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Urolithiasis in gel: Successful journey of an *in vitro* model from vision to reality

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Abstract
This review shares historical glimpses behind the art and science of urinary crystal growth in gel. This successful journey of long and painstaking research consists of both theoretical and experimental knowledge. The survey consists of historical aspects of crystal growth, development of urinary crystal growth in gel as an *in vitro* urolithiasis model and the application of this model to evaluate prophylactic management against kidney stones.

Keywords: Urolithiasis, gel, *in vitro* models, Liesegang rings

1. Introduction

Urolithiasis is one of the oldest, most common and recurrent disease. Urinary calculi are composed of insoluble crystalline compounds of ammonium, calcium, magnesium and phosphorous. Calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddellite), calcium hydrogen phosphate dihydrate (brushite), ammonium acid urate, mono sodium urate monohydrate, uric acid anhydrous, uric acid mono and dihydrate and ammonium magnesium phosphate hexahydrate (struvite) are the examples of these compounds [1]. Crystallization of salt from sea water by burning of earthenware is considered as one of the oldest methods of crystallization. The story of crystal growth in gel medium started when the lead iodide crystals were grown in fruit jelly and jam. The formation of the Liesegang ring in gel turns the history of crystal growth from aqueous to non aqueous media. The series of theoretical and experimental contributions developed "crystal growth in gel" as an *in vitro* technique. The growth of oxalate, phosphate and urate crystals made possible to grow urinary crystals in gel. The promotory or inhibitory effect of herbal extracts on growing urinary crystals provides a pathway for *in vitro* evaluation of risk factors or prophylactic management of kidney stones. The contributions and findings of this successful journey are highlighted in Table-1.

Crystal growth in the gel is a simple, easy and inexpensive *in vitro* technique which provides crystals of different morphologies and sizes along with practical observation of crystal growth stages [2]. Gel medium is very useful for studying crystal deposition diseases such as the formation of atherosclerotic plaque, gall stones, gouty crystals and urinary stones [3]. The gel medium is chemically inert, prevents the turbulence and provides a framework of separated nucleation sites to grow single crystal. The viscous nature, temperature and pH of the gel provide a resemblance with human physiological conditions. However, the size, quality and quantity of growing crystal during the experiment can't be predicted [4, 5]. The basic principle of this technique is generally explained as, "When the specific concentration of two suitable compounds are allowed to diffuse into a gel. These compounds react chemically with reactants present in gel, form a precipitate of periodic bands or rings (Liesegang patterns) and leading to the growth of insoluble crystals of required compound" [2, 4]. Pathologic crystallization is a complex process which causes atherosclerotic plaque, gall stones, gout and urinary stones. Therefore the study to find out crystallization promoting or inhibiting factors is important [6, 7]. The direct observation of crystallization is not possible by *in vivo* models and the mechanism remains unexplained. *In vitro* models not only provide the direct observation of crystal growth, but also devising the meaning of unwanted crystal promotion, modulation or inhibition. Growth of pathologic crystals in gel along with plant extracts and juices gives important information about crystallization promotion, modulation or inhibition by comparing the changes. These changes include shape, size, transparency, approximate number and total mass of crystals [6]. In case of inhibition, it assures prophylactic management by evaluation of nucleation, growth and aggregation of growing crystals.

Therefore, this *in vitro* technique provides a multidisciplinary approach in characterizing the grown crystals and help in formulating a strategy for the prevention or dissolution of urinary crystals. In case of promotion, i.e. increase in size and number of crystals give an idea about risk factors [8]. Crystallization by gel diffusion technique has been divided into following five methods as chemical reaction, chemical reduction, complex dilution, solubility reduction and electrolytic method. Chemical reaction methods are classified as single and double diffusion [9-15]. Hence urinary crystals have been grown by a chemical reaction method. So, contribution regarding this method is mentioned in the survey. Gel technique is not limited to urinary crystals. It has applied to grow different other pathologic crystals as well as crystals of sex hormones such as cholesterol, progesterone and testosterone [16-19]. The same technique is now successfully applied to different areas of biotechnology and nanotechnology.

