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ARTICLE

Mono and Tri-cationic Imidazolium Salts: Use as Stabilizers for Silver Nanoparticles and Anticancer Study

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ABSTRACT

In present strudy, the synthesis and characterization of monocationic 1,3-tetradecylimidazolium; $[(C_{14})_2Im]Br$ and tricationic benzene centered *tris*-tetradecyl/hexadecyl imidazolium bromide salts; *i.e.* $[(C_{14})_3C_6H_3Im]Br_3$ and $[(C_{16})_3C_6H_3ImBr]Br_3$ is reported. The stabilizer role of imidazolium salts to prepare silver nanoparticles (AgNPs) *via* chemical reduction method was investigated. To understand the reaction medium effect on the size and morphology control of AgNPs, monophasic (aqueous medium) and biphasic (DCM/H_2O) approaches were applied. The morphology control was noticed for AgNPs protected with $[(C_{14})_3C_6H_3Im]Br_3$ (show sphere like morphology) and $[(C_{14})_2Im]Br$ (show dendritic structures) *via* biphasic approach. A clear variation in the size and morphology of AgNPs was noticed by varying the type of stabilizers and reaction medium. It was also observed that AgNPs were formed and stabilized only in aqueous medium in both approaches, thus it is assumed that AgNPs surfaces were protected by imidazolium salts with bilayer fashion. Anticancer activity of imidazolium salts was performed by MTT assay against HeLa cancer cell lines. The result shows that cytotoxic activity of tricationic $[(C_{14})_3C_6H_3Im]Br_3$ was more potent than that of monocationic $[(C_{14})_2Im]Br$. The outcome suggests that there is an urgent need to develop new polycationic imidazolium salts for various chemical and medicinal applications.

KEYWORDS

Imidazolium, Stabilizers, Silver nanoparticles, Anticancer.

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INTRODUCTION

The applications of imidazolium salts are growing steadily in various fields of chemistry [1-4]. Imidazolium salts substituted with alkyl chains and various functional groups are now being utilized for chemical, technological and biological applications, some of which include reaction media, chemical sensors, gelators, antimicrobial agents, carbene precursors, electroactive devices, nanoparticle stabilizers, *etc*. [5-22]. To date a large number of attempts have been reported on mono and dicationic imidazolium salts for variety of applications. But still limited information available about the polycationic imidazolium salts and their applications, some of which include reaction media, stationary phases, catalysts, carbene precursors, nanoparticles capping agents and biological agents [20,23-47]. Recently, the use of polycationic imidazolium salts and their hydrogels as stabilizers for silver nanoparticles and silver dendritic structures has been reported by Rondla *et al.* [48]. In continuation of our work to develop new polycationic imidazolium salts to understand their stabilizer role for AgNPs by using different reaction media and as well as to examine their cytotoxic activity against the HeLa cancer cell lines by MTT assay. Herein, the synthesis of monocationic and tricationic imidazolium bromide salts *viz.* $[(C_{14})_3C_6H_3Im]Br_3$ and $[(C_{16})_3C_6H_3ImBr]Br_3$ is reported. The stabilizer role of synthesized imidazolium salts for AgNPs by chemical reduction method is also presented. The size and morphology control of AgNPs by applying monophasic and biphasic approaches using H_2O and DCM/H_2O, respectively and the cytotoxic activity result of imidazolum salts against HeLa cells by MTT assay are also described.

EXPERIMENTAL

Analytical reagent grade chemicals were purchased and used in this study. ^{1}H NMR spectra were recorded on Brucker spectrometer (400 MHz). The IR spectra were recorded on Perkin-Elmer 337 spectrophotometer. The UV-Vis absorption spectra of AgNPs stabilized with imidazolium salts were recorded by Shimadzu UV-2600 spectrophotometer. The morphology images of AgNPs were recorded by using scanning electron microscope-SEM with operating voltage of 20 kV.

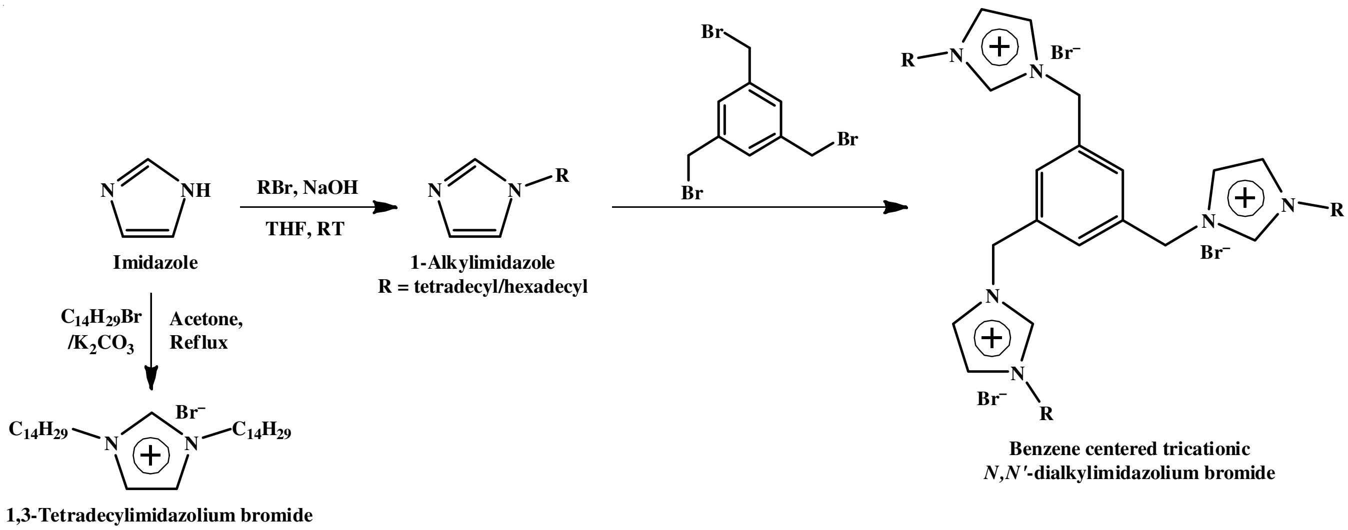
Synthesis: In present study, neutral 1-tetradecyl imidazole $[C_{14}\text{-Im}]$, monocationic 1,3-di(tetradecyl)imidazolium bromide $[(C_{14})_2Im]Br$ and tricationic benzene centered *tris*-tetradecyl/*tris*-hexadecyl imidazolium bromide salts *viz.* $[(C_{14})_3C_6H_3Im]Br_3$ and $[(C_{16})_3C_6H_3ImBr]Br_3$ had been synthesized with NaOH base as reported method [4,18,48]. All the products were obtained in high yield. However, the use of K_2CO_3 base was examined to synthesize C_{14}-Im, which yields a major product of symmetrical $[(C_{14})_2Im]Br$ salt and the neutral $[C_{14}\text{-Im}]$ compound was obtained in very low yield. The schematic representation of synthetic procedure is shown in **Scheme-I**.

