A Review on Ionic Liquids: Unveiling Diverse Application Across Industries

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Abstract:
Ionic liquids (ILs) have been extensively utilized in biomedical and pharmaceutical applications as solvents and permeation enhancers. Recently, there has been increasing interest in leveraging ILs technology to optimize the physicochemical properties of active pharmaceutical ingredients (APIs). Converting APIs into ionic liquids (API-ILs) has demonstrated significant potential for drug delivery by addressing issues such as polymorphism, modifying solubility, enhancing thermal stability, increasing dissolution rates, controlling drug release, modulating surfactant properties, improving API permeability, and adjusting cytotoxicity towards tumour cells. Furthermore, API-ILs are employed in various formulations, including solutions, emulsions, tablets, and nanoparticles. This review aims to summarize the current status of API-ILs, covering the rationale and design, preparation and characterization, improvements in the physicochemical properties of APIs, compatibility with different formulations, and the future prospects of API-ILs in the biomedical and pharmaceutical sectors. This review also outlines recent advancements in synthesizing inorganic nanomaterials using ionic liquids (ILs). The findings suggest that the IL approach can effectively guide the design, production, and application of inorganic nanomaterials in terms of size, shape, composition, and functionality. The examples presented demonstrate that ILs significantly enhance the field of inorganic nanomaterials.

Keywords:
Ionic Liquids, Biodiesel, Active Pharmaceutical Ingredient, Nanomaterial, Catalysis, Energy Storage.

Introduction:

BIODIESEL PRODUCTION USING BASIC IONIC LIQUID AS CATALYST

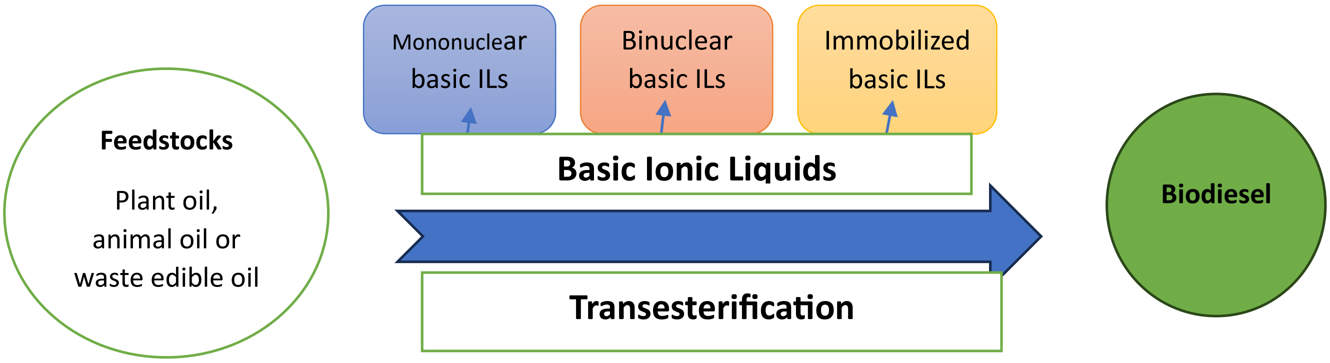
The compounds that are completely composed of ions with melting point below 100°C are defined as ionic liquids. These substances are also known as liquid electrolytes, ionic melts, ionic fluids, ionic salts or ionic glasses.[1] The chemical structure of 1-butyl-3 -methylimidazolium hexafluorophosphate ([BMIM]PF6), a common ionic liquid.

Any salt that melts without decomposing or vaporizing usually yields an Ionic liquid. Sodium Chloride (NaCl), for example, melts at 108°C into a liquid that consist largely of Sodium Cations (Na+) and Chloride Anions. Conversely, when it cooled, it forms an ionic solid-which may be either crystalline or glassy.

