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Implementation of Amino Acid as a Natural Feedstock in Production of *N*-Acylamides as a Biocompatible Surfactants: A Review on Synthesis, Behavior, Application and Scale-up Process

Widharta Surya Alam,[1*] Sabila Gitamara,[1] Riki Wartakusumah,[2] Muhammad Irfan Nurdin,[3] Zuhrina Masyithah,[1]

[1]Department of Chemical Engineering, Faculty of Engineering, University of Sumatera Utara, 20154 Medan
[2]Faculty of Medicine, Public Health and Nursing, University of Gadjah Mada, 55281 Yogyakarta
[3]Department of Chemistry, Faculty of Mathematics and Natural Science, Mataram University, 83115 Mataram

[*]Corresponding e-mail: widhartasuryaalam@students.usu.ac.id

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ABSTRACT

The use of surfactants is extremely widespread for human life. The development of the use of surfactants has not reached detergents anymore, but for drug delivery, biolubricant, emulsifier, cosmetics, enhanced oil recovery (EOR), dispersants and even virus vectors. Unfortunately, the past history of surfactants had given a bad impression since many surfactants are difficult to decompose in nature, are toxic and are not suitable as biological materials. This article will examine the research development and production, syntesis pathway, classification, behaviour and application of *N*-Acyl amino acid (NAAAc) surfactants. Amino acid-based *N*-Acylamides (AAc) or NAAAc surfactants are next-generation biological surfactants. NAAAc can be synthesized by chemical and enzymatic pathway. NAAAc can also be combined with ionic liquids (ILs) to become green surfactants NAAAc ILs which is low in toxicity unlike conventional ILs. The conclusion of this article studied was NAAc production process that had the highest efficiency so far was the production through a catalytic chemical reaction, namely the fatty acid amidation or amino acid acylation process. The application of AAc-based *N*-Acylamides is so promising that it can be considered for scale-up processes in the future.

Keywords: *N*-Acylamides, amino acids, critical micelle concentration, surfactants, ionic liquids, gemini surfactants

INTRODUCTION

High surface tension in hydrophilic-hydrophobic (fat/oil-water) formations can disrupt aquatic ecosystems as well as drug delivery in the body [1]. So we need an active agent that can lower the surface tension which we called a surfactant and act to unite the hydrophilic and hydrophobic components [2]. Surfactants are oleochemical derivatives that are able to reduce surface tension and interfacial tension in two liquids that are difficult to blend, such as oil in water [3].

The demand for surfactants in the world market continues to increase rapidly every year. Surfactant demand in 2018 reached 476,500 tons (2.21 billion USD), and it is predicted that in 2023, the demand for surfactant products will reach 2.69 billion USD [4]. This is based on the use of surfactants in various fields such as detergent, polymer, oleochemical, pharmaceutical,

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energy, petroleum, food and personal care industries [5-9]. However, many surfactant products circulating in the world market in large quantities are produced from petroleum such as LAS, SLS, ABS, imidazolium surfactants and various [10-12]. This type of surfactant is very damaging to aquatic ecosystems since it is a pollutant and toxic [11].

This encourages researchers and industry to compete in the synthesis, production and commercialization of surfactant products that have low toxicity, are eco-friendly, and have the ability to self-assembly in forming aggregations [13, 14]. The candidate surfactants are amino acid (AAc)-based *N*-Acylamides [8, 15]. The advantages of AAc-based *N*-Acylamides are that they're biocompatible and suitable for pharmaceutical purposes such as drug delivery, they are made of biologic materials and this distinguish them from other surfactants [8, 16]. A study that had been reported by Bajani et al. [16], the results of the amino acid-based surfactants they synthesized, namely Na-*N*-lauroylsarcosinate and Na-*N*-lauroylglycine had perfect aggregation properties than petroleum-based surfactants. Both of critical aggregation concentration values were 3.8 and 2.6 mM with a surface Gibbs adsorption of 2.07 and 2.40 million mol/m^{-2}, respectively. The tendency of the Na-*N*-lauroylglycine molecules to form highly ordered crystal-like aggregates was observed from FESEM micrographs with optical microscopy [16].

Meanwhile, amino acid-based *N*-Acylamides (AAc) or commonly called *N*-Acyl amino acids (NAAAc) can be synthesized by reacting amino acid compounds with reactants containing acyl groups (from certain chemicals). In addition, vegetable oils are a new alternative as a type of reactant that contain an acyl groups for the production of environmentally friendly surfactants that have high sustainability. Liu et al. [18] synthesized NAAAc with castor oil as reactant. Some of the surfactants they had successfully synthesized were *N*-acylalanine, *N*-Acylglycine and *N*-Acylserine. Apart from castor oil, the feedstock they had used was cottonseed oil. The surfactant produced with the lowest aggregation concentration was an excellent parameter, since it had a large surface adsorption. Sodium-*N*-Acylglycine produced from this research was 1.09×10^{-3} mol/L [18].

In additions, reactants or raw materials such as castor oil and cottonseed oil are also promising alternatives reactants that contain an acyl group when reacted with amino acids. The high fatty acid composition and abundance in Indonesia can be an opportunity for researchers and industry in Indonesia. As a step forward in the field of surfactant technology, it is hoped that in the future researchers can develop miscellaneous types of eco-friendly amino acid surfactants. Moreover, it will be an added value for the Indonesian economy, if amino acid surfactants use reactants from vegetable oils such as castor oil and cottonseed oil. Exploration of other raw materials is also expected to be the first step for the development of a compact and integrated production. This article will discuss about the research development and production, classification, behaviour and application of *N*-Acyl amino acid (NAAAc) surfactants. Amino acid based *N*-Acylamides (AAc) or NAAAc surfactants are next-generation biological surfactants. Miscellaneous studies in the future are also expected to be applied so that they can be considered for fabrication and scale-up processes.

1. Amino Acid

Amino acids (AAc) consist of amine groups (NH_2), carboxyl (CO_2H) and residues (R) which have neutral, acidic and alkaline properties [15]. When at pH 4.8 – 6.3 this is a manifestation of the dipolar or zwitterionic (isoelectric pH) state [17, 18, 19]. Amino acids that have the -L- configuration are easier to find than the -D- configuration [19, 20]. The selection of AAc in the manufacture of surfactants can substitute polar groups since it is an amphiphilic compound. Sources of AAc are very easy to find and there are more than 20 standard types of

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AAc (-amino acids used in the manufacture of protein biosynthesis) [19-22]. However, the use of -AAc in large quantities in the surfactant industry is still relatively low. The physico-chemical properties of amino acids can be seen in Table 1 as follows:

Tabel 1. The physico-chemical properties of amino acids [23]

Amino Acids	3-letter Abbrev.	Hydrophobicity	Molecular Weight (g/mol)	Molecular Formula
Tryptophan	Trp	-0.9	204.23	$C_{11}H_{12}N_2O_2$
Valine	Val	4.2	117.15	$C_5H_{11}NO_2$
Theronine	Thr	-0.7	119.12	$C_4H_9NO_3$
Arginine	Arg	-4.5	174.20	$C_6H_{14}N_4O_2$
Serine	Ser	-0.8	105.09	$C_3H_7NO_3$
Glutamine	Gln	-3.5	146.14	$C_5H_{10}N_2O_3$
Methionine	Met	1.9	149.21	$C_5H_{11}NO_2S$
Leucine	Leu	3.8	131.17	$C_6H_{13}NO_2$
Lysine	Lys	-3.9	146.19	$C_6H_{14}N_2O_2$
Isoleucine	Ile	4.5	131.17	$C_6H_{13}NO_2$
Histidine	His	-3.2	155.16	$C_6H_9N_3O_2S$
Glycine	Gly	-0.4	75.07	$C_2H_5NO_2$
Glutamic acid	Glu	-3.5	147.13	$C_5H_9NO_4$
Aspartic acid	Asp	-3.5	133.11	$C_4H_7NO_4$
Cysteine	Cys	2.5	121.16	$C_3H_7NO_2S$
Alanine	Ala	1.8	89.09	$C_3H_7NO_2$
Proline	Pro	-1.6	115.13	$C_5H_9NO_2$
Asparagine	Asn	-3.5	132.12	$C_4H_8N_2O_3$

It was reported based on surfactant synthesis research, that the use of AAc with short chain peptides such as L-glycine is an effective candidate for pharmaceutical applications [24]. While the use of long straight chain AAc such as L-lysine in the amidation of reactants will give high yields since surfactants are easier to synthesize [25]. However, it is possible that miscellaneous types of AAc can be derived to surfactant *N*-Acylamides [16, 26]. The miscellaneous types of AAc that can be used as feedstocks in the synthesis of *N*-Acylamides can be seen in Figure 1. as follows.

