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REVIEW ARTICLE

In situ biobutanol recovery from clostridial fermentations: a critical review

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ABSTRACT

Butanol is a precursor of many industrial chemicals, and a fuel that is more energetic, safer and easier to handle than ethanol. Fermentative biobutanol can be produced using renewable carbon sources such as agro-industrial residues and lignocellulosic biomass. Solventogenic clostridia are known as the most preeminent biobutanol producers. However, until now, solvent production through the fermentative routes is still not economically competitive compared to the petrochemical approaches, because the butanol is toxic to their own producer bacteria, and thus, the production capability is limited by the butanol tolerance of producing cells. In order to relieve butanol toxicity to the cells and improve the butanol production, many recovery strategies (either *in situ* or downstream of the fermentation) have been attempted by many researchers and varied success has been achieved. In this article, we summarize *in situ* recovery techniques that have been applied to butanol production through *Clostridium* fermentation, including liquid–liquid extraction, perstraction, reactive extraction, adsorption, pervaporation, vacuum fermentation, flash fermentation and gas stripping. We offer a prospective and an opinion about the past, present and the future of these techniques, such as the application of advanced membrane technology and use of recent extractants, including polymer solutions and ionic liquids, as well as the application of these techniques to assist the *in situ* synthesis of butanol derivatives.

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Introduction

Butanol (1-butanol or n-butanol; simply butanol hereafter) is an interesting industrial chemical that has recently attracted remarkable public attention. It can be used as a fuel source, fuel additive or a chemical feedstock. Butanol has about the same energy content as that of gasoline (one-third higher than ethanol) [1,2] and is less corrosive and hazardous to handle. As a chemical feedstock, butanol has been used as a precursor for methacrylate esters, butyl acrylate, butyl glycol ether, butyl acetate, butyl butyrate, amino resins and n-butylamines [3]. Butanol and its derivatives can also be used for latex surface coatings, enamels and lacquers, flotation agents, cleaners and floor polishers, cosmetics, as a diluent for brake fluid production, as a solvent for hormone and vitamin synthesis, and a swelling agent for textile production [1,3].

Currently, industrial production of butanol named "oxo-process", is mainly based on catalytic hydroformylation of fossil-obtained propylene to butyraldehyde followed by hydrogenation [4]. The oxo-process is economically competitive but not renewable. The intrinsic finite nature of petroleum, the geopolitical concerns and associated environmental problems have driven people to focus their eyes on the biological production of butanol from renewable resources.

The butanol fermentation (called acetone–butanol–ethanol (ABE) fermentation) has two metabolic phases: the acidogenesis corresponding to the exponential growth of cells when the cells produce acetic and butyric acids, and the solventogenesis phase when cellular growth becomes slower and the bacteria re-assimilate the acids produced and meanwhile produce acetone, butanol and ethanol. Butanol usually accounts for no less than 60% (w/w) in the total mixture of ABE in the fermentation. Fermentative butanol production is always limited by the solvent toxicity to the cells, and its usual titer does not exceed 20 g/L in a regular batch fermentation, and the productivity is hard to exceed 0.5 g/L-h [5].

The main mechanism by which Clostridia exerts its self-intoxication has generally been taken to be the

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Supplemental data for this article can be accessed here.

chaotropic effect of butanol on the integrity of the cell's membrane. Various efforts, including conventional mutagenesis and metabolic engineering approaches, were reported for enhancing the butanol tolerance of various solventogenic strains, and indeed, acceptable successes have been achieved [6–8]. However, in spite of those improvements, the general butanol production of the regular fermentation process is still far from being economically competitive.

The downstream processing (separation and purification) for butanol fermentation is more complex and expensive than classic ethanol recovery from a yeast fermentation broth, due to three main reasons: (1) the butanol concentration in the broth is much lower (about 2% of butanol compared to ~15% ethanol); (2) the boiling point of butanol/water azeotrope (93 °C) and that of water (100 °C) are very close (compared with 78.2 °C for the ethanol/water azeotrope); and (3) the final distilled butanol concentration in the aqueous azeotrope is only 55.5% compared to 95.5% for the ethanol analog [9–11]. Therefore, efficient and inexpensive separation or recovery techniques are highly desirable for biobutanol production in order to enhance its economic efficiency.

To mitigate the butanol toxicity during fermentation, process engineering efforts including various recovery strategies have been employed. In this study, we summarized various *in situ* recovery techniques in the butanol fermentation process and meanwhile presented our own prospective with this discussion of the future direction in this area. The intent is to provide relevant references to the research community and meanwhile open discussions. These recovery techniques are experiencing evolution, involving the new tendency of green and clean production and using newly developed advanced chemicals and materials; those integrated with the fermentation process for simultaneous production and removal of solvents that can reduce cell poisoning, increase substrate utilization and improve fermentation productivity and solvent yield [5].

Extraction-based techniques

Liquid–liquid extraction

The *in situ* extraction of butanol is a strategy to reduce the concentration of the toxic butanol in the broth and therefore maintaining the cell culture alive and active longer [9]. Liquid–liquid extraction is performed using a second layer of extractant with or without mixing (Figure 1(a)). The extractant is usually introduced into the process after the acidogenesis phase, because if it is

