UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF A DRUG DELIVERY AGENT BASED ON IONIC LIQUIDS TEMPLATED MESOPOROUS SILICA NANOPARTICLES

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FS 2018 24

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

December 2017

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

DEVELOPMENT OF A DRUG DELIVERY AGENT BASED ON IONIC LIQUID TEMPLATED MESOPOROUS SILICA NANOPARTICLES

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December 2017

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Mesoporous silica nanoparticles (MSNs) has been used as drug delivery agents since 2001 and this is due to their properties such as easy manipulation of physical characteristic, inert, great biocompatibility and easy functionalization. Up to the current date, the most establish template to generate MSNs is anionic surfactant such as cetyltrimethylammonium bromide (CTAB). With the discovery of ionic liquids (ILs), the template materials for MSNs no longer limited to CTAB. This is due to the similarity of core structure between CTAB and ILs which consist of large organic cations and inorganic or organic anions. The most interesting parts regarding ILs is different combination of cations and anions will change the ILs' properties. Therefore, by changing the anions or cations, there is a possibility of obtaining MSNs with different morphologies. In this work, a series of long chain pyridinium ILs (C_nPyBr where n = 12, 14, 16 and 18), two long chain imidazolium ILs (C_nMIMBr where n = 16 and 18) and four pyridinium ILs with different anions (C_{16}PyX where X = BF_4, NO_3, ClO_4 and CF_3COO) were used as templates to synthesized MSNs. By using these different types of ILs, several studies were conducted such as the effect of alkyl chain length, synthesis method, cation and anions. To study the effect of synthesis method, two methods were employed and both syntheses utilized triethanolamine (TEA) as the base catalyst where in one method the TEA undergo pre-treatment process while the other did not. The pre-treatment process involved the heating of TEA and silica source together prior its addition to template water mixture. Besides that, the effects of pyridinium ILs alkyl chain length were also investigated. MSNs generated via both methods exhibited spherical morphology and decreasing average particles size with increasing alkyl chain length of pyridinium ILs. The MSNs porosity were further analyzed through nitrogen sorption analysis where the surface area were in between 71.85 m^2 g^{-1} to 525.02 m^2 g^{-1} and the pore volume was up to 1 cm^3 g^{-1}. It was found that between the two syntheses, the one without pre-treatment process generated MSNs with larger surface area

value. Thus, the method without the pre-treatment was chosen to study the effect of cation and anions. Two imidazolium ILs were used to study the effect of cation and it was found that the MSNs produced using these templates exhibited slightly smaller particles size (50.24 and 34.52 nm) and higher surface area value (570.61 and 598.71 $m^2 g^{-1}$) compared to its counterpart of pyridnium ILs. Anions effect study indicated that different anions exhibited different particles morphology. Some of the morphologies exhibited were spherical, distorted spherical, raspberry and undefined shape with surface area ranging from 92.65 $m^2 g^{-1}$ to 494.96 $m^2 g^{-1}$. From all these previous study, C_{16}PyBr was chosen as the template to be optimized using Response Surface Methodology (RSM) and Box-Behnken Design (BBD) was used. In this design, there were three factors manipulated which were mass of IL, mass of TEA and temperature and two responses were surface area and particles size. From the statistical analysis, surface area and particle size responses were fitted into linear and quadratic models respectively. One MSNs was then chosen from the statistical data for the application in drug delivery studies and the chosen MSNs has the surface area of 999.051 $m^2 g^{-1}$ and average particles size of 28.5 nm. In drug loading studies, evaporation method was chosen and a total of 37 % of drug was successfully encapsulated. Drug release study was conducted in 48 hours and about 32 % of drug has been released. Drug release kinetics study indicated that the release follows the zero order and Hixson-Crowell model.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PEMBANGUNAN EJEN PENGHANTARAN UBAT MENGGUNAKAN NANOPARTIKEL SILIKA MESOPOROS BERDASARKAN CECAIR IONIK

