Biotechnol Lett (2012) 34:187–195
DOI 10.1007/s10529-011-0782-6

REVIEW

Foam mitigation and exploitation in biosurfactant production

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Received: 21 September 2011 / Accepted: 13 October 2011 / Published online: 22 October 2011
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Abstract Biosurfactants could potentially outperform traditional surfactants in many applications whilst being more sustainable to source, manufacture, use and dispose of. However, currently available fermentation production methods are too inefficient to manufacture biosurfactants for these high volume markets. Foaming in an inherent issue with biosurfactant production and adds significantly to the cost of production using traditional unit operations. This review illustrates how the application of process engineering has enabled nuisance foaming to be transformed into a cost saving feature of the production system. The scope of biosurfactants and their application is discussed and the fundamentals of foam generation and control are reviewed. The range of specific phenomena associated with the interaction of foams with bioproducts is assessed. Finally, recent work which has aimed at taking advantage of some of these phenomena in order to intensify the biosurfactant production process is discussed in detail.

Keywords Biosurfactant · Foam fractionation · Separation · White biotechnology

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Introduction

Microbial surfactants produced through fermentation–biosurfactants–could potentially outperform traditional surfactants in many applications, such as oil dispersion, soil remediation, personal care, food and laundry products, whilst being more sustainable to source, manufacture, use and dispose of. However, currently available fermentation production capacity is based around batch/fed batch reactor technology and there are limitations on efficiency, and therefore cost of production, in manufacturing biosurfactants for these high volume markets.

Beyond the normal fermentation challenges of low yield and dilute product streams, biosurfactant systems tend to foam dramatically. The standard recourse for control of foaming in fermentations is to add antifoams, but this is inherently inefficient as, to achieve product functionality, the biosurfactant and antifoam must then be separated downstream. Solid state fermentation is one approach which has been used to avoid the problems of foaming during biosurfactant production (Camilios-Neto et al. 2011); the purpose of this review is to assess the scope for retaining the use of submerged fermentations. There is a market pull for biosurfactants, but price sensitivity is a critical issue and these production limitations currently exclude widespread replacement of cheaper existing synthetic surfactants with biosurfactants. Consequently, this review article summarises past and present information on how foaming effects can be mitigated or exploited in biosurfactant production.

Biosurfactants

Biosurfactants are a diverse group of naturally occurring surfactants of microbial origin (Desai and Banat 1997). They are composed of hydrophilic and hydrophobic groups, like traditional petrochemical and oleochemical surfactants, making the molecules amphiphilic with a predilection for interfaces, which they are capable of adsorbing to and lowering the surface tension of. Biosurfactants are classified according to their chemical structure and microbial origin, with the common types and their origin given in Table 1, adapted from (Abdel-Mawgoud et al. 2010; Banat et al. 2010; Deleu and Paquot 2004; Desai and Banat 1997; Nitschke and Costa 2007; Singh and Cameotra 2004; Van Hamme et al. 2006).

The main types of biosurfactants, listed in Table 1, all differ in their chemistry and structure; glycolipids are low molecular weight carbohydrates with long chain aliphatic acid 'tails' (Desai and Banat 1997). Hydrophobins are a group of small, surface active, fungal proteins (Wessels 1996). Lipopeptides such as surfactin have a cyclic ring structure and a high molecular weight compared to glycolipids, whilst particulate biosurfactants consist of extracellular membrane vesicles (Banat et al. 2010; Van Hamme et al. 2006).

Table 1 Common biosurfactants and their microbial origin

Biosurfactant type	Example	Microorganism
Glycolipid	Rhamnolipids	*Pseudomonas aeruginosa*
	Trehalolipids	*Rhodococcus erythropolis*
	Sophorolipids	*Candida bombicola*
Hydrophobins	HFBI	*Trichoderma reesei*
	HFBII	*T. reesei*
	SC3	*Schizophyllum commune*
Liposaccharides	Alasan	*Acinetobacter radioresistens*
	Emulsan	*Acinetobacter calcoaceticus*
Lipopeptides	Iturin A	*B. subtilis*
	Surfactin	*B. subtilis*
	Viscosine	*Pseudomonas fluorescens*
Phospholipids	–	*Corynebacterium lepus*
Particulate	Vesicles	*Acinetobacter calcoaceticus*
	Whole microbial cells	Cyanobacteria