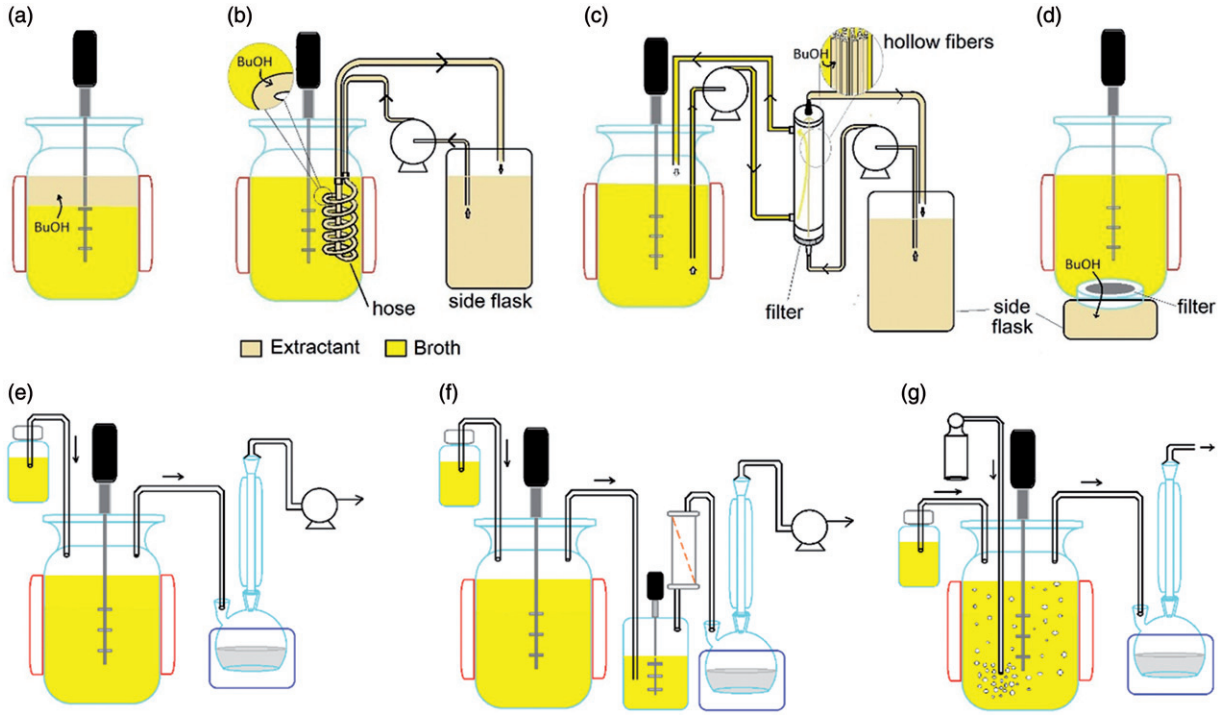

Figure 1. Schematic of various recovery systems (a) Regular solvent extraction through direct contact between the extractant and the broth; (b) "Tube"-type perstraction: extractant is pumped through the fermentation flask without direct contact with the broth; butanol migrates from the broth (in contact with the external of the hose) to the extractant (inside of the hose); (c) Fiber filter perstraction: broth is pumped through the shell and returned back to the bioreactor; the extractant is driven inside of the hollow; (d) Membrane filter perstraction: a circular filter separates the compartment of the broth and the extractant; butanol exchange takes place through the filter; (e) vacuum evaporation; (f) flash fermentation; and (g) gas stripping.

introduced in the earlier stage, it can potentially extract acetic and butyric acids and negatively influence the solventogenesis [12]. The extraction can be continuous or discontinuous. A pseudocontinuous extraction in a batch or fed-batch fermentation can be set up by pumping out the extractant, evaporating the butanol from the extractant and recycling the extractant back into the bioreactor. Such a system can yield a pseudosteady state, whereas the concentration of butanol in the broth remains constant and low, and it reduces the volume of the extractant used inside the bioreactor [9].

The primary characteristics for the extractant to be used in liquid–liquid extraction includes: no or low inhibition to the cell culture growth, high selectivity, high distribution coefficient, no emulsion formation, high stability and low solubility in aqueous solution. Additional desirable characteristics include low/no harmfulness to the environment, density significantly different from the broth for easy phase separation, low viscosity for less energy consumption during extraction, autoclavability, suitable volatility and commercial availability at low cost [9].

For all these processes, the most extensively studied wild-type bacterial strain is *C. acetobutylicum* ATCC 824. Detailed attention has also been paid to: *C. beijerinckii* NCIMB 8052, *C. pasteurianum* DSM 525 and *C. saccharoperbutylacetonicum* N1–4. In addition, a variety of butanol-tolerant mutants have been developed through traditional evolutionary engineering or metabolic engineering approaches [13–15].

Table 1 and supplementary Tables S1, S2 contains a summary of various chemicals tested as butanol extractants in ABE fermentation systems reported in the literature. Partition coefficient (K_D) and selectivity (S) are used to determine the suitability of an extractant for butanol extraction. K_D for butanol ($K_{D\text{-}BuOH}$ hereafter) is the molar ratio between the organic (β) and aqueous phases (α) (Equation (1a)). S is defined as the $K_{D\text{-}BuOH}$ over the $K_{D\text{-}H2O}$ (K_D of water) (Equation (1b)).

$$K_{D-BuOH} = \frac{n^{\beta}_{BuOH}}{n^{\alpha}_{BuOH}} \text{ (a) } S = \frac{n^{\beta}_{BuOH}/n^{\beta}_{H_2O}}{n^{\alpha}_{BuOH}/n^{\alpha}_{H_2O}} \text{ (b)} \quad (1)$$

Both values are dependent on temperature. A summary of $K_{D\text{-}BuOH}$ and selectivities of different extractants for liquid–liquid extraction of butanol is shown in Tables 1 and S2. 35–37 °C is the typical temperature used during *Clostridium* fermentations, and thus, the values reported here are mostly for that temperature range.

Oleyl alcohol is the model extractant in butanol and ABE *in situ* extraction. It is nontoxic and has a relatively good $K_{D\text{-}BuOH}$ (3–4) and good selectivity (200–300), although it is nonvolatile [16,17].

Alkanes are just slightly toxic and highly selective, but their $K_{D\text{-}BuOH}$ is generally low. The more lipophilic the extractant, the lower the extractant concentration in the aqueous phase. It results in a low interaction of the extractant with cell membrane, low dispersion in growth media, low toxicity, low water uptake but also low butanol extraction capability [17]. Aromatic hydrocarbons demonstrate a better $K_{D\text{-}BuOH}$, especially at high temperatures, but most of them are toxic to cells [18].

Various natural oils and triglycerides have been tested as extractants for butanol fermentation. They are expected to be innocuous against bacterial cultures, but some of them show inhibitory effects. Also, some

Table 1. The butanol partition coefficient and selectivity of selected extractants during liquid–liquid extraction with ABE fermentation broth or model solutions.