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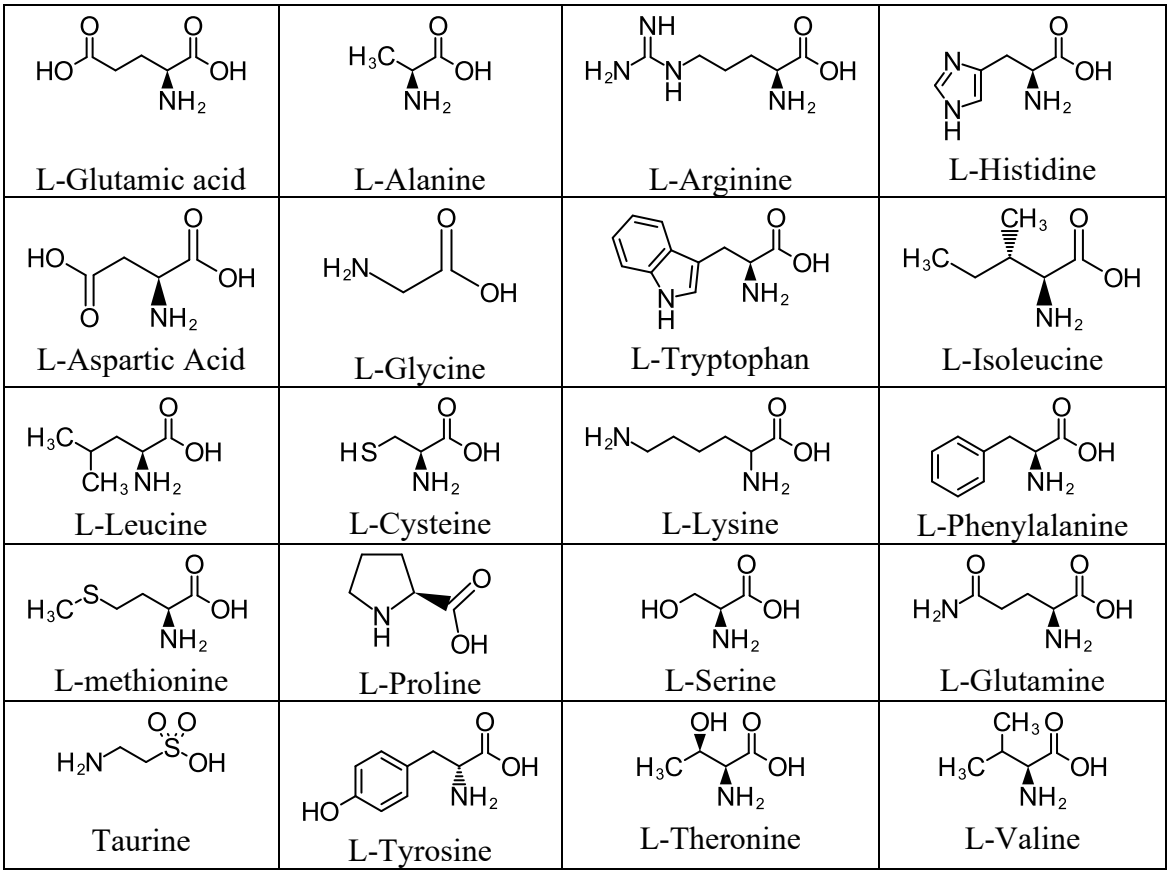

Figure 1. Molecular Structure of Various Amino Acids

According to Kimura et al [27], AAc can be derived to surfactant by reaction with hydrophobic components such as fatty esters, fatty alcohols, or fatty acids. The AAc-based surfactant synthesis pathway is divided into four basic reactions. These reactions are alkylation, acylation, amidation, and esterification. When AAc is reacted with fatty alcohol, it will produce long esteramine surfactant and this reaction is called AAc esterification. Meanwhile, the amidation process of AAc occurs when AAc is reacted together with pure amine with the product in the form of amidoamine surfactant. The AAc acylation reaction process using an acyl group compound will produce *N*-Acylamides or *N*-acyl amino acid (NAAAc) compounds. Meanwhile, AAc will undergo alkylation when it reacts with alkyl halide compounds to form *N*-Alkylamides surfactants or *N*-Alkyl amino acids. The four basic reactions in the AAc surfactant synthesis pathway can be seen as expressed in the diagram in Figure 2 as follows.

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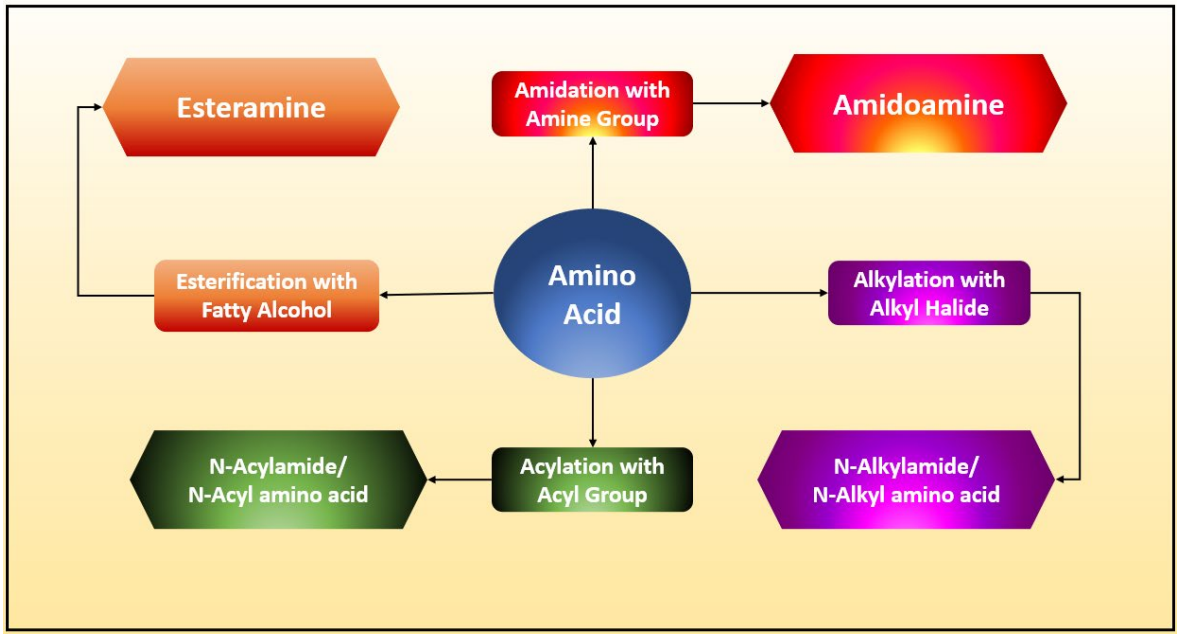

Figure 2. Hierarchical Diagram of Amino Acid-Based Surfactant Production (©author)

Under acidic and neutral conditions, the esterification and amidation pathways of AAc will produce cationic surfactants since they are protonated during the reaction process [16]. The AAc acylation pathway under neutral conditions produces AAc-based nonionic surfactants *N*-Acylamides [27]. The condition of AAc alkylation takes place under alkaline conditions which results in zwitterionic surfactants (types of *N*-Alkylamides or long chain *N*-Alkyl amino acids) [16]. Of the several types of AAc surfactants, the AAc-based *N*-Acylamides have wider applications and uses. Some researchers have found that the acyl group is very suitable to form aggregates of AAc surfactants such as lauroyl, myristoyl, oleyl and so on [19, 20, 27].