The ionic liquids have many applications. These are the solvents that can be used as electrolytes. They have the potential applications in different forms like catalysis, pharmaceuticals, biopolymer processing, nuclear fuel reprocessing, waste recycling batteries etc. Among the bio-renewable energy resources, biodiesel has been a very prospective alternative that has gained extensive interest due to its biodegradable, renewable, high security and non -toxic properties when compared to conventional fossil-based diesel. [2] Chemically biodiesel is defined as a biofuel that mainly consist of long -chain fatty alkyl esters which are originated from animal fats, plant oils or even fried waste oil. And it can also be produced by employing direct use and blending of raw oil, transesterification and micro-emulsification.[3]

Topic	Details
Advantages of Biodiesel	-Biodegradable -Renewable -Nontoxic
Sources of Biodiesel	-Animal fats -Plant oil -Fried waste oil
Production Methods	-Direct use and blending of raw oil -Transesterification -Pyrolysis
Chemical Catalysts	-Homogeneous -Heterogeneous
Biocatalysts	-Environment friendly -Require mild conditions -Avoid soap formation
Ionic Liquids	-Define as molten salts at room temp. -Properties include minimal vapor pressure, low combustibility, high thermal stability
Challenges and Future Prospects	-Need for improvement in conversion rates and product yields

To address the aforementioned hurdles, ILs have been attracting significant awareness as potential solvents or efficient catalysts for a wide variety of reactions or efficient catalysts for a wide variety of reactions. [4] ILs as a new class of materials, are defined as the compounds that are completely composed of ions when melting point below 100°C. Most of the ILs are constituted of organic cations e.g. Imidazolium, pyridinium, quaternary ammonium as well as organic or inorganic anions (e.g. halide, tetra fluoroborate etc.), which give ionic liquids several characteristics like, minimal vapor pressure, low combustibility, chemical stability and environment friendliness when compared to traditional chemicals.[5]



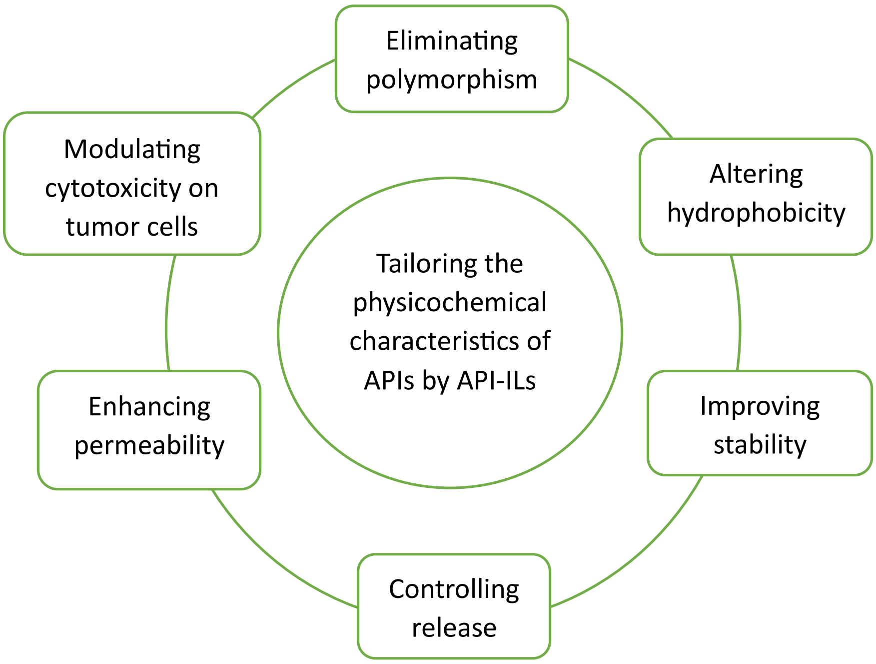
It should be noted that ILs, as a solvent, have shown good performance in the enzymatic synthesis of biodiesel, improving the catalytic efficiency and stability of enzymes.[6] Normally, ILs served as catalysts in the biodiesel production procedure can be divided into two main categories according to reactive sites, that is acidic and alkaline. Acidic ILs, have been extensively applied in production of biodiesel by means of esterification or transesterification.[7] Recently, Lewis and Bronsted acidic ILs have been well studied and widely used in biodiesel manufacturing various oil sources, such as soybean oil, castor oil.[8]

CLASSIFICATION AND SYNTHETIC METHODS OF BASIC IONIC LIQUIDS

Basic ILs can be synthesized by the organization of various cations and anions with various degrees of basicity giving a wide variety of basic ILs.[9] In general, basic ILs can be classified into three main groups depending on the number of alkaline sites and whether the solid supporter is contained in the structure, namely mononuclear basic ILs, binuclear basic ILs, and immobilized basic ILs.[10]

