is successfully used to recover surfactants from industrial wastewater. This separation method is widely used also in industries ranging from metallurgy to chemical industries for the separation of desired

minerals or other solids in aqueous solutions. This method allows the particles and bubbles to collide and if the particles are sufficiently hydrophobic, the bubble and the particle come together and create bubble-particle aggregates. Therefore, the particle-bubble aggregates are transported to the foam zone and collected in a concentrated solution (Han, Han, Kim, Yang, Choi, Kim, et al., 2019).

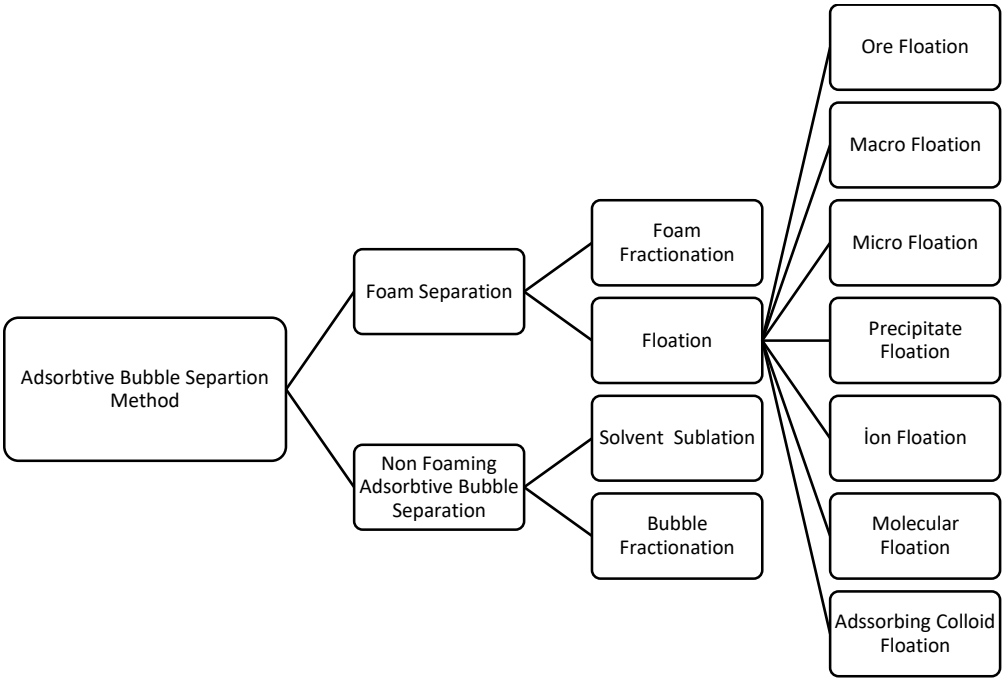

Figure 2.1 Schematic Representation of Adsorptive Bubble Separation Methods (Thompson, 2004).

2. Foam Fraction Method

Ostwald was the first to study foam fractionation for the isolation of natural compounds and in 1920 he obtained patent protection for this technology (Linke, Zorn, Gerken, Parlar, & Berger, 2005). As of today, this method has developed with modern and technological analytical equipment and it is a promising method for the isolation and enrichment of biochemical. It is a method based on the adsorptive bubble separation technique. It's simple as opposed to ultrafiltration and chromatography, so it's cheap and easily scalable. It is environmentally friendly (the use of solvents can be omitted) unlike other methods of purification and it causes only little investment energy (Y.-C. Chen & H. Parlar, 2013; Y. C. Chen & H. Parlar, 2013; Ekici, Backleh-Sohrt, & Parlar, 2005; B. Gerken, Nicolai, Linke, Zorn, Berger, & Parlar, 2006).

Foam fractionation is an ideal method for selectively isolating or enriching molecules dissolved in dilute aqueous solutions (up to 1 × 1010 mol/L) based on their surface activity, hydrophobicity, or ability to associate with other molecules to build hydrophobic complexes. Isolation and enrichment of the molecules occur by adsorption of these molecules on the surface of the foam bubbles formed by the aeration of a foaming solution. the gases used for the enrichment of surfactant substances are e.g. nitrogen, oxygen, air, and carbon dioxide. Surfactants

are used for foam formatıon and foam stabilization (Karaogul, Parlar, Parlar, & Alma, 2016; Thompson, 2004).

In the case of the sufficiently lyophilic analyte, enrichment is possible even without the use of the surfactant agent. Instead, in the case of the analyte with poor lyophibility, the use of the surfactant agent was preferred, which will allow adsorption of the analyte on the bubbles of the surfactant agent.