2. Amino Acid-based *N*-Acylamides Surfactants

N-Acylamide consists of more specific groups such as *N*-Acyl Amino Acid (NAAAc) which has perfect self-assembly properties in emulsifying, tolerance to calcium, and excellent dissolving efficiency [16]. Acyl groups such as palmitoyl and lauroyl can be derived from acyl halides [28], fatty acids [29], oils or triglycerides [30]. AAc such as L-glycine can be derived into *N*-acylamides including *N*-oleoeyl-glycine, *N*-stearoyl-glycine, *N*-arachidonoylglycine [31]. Examples of N-Acylamides synthesized using arachidonic acid or an arachidonoyl halide group with L-phenylalanine will produce *N*-arachidonoylphenylalanine. The structure of *N*-Arachidonoylphenylalanine can be seen in Figure 3 below.

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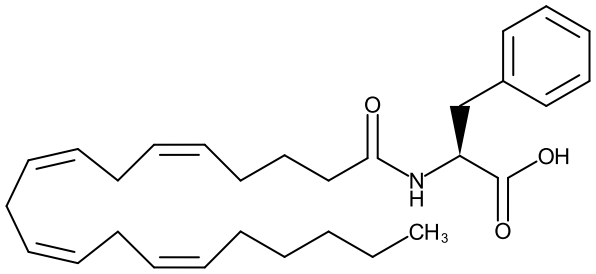

Figure 3. Structure of *N*-Arachidonoylphenylalanine

Surfactants *N*-Acylamides have a polar head equipped with a hydrophobic tail like other surfactants [32]. Observation of self-assembly activity of synthesis *N*-palmitoyl-stearoyl-L-serine exhibits a strong amide group with high polarity [33]. Synthesis of AAc-based *N*-Acylamides can be carried out using either basic, acidic or neutral AAc [15, 16]. Several types of surfactants *N*-Acylamides have long straight chains such as *N*-palmitoyl-L-glutamate and *N*-lauroyl-L-glutamate [34], while those containing cyclic aromatic groups are *N*-acylamides based on L-tyrosine and L-tryptophan. [16, 31] *N*-Acylamides are surfactants which predominantly have nonionic characteristics or do not carry a charge [35].

3. Amino Acid-based Gemini N-Acylamides Surfactants

Recently, researchers discovered a new class of surfactants composed of two hydrophobic groups and two hydrophilic polar heads [36]. This type of surfactant is referred to as the dimer or gemini type. Gemini surfactants have shown remarkable properties compared to conventional surfactants [37]. Gemini surfactants have a lower critical micelle concentration (CMC), which are very suitable for gene therapy drug delivery, even as viral vectors [38, 39].

Gemini surfactants can generally be of two types AAc and have a more complex structure [26]. Unlike conventional nonionic NAAAc, gemini surfactants can be nonionic, cationic, anionic or zwitterionic [26, 36, 38]. N-Acylamides gemini are obtained from the amino acids L-cysteine, D-cysteine [40] L-methionine and L-histidine [26]. Cysteine (Cys) based gemini surfactant $(C_8Cys)_2$ was synthesized by condensation using octyl isocyanate (C_8) in acetone for 24 hours and studied its interaction with -cyclodextrin [40]

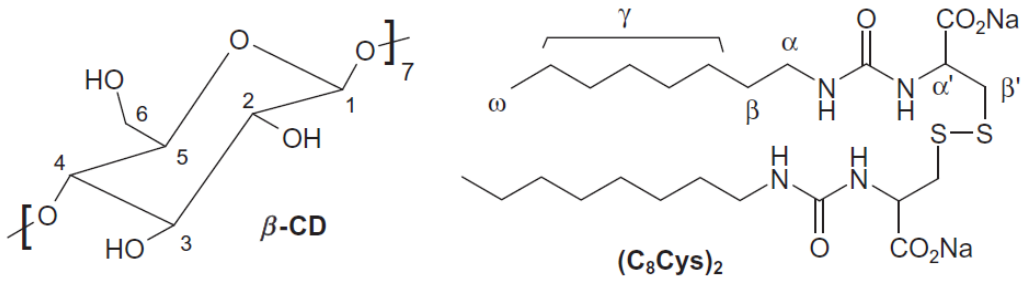

Figure 4. Scheme of Interaction structure between gemini surfactant $(C_8Cys)_2$ Cysteine and -cyclodextrin [40]

Pinazo et al. [25], also synthesized the L-histidine alkylamide-based gemini surfactant NAAAc using various reagents. Gemini NAAAc which has the lowest CMC of 0.025 mM is named Gemini Histidine $C_3(DMHNHC_{16})_2$ [26]. The Gemini surfactant $N^{\alpha}N^{\omega}$-bis-(N^{α}-

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lauroylarginine)-α-ω-alquildiamine or [$C_6(LA)_2$] tested on cervical cancer cells had the lowest EC_{50} of other gemini surfactants, despite the viability value of 50% [41].

4. Ionic Liquids Surfactants *N*-Acylamides based on Amino Acids

Ionic Liquids (ILs) are components of ionic salts in a liquid state [42]. Meanwhile, ILs surfactants are a combination of ILs with conventional surfactants [43]. This type of surfactant has been widely developed, has unique physicochemical properties with very high efficiency [44]. Synthesis of conventional ILs surfactants developed such as imidazolium, pyrrolidinium, ammonium, pyridinium and the like are toxic and do not decompose in the ecosystem [45]. AAc can be converted to *N*-acylamides which is combined with ILs to form AAc-based surfactant *N*-acylamides ILs [46]. NAAAc and choline-based (Cho) ILs surfactants that have been chemically synthesized are dicholine-N-lauroylaspartate, choline-*N*-lauroylsarcosinate, and choline-*N*-lauroylglycinate. The structure of dicholine *N*-lauroylaspartate can be seen in Figure 5 as follows.

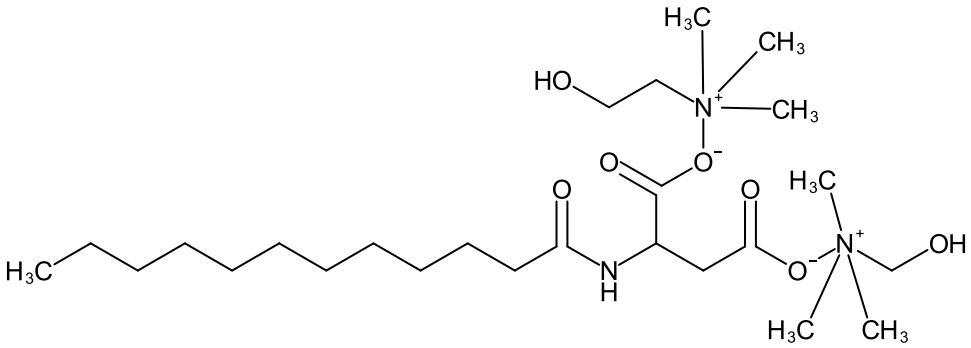

Figure 5. Surfactant Ionic Liquids $(Cho)_2$-*N*-lauroylaspartate [46]

Of the three compounds ILs *N*-Acylamide synthesized by Moshikur et al. [46], Ch_2-*N*-lauroylaspartate gave incredibly excellent results, with the lowest CMC value of 1.5 mM, surface tension CMC 34.5 mM/m. They also performed IC_{50} cytotoxicity testing on L929 mammalian cells which showed that the choline salt on ILs did not exert a significant toxic effect [46].