Synthesis of $[(C_{14})_3C_6H_3Im]Br_3$ and $[(C_{16})_3C_6H_3Im]Br_3$: Imidazole (1 g, 0.014 M) was dissolved in 30 mL of tetrahydrofuran (THF) and few NaOH pellets were added. The reaction mixture was stirred at room temperature for 30 h. After that 3.6 mL of tetradecylbromide ($C_{14}H_{29}Br$) was added and stirred for additional 15 h. The precipitated NaBr was then removed by filtration and the filtrate was extracted two times by using dichloromethane (DCM)/H_2O and dried over anhydrous $MgSO_4$. The yellow liquid product of tetradecylimidazole (C_{14}-Im) was obtained upon evaporation of the solvent by using rotary evaporator. In the next step, $[C_{14}\text{-Im}]$ and 1,3,5-*tris*(bromomethyl)-benzene (3:1 ratio) were added in 15 mL of acetone. The reaction mixture was stirred for 3 h at room temperature. The white crystalline product was collected and removed the solvent. The similar method was followed for the synthesis of $[C_{16}\text{-Im}]$ and $[(C_{16})_3C_6H_3Im]Br_3$.

Synthesis of $[(C_{14})_2Im]Br$: Imidazole (1 g, 0.014 M, 1 equiv.) was dissolved in 30 mL of acetone and 1.824 g of K_2CO_3 (0.9 equiv.), 3.6 mL of $C_{14}H_{29}Br$ (0.9 equiv.) were added. The reaction mixture was allowed for reflux at 55 ºC for 30 h. The reaction mixture was then filtered to remove precipitated KBr. The acetonic filtrate was concentrated to 2.5 mL by using rotary evaporator, which on cooling affords a white solid product (slightly viscous). The product was washed two times by DCM/H_2O. The DCM layer was concentrated and kept at room temperature, which results a solid. Hexane was added to the solid to remove unreacted RBr, but initially the solid was completely dissolved in hexane. The dissolved hexane mixture was then kept in ice bath and stirred for 2 h. After that the white solid product $[(C_{14})_2Im]Br$ was precipitated, which was collected by filtration. The hexane filtrate was concentrated to reduce volume which contains neutral $[C_{14}\text{-Im}]$.

It is to be noted that instead of the expected single yellow liquid product of neutral tetradecylimidazole $[C_{14}\text{-Im}]$, we have obtained a white solid of $[(C_{14})_2Im]Br$ salt as major product in this method.

Synthesis of AgNPs by chemical reduction method *via* monophasic (H_2O) and biphasic (DCM/H_2O) approaches: In this study, AgNPs were prepared by the chemical reduction method with $NaBH_4$ as reducing agent. To prepare AgNPs, the monophasic and biphasic approaches were performed under aqueous and DCM/H_2O media respectively.



Scheme-I: Schematic illustration of the synthesis of neutral 1-tetradecylimidazole, 1,3-ditetradecylimidazolium bromide and benzene centered tris-tetradecyl/hexadecyl imidazolium bromide salts

Preparation of AgNPs *via* biphasic medium (DCM/H_2O) using $[(C_{14})_3C_6H_3Im]Br_3$ salt: A $[(C_{14})_3C_6H_3Im]Br_3$ salt (0.1149 g, 2 mmol) dissolved in 50 mL DCM was taken in round-bottom flask and 10 mL of 1 mmol aqueous $AgNO_3$ was added dropwise and allowed for stirring for 30 min at room temperature. Afterwards, 0.019 g, 2 mmol of $NaBH_4$ was added dropwise until the colourless solution appears in yellow, which is an indicative of the formation of AgNPs. Initially, obtained AgNPs were dispersed in all over the biphasic system, where the brown colour was appeared for DCM and yellow colour was appeared for water phase. This biphasic mixture was transferred into separating funnel and shaken vigorously for 2 min and allowed to stand until the two layers were separated. The AgNPs stabilized with $[(C_{14})_3C_6H_3Im]Br_3$ salt; denoted as $(C_{14})_3$@AgNPs were completely transferred into the upper aqueous phase and the down DCM layer become clear. The similar procedure was applied to prepare AgNPs by using $[(C_{16})_3C_6H_3Im]Br_3$ and $(C_{14})_2$-ImBr salts as stabilizers.