Theoretically, in the case of hydrophilic analytes (non-tensioactive substances), foam fractionation is ineffective. These substances cannot be enriched in the foam through foam fractionation. No adsorption between the molecules of the analyte and the bubbles of the surfactant is possible. In this case, it requires the use of "catcher", the substances capable of forming complexes with the target molecule. The complex formed on the other hand should have the same polarity character with surfactant agent to be transformed along the glass chromatographic column. This type of foam fractionation is called tweezing adsorptive bubble separation (TABS). For enrichment of caffeine from its aqueous solution were conducted foam fractions methods without and with catchers, chlorogenic acid, and n-octylcaffeate. Chlorogenic acid increases the enrichment of caffeine 4 times like that without a catcher. İnstead n-octylcaffeate did not enhance the enrichment of caffeine. This happens because in the case of chlorogenic acid the hydrogen bonds stabilize the complex between caffeine and its catcher. A catcher that is both surface-active and can firmly complex with the target molecule is essential in the process of complexation base foam fractionation (X. Liu, Yu, Xie, Li, Chen, & Li, 2010). İsolation of metalloenzymes by TABS is based on the selective chelation of metalloenzymes (Laccase C, Horseradish peroxidase, MMP-9, and Carboxypeptidase) whit ligand (ADA in these study) (Birte Gerken, Wattenbach, Linke, Zorn, Berger, & Parlar, 2005; Haller, Ekici, Friess, & Parlar, 2010).

In the case of multi-polar molecules, it is possible to have a selective separation based on the isoelectric point of the target molecule. pH corresponding to the isoelectric point of the target molecule allows selective separation of the analyte by İsoelectric Focused Adsorptive Bubble Separation.

Enrichment of Flavokavine A and B from Kava Kava solutions is realized by IFABS at pH 6.5 with adding saponin (M. Backleh, Ekici, Leupold, & Parlar, 2003). Active lipases were isolated from the culture supernatant of the basidiomycetous fungus *Pleurotus sapidus* at pH equal to isoelectric point (pI) by foam fractionation. At pH equal to pI, the gas-liquid interactions are at their maximum. For pH values far from pI-value the enrichment value decreases and the enzymatic activity decreases (Linke, Zorn, Gerken, Parlar, & Berger, 2005).

2.1. The Foam Fraction Device

The foam fraction device is a system consisting of extremely simple and inexpensive parts (fig. 2). It consists of a glass column where the enrichment process takes place, in the upper part of this column there is a container for collecting the foam and a flow meter above it. Under the glass column is the surfactant container connected to a nitrogen cylinder which provided foam.

The enrichment ratios (E) were calculated as follows: (Karaogul, Parlar, Parlar, & Alma, 2016)

$$E = C_{\text{foam}}/C_{\text{Start}}$$

where E is enrichment ratio, C_{foam} is the concentration (μg/mL) of foaming analyte after enrichment with foam fraction, and C_{start} (μg/mL) is the initial concentration of analyte in the sample solution.

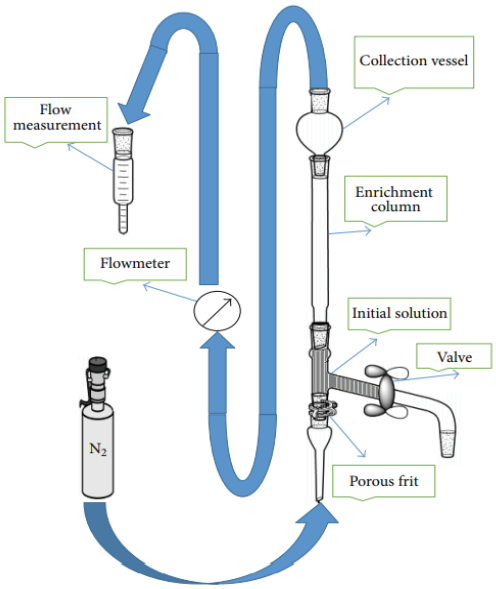

Figure 2. Scheme of the Adsorptive Bubble Separation Device (Karaogul, Parlar, Parlar, & Alma, 2016).

2.2. Factors Affecting Foam Fractionation Efficiency

The adsorption bubble separation method allows the separation and enrichment of the analytes through the mechanism of the interactions between the bubbles and the analyte present in the solution. When the adsorption bubble separation method is applied for the isolation of insoluble materials, separation is happening for suspended solid dispersed materials (Albijanic, Ozdemir, Hampton, Nguyen, Nguyen, & Bradshaw, 2014; Albijanic, Ozdemir, Nguyen, & Bradshaw, 2010; Huang & Wang, 1988; Karaogul, Parlar, Parlar, & Alma, 2016; Kim & Kwak, 2014; Sedwick, Shinn, & Zeitlin, 2006)

This method allows the particles and bubbles to collide and if the particles are sufficiently hydrophobic, the bubble and the particle come together and create bubble-particle aggregates. Therefore, the particle-bubble aggregates are transported to the foam zone and collected in a concentrated solution. Therefore, the bubble-particle attachment mechanism is critical for successful buoyancy (Albijanic, Ozdemir, Hampton, Nguyen, Nguyen, & Bradshaw, 2014; Kim & Kwak, 2014; Sedwick, Shinn, & Zeitlin, 2006).