Table 1: Historical background of urolithiasis in gel.

Year	Contributors	Findings / Contributions	References
Before Christian Era	Not documented	Crystallization of salt from sea water by burning of earthenware (evaporation).	[20]
12th – 13th century	Geber (Jabir Ibn Hayyan, the great Muslim Chemist)	Described the purification of materials by recrystallization, sublimation and distillation.	
1540	Birringuccio	Recorded the leaching of saltpeter and its purification by recrystallization.	
1556	Agricola	Shared the crystallization of alum and vitriol.	
1611	Kepler	Shared the principle of crystallographic forms.	
1602	Caesalpinus	Observed crystals of alum, saltpeter, sugar and vitriol in solutions.	
1665	Hooke	Claimed microscopic arrangement of spherical particles to form crystal.	
1669	Nicolaus Steno	Crystal growth via addition of material from outside not by vegetative mode.	
1773	Bergman	Crystals break into smallest unit (crystal cleavage) and the repetition of smallest unit formation responsible for crystal growth.	
1795	Lowitz	Super saturation of solution is required for crystal formation.	
1813	Schweigger	Minimum size of crystal nuclei is required to initiate crystallization.	
1815	Weiss	Derived the crystal systems.	
1824	Seeber	Lattice type arrangement is responsible to form crystal.	
1849	Bravais	Derived 14 types of crystal lattice.	
1878	Gibb	Determined the total minimum free surface energy needed to generate a nucleus for crystallization.	
1882	Gernez	Quantitatively measured rate of crystal growth.	
1885	Curie	Layer-by-layer adsorption of atoms or molecule is responsible for crystal growth.	[21]
1886	Ostwald	Explained nucleation phenomena which support Liesegang ring formation.	[22]
1891	Marriage	Observed lead iodide crystals in fruit jelly and jam.	[23]
1896	Liesegang	Observed Liesegang ring formation in gel.	[24]
1897	Ostwald	Supersaturation causes Liesegang ring formation.	[20]
1898	Tammann	Quantitatively measured nucleation process to form crystal.	
1900	Ostwald	Derived the thermodynamic formula for the enhanced solubility of small particles. Explained dependence of solubility on particle size.	
1911	Hatschek	First to report that crystals grow better in silica gel than in gelatin or agar. Liesegang rings themselves consist of substantial crystals. He made a systematic study of particle size distribution in these rings.	[25]
1913	Dreaper	Diffusion of reactants through capillary pores of gel aiding efficient crystal formation.	[26]
	Bragg	X-ray crystal structure determination.	[20]
1914	Johnston	Diffusion technique to grow compounds.	
1917	Holmes	Used less acidic silica gel to produce crystalline salts not possible in acidic gel. Grown hexagonal plates of lead iodide, needles of mercuric iodide, sheets of silver acetate and rhombohedral crystals of monosodium phosphate in silica gel.	[27]
1923	Davies	The influence of light in crystal growth.	[28]
1926	Lloyd	Preliminary survey on gel structures.	[2]
	Holmes	Used the dialyzing process for gels to eliminate excess interfering reagents for diffusing components in U-tubes.	
	Endres	Observed growth of ice crystals in ice cream and tartrate crystals in cheese.	
	Fells and Firth	Capillary pores of silica gel were found to be the center of crystal growth.	[29]
1931	Morse and Donnay	Investigated three-dimensional structure of spherulites.	[30]
1947	Plank	Proposed ionic mechanism for silica and silica-alumina gel formation.	[31]
1949	Frank	Crystal growth occurs in spiral fashion by a continuous process.	[32]
1965	Hektisch *et al.*	Described a technique to grow single crystal in silica gel. Further shared that the crystal growth in gel ceases after complete utilization of reactants.	[33]
1966	Kurz	Grown mercuric iodide crystals by chemical reaction method in silica gel.	[34]
		Grown mercuric chloride crystals by chemical reaction method in silica gel.	[35]
1967	Dennis and Henisch	Nucleation of crystal in gel depends on reagent concentration and impurities.	[36]
1968	Halberstadt and	Nucleation of crystal in gel influenced by pH and reagent additives.	[2]