The range of current and potential applications of biosurfactants is large with their use in bioremediation, oil recovery, biomedical sciences and the food industry all being reported (Banat et al. 2010; Singh et al. 2007; Singh and Cameotra 2004; Nitschke and Costa 2007). Biosurfactants are biodegradable and have a low toxicity, properties that make their use particularly attractive to the pharmaceutical, cosmetic, environmental and food industries (Gharaei-Fathabad 2011; Nitschke and Costa 2007). In the following paragraphs some of these current and potential applications of biosurfactants are detailed;

Industrial use of biosurfactants is made by the oil industry, where biosurfactants are used in both oil recovery and processing (Banat et al. 2010). Microbially-enhanced oil recovery involves the use of biosurfactants to increase well productivity through emulsifying the crude oil contained in the well and lowering the interfacial tension of the oil–water interface. The reduction in crude oil viscosity by biosurfactants increases recovery by improving oil drainage into the bore of the well and releasing oil trapped in rock capillaries (Singh et al. 2007). Biosurfactants used for enhanced oil recovery include rhamnolipids, lipopeptides like surfactin and emulsan and others isolated from oilfields and oil contaminated ground (Desai and Banat 1997; Singh et al. 2007).

Singh and Cameotra (2004) report the potential biomedical applications of the lipopeptide biosurfactants iturin A and surfactin from *Bacillus subtilis*. Iturin A is an effective antifungal agent that has been suggested to be effective against fungal skin infections (mycosis) (Tanaka et al. 1997). Surfactin exhibits several interesting antimicrobial and antiviral properties and also inhibits the formation of fibrin clots, which can lead to thrombosis. It is thought that the antiviral action of the surfactin molecule is due to physiochemical interaction involving the lipid membrane of the virus.

Some companies, such as Ecover (BE) (http://www.ecover.com), have commercialised biosurfactant products, in this instance for household cleaning, marketing them based on their environmental benefits (Edser 2011). Biosurfactants have also found use in the food industry, with Jeneil Biotech Inc. (USA)

(http://www.jeneilbiotech.com) commercially producing rhamnolipids and having FDA approval for a biofungicide for the preventing the growth of pathogenic fungi in fruit and vegetable crops. Nitschke and Costa (2007) outline several other ways in which biosurfactants can be used in the formulation of food products, including the stabilisation of aerated products, preventing the formation of fat globule agglomerates and texture improvements of a range of fat and starch based foods. The ability of biosurfactants to tolerate a wider range of pH than traditional surfactants allows their use in harsher environments where petrochemical and oleochemical surfactants cannot be utilised. For example, the pH stability of the exopolysaccharide EPS 71a from a marine strain of *Enterobacter cloacae* has been taken advantage of as a new emulsifying agent and viscosity enhancer with potential for use in food products with acidic pH, due to their containing citric or ascorbic acid (Iyer et al. 2006; Nitschke and Costa 2007). Iyer et al. (2006) found that the biosurfactant EPS 71a was able to emulsify xylene more efficiently than commonly used viscosity enhancers and stabilisers such as arabic and xanthan gum. However, the need to develop manufacturing processes to produce such biosurfactants to the standard required for their use as a food ingredient remains as an obstacle to their commercialisation. Presently it is not possible to market food products containing biosurfactants which are not expressed by organisms which are generally regarded as safe (GRAS).