The yield of the analyte isolation obtained by this method is strictly linked to the interaction mechanism between gas-liquid and/or gas-solid. It is based on the interaction between bubbles of surfactant and analyte present in the sample to be examined. In addition to this, the enrichment yield is also linked to a series of parameters concerning the structure of the equipment and working parameters (Albijanic, Ozdemir, Hampton, Nguyen, Nguyen, & Bradshaw, 2014; Albijanic, Ozdemir, Nguyen, & Bradshaw, 2010; Bando, Kuze, Sugimoto, Yasuda, & Nakamura, 2000; Han, et al., 2019). It is studied the influence of solution properties and operating variables on enrichment ratio in foaming adsorptive bubble separation techniques (A. Suzuki & Maruyama, 2001).

2.2.1. Feed Concentration and Physico-Chemical Properties of Analyte and Surfactant.

In foam fraction, the enrichment is dependent on the analyte concentration in the solution, the concentration of surfactant, and the Physico-chemical properties of surfactant and target molecule.

The bubble-particle attack mechanism was studied on the attack time of the bubble-particle, on colloid-surface characterization, and the strength of the bubble with an atomic force microscope (AFM). It should note that the minimum attack time leads to the maximum recovery of the analyte, and this is possible at the isoelectric point of the analyte. The strength of the bubble particle depends on the bubble surface and particle chemistry (Albijanic, Ozdemir, Hampton, Nguyen, Nguyen, & Bradshaw, 2014; Albijanic, Ozdemir, Nguyen, & Bradshaw, 2010). In the separation of biomolecules by foam fractionation, the protein concentration in the feed should preferably be close to the critical micellar concentration (CMC) of surfactants for adsorption on the surface of the bubbles (Datta, Ghosh, Chakraborty, Gangopadhyay, Prabir, & Datta, 2015).

Increasing the initial analyte concentration decreases the recovery. İnstead İncreasing surfactant concentration in general increases foam formation increases enrichment ratio and increases recovery. The amount of foaming depends on foam stability, type of surfactant, amount, and pH of the solution. At high pH values, the surfactant is thought to degrade (Ekici, Backleh-Sohrt, & Parlar, 2005; X. Liu, Yu, Xie, Li, Chen, & Li, 2010). In the case of the isolation of the enzyme Laccase C from the culture broth by the use of CTAB as a surfactant component, a negative effect on enrichment was obtained. With the increasing concentration of cetyl trimethyl ammonium bromide (CTAB), the enrichment ratio decreased (from 11.7 to 1.8) and recovery increased (from 70.2 up to 80.2%). This is thought to be due to the poor interaction between Laccase C and CTAB (B. Gerken, Nicolai, Linke, Zorn, Berger, & Parlar, 2006). In a study on caffeine enrichment, the effect of different surfactants was investigated. Chlorogenıc acid is a good surfactant for caffeine and has a positive effect on the enrichment ratio. While the n-octylcafeato is a bad surfactant for caffeine, the enrichment ratio of caffeine decreases with the increase in the concentration of n-octylcafeate (X. Liu, Yu, Xie, Li, Chen, & Li, 2010). A comparison study between the various surfactants was carried out by Sulaymon. A comparative study between the various surfactants was carried out during the study of separation and Hydrodynamic Performance of Air-Kerosene-Water System by Bubble Column (Sulaymon & Mohammed, 2010).

2.2.2. Addition of Organic Solvents

The separation of analytes present in solution by foam fractionation assumes that these are highly diluted in the solvent. In foam, fraction water is the traditional solvent. The use of organic solvents in plant extraction poses a problem in terms of foaming and foam stability. In this case, the organic solvent must be removed from the extract (Thompson, 2004). Furthermore, as a result of the studies, it was observed that alcohol has a negative effect on foaming. The addition of ethanol during the enrichment of the alkaloids of α-solanine and α-chaconine from the potato juice influenced the enrichment. It is observed that the addition of alcohol has decreased the formation of foam. Thus consequently the surface tension decreases. This fact is thought to cause precipitation of the proteins present

in potato juice (M. Backleh, Ekici, Leupold, Coelhan, & Parlar, 2004). The same effect of alcohol is observed during the purification of the Kava Kava extract from the substances Flavocavin A and Flavokavin B (M. Backleh, Ekici, Leupold, & Parlar, 2003).