	Henisch		
	Kratochvil *et al.*	Grown hexagonal and triangular shaped gold crystals by chemical reaction method in silica gel.	[10]
1969	Kurz	Grown needles and rhombohedral shaped potassium acid tartrate crystals by chemical reaction method in silica gel.	[11]
1971	Březina and Havrankova	Grown potassium dihydrogen phosphate single crystals in agar gel.	[37]
1973	Banks *et al.*	Grown CHPD, AMPH, strontium hydrogen phosphate and barium hydrogen phosphate crystals in gelatin.	[38]
1975	Bisaillon and Tawashi	Grown single, bipyramidal and rosette shaped COM and COD crystals in silica gel and gelatin.	[39]
1976	Cody	Grown gypsum crystals in bentonite gel.	[40]
	Březina	Growth of lead (II) hydrogen phosphate in polyacrylamide gel.	[41]
1978	Martin and Haendler	Prepared gel inside the horizontal tube opens at both ends.	[42]
1980	Patel and Rao	Modified gel method to facilitate the growth of single larger crystals.	[43]
1981	Arora	Used modified equipment for better crystallization.	[14]
1982	Arend and Connelly	Used tetramethoxysilane gel for crystal growth.	[44]
	Lefaucheux *et al.*	Compared gel grown and solution grown crystals.	[45]
1985	Barber and Simpson	Used ion exchange resins for better crystallization.	[46]
1986	Henisch and Garcia-Ruiz	Explained Liesegang ring formation by Fick's diffusion equation and calculated Liesegang ring masses and spacing on the basis of a simple algorithm.	[47]
1988	Henisch	Designed a simple computer program, to record growth-rate oscillations during Liesegang rings formation.	[48]
	Sperka	Discussed principal features of crystal growth in gels.	[5]
1990	Cipanov *et al.*	Presented experimental and theoretical investigations of the nucleation processes of calcium tartrate crystal formation in gel.	[49]
1991	Chernavskii *et al.*	Explained helix type Liesegang pattern.	[50]
	Plovnick	Grown CHPD crystals from EDTA-chelated calcium in agar gel and these crystals were characterized by IR, SEM and XRD.	[51]
1993	Kalkura *et al.*	Grown platy crystals of uric acid dihydrate crystals in tetramethoxysilane and silica gel.	[52]
	Irusan *et al.*	*Phyllanthus niruri* and *Ocimum sanctum* plant extracts inhibited dendritic and needle shaped CHPD crystals by single diffusion gel method in silica gel.	[53]
1994	Chopard *et al.*	Observed rings, bands and spiral types Liesegang patterns.	[54]
1995	Girija *et al.*	Grown hexagonal cystine crystals by single diffusion methods and these crystals were analyzed by IR and XRD.	[55]
	Kalkura	Grown spherulitic and bow shaped MSUM crystals in tetramethoxysilane and silica gel and characterized these crystals by IR, TGA and XRD.	[56]
1996	Srinivasan and Natarajan	Grown COM, CHPD and AMPH crystals by single and double diffusion method.	[57]
	Garcia-Ruiz	The kinetics of Liesegang pattern formation in gel medium remains unaffected by gravity.	[58]
1997	Natarajan *et al.*	Observed the promotory and inhibitory effect of extracts or juices of *Ananas comosus*, *Borassus flabellifer, Citrus limon*, *Cocos nucifera, Lycopersicon esculentum*, *Tamarindus indica*, *Tribulus terrestris*, *Vitis vinifera* (fruits); *Dolichos biflorus, Hordeum vulgare* (grains or seeds) ; *Mentha spicata* (leaves) ; *Mimosa pudica*, *Hibiscus rosa-sinensis* (plant) ; *Raphanus sativus* (roots); *Musa sapientum* (stem) on COM, CHPD, and AMPH crystals grown by single and double diffusion methods. Same crystals were characterized by XRD and density measurement.	[6]
1998	Sivakumar *et al.*	Grown dendritic, platy and triangular shaped calcium hydrogen phosphate anhydrous (monetite) and CHPD crystals in silica gel and characterized these crystals were by FT-IR, TGA and XRD.	[59]
2002	Ramachandran and Natarajan	Grown needle and spherulite shaped tyrosine crystals by single and double diffusion methods. The grown crystals were characterized by density measurement, FT-IR, TGA and XRD.	[60]
		Grown rectangular and platy hippuric acid crystals in silica gel by double diffusion method. Grown crystals were characterized by density measurement, FT-IR, TGA and XRD.	[61]
2003	Joshi and Joshi	Grown platelet and needle shaped CHPD crystals by single diffusion gel method in silica gel. The crystals were analyzed by FTIR and TGA.	[62]
2004	Ramachandran and Natarajan	Grown hexagonal shaped L-cystine crystals in silica gel by double diffusion method. These grown crystals were characterized by density measurement, FT-IR, TGA and XRD.	[63]
	Kalkura *et al.*	Platy and spherulite shaped HA crystals were grown in silica gel by single diffusion method.	[64]
2005	Joseph *et al.*	*Tamarindus indica* fruit decoction and tartaric acid both inhibited the growth of CHPD crystals grown by single diffusion method.	[65]
	Ramachandran and Natarajan	Grown trapezoidal and platy hippuric acid crystals in silica gel by single diffusion method and characterized these crystals by XRD and density values.	[66]
	Joshi *et al.*	*Tribulus terrestris* fruits and *Bergenia ligulata* leaves extracts inhibited the growth of COM crystals grown in silica gel by double diffusion method.	[67]

