



US008232265B2

(12) **United States Patent**
Rogers et al.

(10) **Patent No.:** **US 8,232,265 B2**
(45) **Date of Patent:** **Jul. 31, 2012**

(54) **MULTI-FUNCTIONAL IONIC LIQUID COMPOSITIONS FOR OVERCOMING POLYMORPHISM AND IMPARTING IMPROVED PROPERTIES FOR ACTIVE PHARMACEUTICAL, BIOLOGICAL, NUTRITIONAL, AND ENERGETIC INGREDIENTS**

(75) Inventors: **Robin D. Rogers**, Tuscaloosa, AL (US); **Daniel T. Daly**, Tuscaloosa, AL (US); **Richard P. Swatloski**, Tuscaloosa, AL (US); **Whitney L. Hough**, Albertville, AL (US); **James Hilliard Davis, Jr.**, Mobile, AL (US); **Marcin Smiglak**, Tuscaloosa, AL (US); **Juliusz Pernak**, Poznan (PL); **Scott K. Spear**, Bankston, AL (US)

(73) Assignee: **Board of Trustees of the University of Alabama**, Tuscaloosa, AL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1208 days.

(21) Appl. No.: **11/545,938**

(22) Filed: **Oct. 10, 2006**

(65) **Prior Publication Data**
US 2007/0093462 A1 Apr. 26, 2007

Related U.S. Application Data
(60) Provisional application No. 60/764,850, filed on Feb. 2, 2006, provisional application No. 60/724,604, filed on Oct. 7, 2005, provisional application No. 60/724,605, filed on Oct. 7, 2005.

(51) **Int. Cl.**
A61K 31/33 (2006.01)
A61K 31/445 (2006.01)
A61K 31/21 (2006.01)
A61K 31/24 (2006.01)
A61K 31/16 (2006.01)
A01N 43/90 (2006.01)
A01N 37/30 (2006.01)
A01N 37/18 (2006.01)

(52) **U.S. Cl.** **514/183**; 514/306; 514/330; 514/513; 514/535; 514/555

(58) **Field of Classification Search** None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,943,176 A	1/1934	Graenacher	260/100
2,004,891 A *	6/1935	Goldberg	514/533
3,223,704 A	12/1965	Shibe	260/247.1
3,344,018 A	9/1967	Shibe	167/22
3,414,569 A	12/1968	Wieden	260/247.1
3,471,423 A	10/1969	Elmer	260/22
4,104,368 A	8/1978	Lala et al.	424/60

4,224,319 A	9/1980	Marcadet	424/238
4,228,162 A	10/1980	Luzzi et al.	424/232
4,491,574 A	1/1985	Seifter et al.	424/10
4,761,164 A	8/1988	Pez et al.	55/16
4,973,456 A	11/1990	Quinn et al.	423/210.5
5,275,820 A	1/1994	Chang	424/426
5,654,337 A	8/1997	Roentsch et al.	514/570
5,679,146 A	10/1997	Kalt et al.	106/166.01
5,683,832 A	11/1997	Bonhôte et al.	429/111
5,731,101 A	3/1998	Sherif et al.	429/102
5,792,399 A	8/1998	Meister et al.	264/101
5,827,602 A	10/1998	Koch et al.	429/194
5,908,697 A	6/1999	Roux et al.	428/402.2
6,759,544 B2	7/2004	Burgard	556/119
6,774,240 B2	8/2004	Seddon et al.	548/347.1
6,808,557 B2	10/2004	Holbrey et al.	106/163.01
6,824,599 B2	11/2004	Swatloski et al.	106/163.01
6,846,926 B1	1/2005	Koppes et al.	544/198
6,906,004 B2	6/2005	Parrish et al.	504/127
6,924,341 B2 *	8/2005	Mays et al.	526/89
6,939,882 B1	9/2005	Cooke et al.	514/336
6,939,974 B2	9/2005	Earle et al.	548/347.1
7,166,641 B2 *	1/2007	Lee et al.	514/561
2002/0010291 A1	1/2002	Murphy	526/133
2002/0161261 A1	10/2002	Bahrman et al.	564/281
2003/0073604 A1	4/2003	McGolf et al.	510/441
2004/0007693 A1	1/2004	Moulton	252/364
2004/0026666 A1	2/2004	Chauvin et al.	252/364
2004/0146549 A1	7/2004	Ben-Sasson et al.	424/449
2004/0234966 A1	11/2004	Bryning et al.	435/6
2005/0058702 A1	3/2005	Ben-Sasson et al.	424/452
2005/0136103 A1	6/2005	Ben-Sasson et al.	424/449

