Applications of primary alkylamines in nanoparticles formation and stabilization

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ABSTRACT
Fatty amines or primary alkyl-amines like hexylamine, Octylamine, Decylamine, Dodecylamine, Tetradecylamine, Hexadecylamine, and Octadecylamine have been used widely in nanoparticles formation, preparation and for stabilization issue; due to their low toxicity and easily utility. The most common use of fatty amines in many research work that has been reviewed is as capping and stabilizing agent for the nanoparticles, and that is related to their abilities to stabilize nanoparticles and reduce Ostwald ripening after nanoparticles formation. Moreover, Fatty amines surfactants have been reported in many research works to assist the formation of monodisperse size because they can be adsorbed on the surface of nanoparticles which limit variability in nanoparticles size and also they can form a coat around nanoparticles that prevent agglomeration or aggregation of nanoparticles. Also, other uses that have been addressed for fatty amines as they served as hydrophobic part due to hydrocarbon chain tail. These tails for fatty amines especially those with long hydrocarbon chain more than 12 carbons like; Dodecylamine C12, tetradecylamine C14, hexadecylamine C16 and octadecylamine C18 can be fabricated and conjugated with other molecules or polymers for many nanoparticles synthesis which can help in the self-assembly of nanoparticles. Moreover, due to their high boiling point; they used as solvents and reaction catalyst facilitate the formation of nanoparticles. Finally, fatty amines surfactant used as the ligating compound also assist the formation of nanoparticles.

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INTRODUCTION

Alkylamines are studied and used widely in many research articles as building blocks in a several discipline including synthesizing of polymers, dyes, pigments, plasticizing agents and also used in pharmaceuticals field as a surfactant that were used extensively in the cleanser and cosmetic agent. Alkylamine plays an important and essential role in chemical industries (Wang et al., 2020). Also, alkyl primary amines are considered of special significance in chemistry field because they serving as intermediates compounds for derivatization reactions, so many researchers focus in their work to produce an economical, safe and efficient synthesis method for the primary amine. This review will mainly focus on the uses of primary alkylamines in nanoparticles formation as a surfactant molecule that has a hydrophilic head (NH₃⁺) and a hydrophobic tail. Surfactant molecule can self assemble into micelle aggregate, so alkylamines for micelles when dissolve in an appropriate solvent. Also, this review mentioned that Alkylamines used in nanoparticles stabilizing as capping agent or stabilizing agent.
Moreover, many articles reviewed that alkylamines can be used as solvent or reaction catalyst assist formation of nanoparticles due to their high boiling point.

APPLICATION OF PRIMARY ALKYLAMINE IN NANO PARTICLES PREPARATION

Nanotechnology

Nanotechnology techniques that produce nanoparticles are considered one of the most potential and promising methods in the drug delivery field. Nanoparticles have been utilized as nanocarriers for the delivery of many anticancer cytotoxic drugs. Moreover, nanoparticles have many applications in clinical cancer diagnosis (Pérez-Herrero and Fernández-Medarde, 2015).

Recently several nanoparticles-based drug delivery approaches were introduced for drug delivery purposes, as shown in Figure 1 including dendrimers, liposomes, inorganic nanoparticles and micelles. Nanoparticles are believed to extend the circulation time in the blood, passively accumulate at tumor sites and avoid distribution to normal tissues (Hema et al., 2018).

As Surfactant unit producing micellar aggregate

Micelles are produced in aqueous media when amphiphilic molecules (comprised of hydrophobic and hydrophilic units) self-aggregate into nano entities consisting of the inner hydrophobic core and an outer hydrophilic shell. The inner core works as a reservoir for the loaded hydrophobic drug(s), which is (are) hold inside either through physical trapping or solubilization. The hydrophilic shell enhances the stability of the micelles and shields them from adsorption, thus promoting their long-term circulation. Moreover; their smaller size that ranges from 10-20 nm[11] permits for their build-up concentration in the pathological area, for example, cancer that has leaky vasculature. Micelles are among the most effective and well-studied tools for delivering lipophilic and cytotoxic drugs that can be loaded within their hydrophobic cores (Hema et al., 2018). Since the alkyl amine has a cationic head which is ionized amine head (NH₃⁺) and a hydrophobic tail characterized by alkyl chain so many studies use primary alkylamines as surfactants molecules which have the ability to form and produce a stable micellar system. Micelle structure was emphasized in Figure 2 (Saha et al., 2019).