Oleh

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Nanopartikel silika mesoporos (MSNs) telah digunakan sebagai ejen penyampai ubat sejak dari tahun 2001 dan ini disebabkan oleh sifat mereka seperti manipulasi ciri fizikal dengan mudah, stabil, serasi secara biologi dan penambahan kumpulan fungsi dengan mudah. Sehingga kini, acuan yang terkenal untuk menjana MSNs adalah surfaktan anionik seperti cetiltrimetilammonium bromide (CTAB). Dengan penemuan cecair ionik (ILs), bahan acuan bagi MSNs tidak lagi terhad kepada CTAB. Ini adalah kerana persamaan struktur teras antara CTAB dan ILs yang terdiri daripada kation organik dan anion tak organik atau organik. Bahagian yang paling menarik tentang ILs adalah gabungan kation dan anion yang berbeza akan mengubah sifat ILs. Oleh it, dengan mengubah anion atau kation, ada kemungkinan MSNs yang dihasilkan akan menjana morfologi yang berbeza. Dalam kerja ini, satu siri ILs pyridinium (C_nPyBr di mana n = 12, 14, 16, dan 18), dua ILs imidazolium (C_nMIMBr di mana n = 16 dan 18) dan empat ILs pyridinium yang berlainan anion ($C_{16}PyX$ di mana X = BF_4, NO_3, ClO_4 and CF_3COO) digunakan sebagai acuan untuk sintesis MSNs. Dengan mengunakan pelbagai jenis ILs, beberapa kajian telah dijalankan seperti kesan panjang rantai alkil, kaedah sintesis, kation dan anion. Untuk mengkaji kesan kaedah sintesis, dua kaedah telah digunakan dan kedua-dua kaedah mengunakan triethanolamin (TEA) sebagai pemangkin di mana dalam satu kaedah TEA telah menjalani proses pra-rawatan manakala yang lain tidak. Selain itu, kesan panjang rantai alkil ILs pyridinium juga disiasat. MSNs yang dihasilkan melalui dua kaedah ini menunjukkan morfologi sfera dan saiz partikel purata menurun dengan peningkatan rantai panjang alkil. Liang MSNs dikaji melalui analisis penyerapan nitrogen di mana kawasan permukaan berada di antara 71.85 m^2 g^{-1} to 525.02 m^2 g^{-1} dan isipadu liang sehingga 1 cm^3 g^{-1}. Dari hasil ini, kaedah tanpa pra-rawatan dipilih untuk mengkaji kesan kation dan anion. Dua ILs imidazolium digunakan untuk mengkaji kesan kation dan didapati MSNs yang dihasilkan mempamerkan saiz partikel yang sedikit kecil (50.24 dan 34.53 nm) dan nilai kawasan permukaan yang lebih tinggi (570.61 dan 598.71 m^2 g^{-1})

berbanding ILs pyridinium. Dari kajian kesan anion, didapati bahawa anion yang berbeza menunjukkan morfologi partikel yang berbeza. Sebahagian daripada morfologi adalah sfera, sfera tidak tepat, raspberi dan bentuk yang tidak dapat ditentukan dengan luas permukaan dari 92.65 m^2 g^{-1} hingga 494.96 m^2 g^{-1}. Dari semua kajian ini, C_{16}PyBr dipilih sebagai acuan yang akan dioptimumkan melalui tindak balas permukaan metodologi (RSM) dan reka bentuk Box-Behnken (BBD) telah digunakan. Dalam reka bentuk ini, terdapat tiga faktor yang dikaji iaitu jisim IL, jisim TEA dan suhu dan dua respon yang dinilai adalah luas permukaan dan saiz partikel. Dari analisis statistik, respon kawasan permukaan mengikut model lurus dan saiz partikel mengikut model kuadratik. Satu MSNs telah dipilih dari data statistik untuk aplikasi penyampaian ubat dan MSNs yang dipilih mempunyai luas permukaan 999.051 m^2 g^{-1} dan saiz partikel purata 28.5 nm. Dalam kajian muatan ubat, kaedah penyejatan telah dipilih dan sejumlah 37 % daripada ubat telah berjaya dirangkum. Untuk kajian pelepasan ubat, dalam masa 48 jam, 32 % ubat telah berjaya dilepaskan. Kajian kinetik menunjukkan bahawa pelepasan ubat mengikut model sifar dan Hixson-Crowell.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my supervisors Dr Haslina Ahmad, Prof Mohd Basyaruddin and Dr Che Azura for their guidance, advice, encouragement and help throughout my studies. The knowledge they have given me are priceless. Thank you for everything.