Preparation of AgNPs *via* monophasic medium (H_2O) using $[(C_{14})_3C_6H_3Im]Br_3$ salt: A $(C_{14})_3C_6H_3Br_3$ (5 mL, 2 mM) in water and 60 mL of 2 mM aqueous $AgNO_3$ solution was mixed and allowed for stirring for 20 min. After that, 4 mM, an ice cold aq. $NaBH_4$ was added dropwise until the solution turns brown and the stirring was continued further for 30 min until the colourless solution appears brown, which is an indicative of the formation of AgNPs. The synthesized AgNPs were extracted from the aqueous medium by centrifugation at 13000 rpm for 20 min. The obtained AgNPs were washed with double distilled water to remove excess of imidazolium salt and other soluble impurities. The similar procedure was applied to prepare AgNPs by using $[(C_{16})_3C_6H_3Im]Br_3$ and $(C_{14})_2$-ImBr salts as stabilizers. The synthesized AgNPs were extracted from the aqueous medium by centrifugation at 13000 rpm for 20 min at room temperature.

MTT assay: For anticancer study, HeLa cancer cell lines were purchased from The National Centre for Cell Science (NCCS), Pune, India. The chemicals DHEM, MTT, PBS, FBS and trypsin were purchased from Sigma Chemicals Co/Gibco. Anticancer activity of the synthesized compounds was tested in Synteny Lifesciences Pvt. Ltd. Hyderabad, India. Anticancer activity of monocationic 1,3-ditetradecylimidazolium bromide; $[(C_{14})_2Im]Br$ and benzene centered tris-tetradecylimidazolium bromide salt; $[(C_{14})_3C_6H_3Im]Br_3$ was evaluated against HeLa cancer cell lines by MTT assay [49].

RESULTS AND DISCUSSION

Spectral analysis: The ^{1}H NMR spectra of the neutral 1-tetradecyl-1*H*-imidazole [C_{14}-Im]; 1,3-ditetradecylimidazolium bromide $[(C_{14})_2Im]Br$ and benzene centered *tris*-tetradecylimidazolium bromide $[(C_{14})_3C_6H_3Im]Br_3$ with the typical chemical shift values (δ ppm) for protons in various chemical environments are shown in Figs. 1-3, respectively. The mass spectra of 1,3-ditetradecylimidazolium bromide and benzene centered *tris*-imidazoliumbromide salt shows the corresponding molecular ion peaks [M]+ at *m/z* 461 and [M]+3 at *m/z* 303 (Figs. 4 and 5), respectively.

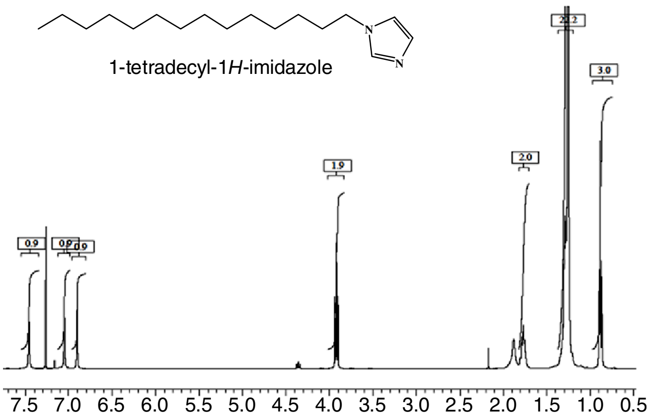


Fig. 1. ^{1}H NMR spectrum of 1-tetradecyl-1*H*-imidazole [48]. ^{1}H NMR (ppm, $CDCl_3$): δ = 7.46 (s, 1H, CH), 7.05 (s, 1H, CH), 6.90 (s, 1H, CH), 3.91 (t, ^3J = 7Hz, 2H, CH_2), 1.76-1.80 (m, 2H, CH_2), 1.22-1.29 (m, 22H, CH_2), 0.88 (t, ^3J = 7Hz, 3H, CH_3)

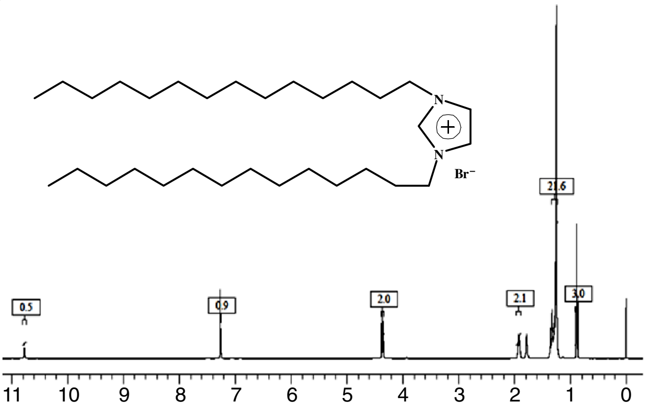


Fig. 2. ^{1}H NMR spectrum of 1,3-ditetradecylimidazolium bromide. ^{1}H NMR (ppm, $CDCl_3$) δ = 10.74 (s, 1 H, CH), 7.24 (s, 2 H, CH), 4.35 (t, ^3J = 7 Hz, 4 H, CH_2), 1.90 (m, ^3J = 7 Hz, 4 H, CH_2), 1.24-1.32 (m, 44H, CH_2), 0.86 (t, ^3J = 7 Hz, 6H, CH_3)