Extractant	Fermentative strain	Toxicity	K_D	Selectivity	T (°C)	References
1-octanol	*C. beijerinckii* LMD27.6	T	10	130	37	[97]
2-ethyl-1-hexanol	*C. acetobutylicum* ATCC 824	NT	7.95	311.1	36	[17]
1-decanol	*C. acetobutylicum* ATCC 4259	T	6.2	ND	34	[98]
	C. beijerinckii LMD27.6	T	8	200	37	[97]
2-Ethyl-1,3-hexanediol	*C. acetobutylicum* ATCC 824	T	8.1	ND	37	[20]
3-Methyl-2,4-heptanediol	*C. acetobutylicum* ATCC 824	T	7.9	ND	37	[20]
[Dec_4N][1-MeCHC]	Aqueous model	ND	8.49	130	25	[99]
[Hex_4N][DHSS]	*C. acetobutylicum* KCTC 1790, *C. beijerinckii* KCTC5579	T	7.99	ND	25	[16]
[$MeOct_3N$][Oct]	Aqueous model	ND	11.29	49	25	[99]
[$MeOct_3N$][Cl]	*C. acetobutylicum* ATCC 824	ND	8.86	41.7	36	[17]
[Oct_4N][2-MNaph]	Aqueous model	ND	21	274	25	[99]
[Ph_3t][$(^{i}C_8)_2PO_2$]	Aqueous model	ND	9.21	55	25	[99]
	Aqueous model	ND	19–59	80–305	25	[100]
[Ph_3t][DCN]	*C. acetobutylicum* KCTC 1790, *C. beijerinckii* KCTC5579	T	7.49	ND	25	[16]
[Ph_3t][Cl]	*C. acetobutylicum* ATCC 824	ND	11.55	83	36	[17]

(1) Ionic liquid cations: [Dec_4N]: tetra(decyl)ammonium, [Hex_4N]: Tetrahexylammonium, [Ph_3t]: Trihexyl(tetradecyl)phosphonium, [$MeOct_3N$]: Methyltrioctylammonium, [Oct_4N]: tetraoctylammonium; (2) Ionic liquid anions: [$(iC_8)_2PO_2$]: bis-2,4,4-(trimethylpentyl) phosphinate, [Cl]: Chloride, [DCN]: dicyanamide, [DHSS]: dihexylsulfosuccinate, [2-MNaph]: 2-methyl-1-naphthoate, [1-MeCHC]: 1-methylcyclohexecarboxylate, [Oct]: octoate; (3) Symbology: T (Toxic), NT (Non-Toxic), ND (No data, non-reported).

A extractant is considered toxic or inhibitory when its presence reduces the cell growth response (OD_{600}; or sugar consumption or gas generation) in more than 10% comparing to the control.

oils can be consumed by bacteria as a carbon source [17]. Ethanol and butanol can be extracted by triglycerides and perform an *in situ* transesterification reaction in order to produce biodiesel [19]. Silicon oil is not metabolizable and has good selectivity, but its $K_{D\text{-}BuOH}$ is low [17].

Esters show a wide scale of values of $K_{D\text{-}BuOH}$ and selectivity. Short chain monoesters are poorly selective but their $K_{D\text{-}BuOH}$ are high. Di- and tri-esters show a very high $K_{D\text{-}BuOH}$, high selectivity and high boiling points [20]. However, the less lipophilic extractant, the more toxic it is to bacterial cells. Short-chain alcohols show high $K_{D\text{-}BuOH}$ due to their structural similarity to butanol but also exhibit the same toxicity mechanism. Branched medium-chain alcohols are less toxic than their linear analogs but are expensive for industrial extraction purposes. The toxicity of alcohols as extractants decreases with the increase in alkyl chains size as well as $K_{D\text{-}BuOH}$ [21]. Some fatty acids are reported as extractants with acceptable their $K_{D\text{-}BuOH}$. When mixed with oleic alcohol, fatty acids increase $K_{D\text{-}BuOH}$ [22]; however, they show undesirable tensioactive behavior.

Polyethylene glycol (PEG) is partially soluble in water and can be used to promote the formation of two aqueous phases, whereas butanol is extracted into the PEG-rich phase. The $K_{D\text{-}BuOH}$ of PEG was reported as 3–4.8, decreasing with an increase in molecular weight above 1200 Da. The laborious water removal from the PEG-rich phase and the high polymer price are both disadvantages [20,23]. However, the study of new polymer solutions opens an area to explore for extracting reagents. In future, smart extractants could be developed by functionalizing polymeric solutions with, for example, supramolecular hosts or a reversible system of chain extenders that permits modification of the affinity against butanol when they are under a controllable characteristic such as pH, temperature, stress or others.

Recent publications tested the performance of water-insoluble ionic liquid (IL) as an extractant for butanol extraction. Quaternary ammonium compounds (Figure S1) such as [Dec_4N][1-MeCHC], [Hex_4N][DHSS], [$MeOct_3N$][Oct] and [$MeOct_3N$]Cl, and trihexyl(tetradecyl) phosphonium compounds such as [Ph_3t][($^iC_8$)$_2PO_2$], [Ph_3t][DCN] and [Ph_3t][Cl] showed $K_{D\text{-}BuOH}$ values considerably higher than previously reported (7.99–21 and 7.49–59, respectively) and meanwhile demonstrated high selectivity. In both groups, the conjugation with the anion bis(trifluoromethylsulfonyl) imide is disadvantageous. In spite of the high butanol recovery capacity, several IL are toxic or inhibitory [16,24].

Due to the ionic nature, the $K_{D\text{-}BuOH}$ of IL increases with their lipophilicity, which is an opposite trend to other solvents. This means that the more capable the IL is for butanol extraction it is less toxic. The 1-alkyl-3-butylimidazolium-based IL increase $K_{D\text{-}BuOH}$ with the size of the side chain, that is [Bmim] < [Hmim] < [Omim] < [Dmim]. The general order of the $K_{D\text{-}BuOH}$ values of various cations is: imidazole-based < quaternary ammonium-based < tetralkyl phosphonium-based. For the IL in the last two groups discussed above, the $K_{D\text{-}BuOH}$ increases with alkyl chain size in a similar manner.

In general, the highest $K_{D\text{-}BuOH}$ has been reported for organic carboxylates, phosphates or sulfonates anions due to their lipophilicity. There are no reports so far to use IL for *in situ* butanol extraction. Researchers have reported such studies with ABE model solutions or downstream extraction [25,26]. This is a relatively new research area.

Perstraction

In the extraction assisted with membranes, termed as perstraction, a semipermeable membrane (which the extractant cannot go across while butanol can) is used. This approach can avoid emulsions and toxicity problems. Extractants with excellent properties (high $K_{D\text{-}BuOH}$ and selectivity) but are very toxic to bacteria, cannot be applied in a regular extractive fermentation. They can be used in membrane-assisted processes instead, since they are not in direct contact with fermentation broth. The main disadvantage for perstraction, however, is that the membrane builds an additional barrier which results in slower diffusion [9,10].