(Continued)

FOREIGN PATENT DOCUMENTS

CA 2619367 A1 7/2009

(Continued)

OTHER PUBLICATIONS

Avent et al., "Evidence for hydrogen bonding in solutions of 1-Ethyl-3-imidazolium Halides, and its implications for ambient temperature Halogenoaluminate (III) ionic liquids," *J. Chem. Soc., Dalton Trans.*, 3405 (1994).
Bates et al., "CO2 capture by a task-specific ionic liquid," *J. Am. Chem. Soc.* 124(6):926-927 (2002).
Bernstein, "Polymorphism of high energy materials," *Polymorphism in Molecular Crystals*, 275-296 (2002).
Bernstein, "Introduction and historical background," *Polymorphism in Molecular Crystals*, 1-28 (2002).
Bernstein, "Crystal structure prediction and polymorphism," *ACA Transactions*, 39:14-23 (2004).

(Continued)

Primary Examiner — Alton Pryor
(74) *Attorney, Agent, or Firm* — McKeon, Meunier, Carlin & Curfman, LLC

(57) **ABSTRACT**

Disclosed are ionic liquids and methods of preparing ionic liquid compositions of active pharmaceutical, biological, nutritional, and energetic ingredients. Also disclosed are methods of using the compositions described herein to overcome polymorphism, overcome solubility and delivery problems, to control release rates, add functionality, enhance efficacy (synergy), and improve ease of use and manufacture.



U.S. PATENT DOCUMENTS

2005/0194561	A1	9/2005	Davis	252/67
2005/0232981	A1	10/2005	Ben-Sasson	424/448
2006/0159632	A1	7/2006	Ishibashi et al.	
2007/0053939	A1	3/2007	Yokoyama et al.	
2007/0054952	A1	3/2007	Hamamoto et al.	
2009/0264664	A1	10/2009	Endo et al.	
2010/0004608	A1	1/2010	Hamamoto et al.	
2010/0029704	A1	2/2010	Hanma et al.	

FOREIGN PATENT DOCUMENTS

DE	93-4308410	3/1993
EP	1405646	* 4/2004
ES	8406412	4/1983
FR	1404697	5/1965
GB	869149	5/1961
GB	1067094	5/1964
GB	1473603	5/1971
JP	61-236818	10/1986
JP	62-198609	9/1987
JP	63-056501	3/1988
JP	2005-82512	3/2005
JP	2005 082512	3/2005
JP	2005082512 A	3/2005
NL	302478	10/1965
WO	WO 95/21806	8/1995
WO	WO 95/21871	8/1995
WO	WO 95/21872	8/1995
WO	WO 97/43012	11/1997
WO	WO 98/51283	11/1998
WO	WO98/51283 A1	11/1998
WO	WO 03/029329	4/2003
WO	WO 2004/075877	9/2004
WO	WO 96/06593	3/2006
WO	WO 2009/060629 A1	5/2009
WO	WO 2009/066457 A1	5/2009
WO	WO 2009/075094 A1	6/2009
WO	WO 2009/119836 A1	10/2009

OTHER PUBLICATIONS

Bhatt et al., "Saccharin as a salt former. Enhanced solubilities of saccharinates of active pharmaceutical ingredients," *Chem. Comm.*, 1073-1075 (2005).

Black et al., "Increased chemical purity using a hydrate," *Crystal Growth & Design*, 4(3) 539-544 (2004).

Bonhôte et al., "Hydrophobic, highly conductive ambient-temperature molten salts," *Inorg. Chem.* 35:1168-1178 (1996).

Bowlas et al., "Liquid crystalline ionic liquids," *Chem. Comm.* 1625 (1996).

Browning et al., "Relationships between antiseptic action and chemical constitution with special reference to compounds of the pyridine, quinoline, acridine and phenazine series," *Proc. Royal Soc. London*, 93(653):329-366 (1922).

Browning et al., "The antiseptic properties of the amino derivatives of styryl and anil quinoline," *Proc. Royal Soc. London*, 100(703):293-325 (1926).

Butcher et al., "Initial screening trials of some quaternary ammonium compounds and amine salts as wood preservatives," *For. Prod. J.*, 27:19-22 (1977).