In research work conducted by Koehler and his colleagues (Koehler et al., 2000). Enhance formation of worm micelles by using a combination of ionic surfactant; one contains cationic head and the second one is an anionic head surfactant. Salt type of alkylamine surfactant cetyltrimethylammonium tosylate has a cationic head and long hydrocarbon tail (C16). This alkylamine recognized to have the capability to form worm micelles when dissolved in an aqueous solvent, but in this work; Koehler and his colleagues enhance worm micelles formation by addition of oppositely charge anionic surfactant (sodium dodecylbenzene sulfonate) to cationic surfactant (cetyltrimethylammonium tosylate). The enhancement effect related to charging neutralization which diminishes potential activity for the micellar surface. In order to investigate the formation of worm micelles; both Small-angle neutron scattering and rheology were used in this study as a method for characterization (Koehler et al., 2000).

In another article conducted by Sahara and Harada (2018), they were used chloride salt of several alkyl amines as a surfactant molecule to prepare a micellar system. Alkyl side chains in this research were ranging from C1 to C12. Only Chloride salt of pentylammonium (C5amine) and -heptylammonium (C7amine) synthesized in this work; by dissolving them in an aqueous mixture of (Ethanol with aqueous HCL) then make recrystallization. The calorimetric experiment used to detect micellar development, so several thermodynamic factors were studied like partial molar enthalpy for the solute, Gibbs energy and entropy.

As emphasized by Mirgorodskaya and his colleagues in their work they showed that Critical Micellar Concentration (CMC) of chloride primary alkyl amines (chloride salt of Decyl and Octyl amine) depend on protonation degree of head group. They conclude that as the percentage of protonation increase, the concentration needs to form micelles also increase (Mirgorodskaya et al., 2000). Table summarized CMC values for chloride salt of Decylamine and Octadecylamine depending on protonation degree of amine head (Table 1).

Also, Revere Micellar system prepared in study promoted by Sarkar and his colleagues (Sarkar et al., 2016) using cationic surfactant then conjugated to carbon dots via a surface modifier. Hexadecylamine (HDA) used to prepare carbon dots and cetyltrimethylammonium bromide for Micellar system preparation in the presence of isooctane/n-hexanol/water. Carbon dot system showed the smallest size ranged between 5 to 7 nm and 15-20 nm size for micellar system, but when micellar system conjugated to hydrophobic carbon dots, the size increased greatly to 200 nm. X-ray photoelectron spectroscopy, Transmission electron microscopy
(TEM), luminescence spectrometer, Dynamic light scattering, FT-IR, and UV-VIS spectrophotometer were used as methods for characterization.

Since the surface-active agent has the ability to get adsorbed on surfaces; Wang et al. (2016) studied adsorption mechanism of dodecylamine (DDA) self aggregate system at different pH 3, 10 and 12. The study revealed that maximum adsorption effect occurs at pH 10 due to tightly hydrophobic layer. The hydrophobic layer tightness decreases at pH 3 and becomes very weaker at pH 12. So the order of tightness depends on pH 10> 3>12. Moreover, they conclude that dynamic molecular simulation strong method for prediction adsorption mechanism of surfactant at mineral oil surfaces.

**As a hydrophobic part fabricated with other molecules to enhance self-assembly of nanostuctures**

Amphiphilic structures can form by conjugating hydrophobic molecules to hydrophilic molecules. When the concentration of these amphiphilic structures higher than aggregation concentration, they will spontaneously self assemble in aqueous media and form nano-entities or nanoparticles like micellar system, liposome and hydrogel.