One of the main barriers to the wider use of biosurfactants in place of traditionally used surfactants is their high cost, which is $\sim$50 times that of petrochemical and oleochemical surfactants, depending on the biosurfactant in question (Deleu and Paquot 2004; Franzetti et al. 2010; Nitschke and Costa 2007). Of these costs, it has been estimated that around 60% are contributed by downstream processing, highlighting the need for the development of more efficient separation techniques for biosurfactants (Mukherjee et al. 2006). In certain high-added value markets, where niche applications of biosurfactants have been identified, the expense of biosurfactant ingredients can be offset to some extent. Deleu and Paquot (2004) suggest that developing alternative routes for biosurfactant production, such as biotransformation of natural products, may help reduce production costs. A summary of biotransformation processes for production of various biosurfactants is given by Desai and Banat (1997). From an engineering and manufacturing perspective it is preferable to exploit established bioprocesses such as fermentation, using technology which is well understood and accepted by the public from its long standing application in the brewing industry. These two factors are key if the novel properties of biosurfactants are to be exploited in the potential food and medical applications discussed previously.

Foam generation and control

Foaming is an important consideration in all fermentation processes, from laboratory to industrial scale, and especially so in the case of extracellular biosurfactant production. Foaming in fermentations is undesirable due to the disruption it causes, including carryover of fermentation broth with the off gas and difficulties with process control (Etoc et al. 2006). When considering process scale up the economy of the chosen foam control method, typically chemical antifoams, and the volume of foaming which can be tolerated must be considered.

A review by Junker (2007) provides a thorough discussion of the causes of foaming during fermentations and the use of chemical antifoams to control foaming. Foam is generated in the fermenter vessel due to the presence of surface-active species in the growth media and also those expressed by the microorganism during the fermentation. Foaming which occurs at the start of fermentations is generally attributable to surface active components of the growth media, whereas if the amount of foaming increases throughout a fermentation the likely cause is proteins and other compounds excreted by the cell population into the fermentation broth (Junker 2007). In biosurfactant-producing fermentations, it is the latter which is usually the source of significant foaming. Operating conditions in fermenters have a large influence on foam generation rates, with the gas flow-rate and amount of agitation required to provide O_2 mass transfer according to the biological O_2 demand of the microorganism determining the foam generation rate to a large extent.

Foam suppression is commonly achieved using chemical antifoams, which are typically comprised of silicone oils and silicone emulsions (Junker 2007). These antifoams function by disrupting the stability of

the liquid films in the foam, increasing the rate at which liquid drains from them and promoting foam collapse (Garrett 1993; Miller 2008). The use of chemical antifoams is undesirable in the production of biosurfactants where the presence of antifoam in the final product could have a detrimental effect on performance. For this reason there is an interest in utilising foaming in biosurfactant fermentation systems through the application of foam separation techniques (Chen et al. 2006a).

Mechanical, acoustic and ultrasonic methods to manage foam within fermenters have also been variously employed, as summarised by Stocks et al. (2005) and Winterburn and Martin (2008). The most common practice is the use of additional impellers on the agitator shaft to disrupt modest rates of foam generation with little additional equipment complexity. These are insufficient for vigorously foaming biosurfactant systems and there has not been widespread application of the other techniques. Other alternative approaches to foam control are also reported, for example 'switchable foam control' using the pH sensitivity of certain biosurfactants (Middelberg and Dimitrijev-Dwyer 2011), but these are generally targeted at biosurfactant application rather than production.

Foam-associated phenomena

The gas hold-up within the broth of an aerated fermenter is a balance between the gas sparging rate, surface entrainment, diffusional transport and surface disentrainment (Yoo and Hong 1986; Dhanasekharan et al. 2005). Surface disentrainment results from the coincidence of bubbles contacting the top surface of the broth and the subsequent bubble film bursting. Any process which tends to stabilise these bubble films and prevent their rupture will reduce the disentrainment rate. Instead of bursting, bubbles will either accumulate at the top surface of the broth or, if agitation is sufficient, they will be mixed back into the broth causing an increase in gas hold up. Foams can result from either of these scenarios.

The interaction of gravity and an accumulation of closely packed gas bubbles on the surface of the broth will lead to relatively dry foams. Gravity drainage of liquid leads to the thinning of films between the bubbles and, in cases where certain forces occur to counteract drainage, polyhedral bubbles separated by a network of thin films can be sustained. The intersections of these films are known as Plateau borders and these intersect at vertices to form a network of channels down which liquid can drain. The network's high liquid surface area to volume ratio gives rise to a number of phenomena.