2.2.3. Addition of Electrolytes and Polyelectrolytes

In foam fractionation, the addition of electrolytes or polyelectrolytes is used to increase the degree of separation. In fractionation of the foam, the electrolytes activate the adsorption of the analytes due to the decrease in the activity of the solvent, and consequently, the solubility of the target molecule decreases. The addition of polyelectrolytes allows it to form complexes with the target molecules to form hydrophobic species. The effect of the addition of the electrolytes in the foam fractionation has been described in the enrichment of active principles of Calendula officinalis (Faradiol Esters), Camellia sinensis (Catechins), Isatis tinctoria (Triptanthirin), and Cannabis sativa (Cannabis) plants (Thompson, 2004).

2.2.4. Addition of Viscosity Enhancers

The addition of small amounts of water-soluble viscous liquids increases the viscosity of the solution and the surface thereby improving the separation in the foam fractionation (Thompson, 2004).

2.2.5. pH of Solution

The effect of pH of the examination solution, on the concentration of the foam and the enrichment ratio of the analytes, is not negligible. For multipolar analytes, the maximum enrichment ratio obtained is at the pH corresponding to the isoelectric point. M. Arulmozhy et al. (2010) carried out an enrichment study on bovine serum albumin and bovine hemoglobin with frothy fraction. A maximum enrichment ratio of 1,199 is obtained at a pH of 5.5 (isoelectric point). İsoelectric point for bovine serum albumin is 4.7, for hemoglobin is 6.8. This is due to the increased hydrophobicity of proteins at their isoelectric point. At this pH value, the Wanderwals attractive force and the electrostatic repulsive force act between the adsorbed proteins on the air-liquid interface. Which electrostatic repulsion between protein molecules adsorbed on the surface of the bubble is weakest, therefor proteins should be more compactly adsorbed on the bubble surface at the isoelectric point (Arulmozhi, Sudha, Meera, Begum, & Narayanan, 2010). Regarding proteins, foaming and foam stability are important in the fractionation of the foam and are influenced by the pH value. Where high PI basic protein foaming is less successful than low PI acidic protein foaming, and foaming of a single protein is less than that of a mixture of acidic proteins (Datta, Ghosh, Chakraborty, Gangopadhyay, Prabir, & Datta, 2015).

In a protein isolation study, protein isolation was performed at different pH values. The proteins were isolated by mass fractionation at pH = 2-3 using SDS as the surfactant. By controlling the pH value, a single protein fraction is obtained. It was possible to isolate bovine albumin, β-lactoglobulin, and α-lactoglobulin from the same sample (milk) under the same working conditions (Ekici, Backleh-Sohrt, & Parlar, 2005). Isolation of the enzyme laccase C from the mushroom culture by a foam fractionation process was accomplished at the isoelectric point. At this pH value, the surface activity, stability, and

gas-liquid interaction are at their maximum. The hydrophobicity of proteins is maximum and the protein-liquid gas interaction is therefore maximum. Enzyme enrichment rate and activity decrease as you move away from the isoelectric point (Linke, Zorn, Gerken, Parlar, & Berger, 2005). pH did not affect foam formation but affected enrichment yield (M. Backleh, Ekici, Leupold, Coelhan, & Parlar, 2004). The same effect of ph is observed during isolation of the Flavokavin A and Flavokavin B substances from the Kava Kava extract. As a result at the optimum pH value coinciding with the isoelectric point for that substance, the highest enrichment efficiency was obtained (M. Backleh, Ekici, Leupold, & Parlar, 2003).

It has been found experimentally the pH value also affects the diameter of the analytes. Maruyama H. et. al. (2006) studied the adsorption of ovalbumin (OA) on the bubble surface at various pHs (3.5, 4.6, 6.0, and 8.0) by separation of the foam technique. In his study of ovalbumin separation, it was revealed that the pH value of the solution affects the diameter of the ovalbumin. Therefore, it affected ovalbumin saturation at the ovalbumin/bubble interface. Consequently, this affected the enrichment yield (Maruyama, Seki, Suzuki, & Inoue, 2006).

2.2.6. Ionic Strength

Ionic strength has a positive effect on the enrichment of molecules by foam fractionation. Adsorption of analytes at the gas-liquid interface may increase with ionic increase force (Kurt, 2006; Thompson, 2004).