Further gratitude I would like to extend towards my lab-mates, Kak Ain, Kak Izzah and Syera for giving me the time and space to conduct the experiments. Not to forget, their advice and helps they have provide to me.

A special appreciation goes to all the lecturers and staff in the Department of Chemistry and Faculty of Science for all their help and advice. Further appreciation is extended towards Mr Hadi, Ms Siti, Mr Akmam, Mr Shahizam and Mr Jufri from MIMOS Semiconductor Sdn Bhd for their assistance in the analysis. Special thanks toward staffs of UM Infra Lab, Mr Irfan and Mr Jasmi, Monash University, Mr Nasrun for all their helps and services for the analysis.

Finally and most importantly, I would like to express my deepest gratitude and love towards my mother for all her love and confidence in me. Without her support and assistance, I would not reach until this level. Thank you very much, forever.

I certify that a Thesis Examination Committee has met on 14 December 2017 to conduct the final examination of Eleen Dayana binti Mohamed Isa on her thesis entitled “Development of A Drug Delivery Agent based on Ionic Liquids Templated Mesoporous Silica Nanoparticles” in accordance with the University and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The committee recommends that the student be awarded the Master of Science.

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LIST OF ABBREVIATIONS

$[EtNH_3][NO_3]$	Ethylammonium nitrate
^1H NMR	Proton NMR
2D	Two dimensional
2FI	Two factorial
3D	Three dimensional
ANOVA	Analysis of variance
BBD	Box-Behnken Design
BET	Brauner-Emmett-Teller
BF_4^-	Tetrafluoroborate anion
BJH	Barett-Joyner-Halenda
C_{12}PyBr	1-dodecylpyridinium bromide
C_{14}OMIM-MSN	1-tetradecyloxymethyl-3-methylimidazolium bromide templated MSNs
C_{14}PyBr	1-tetradecylpyridinium bromide
C_{16}MIMBr	1-hexadecyl-3-methylimidazolium bromide
C_{16}MIMCl	1-hexadecyl-3-methylimidazolium bromide
C_{16}MIM-MSN	1-hexadecyl-3-methylimidazolium bromide template MSNs
$C_{16}PyBF_4$	1-hexadecylpyridinium tetrafluoroborate
C_{16}PyBr	1-hexadecylpyridinium bromide
$C_{16}PyCF_3COO$	1-hexadecylpyridinium trifluoroacetate
$C_{16}PyClO_4$	1-hexadecylpyridinium perchlorate
$C_{16}PyNO_3$	1-hexadecylpyridinium nitrate
C_{16}PyX	1-hexadecylpyridinium anions
C_{18}MIMBr	1-octadecyl-3-methylimidazolium bromide
C_{18}PyBr	1-octadecylpyridinium bromide

C_4MIM^+	1-butyl-3-methylimidazolium cation
C_4MIMBF_4	1-butyl-3-methylimidazolium tetrafluoroborate
C_8MIMCl	1-methyl-3-octylimidazolium bromide
CF_3COO^-	Trifluoroacetate anion
Cl	Chloride
ClO_4^-	Perchlorate anion
CMC	Carboxymethylcellulose
cmc	Critical micelle concentration
C_nMIMBr	1-alkyl-3-methylimidazolium bromide
C_nPyBr	1-alkylpyridinium bromide
CNT	Classic nucleation theory
CTAB	Cetyltrimethylammonium bromide
d_6-DMSO	Deuterated dimethylsulfoxide
DCM	Dichloromethane
DSC	Differential scanning calorimetry
FTIR	Fourier transform infrared spectroscopy
HCl	Hydrochloric acid
I^-	Silicate oligomers
IL	Ionic liquid (singular)
ILs	Ionic liquids (plural)
MAC12	MSNs synthesize via method A using $C_{12}PyBr$ as template
MAC14	MSNs synthesize via method A using $C_{14}PyBr$ as template
MAC16	MSNs synthesize via method A using $C_{16}PyBr$ as template
MAC18	MSNs synthesize via method A using $C_{18}PyBr$ as template
MACn	MSNs synthesize via method A using C_nPyBr as template
MBC12	MSNs synthesize via method B using $C_{12}PyBr$ as template