Perstraction becomes especially important in continuous extraction, either in batch or in continuous fermentation processes. The primary benefit is the increase in fermentation productivity over time. Table 2 summarizes the performance of perstraction for fermentative butanol recovery with the membranes of various materials as reported in the literature. Traditional butanol fermentation experiments have been conducted with silicone membranes, also named as poly(dimethylsiloxane) (PDMS) [27]. The system uses a peristaltic pump to drive the broth through a hose or tube immersed in the extracting solvent as shown in Figure 1(b). In Jeon and Lee's study [27], this system generated an increase in total ABE productivity rate by 0.2–1.19 g/L-h compared with a regular batch fermentation and by 0.07 g/L-h compared with the batch fermentation with direct solvent extraction. Although these values do not represent significant improvement, the length of time that the fermentation can be maintained as active was increased up to 481% of the non-extractive fermentation [28] and 143% of the fermentation with regular liquid–liquid extraction [29].

Table 2. Summary of performance of perstraction for butanol recovery in various batch fermentations for butanol production.

Membrane					Productivity					
					Butanol		ABE			
M	t mm	A m^2	Strain[a]	Solvent	g/Lh	g/Lhm^2	g/Lh	g/Lhm^2	Increase Δ(g/Lh)	References
PTFE	0.075	0.00502	*C. saccharoperbutylaceticum* N1-4	nC_{12}-OH	0.394	78.6	ND	ND	ND	[31]
PTFE	0.075	0.00502	*C. saccharoperbutylaceticum* N1-4	OA	0.32	63.7	ND	ND	ND	[31]
PDMS	0.8	0.227	*C. acetycobutylicum* ATCC 824	OA	0.705	3.07	1.02	4.49	0.54[a]	[28]
PDMS	0.8	0.227	*C. acetycobutylicum* ATCC 824	PPG	0.538	2.34	0.81	3.57	0.33[a]	[28]
PDMS	0.8	0.227	*C. acetycobutylicum* ATCC 824	TBA	0.407	1.77	0.68	3.00	0.2[a]	[28]
PDMS	0.4	0.215	*C. acetycobutylicum* P262	OA	0.16	0.74	0.24	1.12	ND	[101]
PDMS	ND	0.113	*C. acetycobutylicum* P262	OA	0.1	0.88	0.21	1.86	0.07[b]	[29]
PDMS	0.8	0.0714	*C. acetycobutylicum* ATCC 824	OA	ND	ND	2.27	31.79	1.19[a]	[27]
PP fibers	ND	0.1	*C. acetycobutylicum* DSM 1731	OA + dec (50/50)	ND	ND	1.02	10.20	0.39[a]	[30]

A: area; ABE: acetone-butanol-ethanol; dec: decane; M: material; nC12-OH: 1-dodecanol; ND: no data; OA: oleyl alcohol; PDMS: silicone (poly(dimethylsiloxane)); PP: polypropylene; PTFE: polytetrafluoroethylene; t: thickness.
[a]Productivity increment compared with nonextractive fermentation under same conditions.
[b]Productivity increment compared with *in situ* liquid–liquid extraction under same conditions.

This means that the final total amount of butanol or ABE generated from this fermentation has been significantly improved, which is very significant because this would dramatically save the time and efforts that are required for medium preparation, inoculation and reactor setup. The efficiency of silicon hose per unit area is lower compared to other materials such as poly(tetrafluoroethylene) (PTFE).

Polypropylene (PP) fibers with 0.2 μm pores have also been used in a hollow fiber membrane module for butanol recovery as shown in Figure 1(c). This system is able to provide a large contact area in a relatively simple apparatus [30]. It is composed of several porous PP hoses with a small diameter (just a few millimeters) in a plastic shell, whereas the broth is driven through the shell side and the extractant is inside the fibers.

Filters of PTFE with a pore size of 1 μm are relatively highly selective, and butanol recovery per unit area is very efficient [31]. Such a perstraction system (as shown in Figure 1(d), with a PTFE filter disc dividing the flasks of the extractant and the broth) has been tested at temperatures from 303 to 315 K in the solvent container. The extraction capacity increased with temperature. For example, the butanol flux permeate was 0.034 kg/h-m^2 at 28 °C, 0.039–0.042 kg/h-m^2 at 35 °C and 0.049 kg/h-m^2 at 42 °C, when the initial concentration of butanol in the model solution was 12.4 kg/m^3 [32]. Disadvantages include the complicated and laborious setting up and operation, the requirement for specific equipment, the possibility of clogging and cell or biofilm absorption.

Reactive extraction

Butanol is a short-chain alcohol and its distribution coefficient in organic solvents is not as high as desired. But as we mentioned above, some butanol derivatives are very valuable chemicals. Reactive extraction is a chemical reaction occurring at the same time as the extraction. Since some important derivatives are more lipophilic than butanol itself, especially long-chain esters, the reactive extraction can alter the partition equilibrium and thus reduce the butanol concentration in the broth. Supplementary Figure S3 shows some industrially important derivatives that can be obtained from butanol.

Reactive extraction is not easy to perform since most chemicals used to react with butanol are toxic to the cell culture. Additionally, many reactions need to be performed at temperatures higher than the optimal for fermentation. Therefore, there are not many reports in the literature concerning the reactive extraction within butanol fermentation. Nonetheless, two kinds of such processes are feasible, using either biocatalytic enzymes or chemical heterogeneous catalysts (e.g. active sites in the surface of a silicate particle).

Reactive esterification extractions are well studied in lactic acid and many other fermentations [33]. Esterification reactions along with extraction were also reported in *Clostridium* fermentations, using biocatalysts in the organic phase [34]. Lipase catalyzed butyl butyrate production is an easy-to-achieve *in situ* derivatization because the same ABE fermentation can produce both butyric acid and butanol. Ethyl butyrate can be synthesized as coproduct of butyl butyrate, but the yield is very low because ethanol production is usually low in ABE fermentation and ethanol is poorly soluble in the organic phase. Most common extractants for this application are long-chain inert hydrocarbons. Fatty acid butyl esters (applicable as biodiesel) with acyl chain length between 12–20 carbons can also be produced by biocatalysis, from *in situ* butanol extraction with vegetable oils in the presence of a lipase [34]. All of these esters are poorly soluble in the broth and thus favorable for the reaction in the extractant (Figure S2)

[34]. Oleyl alcohol, long-chain secondary alcohols, esters and long-chain hydrocarbons can be used as extractants for reactive extraction, but some secondary products would be expected.