IONIC LIQUIDS AS A USEFUL TOOL FOR TAILORING ACTIVE PHARMACEUTICAL INGREDIENTS

Ionic liquids have been widely used in biomedical and pharmaceutical fields as solvents or permeation enhancers. Recently, more and more researchers focused on optimizing the physicochemical properties of active pharmaceutical ingredient (API) by ILs technology. Converting APIs into ILs (APIs-ILs) has shown great potential for drug delivery by eliminating polymorphism, tailoring solubility, controlling drug release.



Solid forms of active pharmaceutical ingredients (APIs) face several issues like poor solubility,[11] low bioavailability,[12] and polymorphic conversion.[13] To address these problems, researchers have explored various methods such as salt formation, solid dispersions, prodrugs, crystal engineering, nano-suspensions, micellar systems, and adsorption onto high surface area carriers. Among these, converting APIs into salts is a common way to improve solubility, and transforming them into liquid salts can enhance bioavailability and prevent polymorphic conversion. Ionic liquids (ILs) and deep eutectic solvents (DES) are promising materials for drug delivery. ILs are salts that melt below 100°C and consist of asymmetric cations and anions.[14] DES are mixtures of at least two components with a melting point lower than any of the individual components. [15] While DES differ from ILs in composition, they share similar properties, such as easy preparation, non-volatility, recyclability, and biocompatibility. [16-17] DES made from choline chloride ([Ch][Cl]) are sometimes called biocompatible ILs.[18]

By carefully choosing counter-ions, many APIs can be converted into ILs. These API-ILs can be tailored to have better solubility, thermal stability, dissolution rates, and eliminate polymorphism, affecting their pharmacokinetics and pharmacodynamics.[19] There are three types of API-ILs based on how they are formed: direct ionic binding with APIs as anions or cations, covalent linkage to create ionic prodrugs, and a combination of both methods to produce dual active API-ILs. API-ILs can also improve the transdermal or oral mucosal permeation of APIs. [20-22] Despite their potential, there are still many challenges to their application, and specific guidelines could help advance their research and development.

IONIC LIQUIDS FOR SYNTHESIS OF INORGANIC NANOMATERIALS

In recent years, inorganic nanomaterials have garnered significant attention due to their unique chemical and physical properties, which differ markedly from those of bulk solids [23-28]. The size and shape-dependent properties of these nanomaterials have driven scientists to develop methods for synthesizing inorganic nanomaterials with controlled size and structure. Achieving the desired properties in inorganic nanomaterials presents a significant challenge. Typically, water or traditional organic solvents are used in the synthesis of these nanomaterials. Each synthetic route involving these solvents has its own advantages and disadvantages, indicating a need for the development of new synthetic routes using alternative solvents for both fundamental research and application purposes.

Room-temperature ionic liquids (ILs) are organic salts composed entirely of ions, with melting points below 100 °C, and sometimes as low as −96 °C [29]. The first IL with a melting point of 12 °C was reported in 1914 [30]. Since then, numerous analogous compounds have been discovered. The most extensively studied ILs are 1-alkyl-3-methylimidazolium salts, known for their stability in air and moisture. The physicochemical properties of ILs, such as viscosity, solvation, catalytic activity, hydrophobicity, and melting point, can be finely tuned by altering the anion or the length of the alkyl group on the heterocyclic rings [31-32]. ILs have a wide liquidus range, in some cases exceeding 400 °C, and can dissolve a broad range of inorganic, organic, and polymer materials. This ability to combine individual reagents in the same phase makes ILs highly applicable in various fields. Their unusual properties, including high polarity, negligible vapor pressure, high ionic conductivity, and thermal stability, make ILs attractive as environmentally benign solvents for organic chemical reactions, polymer synthesis, separations, and electrochemical applications [33-34]. Numerous books [35-36] and reviews [37-39] have been published on the chemical reactions and physicochemical properties of ILs. Here is a table summarizing the key points:

