



Field-effect calcium sensor for the determination of the risk of urinary stone formation

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ARTICLE INFO

Article history:

Available online 14 December 2008

Keywords:

Field-effect
Calcium sensor
Urolithiasis
Bonn-Risk-Index
EMIS sensor

ABSTRACT

Urinary stone formation has been evolved to a widespread disease during the last years. The reason for the formation of urinary stones are little crystals, mostly composed of calcium oxalate, which are formed in human kidneys. The early diagnosis of the risk for urinary stone formation of patients can be determined by the “Bonn-Risk-Index” method based on the potentiometric detection of the Ca^{2+} -ion concentration and an optical determination of the triggered crystallisation of calcium oxalate in unprocessed urine. In this work, miniaturised capacitive field-effect EMIS (electrolyte-membrane-insulator-semiconductor) sensors have been developed for the determination of the Ca^{2+} -ion concentration in human native urine. The Ca^{2+} -sensitive EMIS sensors have been systematically characterised by impedance spectroscopy, capacitance–voltage and constant–capacitance method in terms of sensitivity, signal stability and response time in both CaCl_2 solutions and in native urine. The obtained results demonstrate the suitability of EMIS sensors for the measurement of the Ca^{2+} -ion concentration in native urine of patients.

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1. Introduction

During the past 20 years in the developed countries, urolithiasis (urinary stone formation) has been evolved to a widespread disease, like diabetes or gout. For instance, in Europe, North America and Japan, 5–15% of the population are struck on urinary stones every year [1–3]. The prevalence in Germany currently ranges around 4.7% and the incidence amounts to approximately 1.5%; this refers to annually 1.2 million patients with a symptomatic first-time or recurrent stone episode [4]. This causes more than 10 million days of disability. Furthermore, most of the first-struck patients become manifest in the age class of 25–50 years, that means in the so-called “rush-hour of life” (family, job) [5,6]. Thus, the socio-economic costs (e.g. in Germany with approximately 175 million €/year) for the health-care systems are enormous.

Urolithiasis is just the symptom of underlying (mostly) multifactorial metabolic disturbances. Alimentary factors, like diets rich in fat and protein, lacking fibre intake combined with inactivity, resembling the so-called modern industrialised life style and

genetic predisposition enhance developing urolithiasis. Typical symptoms of an acute stone colic are, inter alia, agony, sickness and hematuria. Urinary calculus formation is caused by disturbed urinary compositions with altered urinary pH, increased concentrations of lithogenic components as, e.g. calcium, oxalate, phosphate and a lack in inhibitoric substances as, e.g. citrate and magnesium. Calcium oxalate represents the most frequent mineral phase found in uroliths with a frequency of approximately 70–75% [7]. Owing to the high recurrence rate of calcium oxalate stone formation in case of inadequate treatment, evaluation of the individual causes for calcium oxalate urolithiasis is of utmost clinical importance [8].

To improve the early diagnosis and thus, to prevent urinary stone formation at persons with increased risk factors, the Bonn-Risk-Index (BRI) constitutes a trusty method [8–11]. The BRI method is based on the potentiometric detection of the free Ca^{2+} -ion concentration (activity) by means of an ion-selective electrode (ISE) together with an optical determination of the induced crystallisation of calcium oxalate in native urine. The BRI is determined as ratio:

$$\text{BRI} = \frac{[\text{Ca}^{2+}]}{[\text{Ox}^{2-}]} \quad (1)$$

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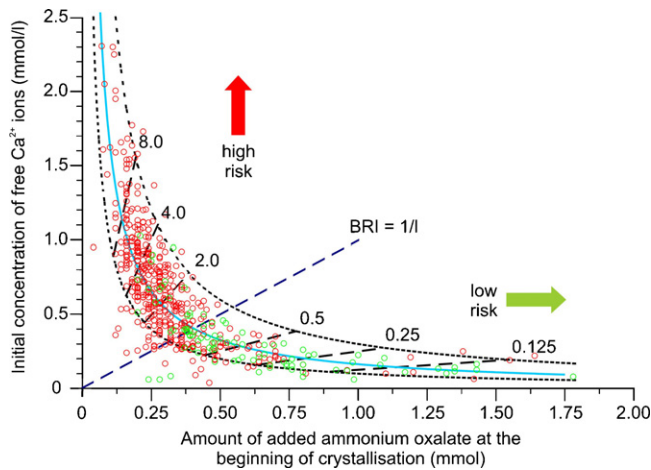


Fig. 1. Diagram for the determination of the Bonn-Risk-Index (BRI); “low-risk persons” and stone patients under successful therapy are differentiated from high-risk persons still “healthy” but prone to calcium oxalate formation and patients with inadequate metaphylaxis at a BRI = 1/l.

where $[Ca^{2+}]$ is the native concentration of free urinary calcium ions, and (Ox^{2-}) is the amount of ammonium oxalate required for crystal formation [8–11].