If the disentrainment from a highly agitated broth continues to lag the bubble incorporation rate then the accumulation of bubbles within the broth will continue to increase. Sufficient agitation will overcome the effects of gravity drainage, which leads to drier foams, and generate a wet foam of largely spherical bubbles. High gas sparging rates will also exacerbate this effect where gravity drainage is outpaced by the gas velocity.

Surfactants present in fermentation broth will adsorb to the gas–liquid surface of bubbles as they make their way through the solution and go on to help stabilise the foam. The quantity of adsorbed surfactant on the films is largely constant but the volume of liquid in the foam layers above the broth decrease significantly as it drains out. Consequently, the average surfactant concentration of the foam increases substantially (Lemlich 1972) and this may be realised by collecting and then collapsing the foam.

In a fermentation broth there will typically be a mixture of more than one surface-active species. Mixtures of low molecular weight surfactants and surface active proteins have been shown to display a variety of intriguing behaviours, the simplest of which is that the smaller molecule will have a higher diffusivity enabling it to populate the interface more quickly than the larger, possibly more surface active, protein. Thus, the composition of the adsorbed layer may be a function of the residence time of bubbles in the fermenter and may change over time. Further complexity arises from direct interaction between the different surfactant species. There has not been extensive study of the practical consequences of these competitive adsorption effects in foams, but its importance has been demonstrated in the case of lung surfactant deactivation (Fernsler and Zasadzinski, 2009) and it has been studied directly in foam films (Angarska et al. 2011).

Particulates within the broth may also interact with the foam and will sometimes adhere to the gas–liquid interface. Van Hee et al. (2006)report that this area has not been greatly studied, but summarise examples of virus-like particles ($\sim$0.06 μm), inclusion bodies

(~0.15 μm) and ampicillin/phenylglycin crystal mixtures (6–62 μm) that have been selectively separated through adhesion to liquid–liquid interfaces. They also summarise cases of whole cell separation using adhesion to gas–liquid interfaces including yeast and bacterial cells.

Denaturation of surface active proteins at gas–liquid interfaces may occur due to the anisotropic surface forces, affecting tertiary and sometimes secondary structure (Clarkson et al. 1999). Less damage will occur in more rigid proteins. Although these are often less surface active, those which are highly surface active and retain their structure commonly make up the community of biosurfactants.

Biosurfactant production intensification by exploiting foams

Foam fractionation is a method for enriching solutions of surface active species. Gas is sparged through a surfactant solution creating new gas–liquid interface onto which the surface active molecules adsorb and stabilise, generating a rising foam whose liquid fraction reduces over time. Overflowing foam is collapsed to recover the adsorbed surfactant in a reduced volume, an enriched liquid known as foamate being obtained. The performance of foam fractionation can be evaluated using two parameters, surfactant enrichment and recovery, defined in Eq. 1 and 2;

$$Enrichment = \frac{C_f}{C_i} \quad (1)$$

$$Recovery = \frac{C_f V_f}{C_i V_i} \times 100 = \frac{C_i V_i - C_r V_r}{C_i V_i} \quad (2)$$

where C_f is the biosurfactant concentration in the foamate, C_i is the initial biosurfactant concentration, C_r is the remaining biosurfactant concentration after foaming, V_f is the foamate volume, V_i is the initial liquid volume and V_r is the liquid volume remaining after foaming.

The use of foam fractionation to separate extracellular biosurfactant from culture broth has the potential to reduce the cost of downstream processing. Foam fractionation can be applied either as a downstream unit operation or as an integrated process for in situ recovery. The application of both these separation strategies is discussed below.

The suitability of foam fractionation for biosurfactant separation is demonstrated by Sarachat et al. (2010), who used a batch foam fractionation process to enrich rhamnolipid present in cell free culture broth. Small volumes of solution containing 326 mg rhamnolipid l^{-1} from *Pseudomonas aeruginosa* SP4 were foamed in a 30 mm internal diameter column of variable height. An investigation into the effects of operating conditions, such as air flow rate and bubble size, on separation efficiency found that for a given column height increasing the air flow rate increased the recovery of rhamnolipid whilst reducing the enrichment. Low enrichments in the range 1.03–4.44 and corresponding recoveries of 94–77% were reported by Sarachat et al. (2010) across the operating conditions studied. Likewise, Winterburn et al. (2011a) illustrate the potential of foam fractionation to separate hydrophobin HFBII from fed batch fermentations and highlight the importance of retaining biomass within the fermenter in order to maintain production rates.