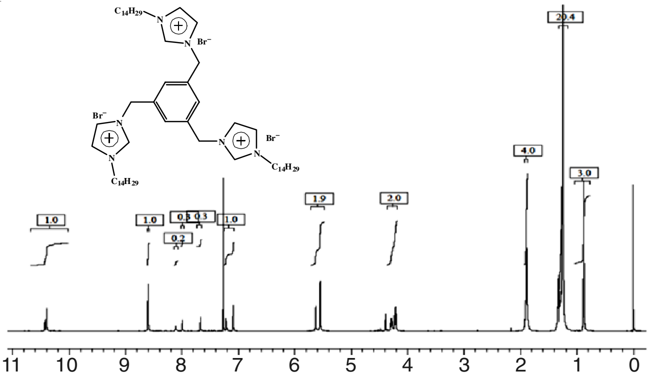


Fig. 3. ^{1}H NMR spectrum of benzene centered tris-tetradecylimidazolium bromide salt [48]. ^{1}H NMR (ppm, $CDCl_3$): δ = 10.4 (s, 3H, CH), 8.6 (s, 3H, CH), 8.1 (s, 1H, CH), 8.0 (s, 1H, CH), 7.7 (s, 1H, CH), 7.2 (s, 3H, CH), 5.6 (s, 6H, CH_2), 4.2 (t, ^3J = 7Hz, 6H, CH_2), 1.9 (s, 12H, CH_2), 1.2-1.35 (m, 60H, CH_2), 0.9 (t, ^3J = 7Hz, 9H, CH_3)

AgNPs stabilized with mono and tricationic imidazolium salts under aqueous (monophasic approach) and DCM/H_2O medium (biphasic approach): In this study, a role of mono and tricationic imidazolium salts as stabilizers for the synthesis of AgNPs *via* chemical reduction method by using monophasic (H_2O) and biphasic medium (DCM/H_2O) approaches were also examined. For ease of understanding, AgNPs stabilized with $[(C_{14})_3C_6H_3Im]Br_3$, $[(C_{14})_2C_6H_3Im]Br_3$ and $[(C_{14})_3$-Im]Br were denoted as $(C_{14})_3$@AgNPs, $(C_{16})_3$@AgNPs and $(C_{14})_2$@ AgNPs

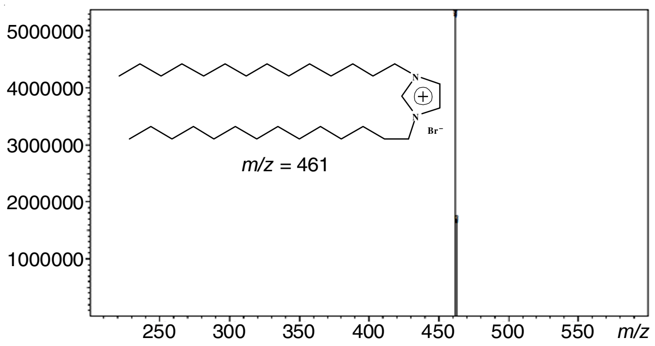


Fig. 4. Mass spectrum of 1,3-ditetradecylimidazolium bromide shows the corresponding molecular ion peak [M]+ at *m/z* 461

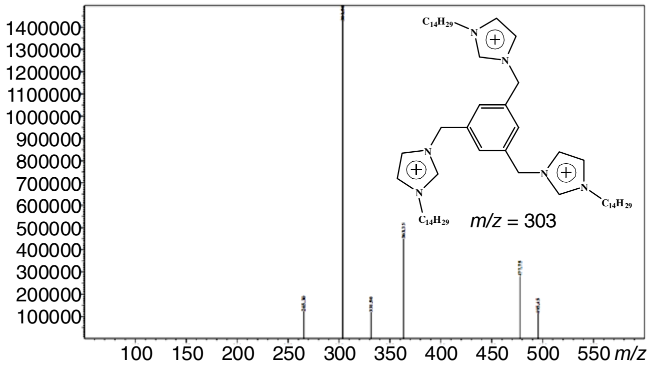


Fig. 5. Mass spectrum of benzene centered tetradecyl substituted tris-imidazolium bromide [48] salt shows the corresponding molecular ion peak [M]+3 at *m/z* 303

respectively. The characterization of AgNPs was carried out by UV-vis spectroscopy, SEM and EDAX analysis.

The appearance of yellow/brown coloured solution during the chemical reduction was the first indicative of formation of AgNPs in both approaches. It is important to note that in the biphasic (DCM/H_2O) approach the AgNPs were formed initially in DCM layer. After sometime the nanoparticles were completely transferred into aqueous layer as shown in Fig. 6a. This phenomenon was noticed with all imidazolium stabilizers. The UV-vis spectra of $(C_{14})_3$@AgNPs, $(C_{16})_3$@AgNPs and $(C_{14})_2$@AgNPs shows the characteristic SPR bands for AgNPs around 420 nm (shown in Figs. 6b, 7a,b and 8a respectively)

The SEM image of $(C_{14})_3$@AgNPs obtained by aqueous medium (monophasic approach) shows ~100-800 nm sized AgNPs with spherical and nanoprism morphology (Fig. 6d) [48]. In case of $(C_{16})_3$@AgNPs, slightly smaller sized AgNPs (~50-500 nm) with spherical shape (Fig. 7c) was observed. The SEM morphology image of $(C_{14})_2$@AgNPs obtained in aqueous medium shows majority of micro sized Ag particles with irregular shapes (Fig. 8c). In the EDX spectra of $(C_{14})_3$@AgNPs, the peak at 3 kev (Fig. 6c) confirmed the formation of AgNPs.