Butcher et al., "Efficacy of acidic and alkaline solutions of alkylammonium compounds as wood preservatives," *J. For. Sci.*, 8:403-408 (1978).

Campanella et al., "Benzylpenicillin PVC membrane electrode for the determination of antibiotics in formulations," *J. Pharm. Biomed. Analysis* 6(3):299-305 (1988).

Campanella et al., "Polymeric membrane electrodes for drug analysis," *J. Pharm. Biomed. Analysis* 6:717-723 (1988).

Carmichael, "A solution in sight," *Chem. Britan* 36 (2000).

Carter et al., "Sweet success: Ionic liquids derived from non-nutritive sweeteners," *Chem. Comm.* 630-631 (2004).

Chawla et al., "Challenges in polymorphism of pharmaceuticals," *CRISPS*, 5(1):9-12 (2004).

Cuppen et al., "Crystal structure and growth behavior of aspartame form I-A," *Crystal Growth & Design*, 5(3) 917-923 (2005).

Davis et al., "Thiazolium-ion based organic ionic liquids (OILs). Novel OILs which promote the benzoin condensation," *Tetrahedron Lett.* 40:1621-1622 (1999).

Davis et al., "From curiosities to commodities: Ionic liquids begin the transformation," *Chem. Comm.* 1209-1211(2003).

Domagk, "A new class of disinfectants," *Deut. Med. Wochenschr.*, 61:829 (1935).

Dupont et al., "Room temperature molten salts: Neoteric "Green" solvents for chemical reactions and processes," *Braz. Chem. Soc.* 11(4):337-344 (2000).

Elaiwi et al., "Hydrogen bonding in Imidazolium salts and its implications for ambient-temperature Halogenoaluminate (III) ionic liquids," *Chem. Soc., Dalton Trans.*, 3467 (1995).

Fannin et al., "Properties of 1,3-Dialkylimidazolium chloride-aluminum chloride ionic liquids. 2. Phase transitions, densities, electrical conductivities, and viscosities," *J. Phys. Chem.*, 88:2614-2621 (1984).

Fraga-Dubreuil et al., "Grafted ionic liquid-phase-supported synthesis of small organic molecules," *Tetrahedron Lett.* 42:6097-6100 (2001).

Freemantle, "Ionic liquids show promise for clean separation technology," *Chem. Eng. News*, 76(34):34 (1998).

Freemantle, "Eyes on ionic liquids," *Chem. Eng. News*, 78(2):37-50 (2000).

Fukumoto et al., "Room temperature ionic liquids from 20 natural amino acids," *J. Am. Chem. Soc.* 2398-2399 (2005).

Geppi et al., "Molecular properties of ibuprofen and its solid dispersions with eudragit RL100 studied by solid-state nuclear magnetic resonance," *Pharm. Res.*, 22(9) 1544-1555 (2005).

Gordon et al., "Fused organic salts. 8. Properties of molten straight-chain isomers of tetra-N-pentylammonium salts," *J. Amer. Chem. Soc.* 100(24):7445-7454 (1978).

Hamaguchi et al., "Structure of ionic liquids and ionic compounds: Are ionic liquids genuine liquids in the conventional sense," *Advances in Chem. Physics*, 131:85-104 (2005).

Hartman et al., "Acid soaps," *J. Applied Chem.*, 41:127 (1928).

Haynes et al., "Occurrence of pharmaceutically acceptable anions and cations in the Cambridge structural database," *J. Pharm. Sci.*, 94(10) 2111-2120 (2005).

Holbrey et al., "Ionic liquids," *Clean Products and Processes* 1:223-236 (1999).

Holbrey et al., "The phase behaviour of 1-alkyl-3-methylimidazolium tetrafluoroborates; Ionic liquids and ionic liquid crystals," *J. Chem. Soc. Dalton Trans.*, 2133-2139 (1999).

Huddleston et al., "Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation," *Green Chem.*, 3:156-164 (2001).

International Search Report and Written Opinion of the International Searching Authority for PCT/US06/39454.

Jacobs et al., "On a new group of bactericidal substances obtained from hexamethylenetetramine," *Proc. Nat. Acad. Sci. USA*, 1:226-228 (1915).

Jacobs et al., "The quaternary salts of hexamethylene-tetramine," *J. Biol. Chem.*, 20:659-683 (1915).

Jacobs et al., "The bactericidal properties of the quaternary salts of hexamethylenetetramine," *J. Exptl. Med.*, 23:569-576 (1916).