Batch foam fractionation has also been used to enrich solutions of surfactin, a cyclic heptapeptide produced by *B. subtilis*. Davis et al. (2001) conducted foaming experiments using both cell free and cell containing broth with surfactin initially at 440 mg l^{-1}, achieving low enrichments of 2.9 and 1.7, respectively, at recoveries of 97.1 and 97.3 %. The batch foam fractionation processes studied by Sarachat et al. (2010) and Davis et al. (2001) both yielded high recoveries, at the expense of low enrichments. Davis et al. (2001) went on to implement in situ recovery of surfactin, using a 25 × 400 mm foam column which was inserted through the vessel headplate and positioned such that the bottom of the column was 50 mm above the broth surface. Surfactin was produced in batch culture by *B. subtilis* ATCC 21332 under O_2 depleted conditions, allowing the stirrer speed to be chosen to control foam formation at a fixed aeration rate. Integrated foam recovery was most effective at a stirrer speed of 146 rpm with an enrichment of 34 at 90 % surfactin recovery. The integrated process has the added benefit of enrichments increased over those obtained from batch foam fractionation, which are likely due to the agitation of the culture broth affecting foaming conditions, such as bubble size, as well as the lower surfactin concentration attained in the fermenter. It would be expected that changing the stirrer speed will alter gas bubble break up and hence bubble

size, which in turn will effect foam wetness and hence surfactin enrichment. Indeed, Davis et al. (2001) reported that at higher stirrer speeds of 204 and 269 rpm "excessive" foaming occurred which both reduced surfactin enrichment, due to the high liquid content of the foam, and productivity.

Integrated foam fractionation for the recovery of surfactin from a batch production process was further investigated by Chen et al. (2006a), who report surfactin recovery and enrichment values that are similar to those of Davis et al. (2001), which is expected as the apparatus and mode of operation are also similar, i.e. foam column penetrating the vessel head-plate. Other work by Chen et al. (2006b) shows the same integrated surfactin production and foam separation strategy applied to a chemostat operated at a dilution rate of 0.2 h^{-1}. With foam fractionation, a low steady state surfactin concentration of 18 mg l^{-1} was reached in the bioreactor with 929 mg surfactin l^{-1} in the collapsed foamate, an enrichment of 50-fold. It is noted that the surfactin concentration in the vessel was maintained below the critical micelle concentration (CMC) with the possibility that other proteins in the culture broth contributed to stable foam generation, allowing surfactin to partition into the foam phase. As the surfactin production and removal rates were not matched with the design of apparatus used not all surfactin produced was collected giving a low recovery of 29% meaning the need to separate surfactin from the outlet stream remained. A limitation of this approach was the significant carryover of biomass with the foam which resulted in low productivity and illustrated the further need for process engineering to improve and scale up the process. Recent work by Martin et al. (2010) and Stevnson et al. (2008) has reinvigorated the coupling of foam drainage mass transport within rising foams and is starting to provide a robust foundation upon which foam fractionation can be engineered for specific systems.

Winterburn et al. (2011b) illustrate this in their presentation of an integrated HFBII product removal process. The process consisted of a foam stripping column through which broth is recirculated via inlet and outlet ports on the head plate of a standard bench top bioreactor. They illustrated that non-foaming low product concentration conditions could be maintained in the bioreactor throughout production through the design of suitable foaming process conditions. The stripping column design was particularly effective at washing biomass from the foam column and returning it to the bioreactor, with a loss of only 5% over the whole fermentation. It is apparent that foam separation of biosurfactant in situ reduces the biosurfactant concentration in the fermenter, which can prevent nuisance foaming.