	Parekh and Joshi	Citric acid inhibited elongated, platelet and star shaped CHPD crystals grown by single diffusion gel method in silica gel.	[68]
2007	Sundaramoorthi and Kalainathan	Grown barium hydrogen phosphate crystals by single and double diffusion methods in silica gel. The grown crystals were analyzed by XRD, TGA/DTA and SEM.	[69]
	Kanchana *et al.*	The nucleation rate of gel grown brushite crystal reduced more in the laser than the sunlight exposed medium. The results were analyzed by XRD, TGA/DTA, and SEM.	[70]
2008	Chauhan *et al.*	Grown dendritic, prismatic, rectangular and star shaped AMPH crystals by single diffusion method by using silica gel. These crystals were characterized by XRD, FT-IR, TGA and dielectric studies.	[71]
	Chauhan and Joshi	*Citrus medica* juice inhibited AMPH crystals grown by single diffusion method.	[72]
	Parekh *et al.*	*Boswellia serrata* (gum resin), *Tribulus terrestris* (fruits), *Rotula aquatica*, *Boerhaavia diffusa* (roots) and *Commiphora wightii* (plant) extracts inhibited the growth of HA crystals grown by single diffusion method. The characterization of grown crystals was confirmed by XRD, FT-IR and dielectric study.	[73]
2009		Roots extract of *Aerva lanata, Boerhaavia diffusa* and *Rotula aquatica* ; gum resin of *Boswellia serrata* inhibited MSUM crystals grown by single diffusion method. These grown crystals were characterized by FT-IR, XRD and TGA.	[74]
	Chauhan *et al.*	*Commiphora wightii* fruit juice inhibited dendritic, prismatic, rectangular, star and needle shaped AMPH crystals grown by single diffusion method.	[75]
	Madhurambal *et al.*	Grown platelet and broad needle shaped CHPD crystals by the single diffusion method in silica gel. The crystals were analyzed by FTIR. Kinetic and thermodynamic parameters were also estimated.	[76]
2010	Rajendran and Dale Keefe	Grown CHPD crystals by single diffusion method and analyzed these crystals by DSC, XRD, FT-Raman, and FT-IR.	[77]
	Valarmathi *et al.*	Grown COM crystals by single diffusion method and analyzed these crystals by FT-IR.	[78]
2011	Choubey	*Ceiba pentandra* bark extract inhibited the growth of MSUM crystals grown by single diffusion method and were characterized by FT-IR, TGA and XRD.	[79]
2012	Kesavan *et al.*	*Costus igneus* stem and rhizome extract inhibited COM crystals grown by single diffusion method. These harvested crystals were characterized by FT-IR, SEM and XRD.	[80]
	Salim	Grown COM crystals by double diffusion method and determined their dielectric properties.	[81]
	Diana and George	*Achyranthes aspera* root extract inhibited the gel grown CHPD crystals by single diffusion method.	[82]
2013		*Ensete superbum* seed extract inhibited the gel grown CHPD crystals by single diffusion method.	[83]
	Chauhan and Joshi	*Citrus medica* (fruit juice) and *Commiphora wightii*, *Boerhaavia diffusa* and *Rotula aquatica* (plant infusions) inhibited the growth of gel grown AMPH crystals.	[84]
2014	Vasuki and Selvaraju	*Citrus limon* and *Tribulus terrestris* fruit extracts inhibited the uric acid crystals grown by single diffusion method. These crystals were characterized by FT-IR, FT-Raman, SEM and XRD.	[85]