Katritzky et al., "1-Butyl-3-methylimidazolium 3,5-dinitro-1,2,4-triazolate: a novel ionic liquid containing a rigid, planar energetic anion," *Chem. Comm.*, 868-870 (2005).

Katritzky et al., "Strategies toward the design of energetic ionic liquids: Nitro- and Nitrile-substituted N,N' dialkylimidazolium salts," *New J. Chem.*, 30:349-358 (2006).

Katritzky et al., "In search of ionic liquids incorporating azolate anions," *Chem. Eur. J.*, 12:4630-4641 (2006).

Klinguer et al., "Lipophilic quaternary ammonium salt acts as a mucosal adjuvant when co-administered by the nasal route with vaccine antigens," *Vaccine* 19:4236-4244 (2001).

- MacFarlane et al., "Pyrrolidinium imides: A new family of molten salts and conductive plastic crystal phases," *J. Phys. Chem.* 103:4164-4170 (1999).
- Martino et al., "Influence of crystal habit on the compression and densification mechanism of ibuprofen," *J. Crystal Growth*, 243:345-355 (2002).
- Matsumoto et al., "Room temperature ionic liquids based on small aliphatic ammonium cations and asymmetric amide anions," *Chem. Comm.* 1726-1727 (2002).
- Meguro et al., "Crystal structure of the low-humidity form of aspartame sweetener," *J. Peptide Res.*, 56:97-104 (2000).
- Merrigan et al., "New fluoros ionic liquids function as surfactants in conventional room-temperature ionic liquids," *Chem. Comm.* 2051-2052 (2000).
- Morrison et al., "Base-promoted reactions in ionic liquid solvents. The Knoevenagel and Robinson annulation reactions," *Tetrahedron Lett.* 42:6053-6057 (2001).
- Ngo et al., "Thermal properties of imidazolium ionic liquids," *Thermochimica Acta*, 357-358:97-102 (2000).
- Oertel, Novel hard to wash-out water soluble wood protecting agents and their application, *Holztechnologie*, 1965, 6:243.
- Ohno et al., "A new type of polymer gel electrolyte: Zwitterionic liquid/polar polymer mixture," *Electrochimica Acta*, 48(14-16):2079-2083 (2003).
- Okamoto et al., "Synthesis, spectra, and reactions of N-triphenylmethylpyridinium salts. Reactions of triphenylmethyl chloride with pyridine under high pressure," *J. Org. Chem.*, 35(11):3752-3756 (1970).
- Oldham et al., "Unusual solvent system shows potential to revolutionize separation and purification technologies," *The Actinide Research Quarterly*, 1st Quarter 50-53 (2004).
- Pernak et al., "Phosphonium acesulfamate based ionic liquids," *Eur. J. Org. Chem.* 650-652 (2005).
- Quinn et al., "Salt hydrates: New reversible absorbents for carbon dioxide," *J. Am. Chem. Soc.* 117:329-335 (1995).
- Rasenack et al., "Properties of ibuprofen crystallized under various conditions: A comparative study," *Drug Dev. Industrial Pharm.*, 28(9) 1077-1089 (2002).
- Remenar et al., "Salt selection and simultaneous polymorphism assessment via high-throughput crystallization: The case of sertraline," *Org. Proc. Res. & Dev.* 7(6): 990-996 (2003).
- Reutzel-Edens et al., "Anhydrates and hydrates of olanzapine: Crystallization solid-state characterization, and structural relationships," *Crystal Growth & Design*, 3(6):897-907 (2003).
- Rogers et al., "Ionic liquids—Solvents of the future," *Science*, 302:792-793 (2003).
- Seddon, "Ionic liquids for clean technology," *J. Chem. Tech. Biotechnol.* 68:351-356 (1997).
- Swatlowksi et al., "Ionic liquids are not always green: Hydroanalysis of 1-butyl-3-methylimidazolium hexafluorophosphate," *Green Chem.* 5:361-363 (2003).
- Trask et al., "Screening for crystalline salts via mechanochemistry," *Chem. Comm.*, 51-53 (2006).
- Visser et al., Task-specific ionic liquids for the extraction of metal ions from aqueous solutions, *Chem. Comm.* 135-136 (2001).
- Visser et al., "Hydrophobic ionic liquids incorporating N-alkylisoquinolinium cations and their utilization in liquid-liquid separation," *Chem. Comm.* 2484-2485 (2001).
- Wasserscheid et al., "Ionic liquids—new "solutions" for transition metal catalysis," *Angew. Chem. Int. Ed. Engl.*, 39:3772-3789 (2000).
- Welton, "Room temperature ionic liquids, Solvents for synthesis and catalysis," *Chem. Rev.* 99:2071-2083 (1999).
- Wilkes et al., "Air and water stable 1-ethyl-3-methylimidazolium based ionic liquids," *J. Chem. Soc.*, 965-967 (1992).
- Application No. 200680046195.7, Sep. 9, 2010, First Office Action. Extended European Search Report for Application No. 06774039.9 dated Jul. 8, 2011.
- International Preliminary Report on Patentability and Written Opinion for PCT/US2009/069652 dated Jul. 7, 2011.
- office Action for AU Patent Application No. 2006302237 dated Aug. 23, 2011.
- Response to Office Action for AU Patent Application No. 2006302237 dated Feb. 6, 2010.
- Response to Office Action for CN Patent Application No. 200680046195 dated Mar. 23, 2012.
- Okutucu et al., Covalent Attachment of Oligonucleotides to Cellulose Acetate Membrances, Artificial Cells, Blood Substitutes, and Biotechnology, 32(4):599-608 (2004).
- Stöllner et al., Activation of Cellulose Membrances with 1,1'-Carbonyldiimidazole or 1-Cyano-4-dimethylaminopyridinium tetrafluoroborate as a Basis for the Development of Immunosensors, *Analytical Biochemistry*, 304:157-165 (2002).