5. Production of *N*-Acylamides via Amino Acid Acylation

The AAc acylation reaction can be carried out chemically or enzymatically [27]. Another name for AAc acylation is fatty acid amidation. The *N*-Acylamides production process is carried out by reacting amines (AAc) with fatty acids or oils [30]. AAc acylation reaction in synthesis *N*-Acylamides of the *N*-stearoyllysine type are illustrated in Figure 5 [29].

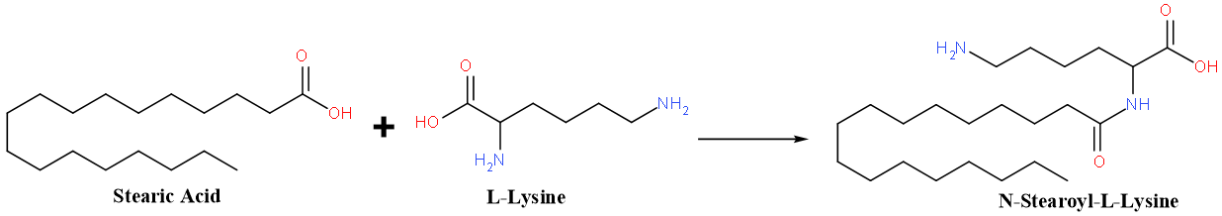

Figure 6. L-Lysine acylation using urea acid in the synthesis of *N*-stearoyl-L-lysine

The acylation conditions can be carried out in single solvent, binary solvent, or solvent free systems [29-31, 47]. In the use of a solvent-free system, catalysis was carried out using Novozym 435® lipase immobilized from *Candida antartica* with purity results in the range of

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20 – 90% [48]. Synthesis in a solvent-free state, sometimes lowers the reaction rate and leads to the deposition of residues, and this has been done in the synthesis of *N*-Oleoylamide [47, 48]. Masyithah et al [50, 51], also synthesized *N*-lauroylamide using immobilized lipase under 50°C, the purity reached 96.5%.

The problem in the enzymatic system for the synthesis of *N*-Acylamides is that the product is formed in small quantities [47, 49]. From the results of research by scientists Masyithah et al [49, 51], the amide production process using a chemical catalyst is the best pathway since the reaction is carried out faster. It was reported that the preferred chemical catalysts in the preparation of *N*-Acylamides include CaO, $ZrCl_4$, and heterogeneous catalysts which are selective on amidation or acylation [29, 49]. The development of research and synthesis of NAAAc via AAc acylation over the last 10 years and its application can be seen in Table 2 as follows.

Table 2. Previous research on the synthesis of NAAAc via acylation reaction.

***N*-Acylamides**	**AAc and Reactant**	**Research Purposes**	**Result**	**Ref.**
N-Stearoyl-L-lysine	L-lysine & Stearic Acid (SA)	Synthesis Optimization of Conversion	the optimum conditions, ratio of AAc/SA = 4/1, solvent ratio of 3/1, CaO 5% and the conversion reached 85.20%	[29]
N-Acylarginine	L-Arginine & Dodecanol (D)	Synthesis Optimization of Conversion	the optimum conditions, ratio of AAc/D = 4/1, solvent ratio at 3/1, catalyst concentration CH_3ONa at 3%, reaction time at 3 hours, temperature 70°C and the conversion reached 90%	[52]
N-Acylarginine	L-Arginine & tetradecanol (TD)	Synthesis Optimization of Conversion	the Optimum conditions at 7% CH_3ONa, 1/3 solvent ratio, AAc/TD mole ratio = 4/1, temperature at 90°C. Conversion reached 91.6%	[53]
N-Acylalanine	L-Alanine, castor oil	Aggregation testing	Reaction conditions 160°C, 5 hours yielded a hydrodynamic diameter of 150 nm, CMC 1.49×10-3 mol/L, CMC γ_{CMC} 38.79 mN/m and ΔG_{mic} = -11.33 kJ/mol.	[18]
N-Tetradecanoyl Phenylalanine (NTDP)	L-Phenylalanine, Tetradeconyl Chloride	Micellization and Solution Behavior Testing	The aggregation number (N_{Agg}) is >210 in the 100% NTDP fraction.	[54]

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Acylation can take place well when a polar solvent that dissolves amides (AAc) such as alcohol is used, as well as a non-polar solvent that is useful in dissolving fatty acids [53]. Some solvents that have been used include a mixture of distilled water and DMSO, n-hexane, isopropanol, and tert-amyl alcohol [29, 53]. Unfortunately, the selection of conventional organic solvents needs to be considered since that many are toxic and are not suitable when applied to pharmaceutical and food products.

The ratio of reactants or the ratio of AAc to fatty acids determines the conversion of the reaction. In the production of *N*-stearoy-L-lysine, the optimum ratio of lysine to stearic acid is 4/1 [29]. The optimum ratio value will differ depending on the type of AAc and process conditions [34]. The product *N*-Acylamides can be referred to as superamides when the reaction proceeds at an amide/fatty acid mole ratio of 1/1 [55]. Generally, fatty acid amidation takes place for 2-6 hours by chemical catalysis and last more than 24 hours enzymatically [47, 49, 52].

6. Parameters of *N*-Acylamides Surfactant

Critical Micelle Concentration and Surface Tension of *N*-Acylamides

In order to act as an efficient surfactant, NAAAc must be adsorbed to reduce surface tension (γ) and also form aggregates at a certain concentration [31]. Critical Micelle Concentration (CMC) is a parameter of an aqueous surfactant solution (in media) at various concentrations obtained from a semi-log plot of γ value [56]. Moshikur et al. [46], have measured γ ILs of NAAc choline-*N*-lauroylglycinate using a Kruss K100 automatic tensiometer (Hamburg, Germany) with an accuracy of 0.3 mM/n, γ water of 71.9 mN/m ± 1°C [46]. Other studies also use a similar method and the results of the analysis of CMC and γ_{CMC} can be seen in Table 3 as follows.

Table 3. Analysis of CMC and γ_{CMC} Surfactants NAAAc in Previous Researches.

N-Acylamides	CMC (mM)	γ_{CMC} (mN/m)	Ref.
Gemini Histidine $C_3(DMHNHC_{16})_2$	0.025	34.00	[26]
Gemini Histidine $C_3(DMHNHC_{14})_2$	0.040	36.00	[26]
N-Acylglycine	2.810	6.24	[30]
Cho-*N*-lauroylglycinate	2.400	36.50	[46]
$(Cho)_2$-*N*-lauroyaspartate	1.500	34.50	[46]
N-Acylalanine	1.860	38.25	[18]
N-Acylserine	5.860	35.70	[18]
Na-Cocoylalaninate	7.940	31.21	[56]
Na-*N*-Oleoylglutamate	0.220	31.42	[57]
Na-*N*-Capriloylglycinate	1.195	38.17	[57]

A low value of γ and CMC will be highly efficient in forming aggregates [46]. Based on Table 3, the surfactants with the lowest CMC were gemini NAAAc, followed by NAAAc ILs, and standard NAAAc. The extremely low CMC values in gemini NAAAc are due to multi-amide bond interactions. The increase in the gemini NAAAc γ value occurred along with the decrease in the hydrophobic chain length of the surfactant (C_{16} to C_{14}) [25]. Histidine amides support the formation of intermolecular hydrogen bonds of surfactants in forming aggregates [58, 59, 60]. The histidine-based Gemini NAAAc is composed of two charged cationic groups on the imidazolium, two hydrophobic alkyl groups that have similar behavior to gemini imidazolium [26]. Meanwhile, The CMC of NAAAc ILs and standard NAAAc have γ values

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that are not much different. The CMC of NAAAc ILs follow the properties of water, since the choline cation has similar properties to water [46]. The double-phase choline substituent (dicholine) in dicholine-*N*-lauroyaspartate is also thought to reduce CMC values [46, 59].