Topic	Details	References
Interest in Inorganic Nanomaterials	Unique chemical and physical characteristics compared to bulk solids. Size and shape dependent properties have led to efforts to control size and structure.	23,24,25,26,27,28
Challenges in Synthesis	Synthesis involves water or traditional organic solvents, each with advantages and disadvantages. New synthetic routes with each other solvents are necessary.	
Types of Ionic Liquids	The most studied ILs are 1-alkyl-3-methylimidazolium salts due to their stability. Properties can be finely	31,32

	tuned by altering the anion or alkyl group length.	
Applications of ILs	ILs have unusual properties like high polarity, negligible vapor pressure, high ionic conductivity and thermal stability, making them attractive for various applications.	33,34
Development in Nanomaterial Synthesis	The advantages of ILs in inorganic nanomaterial synthesis have been gradually realized. New pathways for creating unique inorganic nanomaterials have been reported.	40,41,42,43,44

Recently, the advantages of ILs in the synthesis of inorganic nanomaterials have been increasingly recognized. Various approaches have been reported for fabricating inorganic nanomaterials with unique structures and properties in ILs. Notably, ILs can not only reproduce conventional inorganic nanomaterials but also facilitate the synthesis of new inorganic nanomaterials with properties that are challenging or impossible to achieve using conventional processes. The synthesis of inorganic nanomaterials in ILs is a relatively new field, having emerged over the past decade [40-44]. Given the significance and rapid development of ILs in this area, a review of recent advances in the synthesis of inorganic nanomaterials in ILs is timely. This review will focus on these advancements, excluding the inorganic-organic hybrids such as metal-organic frameworks synthesized in ILs, which have been recently reviewed by Parnham and Morris [45].

Conclusion:

Biodiesel presents a promising alternative to traditional petroleum-based fuels due to its renewable, biodegradable, and environmentally friendly properties.[46] The predominant method for producing biodiesel is through the transesterification of various feedstocks with methanol, which has received considerable attention. In this process, the catalyst is essential for facilitating the efficient conversion of raw materials into biodiesel.[47]

This review has highlighted the advantages and application of API-ILs in pharmaceutics.[48] Initially, converting APIs into ILs was suggested by focusing on eliminating the polymorphism of solid APIs.[49] Subsequently, API-ILs showed great potential for drug delivery by tailoring solubility, improving thermal stability, increasing dissolution, controlling drug release, modulating the surfactant properties, enhancing the permeability of APIs and modulating cytotoxicity on tumour cells.[50]

The recent advancements in the synthesis of inorganic nanomaterials using ionic liquids (ILs) reviewed in this article demonstrate the significant value ILs bring to the field of inorganic nanomaterials.[51] The inherent adaptability and versatility of ILs offer a novel, flexible, and potent method for fabricating novel, complex nanostructures through chemical techniques.[52] The utilization of ILs in inorganic nanomaterials remains in its nascent stages.[53]

References:

1 Hallett, J. P.; Welton, T. Room-Temperature Ionic Liquids: Solvents for Synthesis and Catalysis. 2 Chem. Rev. 2011, 111, 3508– 3576 DOI: 10.1021/cr1003248
2 Bara, J. E.; Carlisle, T. K.; Gabriel, C. J.; Camper, D.; Finotello, A.; Gin, D. L.; Nobel, R. D. Guide to CO2 Separations in Imidazolium-Based Room-Temperature Ionic Liquids Ind. Eng. Chem. Res. 2009, 48, 2739– 2751 DOI: 10.1021/ie8016237
3 Lei, Z.; Dai, C.; Chen, B. Gas Solubility in Ionic Liquid Chem. Rev. 2014, 114, 1289– 1326 DOI: 10.1021/cr300497a
4 Lei, Z.; Dai, C.; Zhu, J.; Chen, B. Extractive Distillation with Ionic Liquids: A Review AIChE J. 2014, 60, 3312– 3329 DOI: 10.1002/aic.14537
5 Chatel, G.; MacFarlane, D. R. Ionic Liquids and Ultrasound in Combination: Synergies and Challenges Chem. Soc. Rev. 2014, 43, 8132– 8149 DOI: 10.1039/C4CS00193A
6 Mai, Y. M. Computer-Aided Design of Ionic Liquids for High Cellulose Dissolution ACS Sustainable Chem. Eng. 2016, 4, 541– 547 DOI: 10.1021/acssuschemeng.5b00958
7 Gurkan, B. E.; de la Fuente, J.; Mindrup, E. M.; Ficke, L. E.; Goodrich, B. F.; Price, E. A.; Schneider, W. F.; Brennecke, J. F. Equimolar CO2 Absorption by Anion-Functionalized Ionic Liquids J. Am. Chem. Soc. 2010, 132, 2116– 2117 DOI: 10.1021/ja909305t
8 Ruckart, K. N.; O'Brien, R. A.; Woodard, S. M.; West, K. N.; Grant, T. Glover Porous Solids Impregnated with Task-Specific Ionic Liquids as Composite Sorbents J. Phys. Chem. C 2015, 119, 20681– 20697 DOI: 10.1021/acs.jpcc.5b04646
9 Qian, W.; Texter, J.; Yan, F. Frontiers in Poly(ionic liquid)s: Syntheses and Applications Chem. Soc. Rev. 2017, 46, 1124– 1159 DOI: 10.1039/C6CS00620E
10 Rojas, M. F.; Bernard, F. L.; Aquino, A.; Borges, J.; Dalla Vecchia, F.; Menezes, S.; Ligabue, R.; Einloft, S. Poly(ionic liquid)s as Efficient Catalyst in Transformation of CO2 to Cyclic Carbonate J. Mol. Catal. A: Chem. 2014, 392, 83– 88 DOI: 10.1016/j.molcata.2014.05.007
11 A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: solubility and permeability studies
Eur. J. Pharm. Biopharm.
(2017)
A. Balk et al.
12 Transformation of acidic poorly water soluble drugs into ionic liquids
Eur. J. Pharm. Biopharm.
(2015)
Y. Shi et al.

13 Oral delivery of sorafenib through spontaneous formation of ionic liquid nanocomplexes
J. Control. Release
(2020)
X. Wu et al.
14 Improving dermal delivery of hyaluronic acid by ionic liquids for attenuating skin dehydration
Int. J. Biol. Macromol.
(2020)
Q.M. Qi et al.
15 Mechanistic study of transdermal delivery of macromolecules assisted by ionic liquids
J. Control. Release
(2019)
P.W. Stott et al.
16 Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen
J. Control. Release
(1998)
M.H. Zainal-Abidin et al.
17 Emerging frontiers of deep eutectic solvents in drug discovery and drug delivery systems
J. Control. Release
(2019)
L. Kang et al.
18 Physicochemical studies of lidocaine-menthol binary systems for enhanced membrane transport
Int. J. Pharm.
(2000)
P.W. Stott et al.
19 Mechanistic study into the enhanced transdermal permeation of a model beta-blocker, propranolol, by fatty acids: a melting point depression effect
Int. J. Pharm.
(2001)
E.E.L. Tanner et al.
20 Transdermal insulin delivery using choline-based ionic liquids
J. Control. Release
(2018)
D. Yang et al.
21 The molecular design of drug-ionic liquids for transdermal drug delivery: mechanistic study of counterions structure on complex formation and skin permeation
Int. J. Pharm.
(2021)
R. Yang et al.
22 Synergy between chemical permeation enhancers and drug permeation across the tympanic membrane
J. Control. Release

(2018)
S. Rathi et al.
M. Zäch et al.
23 Nanoscience and nanotechnology for advanced energy systems
Curr Opin Solid State Mater Sci
(2006)
K.W. Kolasinski
24 Silicon nanostructures from electroless electrochemical etching
Curr Opin Solid State Mater Sci
(2005)
J.M. Macak et al.
25 TiO2 nanotubes: Self-organized electrochemical formation, properties and applications
Curr Opin Solid State Mater Sci
(2007)
K.W. Kolasinski
26 Catalytic growth of nanowires: Vapor–liquid–solid, vapor–solid–solid, solution–liquid–solid and solid–liquid–solid growth
Curr Opin Solid State Mater Sci
(2006)
P. Kubisa
27 Application of ionic liquids as solvents for polymerization processes
Prog Polym Sci
(2004)
I. Mukhopadhyay et al.
28 Electrodeposition of Ti from TiCl4 in the ionic liquid l-methyl-3-butyl-imidazolium bis (trifluoro methyl sulfone) imide at room temperature: study on phase formation by in situ electrochemical scanning tunneling microscopy
Electrochim Acta
(2005)
S. Zein El Abedin et al.
29 Electrodeposition of nanoscale silicon in a room temperature ionic liquid
Electrochem Commun
(2004)
P.Y. Chen et al.
30 Electrochemistry of Cd(II) in the basic 1-ethyl-3-methylimidazolium chloride/tetrafluoroborate room temperature molten salt
Electrochim Acta
(2000)
P.Y. Chen et al.
31 Electrochemical study of copper in a basic 1-ethyl-3-methylimidazolium tetrafluoroborate room temperature molten salt
Electrochim Acta
(1999)
J.F. Huang et al.