In systems where product inhibition or degradation occurs, limiting production efficiency, foam separation can be used to attain low steady state product concentrations in the fermenter, reducing product inhibition. Liu et al. (2010) reported on the production of nisin, an antimicrobial peptide, produced from fermentations of *Lactococcus lactis* subsp. *lactis* ATCC11454, whose production is hindered by feedback inhibition. They integrated *L. lactis* nisin production with foam fractionation, with aeration being started part way through the fermentation to generate foam and remove the nisin produced. Foaming increased the specific productivity of fermentations by 30%, compared to a control fermentation which was not aerated (foamed), through reduction of feedback inhibition. In this case, the recovery of nisin was 37% at an enrichment of 10.8, although the increased production is the more important consideration. A summary of the salient results from each of the papers discussed here is given in Table 2. It is noted that the majority of studies of biosurfactant foam recovery from fermenters have so far been limited to small laboratory scale fermentations of no more than 2 l working volume.

Summary

Recent work in the area of biosurfactant production has been reviewed with the purpose of illustrating the potential for bioprocess intensification by taking advantage of foaming phenomena. Integrated foam fractionation processes have now been demonstrated on a number of different fermentation systems and illustrate the ability to achieve product enrichment and high recoveries whilst retaining biomass within the fermenter. In general this has illustrated the value of applying unit operation characterisation to bioprocessing equipment. Provided the production volume is great enough, deviation of the process away from the most conventional technology can significantly improve process economics.

Table 2 Summary of previous biosurfactant foam separation

Paper	Foam producing compound	Description	Foam generation	Enrichment (–)	Recovery (%)	Initial concentration (mg l^{-1})	Gas flow rate (ml min^{-1})	Bioreactor working volume (l)	Sparger type
Chen et al. (2006a)	Surfactin from *B. subtilis* BBK006	Integrated recovery during batch operation	Uncontrolled	55.0	92.3	–	–	1.0	Sintered glass disc
Chen et al. (2006b)	Surfactin from *B. subtilis* BBK006	Integrated recovery during steady state continuous operation	Uncontrolled	50.1	28.7	18	400	1.0	Sintered glass disc
Davis et al. (2001)	Surfactin from *B. subtilis* ATCC 21331	Cell-free broth, separate foam fractionation	Controlled	2.9	97.1	440	60	–	Sintered glass disc
		Cell-containing broth, separate foam fractionation	Controlled	1.7	97.3			–	
		Integrated recovery stirrer speed 146 rpm	Uncontrolled	34.0	90.0	–	1000	1.0	–
Heyd et al. (2011)	Rhamnolipid from *P. aeruginosa*	Cell-free broth, separate foam fractionation	Controlled	53.0	–	21	50–150	1.0	–
				2.1	–	402			–
		Integrated recovery with magnetic separation of cells	Uncontrolled	15.0	–	–	1000	10.0	Metal ring
Liu et al. (2010)	Nisin from *L. lactis* ATCC 11454	Integrated recovery	Controlled	10.8	37.3	–	20	0.5	Sintered glass disc
Sarachat et al. (2010)	Rhamnolipid from *P. aeruginosa*SP4	Cell-free broth, separate foam fractionation	Controlled	4.0	97.0	362	30	–	Sintered glass disc
Winterburn et al. (2011a)	HFBII from *T. reesei* expressed in *S.cerevisiae*	Integrated recovery	Uncontrolled	54.6	98.1	–	1000	1.7	Standard metal sparger
(Winterburn et al. 2011b)	HFBII from *T. reesei* expressed in *Saccharomyces cerevisiae*	Foam fractionation integrated as a separate unit operation	Controlled	–	42.7	–	600	1.7	Sintered glass disc
				6.6	69.8		1000		
Zhang et al. (2007)	Cellulase from *T. reesei* Rut C-30	Cell-containing broth, separate foaming	Uncontrolled	1.2	11.6	0.25 (FPU ml^{-1})	2,300	–	Sintered glass disc

Table two is an expanded version of a table previously published in Winterburn et al. (2011a)

Acknowledgment The authors gratefully acknowledge support through an EPSRC PhD Plus award which facilitated this review.

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