* cited by examiner

Figure 1

[Hex]Sulfacetamide, [Hex]Cl & Na Sulfacetamide Dissolution

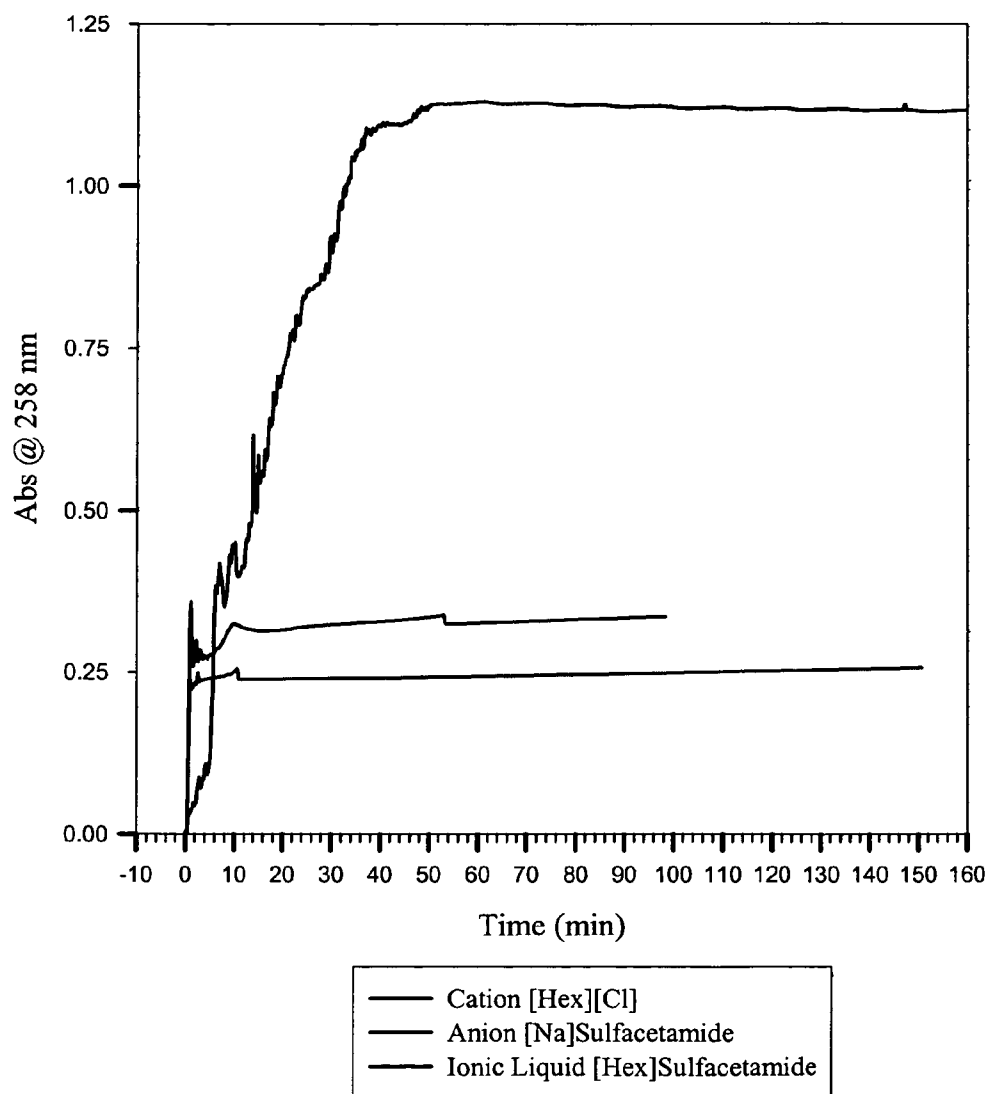