7. Toxicity of *N*-Acylamides

The use of surfactants for the pharmaceutical and environmental fields must be low in toxicity. Conventional surfactants are mostly very toxic to aquatic life, especially the cationic group. Toxic surfactants are more dangerous if they have a low CMC since they increase adsorption to the dispersion interface [46]. The increase in toxicity rates is also generally due to an increase in hydrophobic molecules [46, 60, 61]. NAAAc is dominated by non-ionic surfactants which are claimed to be low in toxicity [34]. Zhang et al. [62], tested the toxicity of surfactant *N*-lauroylsericin by CCK8 method on lymphoma, ramous and CEM cells. Promising results were found in CEM-type cells, that cell survival was up to 80%, and it was claimed that there was no significant cytotoxicity in these cells [62]. Moshikur et al. [46], also compared the toxicity of conventional surfactants SDS and Tween 80 with the three synthesized NAAAc IL surfactants namely choline-*N*-lauroylsarcosinate, choline-*N*-lauroylglycinate and dicholine-*N*-lauroylaspartate in mammalian cells. The results showed that the three surfactants had IC_{50} values > 100 M, while the comparison surfactants IC_{50} < 100 [46]. The higher IC_{50} value indicates that the surfactant has low toxicity [62].

8. Applications of *N*-Acylamides in Industry

Many claims from research results prove that AAc-based *N*-acylamides (NAAAc) are surfactant candidates that have biocompatible properties in miscellaneous fields. The Ajinomoto Company uses L-arginine, low-toxic L-glutamic acid and L-lysine-based NAAAc for the manufacture of shampoos, cosmetics and detergents [63]. The application of NAAAc into several versatile products can be seen in Table 4 below.

Table 4. Industrial Applications of NAAAc Surfactants in various fields.

***N*-Acylamides**	**Amino acid and Reactants**	**Applications**	**Ref.**
N-Palmitoylglycine	L-glycine, Palmitic acid or Palmitoyl chloride	Lipids Receptor G2A/GPR132	[31]
Gemini $(C_8Cys)_2$	L-Cysteine, Octyl isocyanate	Its Interaction on β-cyclodextrin	[40]
Ch-*N*-lauroyl sarcosinate	Sarcosine, lauroyl chloride, ChCl	Ionic Liquids Mixture	[46]
Na-*N*-Capriloylglycinate	L-Glycine, capric acid	Antibacteria Application	[57]
Na-*N*-oleylglutamate	L-glutamic acid, oleic acid	Antibacteria Application	[57]
Na-*N*-Lauroylsericin	Sericin, Lauroyl Chloride, & NaOH	Anti-tumor Drug Delivery	[62]
N-lauroyl-L-aspartic acid	L-aspartic acid, lauroyl chloride	Enhanced Oil Recovery	[64]
N-Oleoyltaurines	Taurine, oleic acid or oleoy lchloride	Endogenous Lipid Messenger	[65]

The application of NAAAc surfactants is a promising potential in miscellaneous fields. Several studies have also been carried out on the manufacture of biolubricant based on glutamic acid-derived NAAAc [66]. Gemini N^{α}-lauroylarginyl-phenylalanine and glutamic acid

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derivatives are also used as antimicrobials in the pharmaceutical industry [15]. The study conducted by Zhang et al. [62], silk protein is fermented to the amino acid sericin for the production of *N*-lauroylsericin. When the concentration of *N*-lauroylsericin was 100 µg/ml, this surfactant was able to deliver the drug cytarabine to inhibit the growth of CEM and ramous tumors with an inhibition level of 82.09±2.69% after 48 hours [62]. The mechanism for the formation of surfactant aggregation with an amino acid polymer (protein) myoglobin can be seen in Figure 7 [67].

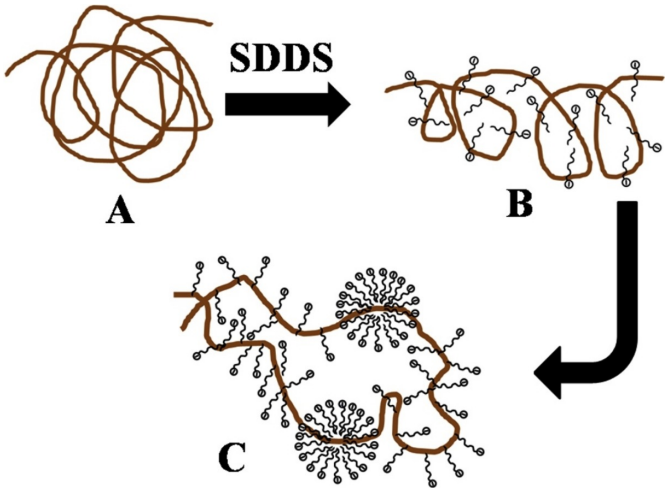

Figure 7. Application of sarcosine amino acid surfactant for myoglobin protein binding [67].

Pharmaceutical applications can be seen from Mondal et al. [67] who studied the interaction of Sodium-*N*-dodecanoylsarcosinate (SDSS) with myoglobin (an oxygen-rich storage protein). The results showed that the surfactant formed aggregates with the myoglobin protein. Based on (Figure 7) Myoglobin (A) with a helical structure undergoes binding (B) when the concentration of Na-*N*-dodecanoylsarcosinate is increased. JASCO J-815 CD (circular dichroism) spectrometer. when the highest surfactant concentration was at 2.40 mM, it was found that protein random coils had reached 45.42% greater than other conditions. This random coil is a manifestation of the formation of aggregate bonds between surfactants and myoglobin (C).

In the petroleum industry, *N*-lauroyl-L-aspartic acid was applied as an enhanced oil recovery (EOR) with results showing that the oil recovered 11.19% at a salinity of 2000 ppm [64]. In petroleum drilling, the surfactant NAAAc had applied as a wetting agent and EOR. The mechanism of wetting of carbonate rocks through hydrophobic interactions on petroleum molecules can be observed in Figure 8 [56].

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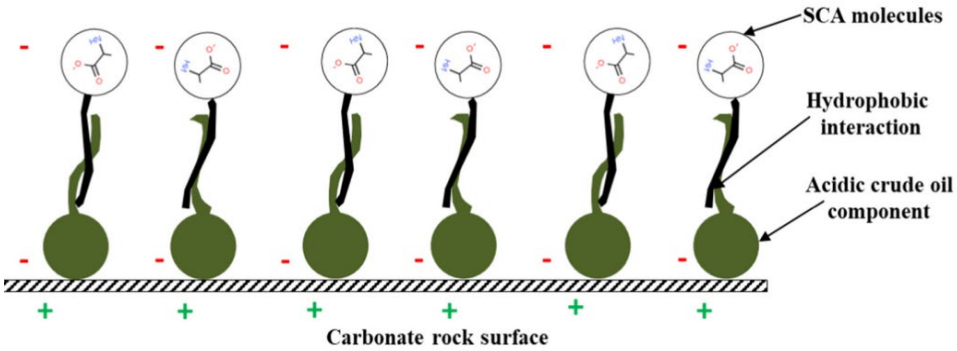

Figure 8. The mechanism of wetting of carbonate rocks via hydrophobic interactions [56]

Sodium-*N*-Cocoylalaninate (SCA) was applied as the EOR. SCA even showed excellent performance at high salinity conditions. the wetting mechanism of the hydrophobic group heads in the oil recovery process can be seen in Figure 8 [56]. The aggregation phenomenon is characterized when the SCA concentration is increased to the highest state. There is a change in enthalpy and entropy due to dehydration of the hydrocarbon chain (crude oil). SCA has also been shown to be effective in increasing the wettability of quartz and $CaCO_3$ rocks, as well as forming thermodynamically stable micelles during the recovery process.