The SEM image of $(C_{14})_3$@AgNPs obtained *via* DCM/H_2O medium (biphasic approach) shows ~100-500 nm sized AgNPs with sphere like morphology (Fig. 6e). While in case of $(C_{16})_3$@AgNPs micro sized cubic and irregular shaped Ag particles (Fig. 7d) were observed. The SEM image of $(C_{14})_2$@

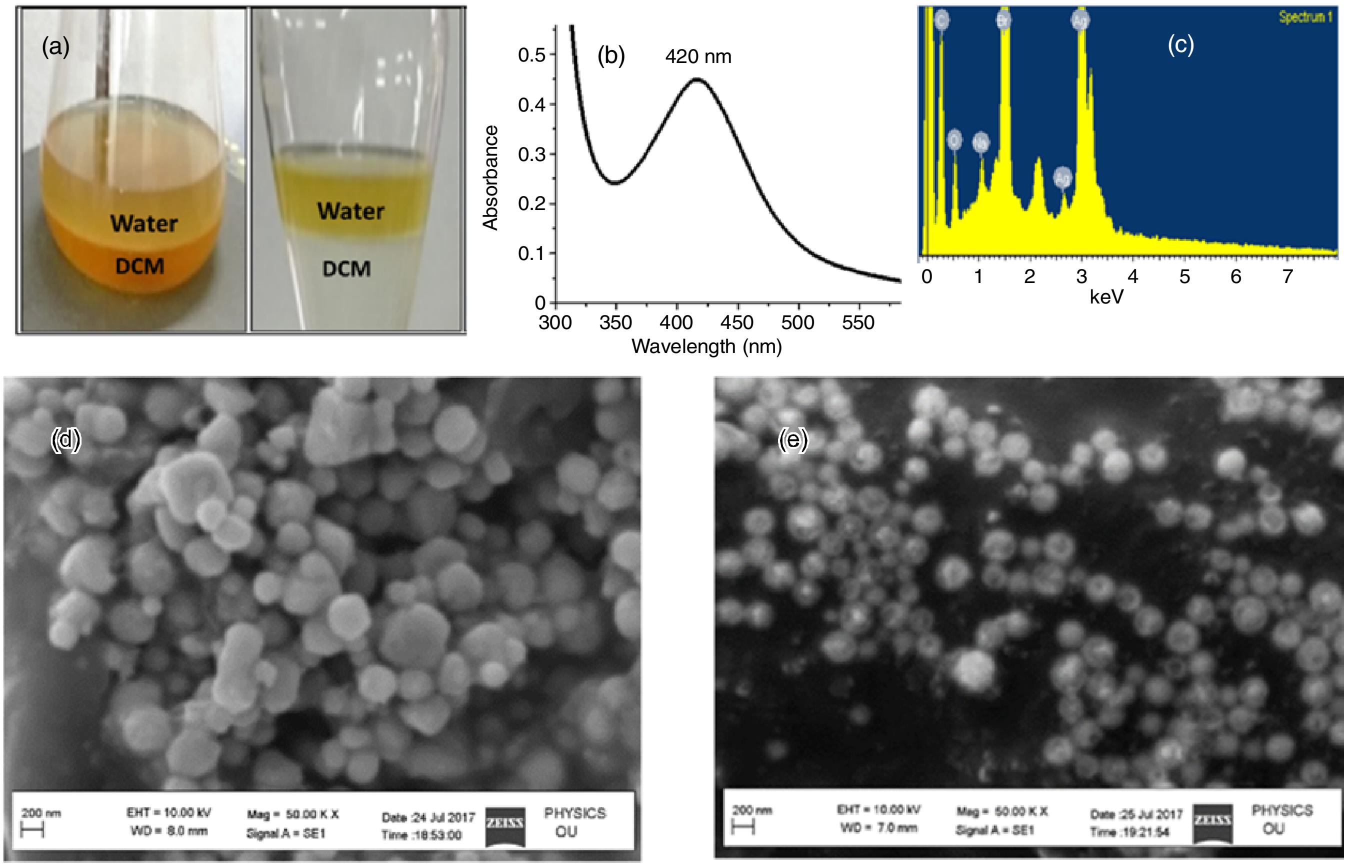


Fig. 6. a) Transfer of AgNPs from DCM layer to aqueous layer; b) $(C_{14})_3$@AgNPs exhibits SPR band at 420 nm; c) EDX spectra of $(C_{14})_3$@AgNPs shows the peak at 3 keV, confirms the AgNPs d) SEM images of $(C_{14})_3$@AgNPs obtained in aqueous medium shows spherical and nanoprism morphology [48]; and e) SEM image of $C_{14})_3$@AgNPs obtained in DCM/H_2O medium shows sphere like morphology