2.2.7. Gas and Gas Flow Rate

In the fractionation process of the foam, air or N_2 is mostly used as gas that feeds the solution. In addition to these gases, O_2, Co_2 or inert gases can also be used. In literature, there are studies on the adsorption mechanisms of these gases at the gas-liquid interface. A comparison of the gas-liquid adsorption mechanism of CO_2 and air was carried out by Kim and Kwak. CO_2 and air bubbles were used as particle collectors in the flotation process. The gas separation capabilities were investigated by examining the diameter distribution of the bubbles and the collision effects of air and CO_2. Bubble size is a key factor in bubble adsorption separation. Xu, X., et al. (2015) in their study on the effect of bubble diameter on enrichment they achieved: separation efficiency for 30-mu m bubbles increases from 29.67% to 99.53% when the bubble diameter changes from 30 mu m to 100 pm (Kim & Kwak, 2014; Kurt, 2006; Maruyama, Seki, Suzuki, & Inoue, 2006; Panjipour, Karamoozian, & Albijanic, 2021; Xu, Yang, Wang, & Wang, 2015).

In the foam fraction method, the flow rate significantly affects the yield. In the foam fractionation process, gas flow rates of 10-60 ml/min are generally employed (Ekici, Backleh-Sohrt, & Parlar, 2005; B. Gerken, Nicolai, Linke, Zorn, Berger, & Parlar, 2006; Karaogul, Parlar, Parlar, & Alma, 2016; Linke, Zorn, Gerken, Parlar, & Berger, 2005; X. Liu, Yu, Xie, Li, Chen, & Li, 2010; Nicolai, Friess, & Parlar, 2008). However, there are also studies conducted at high flow rates such as 24-330 ml/min (Thompson, 2004). It is necessary to provide the required foam height for successful separation. The optimum flow rate can be determined by the concentration of the surfactant and the stability of the foam.

2.2.8. Height of Foam Tower

In the foam fraction method, the foam height causes a change in the interfacial and overall transfer process of drainage and internal

reflux. Hence different foam heights show a significant effect on separation. Ahmad (1975) and Uraizee and Narsimhan (1996) studied the effect of foam height on enrichment efficiency (Ahmad, 1975; Thompson, 2004).

2.2.9. Temperature

It was thought that the temperature did not affect the enrichment. So the effect of temperature on the literature of biochemicals has not been much studied. Instead, in the study of Merz.J et. al. (2010) on purification of a fungal cutinase by adsorptive bubble separation, a strong effect of temperature on enrichment and recovery is observed. High temperatures improve enrichment and low temperatures improve recovery of the active enzyme. It is assumed that high temperatures cause a decrease in viscosity and consequently a decrease in the stability of the foam (Kurt, 2006; Merz, Zorn, Burghoff, & Schembecker, 2011).

3. Application Areas of Adsorption Foam Separation Methods (ABSM)

The adsorption foam separation techniques are used in three different areas for three different purposes, such as: for the purification of wastewater from industrial factories, from geopolitical and municipal waters, for the separation of some oil fractions in refineries, and the isolation of active substances from herbs and some food products.

3.1. Purification Applications

There are many studies on the purification of wastewater from heavy metals, different organic pollutants such as pesticides and harmful microorganisms using adsorption foam separation methods. The separation technique on adsorption bubbles accompanied by organic precipitating reagents is an example being studied on the removal of cobalt (Bleasdell, Calma, & Zeitlin, 1982; Huang & Wang, 1988; Sedwick, Shinn, & Zeitlin, 2006), nickel, copper, and manganese metals from sulfated deepwater ferromanganese nodules (Boardman, Vanleigh, Nolan, & McTernan, 1985; Sedwick, Shinn, & Zeitlin, 2006).

The enrichment of metal in wastewater was studied by modifying the equipment and operating conditions (foam flow rate and metal concentration in foam flow) in the bubble column foam separation method. The foam flow ratio increases with increasing gas velocity, decreasing liquid velocity, decreasing the height of the foam layer, and decreasing metal concentration in the sample. Enrichment of the metal shows reverse trends. When a draft tube is inserted into the bubbler layer, the foam flows rate decreases. Enrichment is strongly governed by the foam f

low ratio. Since the value of the foam flow ratio is related to the structure of the equipment and the operating conditions (Bando, Kuze, Sugimoto, Yasuda, & Nakamura, 2000).

The removal of non-ionic organic pollutants such as Heptachlor and Hydroxychlordene from aqueous solutions was performed by air stripping, sublation processes with solvent and foam fractionation. Furthermore, the effect of the airflow, the addition of salt, the addition of ethanol, and the addition of surfactants on the removal of organic impurities was investigated. Foam fractionation was the most efficient method (Chiu & Huang, 1991). In a study on the removal of organophosphorus pesticides (ddvp (phosphoric acid 2,2-dichlorovinyl dimethyl ester) and phorate (phosphorodithioic acid o,o-diethyl s-(

(ethylthio)methyl ester) from wastewater, the greatest success was achieved with solvent sublation between the methods of air stripping, solvent sublation, and adsorbent colloidal flotation. The removal of ddvp by adsorbent bubble separation techniques is poor. ddvp is a hydrophobic molecule so presumably, it has much greater solubility than phorate and this makes ddvp more difficult to remove by the adsorbent bubble separation techniques (Lu & Huang, 1992). In a study on the isolation of dinitrophenol, the foam fractionation method (whit hexadeeyltrimethylammonium bromide(HTA) like surfactant) was found to be more effective, between fractionation of the foam, sublimation of the solvent, and flotation of the colloid with Fe(OH)3 (Sulaymon & Mohammed, 2010). Silica isolation from geothermal fluids has been successfully performed by adsorptive bubble chromatography (De Carlo & Ronay, 1987), butyl acetate from discharged wastewater during penicillin production has been successfully performed by nonfoaming bubble separation (Sun, Chang, Hu, Shen, & Liu, 2005).