A combination of chemical reaction with fermentation is a promising area to study in future to increase productivity and the economic viability of a bioprocess. Derivatives might be less soluble and less toxic, keeping the fermentation actively running for a longer time. Heterogeneous chemical catalysis, such as a metallic redox system, could be used to synthesize *in situ* chemical derivatives of butanol without introducing harmful chemicals to the broth. On the other hand, biocatalysts have increasing importance in the industry. Lipases, nitrilases, amidases, lyases, acylases, hydroxylases and many other enzymes are essential to various industrial processes [35,36]. The discovery, isolation and immobilization of new stable enzymes will facilitate the attempt of chemical reactive extraction during butanol fermentation.

Additionally, the attempt of *in situ* recovery of butanol or ABE, followed by a chemical catalysis process to convert the solvent to long-chain hydrocarbons, has achieved great success. In one study, the ABE mixture was recovered through *in situ* extraction with glyceryl tributyrate and was then efficiently converted into ketones by a palladium-catalyzed alkylation [37]. In a recent report, hydrolysates generated from corn stover was fermented with *C. beijerinckii* CC101, followed by recovery using gas stripping and pervaporation, and the ABE mixture was then used to synthesize 5–15 carbon ketones as a substitute for jet fuel [38]. High conversion efficiency and stable conversion rates were demonstrated in such a process.

Adsorption-based techniques

There are different models explaining adsorption phenomena, depending on the nature of the material, types of interaction with adsorbates, pore size, surface area, concentration of adsorbates and the presence of other adsorbates. During ABE fermentation, the concentration of the substrate, organic acids, acetone, ethanol and butanol are all changing during the process, and any of these substances can be adsorbed. Therefore, from the literature, researchers used different models to study the adsorption of butanol. Here, a critical comparison among them is attempted.

When the adsorbate concentration is well below saturation, some adsorbents behave close to linearity while others do not. Some researchers determined a partition coefficient as an approximation (assuming linear behavior) for preliminary screening of the best adsorbents. Adsorption at saturation is another approach used for the same purpose. Supplementary Table S3 summarizes various adsorbents reported for biobutanol recovery for some of which the solid/liquid partition coefficients ($K_{s/w}$) and the saturation loading capacity for butanol (L_{BuOH}) have been determined. By comparing L_{BuOH} in mg of butanol per gram of adsorbent from various literatures [9,10], we define it as $0 <$ "very low" $< 25 \leq$ "low" $< 50 \leq$ "medium" $< 75 \leq$ "high" $< 150 \leq$ "very high".

Activated carbon is the most employed adsorbent. L_{BuOH} of active carbon has been reported as 68–300 mg/g (commonly very high values) in a single or binary component. L_{BuOH} decreases dramatically when the solution composition becomes complicated for some forms of carbon such as Witco 517 or Nuchar WV-G [39]. The second group of adsorbents is composed of silicates and aluminosilicates. Silicalite is an aluminum-free zeolite analog with the same crystal structure of the zeolite ZSM-5. Silicalite is a selective adsorbent, and L_{BuOH} is reported to be 64–100 mg/g even in complex media. The selectivity of silicalite for alcohols increases with an alkyl chain from 1 to 5 carbons [40]. Polymer resins with micro- or macropores are used as synthetic adsorbents. Aromatic resins are common because aromatic groups have a large surface area for nonpolar interactions. Polystyrene, crosslinked with divinylbenzene P(S-co-DVB), is the most common polymer-based adsorbent. Commercial resins of P(S-co-DVB) are manufactured by Dowex, Donopore, Amberlite (Fluka), Diaion, Hytrel and Reillex are reported with L_{BuOH} from low to high (1.7–97.5 mg/g), though some of them are already discontinued. These resins are relatively highly selective, because they are nonpolar, and the interactions with cells, glucose and small alcohols are minor. Crosslinked polystyrene resins can be also functionalized with side groups to increase their polarity. Optipore SD-2 and M43 are functionalized with a tertiary amine, and Diaion HP-20 with a sulfonic acid [41]. Functionalization can promote hydrogen bond interactions with butanol, increasing the affinity but reduce the affinity when functional groups significantly increase the polarity. KA-I resin is a complex adsorbent of the polystyrene framework, functionalized with ester groups developed by the National Engineering Technique Research Center for Biotechnology (Nanjing, China) [42]. KA-I was well studied and it showed L_{BuOH} (84–93 mg/g) and good selectivity even in complex mixtures [42]. Polyvinylpyridine is another aromatic resin reported with an acceptable $K_{s/w}$ [43]. Mild polar resins have also been reported in literature [41,43,44]. Acrylate

and methacrylate polymers and ester derivatives are used and have low-to-medium values of L_{BuOH}. Metal-organic framework (MOF) is a modern type of adsorbent with an ordered porous 3 D structure composed by a metal interaction with an organic structure. ZIF-8 is a MOF containing zinc, it shows very high L_{BuOH} and selectivity for butanol recovery [44].

Generally, two models are widely used to study adsorption phenomena: Langmuir isotherm and Freundlich isotherm. The Langmuir model (Equation (3)) is applicable for samples approximating the following: solution behavior is ideal; just a monolayer is adsorbed; adsorption sites have the same affinity; adsorbed molecules are localized; there is no lateral interactions and adsorbed molecules are in dynamic equilibrium [45]. In addition, Langmuir model studies the enthalpy of adsorption and is the most extensively used adsorption model reported in the literature as shown in supplementary Table S4 for many adsorbents.

$$q = \frac{q_{max} B C_{eq}}{1 + B C_{eq}} \tag{3}$$

where q is the adsorption capacity, q_{max} is the maximum adsorption capacity, B is the Langmuir constant, C_{eq} is the solute concentration at equilibrium in liquid phase [46]. The physical meaning of q_{max} (for butanol hereafter) is an analog to L_{BuOH} when saturation is reached, and the Langmuir constant (B) is similar as $K_{s/w}$. B describes the affinity of the adsorbent and the adsorbate, or the relation between empty and occupied sorption spots. B and q_{max} can be obtained from the mathematic linearization of Langmuir model. B and q_{max} values mentioned hereafter correspond to butanol adsorption.