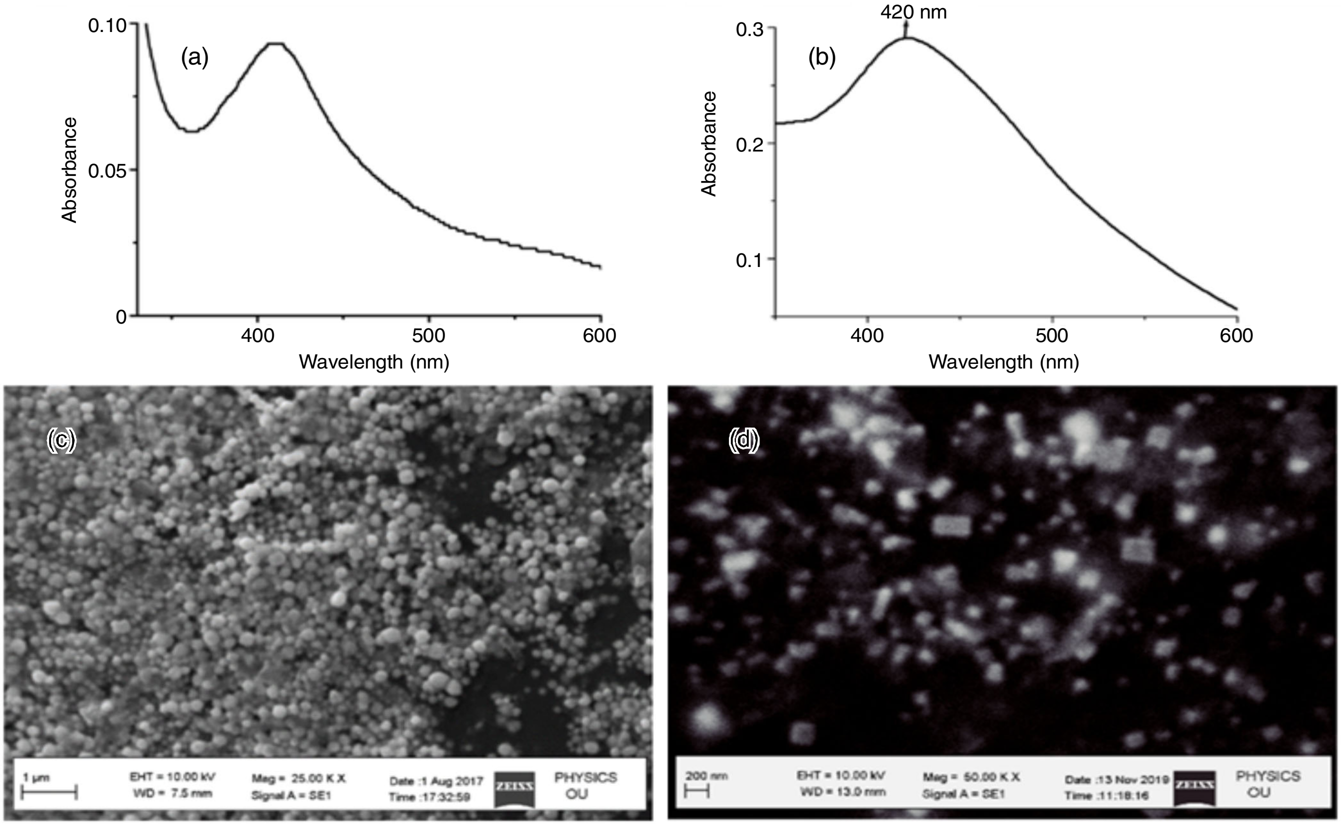


Fig. 7. a) & b) $(C_{16})_3$@AgNPs obtained *via* mono phasic and bipjasic approaches exhibits SPR bands around 420 nm; c) SEM images of $(C_{16})_3$@AgNPs obtained in aqueous medium shows spherical morphology; and d) SEM image of $C_{16})_3$@AgNPs obtained in DCM/H_2O medium shows cubic and irregular morphology