9. Considerations for the Use of Bioreactors for the Production of N-Acylamides in the Biosynthetic Pathway

Chemical synthesis of NAAAc is a cost-effective production process since it is obtained in a short time and does not require expensive raw materials. However, the product cannot be applied to pharmaceuticals and foods. NAAAc for pharmaceutical and food purposes must be produced biosynthetically. Kubicki et al. [68] explained that in the biosynthetic pathway, fatty acids and hydroxy fatty acids are a source of metabolism for bacteria. In (Fig. 9), it is hypothesized that amino acids are catalyzed by acyltransferase to produce a class of lipoamino acid biosurfactants.

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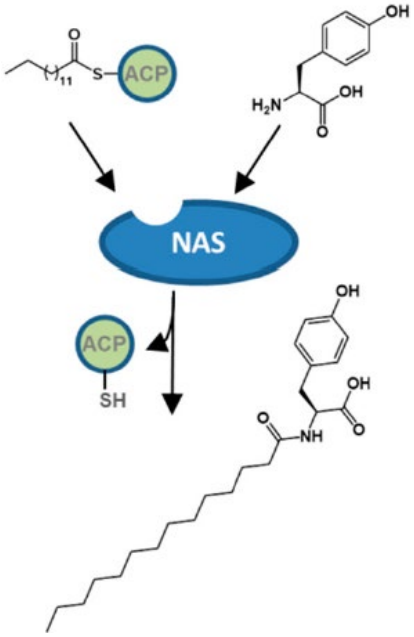

Figure 9. Scheme of NAAAc biosynthesis mechanism with amino acids and hydroxy fatty acids [68]

Biosynthesis of the lipoamino surfactant *N*-Myristoyltyrosine via acyltransferase or synthase. The production of NAAAc in the biosynthetic pathway is a very expensive step, since in addition to being quite a long process, it requires cell culture (microbes) or enzymes which are very expensive and complicated isolation. The NAAAc product obtained from biosynthesis is a class of NAAAc biosurfactants. These problems are a demand for researchers and the biotechnology industry in developing bioreactors for the biosurfactant production process.

In the process of designing the bioreactor so far, it is still used on a laboratory scale. In the design of the bioreactor for the synthesis of NAAAc surfactants, the selection of construction materials such as grade A stainless steel is dominated by food grade materials. Other dimensional parameters such as the volume of the bioreactor shell (V_s), shell thickness (t_s), the volume of the bioreactor head (V_h) and the total bioreactor volume (V_t), as well as the design of the agitation system are needed. In determining the volume of the biochemical reactor shell and head, it is generally possible to refer to equations (1), (2), and (3) which are expressed as follows.

$$V_s = \frac{1}{4}\pi D_t^2 H_s \quad (1)$$

$$V_h = \frac{\pi}{24} D^3 \quad (2)$$

$$V_t = V_s + n.V_h \quad (3)$$

The design of biochemical reactors is usually determined by the ratio dimentions of the bioreactor height to its diameter (H_s/D_t). The value of n is the number of head designed for the biochemical reactor [69]. The NAAAc biosynthesis process using bacteria is analogous to the production of surfactin (*Baciullus subtilis*) to produce sulfuric organic gases [70]. Several researchers have also carried out the production of surfactants using bioreactors. The enzymatic process of amino acids can also be controlled by pH and temperature in a bioreactor [71].

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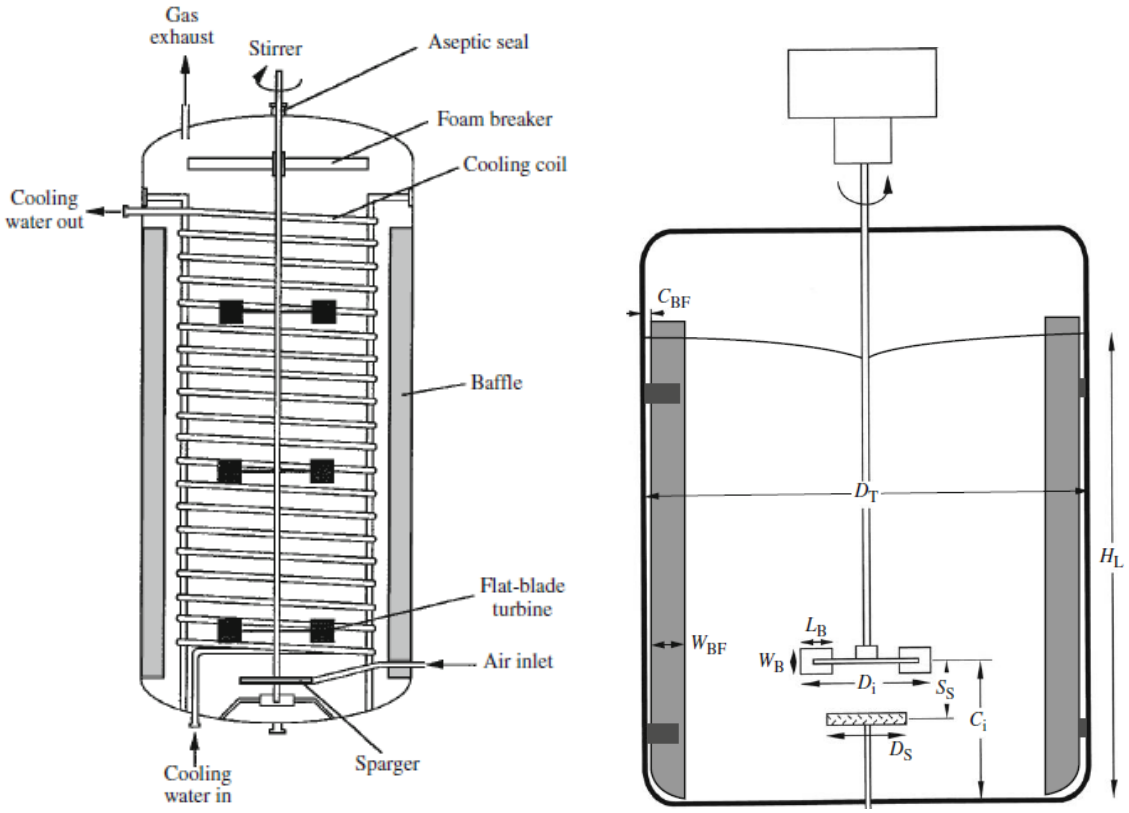

Figure 10. Bioreactor design: (a) Design of a biochemical reactor with agitation system (b) geometric specifications of a bioreactor for the production of surfactant NAAAc with a stirrer [71].

Where C_{BF} = baffle clearance, W_{BF} = baffle width, W_B = blade width, C_i = impeller clearance, D_S = sparger diameter, S_S = sparger separation, D_i = impeller diameter, D_T = bioreactor diameter, L_B = blade length and H_L = liquid height [71, 72]. In the construction of bioreactors it is suggested to increase the capacity by 20% as a factor of safety [69]. Several production systems of amino acid surfactants and other biosurfactants that have been integrated with the purification/separation of the mixture have become very interesting studies. The design of the biofilm bioreactor developed for the production of amino acid-based surfactin and the bacteria Bacillus subtilis by Brück et al. [73], can also be applied in enzymatic pathways and acyltransferase for the manufacture of NAAAc. The reactor model that can be developed for NAAAc products can be seen in Figure 11 as follows.