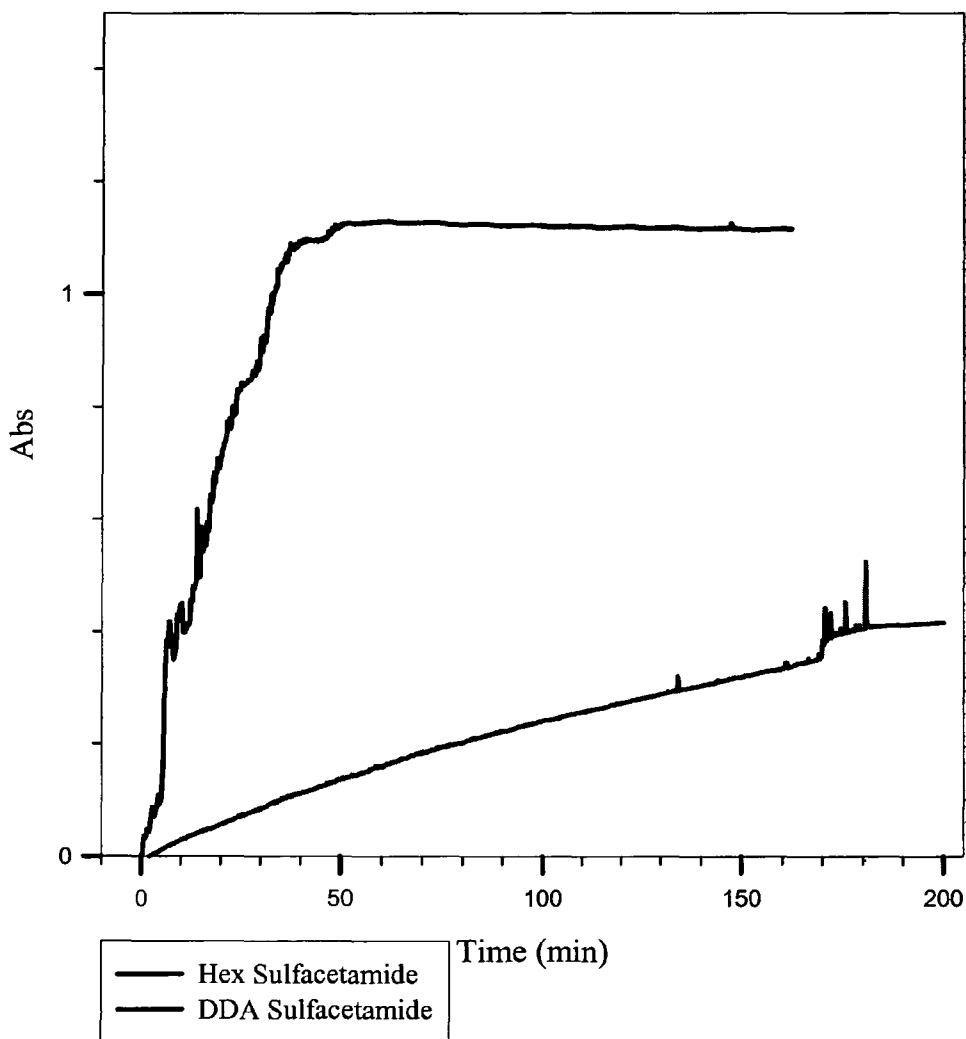


Figure 2

Hex Sulfacetamide and DDA Sulfacetamide Dissolution



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.