A pilot-scale bubble separation system was installed to isolate starch and mucilage from yam. The sample was purified from Salmonella and Escherichia coli using a UV-guided bubble separation system (Fu, Hung, & Huang, 2014).

In another study, it was possible to purify the sample of bacteria (viable bacteria, enterococci, Vibrio, and Salmonella-like bacteria) using milk casein as a surfactant in a batch (80%) and continuous (70%) system (Y. Suzuki, Hanagasaki, Furukawa, & Yoshida, 2008). In another similar study, milk casein was used as a surfactant and the municipal wastewater sample was purified from Norovirus (Y. Suzuki, Narimatsu, Furukawa, Mekata, Kono, Sakai, et al., 2009). Thus, it has been seen that the foam fraction method can also be used to purify the environment from harmful microorganisms.

Until 20-30 years ago, the studies done for the removal of metallic or organic pollutants from geopolitical and wastewater samples were focused on floatation techniques while today the studies are focused more on the separation process of the foam column. Adsorptive bubble separation methods still have enormous potential for research work and biotechnology applications, as well as for pollution control of final waste in the industry.

3.2. Enrichment Application

The adsorptive bubble separation method was used to enrich the active principle substance, the primary and secondary metabolite of aromatics, seeds, mushrooms, food products, and more. In the literature, the main emphasis has been on the enrichment of proteins, glycoproteins, enzymes, glycoalkaloids, phenolics, polymers, and other substances of industrial importance.

3.2.1. Enrichment of Enzymes and Proteins

Purification is a fundamental step for the production of recombinant proteins. But also in food or pharmaceutical industries, the use of various enzymes and proteins requires their isolation from biological sources. Purification is a fundamental step for the production of recombinant proteins. Separation techniques such as salting, dialysis, or ultrafiltration are frequently applied, followed by chromatographic purification processes. However, each of these steps leads to a loss of enzymatic activity (Birte Gerken, Wattenbach, Linke, Zorn, Berger, & Parlar, 2005; Maruyama,

Suzuki, & Seki, 2000). A significant number of phytonutrients are heat sensitive and are chemically degraded due to oxidation. Foam fractionation has become useful for the isolation and enrichment of natural substances at room temperature employing an inert gas and without the addition of reactive additives. Further development of this technique will offer good potential in the biotechnological and industrial applications for the enrichment and purification of natural products. In China, there is a successful industrial-scale application for the production of nisin (a polypeptide antibiotic from *Streptococcus lactis* active against *Mycobacterium tuberculosis*, *Streptococcus*, and *Clostridium*) (Datta, Ghosh, Chakraborty, Gangopadhyay, Prabir, & Datta, 2015; Kurt, 2006; Maruyama, Suzuki, & Seki, 2000).

A study on the enrichment of bovine serum albümin (BSA) and bovine hemoglobin (HBB) was carried out (enrichment ratio of 1.42 at PH 5.5) for foam fraction by studying effects of gas flow rate, protein concentration, solution pH, liquid tank height and foam height on the enrichment of proteins (Arulmozhi, Sudha, Meera, Begum, & Narayanan, 2010). In another study, the enriching mechanism of Hemoglobin and Ovalbumin in continuous foam separation was studied. The experimental isotherms for HB and OA were compared to the Langmuir isotherm, and the adsorption parameters like as the equilibrium constant, K, and the saturated density, γ, at each pH were determined. γ values obtained for OA and HB showed maxima at their isoelectric point (i.e.p., pH 4.6 for OA and pH 6.8 for HB) (Maruyama, Suzuki, & Seki, 2000). İn another study separation of BSA and HBB from an aqueous solution mixture was obtained at pH 3.9. To characterize the surface activity of these two proteins in an aqueous solution, the surface tensions of the BSA and HBB solution at different pH and ionic strengths were measured (Z. H. e. a. Liu, 1996). Enrichment of α,β-unsaturated bovine insulins-(C12)n from the synthesis solution was made at pH 8 for the use of BSA as a tweezing agent and surfactant agent (Nicolai, Friess, & Parlar, 2008). There are several studies on the isolation of milk proteins using different surfactants. Immunoglobulins represent an important class of protein in the life sciences, with numerous biotechnological or pharmaceutical applications, such as infection control, prenatal therapy, disease treatment, functional foods, and various research applications. Isolation of İgM and İgG immunoglobulins, at isoelectric pH, was achieved using albumin as the surfactant agent (Y.-C. Chen & H. Parlar, 2013; Y. C. Chen & H. Parlar, 2013). Another study on protein isolation from milk was carried out by bulk fractionation at pH=2-3 using SDS as a surfactant. And by performing pH control, albumin bovine, β-Lactoglobulin, and α-Lactoglobulin proteins were isolated from the same sample under the same conditions (Ekici, Backleh-Sohrt, & Parlar, 2005).