MBC14	MSNs synthesize via method B using C_{14}PyBr as template
MBC16	MSNs synthesize via method B using C_{16}PyBr as template
MBC18	MSNs synthesize via method B using C_{18}PyBr as template
MBCn	MSNs synthesize via method B using C_nPyBr as template
MM16	MSNs synthesize using C_{16}MIMBr as template
MM18	MSNs synthesize using C_{18}MIMBr as template
MMn	MSNs synthesize using C_nMIMBr as template
$MSBF_4$	MSNs synthesize using $C_{16}PyBF_4$ as template
$MSCF_3COO$	MSNs synthesize using $C_{16}PyCF_3COO$ as template
$MSClO_4$	MSNs synthesize using $C_{16}PyClO_4$ as template
$MSNO_3$	MSNs synthesize using $C_{16}PyNO_3$ as template
MSN-Q	MSNs loaded with drug Q
MSNs	Mesoporous silica nanoparticles
MSX	MSNs synthesize using C_{16}PyX as template
N_2	Nitrogen gas
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance
NO_3^-	Nitrate anion
PBS	Phosphate Buffer saline
PS	Particle size
Py ILs	Pyridinium ILs
Py ILs-MSNs	MSNs containing pyridinium ILs
Q	Quercetin
R^2	Determination coefficient
rpm	Rotation per minute

RSM	Response surface methodology
RTILs	Room temperature ionic liquids
$RuCl_6$	Ruthenium hexachloride
RuO_2	Ruthenium dioxide
S.D	Standard deviation
S^+	Cationic template
S1	Solution 1
S2	Solution 2
SA	Surface area
TAOS	Tetraalkylorthosilicate
TBOS	Tetrabutylorthosilicate
TEA	Triethanolamine
TEM	Transmission electron microscopy
TEOS	Tetraethylorthosilicate
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TMOS	Tetramethylorthosilicate
TMS	Tetramethylsilane
TPOS	Tetrapropylorthosilicate
UV-Vis	Ultraviolet-Visible Spectrophotometry
XRD	X-Ray diffraction

CHAPTER 1

INTRODUCTION

1.1 Introduction

Cancer has been the world's greatest concern as it leads the chart as the major cause of death. Based on GLOBALCON, in the year 2012 alone, there were 14.1 million new cases recorded and 8.2 million people died due to cancer worldwide (Torre et al., 2015). The most common types of cancer diagnose are lung, breast, bowel, prostate and others in decreasing percentage respectively (Torre et al., 2015). Up to the current date, the most widely used treatment for these patients is chemotherapy where the drugs are intravenously injected to the body. However, the main apprehension with these drugs are its side effects (Babu, Templeton, Munshi, & Ramesh, 2013). Therefore, the main priorities in cancer-based researches are either to discover drugs with higher efficacy against cancer cells or to develop and improve the whole drug delivery systems which then increase the drug effectiveness against cancerous cell. Ironically, even with drug discovery, without the perfect vehicle, the drugs will not exhibit a better result than the current ones.

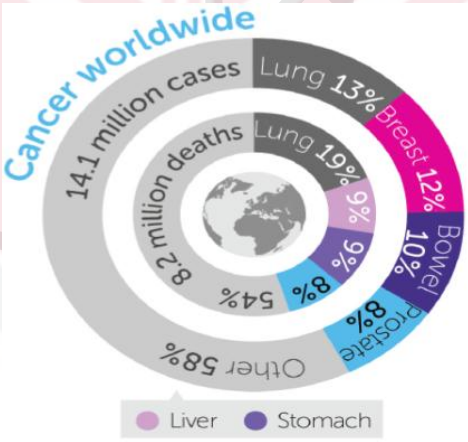

Figure 1.1: **Global statistic on cancer** (Torre et al., 2015)

1.2 Cancer therapy evolution

Battles against cancer have been occurring throughout the human history and many questions and theories have been raised regarding this disease. Until now, most of these questions and theories are still being tested. In these past centuries, there were a lot of major breakthroughs made in cancer treatment such as movement from conventional and non-targeted therapy to targeted therapy. Figure 1.2 shows cancer therapy timeline and its transition (Bae et al., 2013).