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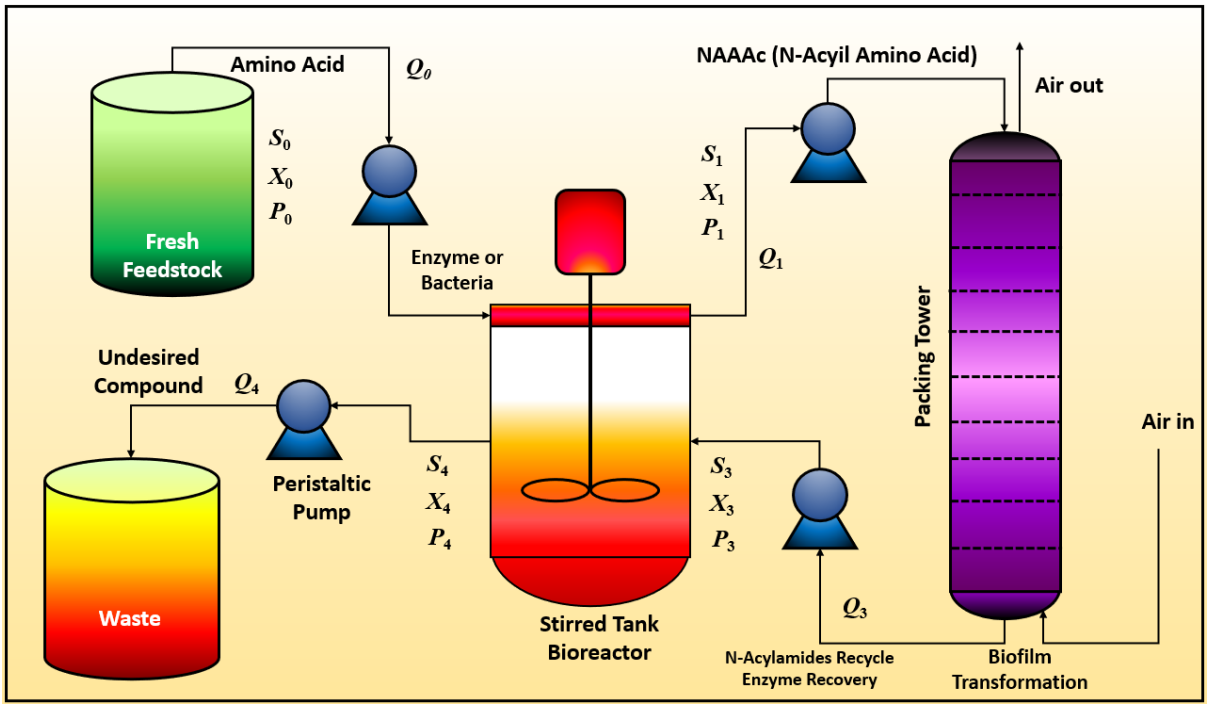

Figure 11. Process Flow Diagram of the NAAAc Production using a bioreactor (©author)

Amino acid feedstock or amino hydroxy amino acids are incubated and undergo biochemical reactions enzymatically or forming complex bioreaction processes in the bioreactor. According to Bruck et al. [72], the use of biofilm in surfactin biosynthesis from *Basillus subtilis* substrate will also increase its productivity and this result is 37% larger than not using a biofilm. The production model in Fig. 11 can be used as a consideration for the production process. In the above case, the simple substrate mass balance (S) follows the law of conservation of mass and this is assumed to be in a continuous state in the bioreactor..

$$(Q_0S_0 + Q_3S_3) - (Q_1S_1 + Q_4S_4) + r_sV = V\frac{dS}{dt} \quad (4)$$

Simply, Q is the volumetric flow rate, S is the substrate concentration, r_s is the specific substrate consumption rate and V is the volume of fluid during the process. In industry, generally the volumetric flow rate is controlled continuously ($Q_0 = Q_1 = Q_3 = Q_4$) and the process becomes steady. As a result, the accumulated value of $dS/dt = 0$ or there is no process accumulation. Thus, it can be seen how much the rate of consumption of feedstock needed is equivalent to equation (5) which is expressed as follows.

$$-r_s = \frac{Q}{V}\{Q_0 + Q_1 + Q_3 + Q_4\} \quad (5)$$

In another study, Guez et al. [74], designed a bioreactor system for the production of biosurfactants through a biosynthetic process. The surfactin they produce given a lot of foam during the bioreaction process, so it is designed with a foam collector system as shown in Figure 12 below

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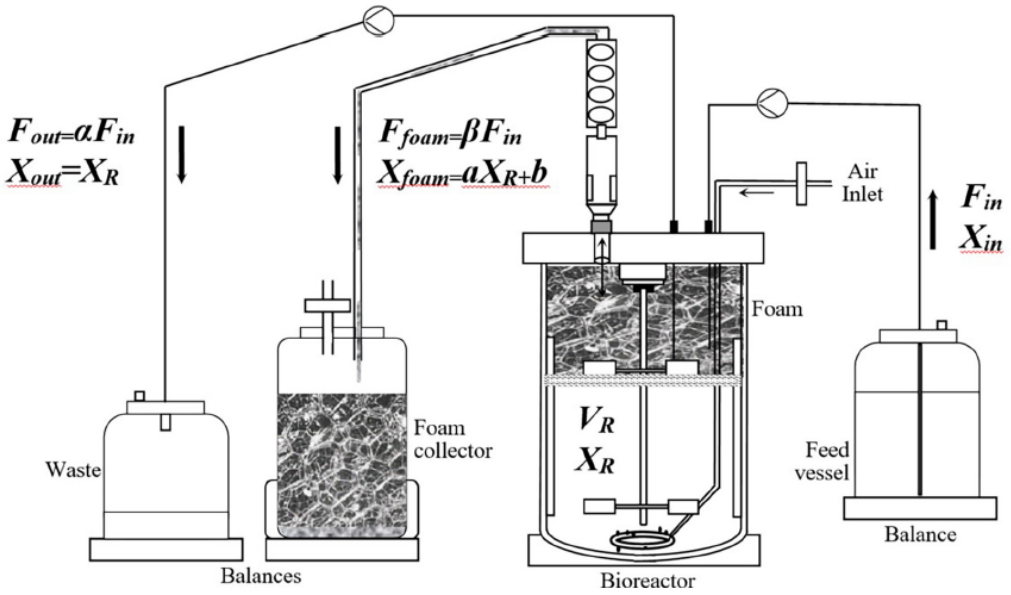

Figure 12. Schematic Process of Surfactant Production with an overflowing continuous culture system [72]

Both surfactin or NAAAc are derivative surfactants of amino acids (AAc). So for the production of NAAAc using bioreactor technology can be considered. The theoretical model for this overflowing condition can be expressed in the following mass balance [72].

$$V_R \frac{dX_R}{dt} = X_{in}F_{in} + V_R \mu X_R - X_R F_{out} - X_{foam}F_{foam} \quad (6)$$

Where the specification V_R is the volume of the bioreactor, X_R is the concentration of biomass in the reactor, X_{in} is the inlet concentration, F_{in} is the water inlet rate, F_{out} is the outflow rate, X_{out} is the output concentration in the waste. While the foam subscript indicates the state when the foam was formed [72].

10. Considerations for Scale-up Process for Production of N-Acylamides

Based on studies of biosurfactant production using previous bioreactors [70 – 72], the results obtained were larger, since they utilize a larger scale than used glass equipment. Processes can also be controlled. The complex synthesis of NAAAc is indeed very expensive, especially the costs for the purification and isolation of the product. However, the scale-up process is believed to be able to reduce costs since it can be carried out continuously and further control processes can be guaranteed. Although the capital required for the development of a scale-up bioreactor to process amino acid-based NAAAc products is quite large, it is necessary to study the economics of the surfactant industry. Evenmore, NAAAc products have very wide applications and are needed in almost all areas of life. In addition, Ajinomoto Company currently produces a lot of oleofood and oleochemical products based on amino acids, including NAAAc products.