The adsorptive bubble separating method (ABS) can be used too in qualitative analysis. Sample with a low concentration of the analyte leading to negative results in routine analysis, thanks to this method could be tested positively. It was used for the enrichment of prion protein (PrPSc) from very weak contaminated cattle brains, which lead to negative results in the routine analysis. So the prion protein (PrPSc) was enriched 140 fold in the foam phase using sodium dodecyl sulfate (SDS) as a surface-active component (Berner, Friess, Ekici, & Parlar, 2012).

The purification level of the enzymes is the key criterion for their application in the biotechnology field. Most of the metalloenzymes purified by the foam fraction method have been realized for the use of a "tweezing agent". This class of enzymes contains metals capable to form complexes with specific tweezing agents. For enrichment of MMP-9 and Carboxypeptidase A from a biological sample (Haller, Ekici, Friess, & Parlar, 2010) and the enrichment of Laccase C (13.3-fold enrichment and 66.31% recovery) and Horseradish peroxidase (17.8-fold enrichment and 85.34% recovery) (Birte Gerken, Wattenbach, Linke, Zorn, Berger, & Parlar, 2005) was used ADA as a tweezing agent and C8 as a surfactant component. Laccase C has been enriched too without the use of tweezing agent from the culture broth. Only CTAB (Cetyl trimethyl ammonium bromide) was used as a surfactant component (11.7-fold enrichment and 70.2 % recovery). Active Lipases were isolated from the culture supernatant of the basidiomycetous fungus *Pleurotus sapidus* at the isoelectric point of the enzymes by foam fractionation method. Maximum recovery (95%) of enzymes was obtained at pH 7 (Linke, Zorn, Gerken, Parlar, & Berger, 2005). An extracellular esterase (Cutinase) was isolated from culture supernatants of the Basidiomycete Coprinopsis Cinerea at Ph 7 with an enrichment factor of 10.5 and a recovery of 79% by foam fraction method. As regards optimization of the foam fractionation process, the following have been studied various parameters of interaction and influence through Design of Experiments (DoE) (Merz, Schembecker, Riemer, Nimtz, & Zorn, 2009; Merz, Zorn, Burghoff, & Schembecker, 2011).

3.2.2. Enrichment of Seconder Methabotics Substances

Plants are sources of active substances with pharmacological and biological activities. Herbal active principles are inexpensive compared to synthetic active ingredients. For this reason, the pharmaceutical, and cosmetic industries have looking to use plant-active ingredients for the production of pharmaceuticals and cosmetic products. A selective enrichment method has been developed for active principles of plant Calendula officinalis (Faradiol Esters), Camellia sinensis (Catechins), Isatis tinctoria (Triptanthirin), and Cannabis sativa (Cannabis) taking into account the basic principles of fractionation as Physico-chemical aspects of the foam and properties of the active ingredients and the supplementing condition of the foam fractionation process. With foam fractionation, it is possible to enrich the active principles of herbs in an economical, effective, and selective way (Thompson, 2004). Farradiol esters, tryptanthinin, and cannabis are hydrophobic molecules. These are enriched by the solutions of their plants with the addition of organic surfactant, organic solvent, and a viscosity enhancer. The enrichment of tryptanthinin occurs at alkaline pH instead of cannabis occurs at acidic pH. The catechin molecules, being hydrophilic molecules, have been enriched by the formation of the complex with the caffeine present in the extract solution at an acidic pH and by the addition of an electrolyte (Thompson, 2004). For the successful enrichment of active substances, the molecules need to be surface-active, hydrophobic, or capable of binding with other molecules to form a hydrophobic complex. In the case of multicomponent mixtures such as plant extracts, the hydrophobicity can be

varied with the pH value, the addition of electrolytes, or organic solvents. On the other hand, for multicomponent mixtures, it is a disadvantage, the presence of high quantities of undesired surface-active and hydrophobic molecules or complexes. Especially if their properties cannot be modified by derivatization, complexation, or degradation (Thompson, 2004).