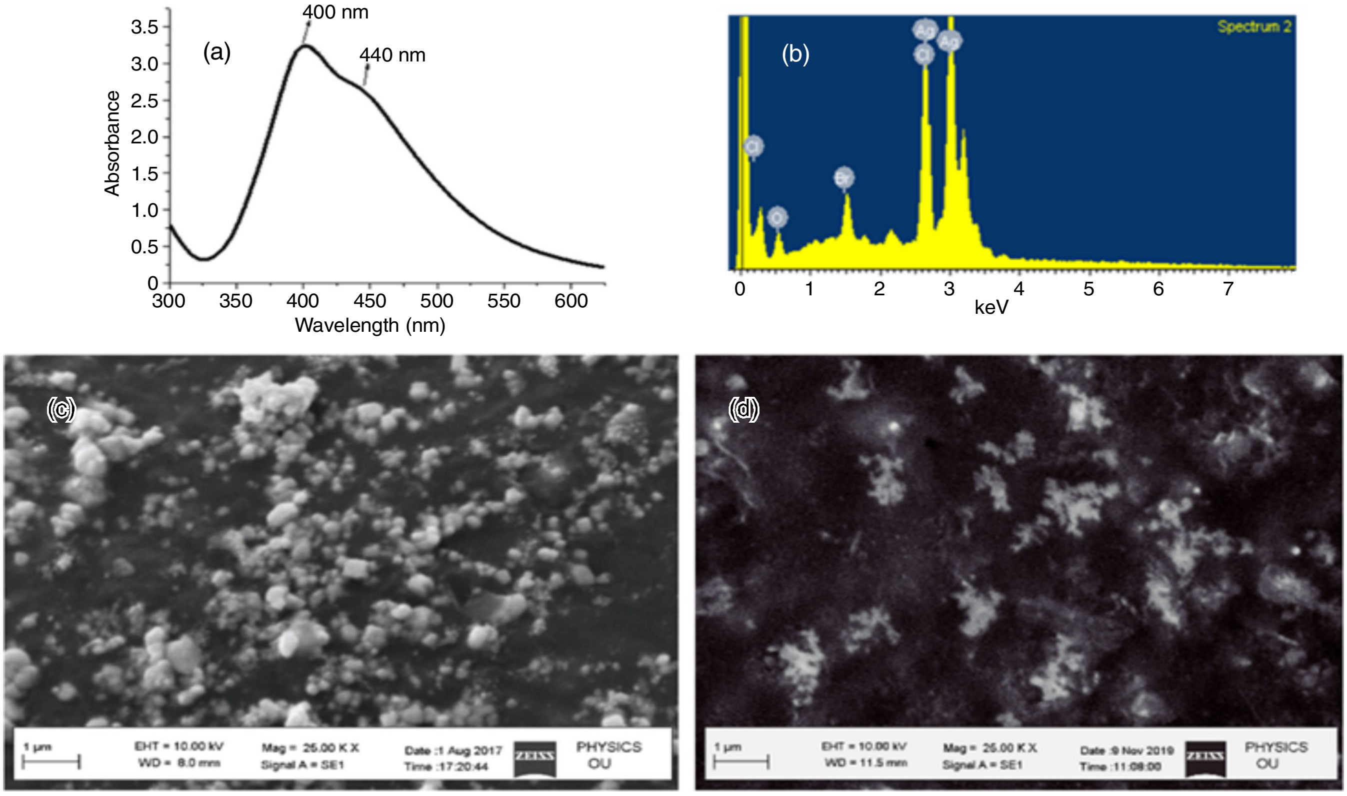


Fig. 8. a) $(C_{14})_2$@AgNPs exhibits SPR bands at 400 and 440 nm, possibly due to the agglomerated AgNPs; b) EDX spectra of $(C_{14})_2$@AgNPs exhibits the peak at 3 keV, which indicates the silver metallic structures; c) SEM images of $(C_{14})_2$@AgNPs obtained in aqueous medium shows irregular shaped microparticles; and d) SEM image of $(C_{14})_2$@AgNPs obtained in DCM/H_2O medium shows silver dendritic morphology

AgNPs obtained *via* biphasic approach shows dendritic Ag nanostructures (Fig. 8d) with the length of ~1 µm. The EDX spectra of $(C_{14})_2$@AgNPs obtained in aqueous medium shows the peak at 3 kev (Fig. 8b), which indicates the formation of metallic AgNPs.

The results show that the AgNPs obtained *via* biphasic approach were completely transferred into aqueous layer (Figs. 6a and 9a) and thus in all the experiments AgNPs were obtained in the water irrespective of the type of approach. Possibly the AgNPs surfaces are protected by the imidazolium salts in bilayer fashion [49] as shown in Fig. 9b. There is a clear variation in the size and morphology of AgNPs by varying the type of stabilizers and as well as reaction medium. One could achieve the morphology control of AgNPs for $(C_{14})_3$@AgNPs and $(C_{14})_2$@AgNPs by varying the reaction medium. Because $(C_{14})_3$@AgNPs obtained *via* monophasic approach (H_2O) shows spherical and nanoprism morphology, whereas they show uniform sphere like morphology *via* biphasic medium (DCM/H_2O). On the other hand, $(C_{14})_2$@AgNPs with irregular morphology obtained *via* monophasic approach, whereas the dendritic structures were obtained *via* biphasic approach.

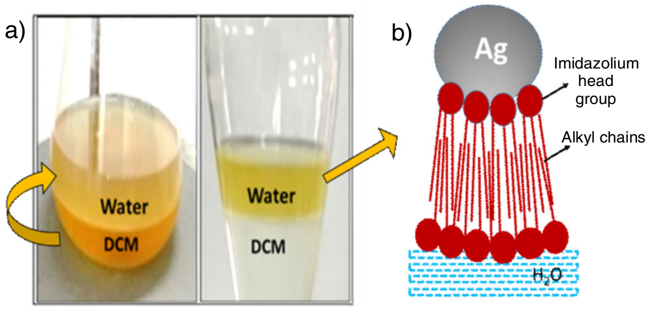


Fig. 9. a) Transfer of AgNPs from DCM layer to aqueous layer in the biphasic approach; b) Proposed bilayer fashion of imidazolium salt protected AgNPs

Cytotoxic effect of mono and tricationic imidazolium salts by MTT assay: Anticancer activity of monocationic 1,3-ditetradecylimidazolium bromide $[(C_{14})_2Im]Br$ and tricationic benzene centered *tris*-tetradecylimidazolium bromide salt $[(C_{14})_3C_6H_3Im]Br_3$ was evaluated against HeLa cancer cell lines by MTT assay [50]. The monocationic $[(C_{14})_2Im]Br$ and tricationic $[(C_{14})_3C_6H_3Im]Br_3$ compounds show IC_{50} values 39.08 (µg/mL) and 22.7 (µg/mL), respectively (Tables 1 and 2). The