**Micelles**

The hydrocarbon chains of alkylamines, especially Long hydrocarbon chain of HAD and ODA were used as hydrophobic part fabricated with polymers or other hydrophilic parts to produce new surfactant which has good balance between hydrophilic and hydrophobic part. Consequently, this will enhance self aggregate characteristics properties of surfactant molecule leading to form a micellar system. This was shown in a study conducted by Castelli et al. (2005) which synthesize a novel surfactant molecule by incorporate HDA as a hydrophobic part in aspartamide molecule and made new modified aspartamide surfactant. Modified aspartamide used to prepare the micellar system in order to enhance entrapment and release efficiency for ketoprofen drug and also to decrease ketoprofen side effects, especially on Gastrointestinal and renal system. In another work conducted by Saha et al. (2019), they used hydrocarbon chain of dodecylamine to facilitate the formation of bovine serum albumin nanoparticle through conjugation between carboxyl groups of amino acid with the amine group of Dodecylamine via amide coupling reaction. Once the reaction formed, protein spontaneously self assemble in nanoparticles with a positive surface charge, as shown in Figure 2, which improve doxorubicin encapsulation.

Moreover in this area Le and Kim in their work they enhanced polymeric micellar formation; by grafting a hydrophobic and hydrophilic part to polyeuccinamide backbone. C18 fatty amine (Octadecylamine) used as a hydrophobic part in that grafted polyeuccinamide polymer (Le and Kim, 2019).

**Liposome**

Only one research study conducted by that used primary alkyl amine as an enhancer for liposome formation. In this study, polysialic acid was conjugated to octadecylamine (Luo et al., 2018).

**APPLICATION OF PRIMARY ALKYLAMINE IN NANO PARTICLES STABILIZATION**

**Capping agent and Stabilizing agent**

The main reason for unwanted and frequently irreversible processes for synthesized nanoparticles with a modified surface is the aggregation or agglomeration; which defined as the presence of excessive chemical activity on these surfaces of nanoparticles. When Nanoparticles aggregated to each other, this will lead to a decrease in; surface area, interfacial free energy and eventually lead to stopping nanoparticles activity as shown in Figure 3. So it is very important to produce nanoparticles with reasonable stable surfaces. As mentioned by Arora and Jagirdar (2012), many of stabilization techniques involve the addition of dispersant molecules like, for example, electrolytes or surface-active agent. A variety of stabilizing agents is used to reduce nanoparticles aggregating and also used to functionalize the nanoparticles for the desired applications.
Table 1: Schematic representation for some primary alkyl amine CMC

| Alkylamine                  | Degree of protonation (%) | CMC * (mol/l) |
|-----------------------------|---------------------------|---------------|
| Chloride salt of Decylamine | 0                         | 0.00095       |
|                             | 25                        | 0.001         |
|                             | 50                        | 0.0013        |
|                             | 75                        | 0.0027        |
| Chloride salt of Octadecylamine | 0                     | 0.008        |
|                             | 50                        | 0.01          |
|                             | 75                        | 0.0135        |

CMC critical micellar concentration

Figure 3: Effect of applying of Alkylamines like Hexadecylamine (HAD) as capping and stabilizing agent

Figure 4: Different shapes of organogel according to chain length of alkylamine

It is well known that nanoparticles suffer from aggregation and clumping due to instability issues especially after solvent drying or through drying step, so in order to increase the stability of nanoparticles, alkylamines were added as capping and stabilizing agents. Alkylamines were able to form a protective layer around nanoparticles prevent their aggregation.

In work done by Wasiakan and his colleagues that involve investigation effect of primary alkyl amines as stabilizing agents stabilizing agent for polymeric nanoparticles. Alkylamines used were Hexylamine, Octylamine (OA), Decylamine (DA), and Benzylamine. Dextran was modified by reacting with alkylamines, so alkylamines form the backbone of dextran and consequently enhances the formation of nanoparticle. Morphology of nanoparticle tested using SEM and size analysis. Stability of nanoparticle was tested using different pH (Wasiak et al., 2016).