	Suryawanshi and Chaudhari	Grown dendritic and prismatic COM crystals by single and double diffusion method in agar-agar gel and characterized these crystals by FT-IR, TGA and XRD.	[86]
		Grown dendritic, needle, platy, prismatic, rectangular and star shaped crystals by single diffusion and dendritic shaped CHPD crystals by double diffusion method in agar-agar gel. These crystals were analyzed by FT-IR, SEM, TGA and XRD.	[87]
		Grown platy, prismatic, star shaped crystals by single diffusion and dumbbell, star and platy shaped struvite-k crystals by double diffusion method in agar-agar gel. These crystals were analyzed by EDS, FT-IR, SEM, TGA and XRD.	[88]
2015		Grown dendritic, needle, platy, prismatic, rectangular and star shaped CHPD crystals by the single diffusion method in agar-agar gel. The crystals were analyzed by stereoscope and EDS.	[89]
	Popalghat and Bhagat	Grown elongated rod shaped COM crystals by single diffusion method in silica gel and characterized these crystals by FT-IR and XRD.	[90]
	Ahmed *et al.*	Grown spherical ring banded dumbbell and composite spherulites of MSUM crystals on a glass slide in silica gel and observed under compound microscope.	[91]
	Bindhu *et al.*	*Phyllanthus emblica* fruit extract inhibited the growth of AMPH crystals grown in silica gel by single diffusion method. Grown crystals were characterized by FT-IR, SEM, TGA and XRD.	[92]
2016	Joshi	*Citrus limon* fruit juice and *Hordeum vulgare* seed extract, citric acid and tartaric acid affected the growth of gel grown CHPD crystals. The growth inhibition and reduction were measured by a reduction in the number of Liesegang rings and size of grown crystals.	[93]
	Ahmed *et al.*	Grown arborescent, donut, dumbbell, needles, platy, prismatic, rosette, crystal with round edges, loose agglomerate and compact aggregates of COM crystals on a glass slide in silica gel and observed under compound microscope.	[94]
		Grown needle, platy (with spatial branches and radiating assemblage), star, tetragonal bipyramidal shaped crystals of CHPD on a glass slide in silica gel and observed under compound microscope.	[95]
	Selvaraju and Sulochana	*Tribulus terrestris* fruits extract inhibited the growth of COM crystals grown in silica gel by single diffusion method.	[96]

	Muryanto *et al.*	*Orthosiphon aristatus* leaves extract inhibited the growth of AMPH in gel. The grown crystals were characterized by FT-IR, SEM and XRD.	[97]

Keys: AMPH: ammonium magnesium phosphate hexahydrate or struvite, CHPD: calcium hydrogen phosphate dihydrate or brushite, COD: calcium oxalate dihydrate or weddellite, COM: calcium oxalate monohydrate or whewellite, DSC: differential scanning calorimetry, EDS: Energy-dispersive X-ray spectroscopy, FT-IR: Fourier Transform Infrared spectroscopy, HA: hydroxyapatite, IR: infra red spectroscopy, MSUM: Monosodium urate monohydrate, Saltpeter: potassium nitrate, Silica gel: sodium meta silicate gel, TGA/DTA: Thermogravimetric analysis / Differential thermal analysis, Vitriol: sulphuric acid, XRD: X-ray powder diffraction.

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