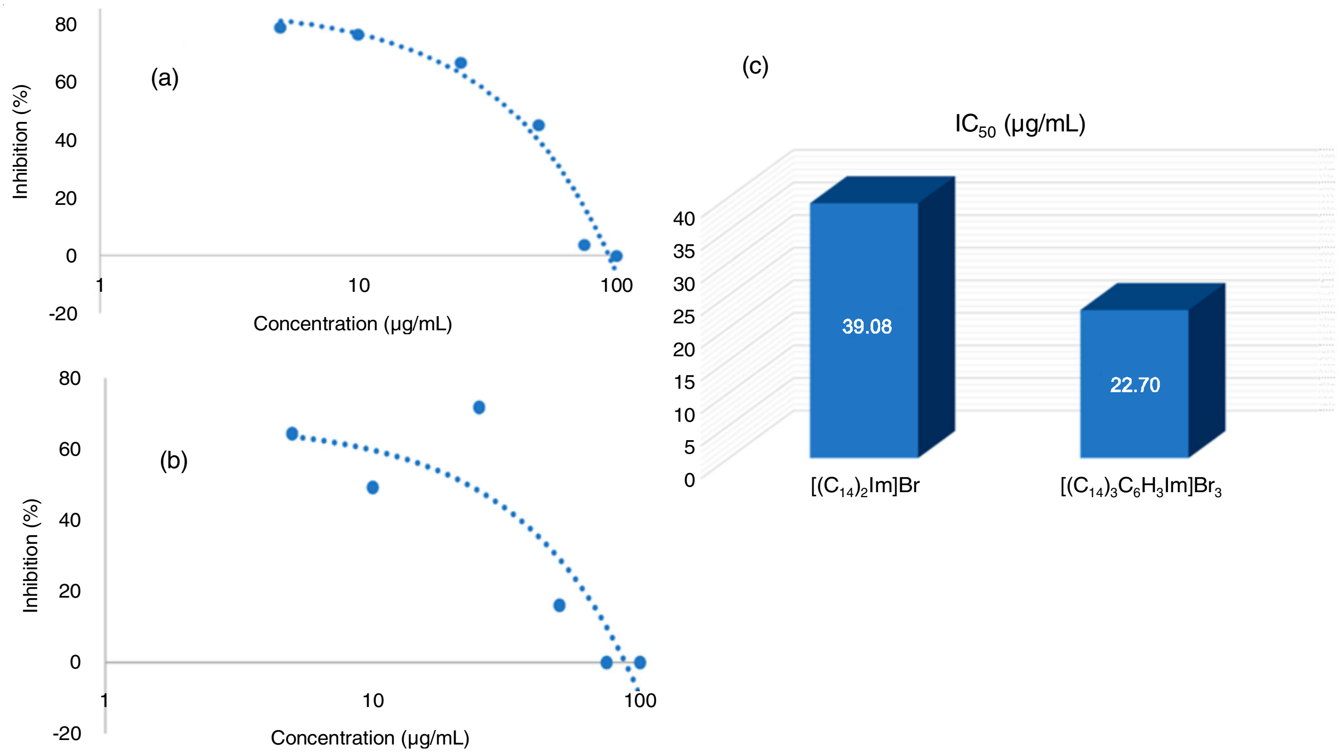


Fig. 10. Graphical representation of cytotoxic effect of $[(C_{14})_2Im]Br$ **(a)** and $[(C_{14})_3C_6H_3Im]Br_3$ **(b)** compounds on HeLa cells and the comparison chart (c)

TABLE-1
RAW DATA OF CYTOTOXIC EFFECT OF $[(C_{14})_2Im]Br$ COMPOUND ON HeLa CELLS

Conc. (µg/mL)	Absorbance at 570 nm			Cell viability (%)			Average	Cytotoxicity (%)	IC_{50} (µg/mL)
100	2.030	2.000	1.985	100	100	100	100	0	39.08
75	0.667	0.658	0.693	95.6	94.40	99.4	96.4	3.6	
50	0.387	0.375	0.386	55.5	53.8	55.43	54.91	45.09	
25	0.243	0.230	0.219	34.8	32.9	31.4	33.03	66.97	
10	0.232	0.231	0.232	33.2	33.1	33.2	23.16	76.84	
5	0.140	0.149	0.145	20.0	21.3	20.80	20.7	79.3	

TABLE-2
RAW DATA OF CYTOTOXIC EFFECT OF $[(C_{14})_3C_6H_3Im]Br_3$ COMPOUND ON HeLa CELLS

Conc. (µg/mL)	Absorbance at 570 nm			Cell viability (%)			Average	Cytotoxicity (%)	IC_{50} (µg/mL)
100	1.433	1.422	1.399	100	100	100	100	0	22.7
75	1.017	1.115	1.119	100	100	100	100	0	
50	0.577	0.589	0.590	82.7	84.5	84.6	83.9	16.1	
25	0.196	0.200	0.195	28.1	28.6	27.9	28.2	71.8	
10	0.350	0.354	0.358	50.2	50.7	51.3	50.7	49.3	
5	0.227	0.230	0.290	32.5	32.9	41.6	35.6	64.4	

graphical representation of cytotoxic effects of applied imidazolium compounds on HeLa cells determined by MTT assay is shown in Fig. 10. It appears that $[(C_{14})_3C_6H_3Im]Br_3$ displayed high activity against Hela cancer cell line with the IC_{50} 22.7 µg/mL. This result supports literature stating that the polycationic imidazolium salts show higher anticancer activity than that of mono and dicationic imidazolium salts [51].

Conclusion

In this work, synthesis of monocationic and tricationic-imidazolium bromide salts and their stabilizer role for AgNPs *via* chemical reduction method was presented. To examine the effect of reaction medium on the size and morphology control of AgNPs, the monophasic (aqueous medium) and biphasic approach (DCM/H_2O) were applied. It was observed that AgNPs were formed and stabilized in aqueous medium in both approaches. Thus it was assumed that AgNPs surfaces are protected by the imidazolium salts in bilayer fashion. The cytotoxic activity against HeLa cancer cells shows that tricationic imidazolium salts ($[(C_{14})_3C_6H_3Im]Br_3$) are more potent than that of monocationic imidazolium ($[(C_{14})_2Im]Br$) salts.

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