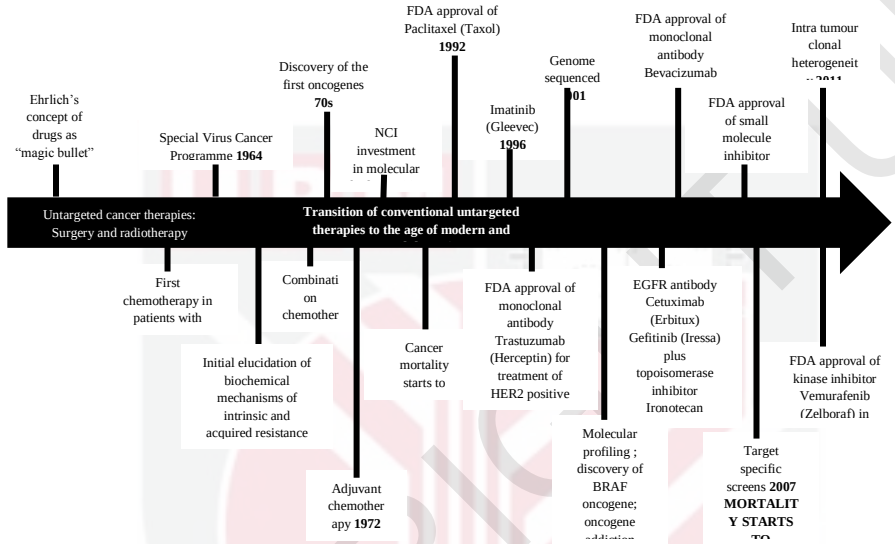

Figure 1.2: Cancer therapy timeline (Bae et al., 2013)

Conventional and non-targeted therapies such as surgical procedure, radiotherapy and chemotherapy dominate in the field of cancer treatments for a very long time. Even now, surgical procedure has the highest success rate provided that all the cancer cells or tumour are completely removed. In the cases where only majority of the cancer cells were removed or when surgical intervention is impossible, other treatments are required such as radiotherapy and this is before the discovery of chemotherapy. Radiotherapy is completely different that surgical procedure where it only targets the specific cancerous area and affect the cells division process. Through much advancement of technologies, the current radiotherapy is very effective but it still show several drawbacks. This treatment uses high energy radiation which can damage the noncancerous cells. Besides that, the patients also suffer from several side effects such as skin erythema, peeling skin, nauseous and diarrhoea (Bae et al., 2013). Another non-targeted cancer treatment and the most popular is chemotherapy and this treatment uses drugs which are able to kill the cancer cells (Bae et al., 2013). However, the drugs used exhibited non-specific distribution and poor bioavailablity (Qin, Zhang, Cheng, Rong, & Zhang, 2017).

The problems pose by conventional and non-targeted therapies push the effort in finding targeted therapies. The main purpose of targeted therapies is to ensure that the drugs accumulate at the target area specifically, independent of the site and method of its administration. The overall advantages of targeted therapies are simplification of treatment process, reduction of drug quantity for the effectiveness of the therapy and the raise of the drug concentration without affecting the non-targeted components are feasible (Torchilin, 2010).

1.3 Nanotechnology in cancer therapies

In effort of developing better drug delivery system, nanotechnology has been explored as one of the main platform in these last few decades. Nanomaterials can be generally defined as materials with the size ranging 1-100 nanometers. However in the field of medicine, nanomaterials which are being used as drug delivery agent, commonly referred as nanomedicine, are not restricted to the size range defined. The size typically reaches up to several hundred nanometers (Tan & Wu, 2016). Nanoparticles are like blank canvas and the main advantages of it in development of nanomedicine are it able to increase drug bioavailability, better interaction with biological system within the same size, high surface area and functionality, possibility of changing its physical properties and the possibility of multifunctional system with different properties (Bae et al., 2013; Grazú, Moros, & Sánchez-Espinel, 2012). Nanomedicine has been found in many different applications but majority of researches being done focus on cancer therapy. Many designs and concepts of nanomedicine were found through cancer therapy research and it can be categorized according to Figure 1.3 (Torchilin, 2010)