32 Electrodeposition of PtZn in a Lewis acidic ZnCl2–1-ethyl-3-methylimidazolium chloride ionic liquid
Electrochim Acta
(2004)
J. Du et al.
33 Synthesis of mesoporous SrCO3 spheres and hollow CaCO3 spheres in room-temperature ionic liquid
Micropor Mesopor Mater
(2005)
Z. Li et al.
34 Synthesis of LaCO3OH nanowires via a solvothermal process in the mixture of water and room-temperature ionic liquid
Mater Lett
(2005)
P. Singh et al.
35 Copper nanoparticles in an ionic liquid: an efficient catalyst for the synthesis of bis-(4-hydroxy-2-oxothiazolyl)methanes
Tetrahedron Lett
(2008)
Z. Li et al.
36 Synthesis of single crystal BaMoO4 nanofibers in CTAB reverse microemulsions
Mater Lett
(2005)
Z. Li et al.
37 Preparation and self-assembly of nanostructured BaCrO4 from CTAB reverse microemulsions
Mater Chem Phys
(2005)
Z. Li et al.
38 Preparation of silica microrods with nano-sized pores in ionic liquid microemulsions
Colloids Surf A
(2006)
39 Semiconductor clusters, nanocrystals, and quantum dots
Science
(1996)
A. Henglein
40 Small-particle research: physicochemical properties of extremely small colloidal metal and semiconductor particles
Chem Rev
(1989)
K.R. Seddon et al.
41 Influence of chloride, water, and organic solvents on the physical properties of ionic liquids
Pure Appl Chem
(2000)

P. Walden, Bull Acad Imper Sci [St. Petersburg] 1914;...
A.E. Bradley et al.
42 Small-Angle X-ray Scattering Studies of Liquid Crystalline 1-Alkyl-3-methylimidazolium Salts
Chem Mater
(2002)
H.L. Ngo et al.
43 Thermal properties of imidazolium ionic liquids
Thermochim Acta
(2000)
R. Sheldon
44 Catalytic reactions in ionic liquids
Chem Commun
(2001)
J.G. Huddleston et al.
Room temperature ionic liquids as novel media for 'clean' liquid–liquid extraction
Chem Commun
(1998)
E.V. Dickinson et al.
45 Hybrid redox polyether melts based on polyether-tailed counterions
J Am Chem Soc
(1999)
46 Lei, Z.; Dai, C.; Chen, B. Gas Solubility in Ionic Liquid Chem. Rev. 2014, 114, 1289– 1326 DOI: 10.1021/cr300497a
47 Lei, Z.; Dai, C.; Zhu, J.; Chen, B. Extractive Distillation with Ionic Liquids: A Review AIChE J. 2014, 60, 3312– 3329 DOI: 10.1002/aic.14537
48 A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: solubility and permeability studies
Eur. J. Pharm. Biopharm.
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A. Balk et al.
49 Transformation of acidic poorly water soluble drugs into ionic liquids
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(2015)
Y. Shi et al.
50 Oral delivery of sorafenib through spontaneous formation of ionic liquid nanocomplexes
J. Control. Release
(2020)
X. Wu et al.
51 Nanoscience and nanotechnology for advanced energy systems
Curr Opin Solid State Mater Sci
(2006)

K.W. Kolasinski
52 Silicon nanostructures from electroless electrochemical etching
Curr Opin Solid State Mater Sci
(2005)
J.M. Macak et al.
53 TiO2 nanotubes: Self-organized electrochemical formation, properties and applications
Curr Opin Solid State Mater Sci
(2007)
K.W. Kolasinski