Enrichment of the glycyrrhizic acid ammonium salt from Licorice roots (Glycyrrhiza glabra L.) was performed by bubble separation technique using four surfactants such as β-lactoglobulin (368.3 times enriched), bovine albümin (90,4 times) and starch soluble (9,9). lower enrichment values determined for application without additive (5.9 times) (Karaogul, Parlar, Parlar, & Alma, 2016).

Kava-Kava (*Piper methysticum G. Forst*) extract has relaxing and anxiolytic properties. Flavokavines A and Flavokavines B are phenolic aromatic substances present in Kava Kava extract. Removal of undesirable Flavokavines A and Flavokavines B from the Kava Kava extract was achieved by foam fractionation. Saponin was used as a surfactant and the substances Flavokavin A and Flavokavin B were removed from the Kava Kava extract by adjusting the amount of saponin, pH, and gas flow (M. Backleh, Ekici, Leupold, & Parlar, 2003).

Glycoalkaloids α-solanine and α-chaconine at pH 6 and without the use of surfactant it was 100% recovered from potato juice by adsorptive bubble separation (ABS). The enrichment into the foam was influenced by bubble size, pH value, and gas flow rate (M. Backleh, Ekici, Leupold, Coelhan, & Parlar, 2004).

The caffeine (alkaloids) is also enriched in another study from its aqueous solution without and with catchers, chlorogenic acid, and n-octylcaffeate. The greatest enrichment was obtained with chlorogenic acid (X. Liu, Yu, Xie, Li, Chen, & Li, 2010).

A study emphasizing the success of the foam separation process over other separation processes was conducted by Fu.Y.C (2005). Choline (base substance) separation analysis was performed with an old separation process (AACC) from 3 different grains (wheat, rice, and oat flour) and 3 different Dioscorea (yam) tubers (*D. pseudojaponica Y., Yangmingshan yam, and Ming-Chien yam*) after this method was modified by a foam separation process and the separation efficiency of choline was investigated. When tested on cereals, the choline estimated by the modified method was 34.0-45.3% higher than that of the original AACC method. In the case of Dioscorea (yam) tubers 231-306% higher than when the original AACC method was used (Fu, Chen, Huang, & Li, 2005). Starch and mucilage isolation from sweet potato has been achieved successfully with a continuous foam separation process (Fu, Huang, & Chu, 2005; Fu, Hung, & Huang, 2014). Separation and purification of drug component (gentamycin Sulphate) from an enantiomeric drugs mixture and a plant source and removal of drug component from wastewater are carried out through foam separation method using dioctyl sodium sulfosuccinate (DOSS) and sodium lauryl sulfate (SLS) as surfactant components. Drug recovery was 69.55 and 80.32, respectively (Mukhopadhyay & Khanam, 2009).

For the first time, the unstable antioxidative diterpene carnosic acid was enriched from the extract of rosemary (Rosmarinus officinalis L.),

by isoelectric focused adsorptive bubble chromatography. In the presence of saponin as surfactive substance, the maximum enrichment (%100) was obtained at pH 4 was, the conversion of carnosic acid to carnosol was negligible (Marlène Backleh, Leupold, & Parlar, 2003).

Foam fractionation is described as a new method to remove and separate biosurfactants from cultivation. İt has also been used for the enrichment of a bacterial secondary metabolite. For the enrichment of antiviral-antibacterial surfactin from the culture of *Bacillus subtillis* the fermentation reactor was connected to a fractionation column of the foam in batch and continuous mode. Thus the amount of surfactin increased from 92 mg/L to 136 mg/L (Chen, Baker, & Darton, 2006). This method was also applied to the cultures of *Bacillus subtilis,* in which the lipopeptide antibiotic fengicin and polyketide antibiotic bacilli were enriched (Glazyrina, Junne, Thiesen, Lunkenheimer, & Goetz, 2008).

3.2.3. Enrichment of Polymers

for selective separation of chitosan from their mixed hydrophobic aqueous solution, bubble flotation chromatography was proposed as a successful separation method. The analytical solution contains chitosan (Ch) and hydrophobically modified chitosan (% 5 mol n-dodecyl side chains HMCh). These two polymers have the same molecular weight (M = 300000 g mol–1) and the same degree of deacetylation (DA = 0.85). Usually is used high-performance liquid chromatography (e.g., gel permeation chromatography) for the separation of polymers and the establishing of their molecular weights. But it is difficult for polymers that have the same molecular weight. İnstead whit bubble flotation chromatography it was possible because it allows separation on different hydrophobicity. HMCh has greater surface activity at the air/water interface so it is a powerful foam stabilizer. The capture coefficient for modified chitosan is 12% instead of chitosan is 5%. The chitosan polymer is a poor foam component (Babak, Tikhonov, Lachashvili, Philippova, Khokhlov, & Rinaudo, 2003).

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