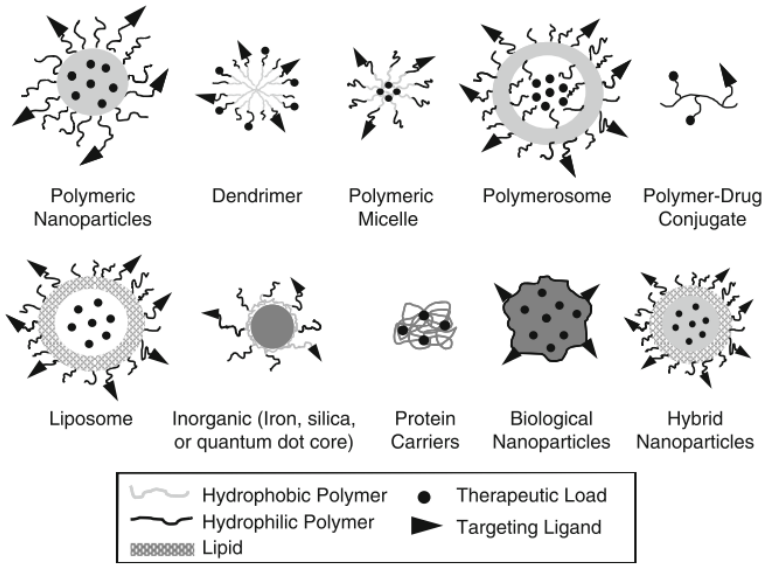

Figure 1.3: Major nanotechnologies for cancer therapies (Torchilin, 2010)

1.4 Inorganic nanomaterials

One of nanomaterials that are being extensively research is inorganic nanomaterials. This material has advantages over organic nanomaterials in terms of its stability while organic nanomaterials still facing unsolved problems of limited chemical and mechanical stability and swelling (Salas, Costo, & Morales, 2012). Inorganic nanomaterials typically made out of metal complexes and high probability of monodispersity through the synthesis method (Torchilin, 2010). It possesses unique physiochemical properties such as size, shape, chemical composition, large surface area, easy functionalization. Some of the applications of these materials in medicinal field are drug delivery and therapy, bioimaging, biomedical sensoring and biocatalysis (Ma et al., 2015).

Inorganic nanomaterials can be synthesized through two common methods which are the top-down and bottom-up approaches. In top-down approach, as its name, it involves obtaining smaller materials by breaking a larger material. However, this method is not preferable due to the inconsistent results obtained such as wide size distribution and different particle shape. Besides that, it also contains impurities due to the method used and surface and crystallographic defect. Bottom-up method is much more common and it involves the growing of nanoparticles from single atom. The materials obtained from this approach have narrow size and shape distribution (Salas et al., 2012). Some of the most common inorganic nanoparticles that under investigation for biomedical application are gold nanoparticles, iron oxide nanoparticles, mesoporous silica nanoparticles and quantum dots (Ojea-Jiménez et al., 2013).

1.5 Mesoporous silica nanoparticles (MSNs)

MSNs can be defined as silica materials within the size of nanometers that contain porosity. The term porosity were given according to the IUPAC classification where when the pores with diameter less than 2 nm, between 2 and 50 nm and more than 50 nm are defined as micropores, mesoporous and macroporous respectively (J. Zhang, Ma, Shi, Liu, & Deng, 2009). Mobil Oil Research discovered the first ordered MSNs in the year 1992 and it was named M41S (Johansson, 2010; Zhen Li et al., 2008). The first MSNs for the application of drug delivery began in 2001 and since then, there were increasing number of research in medical field using this material (Tang, Li, & Chen, 2012). This is due to the properties of MSNs which are easy manipulation of physical characteristic, inert, great biocompatibility and easy functionalization. Furthermore, all these characteristics make it a great platform in development of delivery vehicle for theranostic purposes (Ma et al., 2015; Tan & Wu, 2016).