A recent study demonstrated very high q_{max} in active carbon Norit ROW 0.8 even in a complex solution [47]. The authors also demonstrated the applicability of this material in a real *in situ* fermentation process and achieved up to 54.6 g/L butanol [47]. The $q_{\max}$ of zeolites, silicalite and polystyrene adsorbents show the same trend as L_{BuOH} as discussed above. Silicalite, compared to regular zeolites, is more selective for butanol than water [46]. Polystyrene resins show Langmuir constant values between 0.2 and 0.4 for single components and some multicomponents solutions, and they remain at an acceptable value until the concentration of a second component is very high as shown in a binary model by Jiao et al. [48]. Zeolites show the highest affinities (B), behavior concordant with oxophilicity of aluminum, though a very high value can be counterproductive during the desorption stage.

The Freundlich isotherm empirical model usually fits the adsorption behavior better than Langmuir without complex calculations. The model is expressed in Equation (4).

$$q = K_f C_{eq}^{1/n} \tag{4}$$

where K_f and n are Freundlich constants (values for butanol hereafter). The equation does not indicate a finite uptake capacity, and thus, it is functional in the low-to-medium concentration ranges [49]. If $n = 1$, the expression becomes linear since $K_f = K_{w/s}$. So, n is related to the deviation from this ideal behavior caused by the heterogeneity of the surface adsorption sites. When *1/n* is close to zero, the surface is highly heterogeneous [50]. Therefore, K_f is an improved $K_{w/s}$ and represents the quantity of adsorbate in the solid required to maintain at one unit for the concentration in the solution (i.e. mmol/L). Consequently, K_f is also related to the adsorption capacity [50]. Researchers have used Freundlich models to describe the butanol adsorption with various adsorbents (supplementary Table S5). According to analysis of Freundlich model, activated carbon showed the highest k_f, followed by other adsorbents, such as KA-I, and finally, the Optipore L493 and SD2. Diaion HP20, HP2MG and Hytrel 8206 demonstrated relatively low k_f [51].

Other adsorption models like Brunauer, Emmett and Teller (BET) isotherm, or Lagergren's equation for pseudoorders are also used and can usually fit better for the experimental data [52]. However, they are not widely used due to their complexity, and because the physical meaning of their constants is hard to represent. In one example, the BET model was employed when SiO_2 functionalization with calixarene was used as an adsorbent for butanol [52], which demonstrated that butanol adsorption is dependent on the calixarene content on the supramolecular conjugate.

It needs to be pointed out that some adsorbents can be inhibitors for cell growth. For example, resins Diaion HP-20 and Dowex M43 demonstrated severe inhibition on cell growth in the clostridial fermentation, reducing butanol production by 87–99% [41]. Nontoxic adsorbents are preferable when they need to be in direct contact with the cell culture. Another approach to mitigate the adsorbent inhibition is to pump the culture through a cell filter followed by a cartridge with the adsorbent [53]. This is usually a common procedure when adsorption is used for butanol recovery, and therefore, the toxicity of adsorbents to the fermentation culture is not often studied.

Desorption process is also very important for overall butanol recovery. A good adsorbent should have low affinity at high temperature. The heat required for desorption is highly decisive for the cost of the whole

process. For example, zeolites CBV28014 and CBV901 require 275 J/g and 355 J/g for the desorption of butanol, respectively [54], while Norit Row 0.8 requires up to 14,127 J/g [47]. Competitive adsorption (e.g. pressurized CO_2), gas stripping, elution and other techniques can be considered as alternatives for desorption, but they are not necessarily less expensive [54].

Future adsorption development is dependent on the discovery of new materials. Some of the MOFs are catalysts of chemical reactions with butanol and they exhibit high adsorption and selectivity for butanol as shown above. Therefore, this characteristic can be used to explore possible *in situ* or *ex situ* chemical transformation of the adsorbed butanol. Future intelligent adsorbents should have programmable adsorptivity: strong under fermentation conditions and weak during desorption. Such behavior could be achieved if the structure of the adsorption sites change when conditions are changed. They should also be easy to recover and reuse. Materials with supramolecular structures are one of the most feasible candidates as smart adsorbents.

Evaporation-based techniques

Pervaporation

Pervaporation is a separation process that combines permeation through a membrane and vacuum evaporation. This traditional technique is considered to be one of the most energetic and timely efficient approaches for butanol recovery, especially in the context of recent advances that the novel membranes can allow the permeation of high flux of butanol with high selectivity [55,56]. Temperature, membrane thickness, vacuum pressure, the concentration and presence of other components are slightly related with the pervaporation performance. Drawbacks for this approach include the chance of membrane contamination and clogging, the price of highly specific membranes and the accumulation of non-condensable gases on vacuum pumps [57,58]. Therefore, we propose to critically discuss and compare the efficiency of pervaporation during real fermentation conditions.

Most studies, employing pervaporation for butanol recovery have been conducted using a silicon membrane (PDMS, polydimethylsiloxane), PDMS blend or PDMS derivative. Qureshi and Blaschek evaluated a PDMS perstraction membrane for ABE recovery in a batch fermentation with *C. beijerinckii* BA101 [59]. The total solvent productivity was increased from 0.35 g/L-h in a regular batch fermentation to 0.98 g/L-h in the pervaporation integrated fermentation, and a final solvent titer of 165.1 g/L was achieved. Kong et al. [60] achieved a solvent productivity of 0.98 g/L-h, with a butanol and ABE titers of 93.49 and 150.06 g/L, respectively, (which was 7.13 and 7.98 times, respectively, higher than in a regular batch fermentation) when they applied pervaporation coupled with a batch fermentation using the mutant BT14 of *C. beijerinckii* NCIMB 8052.

Some reinforcements or fillers can be used in PDMS matrix for increasing the efficiency of the membranes. Filler permeability is related with the parameters mentioned above such as $K_{w/s}$, L_{BuOH} and isotherms constants [61]. Fillers with high L_{BuOH} improve butanol permeability and fillers with good selectivity increase the butanol concentration of the permeate. PDMS/zeolite composites show a lower total flux permeate yet higher butanol flux when zeolite concentration is increased from 0% to 80% [55,62]. PDMS/ceramic composites were reported for *in situ* pervaporation during fermentation with *C. acetobutylicum* XY16 and showed a total flow of 661 g/m^2-h, a butanol flux of 3.5 g/m^2-h, and an increase in productivity from 0.20 g/L-h in the control fermentation to 0.410 g/L-h in the pervaporative fermentation [63]. Model of PDMS/silicalite-1 showed a total flow of 1233 g/m^2-h, with a butanol flux of 611 g/m^2-h [56].