Growth mechanism of Cd-Se nanoparticles capped by HDA was studied by Oluwafemi and Revaprasadu (Oluwafemi and Revaprasadu, 2009). The result indicated that there are two different growth period. First growth period occurred within 10 minutes of preparation implicated by fast growth and narrow size distribution then the second period occurred in the final state characterized by the slow rate of growth and broad size distribution. Morphology result showed that nanoparticles have a spherical shape with Final diameter size equal to 3 nm and small standard deviation equal to ± 8 nm (Oluwafemi and Revaprasadu, 2009), so this study indicates strongly that alkylamines affect and control the size of nanoparticles prepared.

In order to increase the stability of iron oxide; a hybrid nanostructure was synthesized, which consist of nanoparticles and nanotubes. Iron oxide was incorporated in both structures and capped by hexadecylamine. 2.1 nm reported to be diameter size for nanotube loaded with iron oxide. Amount of iron was determined and calculated using Instrumental Neutron Activation Analysis (Saleta et al., 2008).

Miscellaneous uses or other uses for alkylamines in nanoparticle formation

Luo et al. (2009) in their study used octadecylamine as an agent to determine the crystallinity phase for nickel nanoparticle. They conclude that octadecylamine ensure the formation of hexagonal face packed for nickel nanoparticles. Han et al. Developed a new method for preparing nanoparticles in the presence of alkylamines as ligating solvent (Han et al., 2009).

Octadecyl-amine and Dodecyl-amine were shown to enhance gold nanoparticles formation by working as a catalyst Ligand that enhances the transfer of gold nanoentity from the aqueous phase to the organic
phase (Li et al., 2013). Moreover, Yu et al. (2006) in their study used alkylamine as Hydrolysis catalyst in the preparation of Silicon dioxide microparticles and they have been shown that as the size of dodecylamine increase the diameter increase. In another study conducted by Nethravathi and Rajamathy (2006), they prepared a Colloidal system by using alkyl-amines as an intercalating agent because Alkylamines can intercalate with graphite oxide and form nanoparticles.

Liu et al. (2013) confirmed that alkylamine could form many H-bonding with polymer (ethylene glycol) and work as gelator and end with the formation of gel network as shown in Figure 4, also they conclude that Alkyl chain length affects consistency and shape of organogel formed: Lamellar shape formed in organogel contains dodecylamine, Worm-like structure formed with tetradecylamine, Thread balls structure formed with hexadecylamine and finally polyhedral shape formed with octadecylamine. Figure 4 shows the different shapes of organogel.

Sun et al. (2013) found that alkylamines work as Size reducing agent or size controlling agent because they have the ability to Change particle size distribution, and transformed the polydispersed colloid into a monodispersed colloid.

Huang et al. (2020) use alkylamine as a Backbone molecule to enhance the buffering capacity of chitosan due to multiple amines presence in structures of alkylamine, so they attached chitosan covalently to three different types of primary alkyl amine propylamine, (diethylamino) propylamine and N,N-dimethyl-dipropylendiamine.

Finally, Fatty amines characterized by high boiling point above 100 c, which makes them good solvent and powerful solubilizing agents for nanoparticles (He et al., 2019). octylamine serves as the solvent in cadmium selenium quantum dots preparation (Jeong et al., 2016).

CONCLUSION

This review showed all the significant aspects of the versatility and suitability of primary alkylamines in the preparation of nano entities materials. We illustrated the different roles and functions of primary alkylamines in nanoparticles preparation. Even though studies reviewed showed capping agent is one of the important and main uses of primary alkylamines, but also there are other roles for alkylamines such as it used as size controller for nanoparticles; convert polydisperse to monodisperse size. Moreover, studies showed that alkylamine used to prepare micellar system since alkylamine has in their structures a hydrophilic head that can be ionized at acidic Ph and an alkylchain represent a hydrophobic tail so it can be used as a surfactant molecule. In other studies, alkylamines used as a catalyst when added to nanoparticle preparation. Finally, alkylamines used as gelator; means that form hydrogen bonds with the polymer to form organogel.

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Conflict of Interest

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