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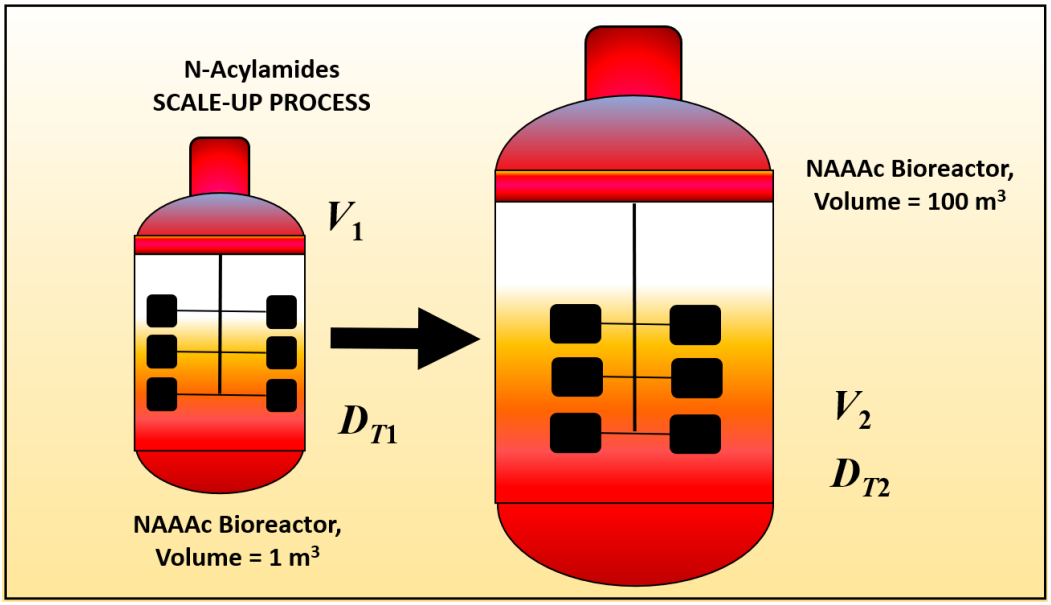

Figure 13. Scheme of Bioreactor Scale-up Process for Production of NAAAc (author ©)

The most important thing before doing a scale-up process is compiling and determining the production process based on the flow process diagram and how the production process system is. Industrial experts and process scientists have developed miscellanoeus methods or processes that are more economical. The construction of a bioreactor with a larger size than the previous size is also not arbitrary. The approach that is usually used for that is the scale-up ratio which is expressed as equations (7) and (8) below.

$$\frac{V_2}{V_1} = \left(\frac{\frac{\pi D_{T2}^3}{4}}{\frac{\pi D_{T1}^3}{4}}\right) = \left(\frac{D_{T2}^3}{D_{T1}^3}\right) \quad (7)$$

$$R = \left(\frac{V_2}{V_1}\right)^{1/3} = \left(\frac{D_{T2}}{D_{T1}}\right) \quad (8)$$

R is the ratio of the scale-up process, while the subscripts (1) and (2) represent the variables of the bioreactor diameter and volume before and after scale-up respectively [73]. For NAAAc production, the implication is that the mixing time required when scale-up is carried out will increase. The feedstock mixing time in the bioreactor is expressed in equation (9) [71].

$$t_m = 5.9\, {D_T}^{2/3} \left(\frac{\rho V_L}{P}\right)^{1/3} \left(\frac{D_T}{D_i}\right)^{1/3} \quad (9)$$

It is known that t_m is the mixing time to be achieved, ρ is the density of the feedstock of amino acids and other reactants. V_L is the volume of liquid, while P is the power required to drive the agitator [71], that is during the feedstock stirring process in the bioreactor for the production of NAAAc.

This causes another variable to increase when scale-up is carried out, namely the power variable (P). The enlarged volume of the bioreactor will increase the amount of power required, since the size of the agitator in the bioreactor is also enlarged, thus requiring more energy. The phenomenon is described in the equation which is expressed as follows.

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$$5.9\ {D_T}^{\frac{2}{3}}{}_1\left(\frac{\rho_1 V_{L_1}}{P_1}\right)^{1/3}\left(\frac{D_{T_1}}{D_{i_1}}\right)^{1/3} = 5.9\ {D_T}_2{}^{\frac{2}{3}}\left(\frac{\rho_2 V_{L_2}}{P_2}\right)^{\frac{1}{3}}\left(\frac{D_{T_2}}{D_{i_2}}\right)^{\frac{1}{3}} \quad (10)$$

$$D_T{}^{\frac{2}{3}}{}_1\left(\frac{V_{L_1}}{P_1}\right)^{1/3} = {D_T}_2{}^{\frac{2}{3}}\left(\frac{V_{L_2}}{P_2}\right)^{\frac{1}{3}} \quad (11)$$

The D_T/D_i ratio is considered the same if the geometry of the bioreactor does not change. Likewise, the density of amino acid raw materials and reactants did not change before and after scale-up, so that equation (11) was obtained. If rearranged, the following equation will be obtained.

$$P_2 = P_1\left(\frac{V_{L_2}}{V_{L1}}\right)\left(\frac{D_{T_2}}{D_{i_2}}\right)^2 \quad (12)$$

Based on equation (12) above, this is where the statement appears that it is necessary to consider various aspects before carrying out the scale-up process. P_2 is the power required after the scale-up process and this is needed to drive the motor during the bioreactor stirring process [71]. If the volume of the bioreactor undergoing scale-up is getting bigger, then a longer mixing time of amino acid reactants is required, and the effect is also caused by a large diameter, so a larger agitator/impeller diameter is required. The large diameter of the agitator increases the power requirement (P_2), so that the use of electric current is greater and increases the cost.

However, the above are common obstacles and challenges that are usually faced in several industries. The next is how to develop a system and use more efficient energy and exergy and its realization. As far as the review that has been carried out, based on the data that has been summarized as in Tables 1 – 4, the use of AAc as a natural feedstock for the production of N-Acylamides is highly considered and recommended so that a scale-up process can be carried out in the future. Further study of the scale-up process is also needed as an initial step in industrial development so that the optimization of the use of amino acids in the production of biocompatible surfactants on a large scale can be further developed.

CONCLUSION

This article summarized study on the use of AAc as a natural feedstocks for the production of various *N*-Acylamides. The hierarchy of combining amino acids with hydrophobic tails (fatty compounds) in the synthesis of *N*-Acylamides could be traversed from various reaction pathways. The results of the synthesis of *N*-acylamides based on AAc had high biocompatibility properties and were proven to be less toxic than any conventional surfactants. Although the use of AAc was still low due to high production costs, the development for the production of NAAc was very suitable for the food, pharmaceutical and environmental fields of the future. The development of more advanced surfactant technology could be seen from AAc-based gemini surfactants which were biological and had very low CMC. Catalytic process was the most efficient pathway to produce amide since the reaction was carried out faster by using chemical heterogeneous catalyst.

The biggest obstacle and challenge in exploiting the current use of AAc was the high cost of production. This was due to the demand for purity of AAc by the isolation process. The high cost of producing AAc-based *N*-Acylamides for food, cosmetic and pharmaceutical uses was also a major problem since these surfactant products were required to be free from toxic chemicals such as solvents and other supporting materials. Researchers and scientists from

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around the world are also working hard to minimize this problem by reducing cost-effective process optimization. AAc-based *N*-Acylamides had strong potential for widespread application in various industries. The NAAc production process that had the highest efficiency so far was the production through a catalytic chemical reaction, namely the fatty acid amidation process or amino acid acylation. While the biosynthetic pathway with enzymes and bacteria had low production efficiency, the resulting product was quite compatible with the highest purity. The application of AAc-based *N*-Acylamides in various fields is very promising so that it can be considered for scale-up processes in the future.

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