Polymeric blends containing PDMS and its composites were also tested for butanol recovery through pervaporation. Polyvinylidene fluoride inclusion (PDMS/PVDF) increases the permeation of butanol from 4.1–4.6 to 20.0 g/m^2-h and the total flux from 38.8–45.6 to 120 g/m^2-h [64]. Composites of PDMS/PVDF containing metal complexes of Co and Fe increased the total flux up to 331 g/m^2-h in model solutions [65]. Polyacrylonitrile blend (PDMS/PAN) achieved a flow of 557 g/m^2-h and generated a high butanol concentration of 122.4 g/L in the permeate solution [66]. When PDMS membranes were replaced by triblock copolymer of styrene-silicone-styrene (SDS) in a *C. acetobutylicum* fermentation, the butanol flow was increased from 110 to 220 g/m^2-h, and butanol selectivity from 14 to 21, due to the solvent passing through noncrosslinked joint between the rigid polystyrene and the crosslinked PDMS [67]. A butanol flow of 12–27 g/m^2-h could be reached with polyimide-silicon (PDMS/PI) [68], and a butanol flow of 4–12 g/m^2-h was reported with polyethylene, silicon and metal particle system (PDMS/PE/metal) used for the pervaporation [69].

Polypropylene hollow fibers are used for pervaporation membranes with low flux (7.1 g/m^2-h), and they are used on high surface area devices [70]. Polyether-block-amide (PEBA) can be also used as a membrane, alone or combined with carbon nanotubes (CNT). PEBA/CNT has lower permeate flow than PEBA alone (147 g/m^{2}h and

167 g/m^{2}h, respectively) and higher butanol flux (0.58 and 0.45 g/m^{2}h, respectively). Other materials, such as the polymers of intrinsic microporosity PIM-1, PEBA/ceramic hollow fiber, stainless steel/silicalite, Hyflon AD/PVDF (poly(2,2,4-trifluoro-5-trifluoromethoxy-1,3-dioxole-co-tetrafloroethylene)/poly(vinylidene fluoride)), poly(octhylmethyl siloxane) (POMS), poly(1-trimethylsilyl-1-propyne) (PTMSP), PDMS/silicalite, have also been used for pervaporation membranes for butanol recovery [71–76].

Membranes swelled in a water-insoluble liquid and coated, can be used to improve pervaporation selectivity [77]. Similar as extraction, liquids with high L_{BuOH} and selectivity are good candidates for these "liquid membranes". A liquid membrane composed of oleyl alcohol with polypropylene support produced 3.3 g/m^2 h of butanol flux and a total permeate flux of 14.3 g/m^2 h [78]. A preliminary screening of IL immobilized in Nylon/PDMS showed the best results for [Dmim][B(CN)$_4$] > [Ph$_3$t][B(CN)$_4$] > [Dmim][FAP], and the total flux for [Dmim][B(CN)$_4$] was up to 550 g/m^2 h [58]. PDMS/[Omim][Tf$_2$N] produced a butanol flux of 6.2 g/m^2 h compared with 1.75 g/m^2 h with PDMS alone [77], and PDMS/[Pr$_4$N][B(CN)$_4$] generated a butanol flux of up to 15 g/m^2 h [79]. B(CN)$_4$ anion shows the best performance which are demonstrated when membranes are very thin and there were no significant differences among various IL under those conditions [79].

Vacuum and flash fermentation

Vacuum fermentation (Figure 1(e)) and flash fermentation (Figure 1(f)) are well known methods, which are especially suitable for continuous fermentation. Butanol and other products are removed from a bioreactor under vacuum at normal temperatures during vacuum fermentation. The flash fermentation is carried out using a bioreactor at normal pressure, while the broth is driven through a vacuum chamber, where distillation occurs [80]. Broth is filtered in front of the vacuum chamber in order to retain the cells in the reaction vessel.

Vacuum fermentation for butanol production using *C. beijerinckii* NCIMB 8052 or *C. beijerinckii* P260 has been reported [81]. Butanol and water generate an azeotrope mixture, with a boiling point of 92.4 °C. Vacuum distillation of butanol generated a more concentrated product. Fermentations were conducted under a vacuum of 711–737 mm Hg at 35 °C, starting with a constant or a cyclic vacuum 18 h after fermentation. The total production in a 7-L batch reactor was increased from 80.6 to 106.0 g of butanol and from 110.1 to 132.4 g of total ABE, respectively. When continuous vacuum is used, the production rose to 120.1 g of butanol and 141.2 g of total ABE for cyclic vacuum [81–83].

Optimization of flash vacuum parameters was conducted for continuous fermentation and distillation purification of butanol. Computer simulations assisted the increase in butanol productivity from 4.51 to 7.70 g/L h in a flash vacuum fermentation [84]. Flash fermentation could permit a feed of substrate up to 100–300 g/L (sugars or others). The disadvantage was the decrease in sugar conversion efficiency from 98.5% to 92.9% [83,85].

Gas stripping

Gas stripping is a simple, inexpensive and nontoxic recovery process. Gas stripping is conducted by bubbling a gas (or gas mixture) into the fermentation broth to promote the evaporation of volatile compounds in the gas stream (Figure 1(g)). Gas stripping can be carried out in the bioreactor or in a side chamber. Then, the evaporated stream is condensed in a cold trap and/or a condenser (heat exchanger). A low-cost inert gas like nitrogen (N_2) or the gas(s) (CO_2 and H_2) generated from the ABE fermentation process is typically used. Gas stripping allows the usage of high concentration of substrate stock, reducing the volume needed for fermentation [86,87]. Total butanol production was increased from 11.9 g/L in the control to 16.4–46.4 g/L [86] and from 16.2 g/L to 19.8 g/L [88] with gas stripping coupled with batch or fed-batch fermentations. High butanol titer was also demonstrated by Xue, et al. [13], using intermittent stripping cycles in a fed-batch reactor. In their fermentation, 113.3 g/L butanol was obtained from 474.9 g/L glucose within 326 h.