Ideal MSNs for many applications especially in the medical field should exhibit desirable characteristics such as stable in solution, controllable pore size and uniform particle size and large pore volume (Si-Han Wu, 2013). The main

principle in obtaining MSNs is through the condensation of silica source guided by the templates (Sun, 2012). In general, the processes involve two reactions which are hydrolysis and condensation process under basic condition. The two most well establish methods are modified Stöber and co-condensation method. In Stöber and co-condensation methods, ammonia and sodium hydroxide (NaOH) solutions were utilized respectively as the bases and catalysts (Huh et al., 2003; Zongxi Li, Barnes, Bosoy, Stoddart, & Zink, 2012). Besides the base, the template and silica source are the two other main components in the synthesis process. Silica source and template that commonly used are tetraalkylorthosilicate (TAOS) and surfactant or polymer respectively. Currently, the main focus is on the templates used where by changing the template, the possibility of obtaining MSNs with different morphologies exist.

1.6 Ionic liquid (IL)

The first IL, ethylammonium nitrate ($[EtNH_3][NO_3]$) with melting point of 13-14°C was discovered in the year 1914 (Petkovic, Seddon, Rebelo, & Pereira, 2011). Since then, there are lot of researches being done in discovering new ionic liquids (ILs). In general, ILs can be defined as salts with melting point below the boiling point of water (Wasserscheid & Welton, 2002). ILs that are molten at room temperature are defined as room temperature ionic liquids (RTILs) (Chellappan, 2012). They received a lot of attention in the field of green chemistry due to its properties such as essentially zero vapour pressure, high thermal stability and nonflammibility which minimize air pollution compared to organic solvents (Jaitely, Karatas, & Florence, 2008; Xiaoyu Li, Ma, & Wang, 2015; J. Zhang et al., 2009). ILs consist of two core components, large organic cations and inorganic or organic anions (Dobler, Schmidts, Klingenhöfer, & Runkel, 2013). The most interesting parts regarding ILs is different combination of cations and anions will change the properties of ILs. Thus the desired characteristic of ILs can be tailored according to the cations and anions. Figure 1.4 shows the common cations and anions for ILs (Mallakpour & Dinari, 2012). Since the core components of ILs is similar to anionic surfactant used in MSNs synthesis, there is potential of utilizing ILs as templates in MSNs synthesis.

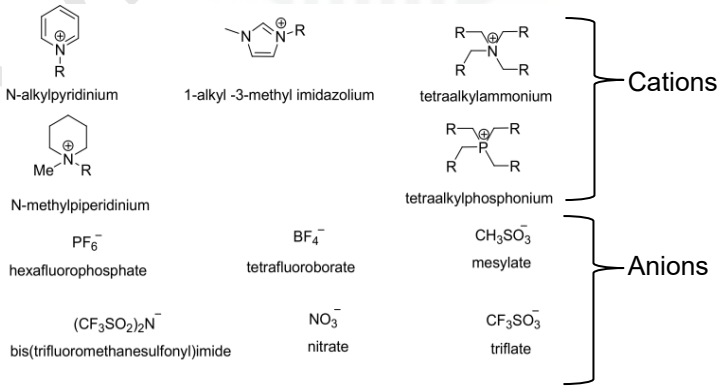

Figure 1.4: Common cations and anions for ILs (Mallakpour & Dinari, 2012)

1.7 Problem statement

Cancer can be defined as a disease which abnormal cells divide without control and can invade nearby tissues. The scariest part about it is, it can spread to other body parts through the blood and lymph systems. The current and most popular treatment is chemotherapy and it is really effective in killing the cancer cells. However, the drugs used in the treatment are prone to leakage and ironically kill the healthy cells as well. Therefore, developing a suitable delivery agent which can contain this problem is of priority.

One of the most common inorganic delivery agents is MSNs and a lot of researches being done on it due to its properties. Currently, the most commonly used template to develop MSNs is limited CTAB and with the discovery of ILs, the possibility of discovery alternative source template is available. Furthermore, the properties of the MSNs can be altered according to the purpose by varying the type of ILs used and its synthesis method.

1.8 Research objectives

This research main aim is to prove that ILs can serve as template in the MSNs synthesis as well as varying its morphology. Hence the objectives of this research are as follow:

I. To synthesize and characterize MSNs based on a series of pyridinium ILs via two methods.
II. To investigate the effect of anions and cations on the MSNs synthesized.
III. To optimize the synthesis parameters of MSNs via response surface methodology
IV. To determine the drug loading, drug release and drug release kinetics of drug using the optimized MSNs.

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