The simplicity of gas stripping makes this technique especially suitable to be combined with other recovery techniques for hybrid recovery purposes. With recent innovative methods using a double gas trap or a double stripping process, the recovered butanol concentrations have been reported to be impressive at 515.3 g/L [89], 175.6–420.3 g/L [88] and 441.7 g/L [90]. Gas stripping has also been employed in combination with pervaporation, generating a final butanol concentration of 521.3 g/L in a fermentation with *C. acetobutylicum* JB200 [90]. In another study, gas stripping coupled with oleic alcohol extraction generated a final butanol titer of 549 g/L in a fermentation with *C. acetobutylicum* ATCC 824 [91]. Xue et al. [92] summarized and highlighted the increasing importance of these "hybrid methods" in the recent literature.

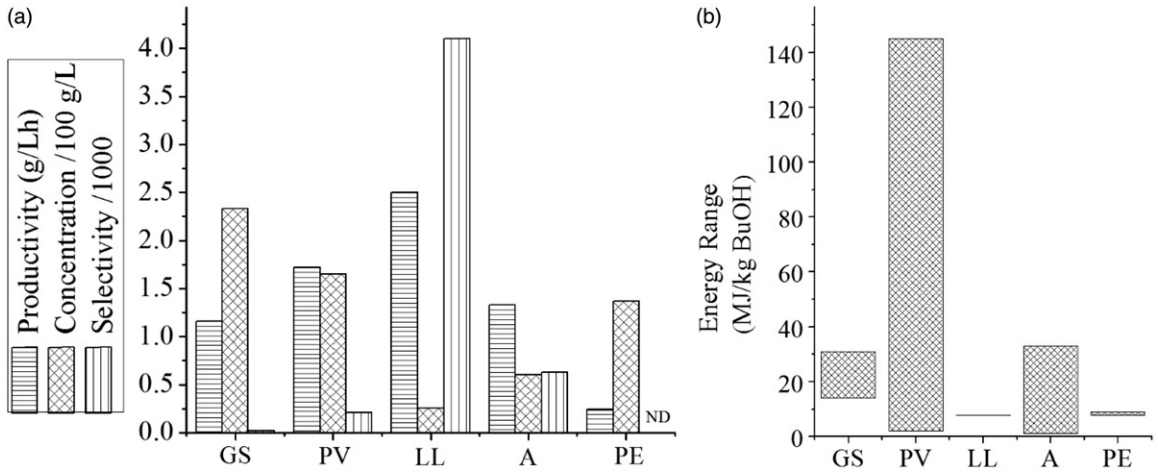

Figure 2. Comparison of several primary recovery techniques [2,53,102,103]. (a) highest productivity, concentration and selectivity (PE selectivity not reported) (b) estimated energy consumption range. GS: gas stripping; PV: pervaporation; LL: liquid–liquid extraction with oleyl alcohol; A: adsorption; ND: no data; PE: perstraction.

Comparison of performance and energy requirement

Butanol has an energy content of 36.2 MJ/kg, and the direct distillation from 2% in broth consumes about the same energy. Lowest values for energy consumption during recovery were reported for pervaporation and adsorption, but the range of energy consumption for these techniques is wide as shown in Figure 2(b) [2,53]. The energy consumption in gas stripping, pervaporation and vacuum flash is significantly associated with the energy used and the condensate purified product. A very low temperature in the condenser can reduce the loss of butanol but increase the cost [93]. In vacuum-based techniques, intermittent vacuum fermentation was energetic superior to the continuous one because distillation occurs when butanol is more concentrated and the low butanol concentration after each vacuum cycle keeps the bacteria culture at an active growth phase for longer [82]. The energetic consumption in adsorption is highly linked to the desorption process as well.

Figure 2(a) illustrates the comparative best performance and energy consumption for various butanol recovery techniques. Gas stripping, pervaporation and perstraction can generate higher titers. Pervaporation and adsorption consume the lowest or highest amount of energy, depending on the conditions. The overall costs of the adsorption and extraction processes are also highly dependent on the prices of the used adsorbents and extractants. Gas stripping is particularly interesting when it is used combined with other techniques because of its simplicity. It has been reported that a double gas stripping system required less than 5 MJ/kg of energy to generate about 500 g/L butanol in an integrated ABE fermentation process [88]. A combination of some of the recovery techniques can make the process more efficient and cost effective. For example, high butanol concentrations from 400 to 550 g/L have been obtained with hybrid gas stripping/pervaporation [90], double gas stripping [88] and double pervaporation [94] in a single integrated process. In addition, fermentation with *in situ* extraction and distillation has also been reported [95].

Conclusions and prospects

Intrinsic advantages of butanol as a fuel or fuel additive are extensively noticed, but butanol production through the biological fermentation route is still not economically viable. The simple rule is that the produced butanol should possess more energy than that required to produce and purify itself. A regular distillation process from a dilute solution of butanol requires about the same amount of energy as the heat energy that can be generated through theoretical combustion of the same amount of butanol [10]. *In situ* recovery techniques have a significant effect on the whole process and must be taken seriously into account.

Vacuum distillation, flash fermentation and gas stripping do not show significant progress and current research in this areas applied to butanol fermentation is generally related to process optimization and industrialization studies. However, these techniques (besides pervaporation) are the current best candidates for potential commercial-scale production.

Membrane-associated technologies (pervaporation and perstraction) enjoy coevolution with the development of new materials. The discovery and development of advanced materials can change the general

performance of these techniques. Recently, developed membrane materials, including the MOF and liquid membranes, are suitable for butanol recovery [96].

Liquid–liquid extraction and relevant methods have been proved to be the highest selective techniques, but they are also the most expensive. Polymer solutions, such as poly(ethylene glycol) and IL, are the best current available options. The future development in liquid–liquid extraction should reside in their application for the production of butanol derivatives such as high-value fine chemicals.

Reactive extraction and a hypothetical reactive pervaporation could constitute a one pot, tandem or multicomponent biotechnological/chemical reaction. Functionalized silicate heterogeneous catalysts are candidates for *in situ* synthesis of butanol derivatives. Reactions catalyzed by enzymes (immobilized or in the free form) are also promising. The discovery, development and isolation of new enzymes are going to widen the spectrum of these chemical derivatives.

Disclosure statement

The authors report no declarations of interest.

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