Although just defined by only two parameters, high significance is reached by BRI in discrimination between persons “without risk” and persons “at risk” (see Fig. 1). Based on this method, the risk for urinary stone formation can be automatically determined by using the commercially available device “Urolizer[®]” [12]. However, the big sizes and high costs of ISEs used, the necessity of their careful cleaning and frequent calibration after the measurement in urine with cost-intensive solutions as well as low life-time in urine, limit a broad implementation of these devices in routine medical practices.

In the present work, miniaturised field-effect capacitive Ca^{2+} -sensitive EMIS (electrolyte-membrane-insulator-semiconductor) sensors have been developed for the determination of the free Ca^{2+} -ion concentration in native urine of high-risk patients. The advantages of capacitive EMIS sensors are robustness, small sizes, simple layout, and easy and cost-effective fabrication by using silicon technology (usually, no photolithographic or complicated encapsulation processes are needed) [13–15].

2. Experimental

Fig. 2 shows the measuring set-up (a) and a cross-section of the layer structure (b) of the developed EMIS sensor. The EMIS sensor consists of an Al-p-Si-SiO₂-Ta₂O₅ structure (300 nm Al film as rear-side contact layer, p-Si with $\rho = 5\text{--}10\ \Omega\text{ cm}$, $\sim 30\text{ nm}$ thermally grown SiO₂ and 50–60 nm Ta₂O₅, chip size: 10 mm × 10 mm) modified with an ion-selective polyvinyl chloride (PVC) membrane containing the Ca^{2+} ionophore ETH 1001. The Ta₂O₅ layer has been prepared by means of thermal oxidation of sputtered Ta in an oxygen atmosphere at 520 °C for about 2 h.

To improve the adhesion of the Ca^{2+} -sensitive PVC membrane onto the Ta₂O₅ layer, prior to the membrane deposition, the sensor surface has been cleaned by helmanex solution, iso-propanol, ethanol and DI-water for 5 min in an ultrasonic bath. Then, the sensors have been dried in N₂ flow following of dehydrating on a hotplate at 160 °C for 10 min. After the cleaning process, the Ta₂O₅ surface has been silanised by means of pipetting hexamethylsilazane (HMDS) and treated on a hotplate at 100 °C. The silanised sensor surface has been characterised by contact angle method (the contact angle was $\sim 60^\circ$). The Ca^{2+} -ionophore-based PVC membrane has been deposited onto the silanised Ta₂O₅ layer by dropping a commercial membrane cocktail (C-Cit, Wädenswil)

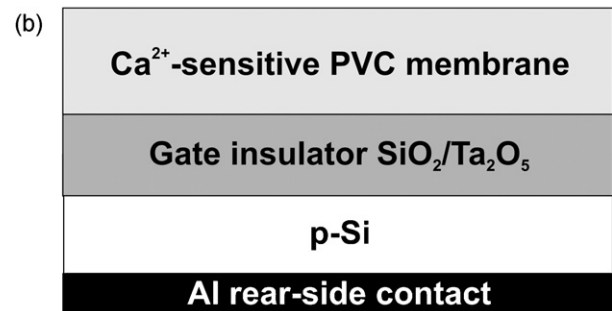
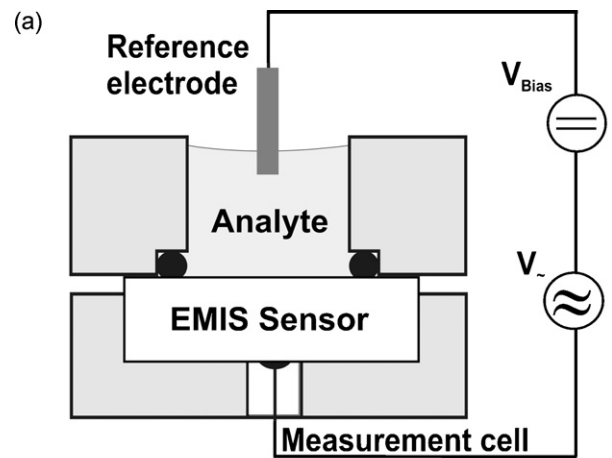


Fig. 2. Measurement set-up (a) and cross-section (b) of the layer structure for the capacitive EMIS sensor with a polymeric membrane.

onto the sensor surface. For evaporating the solvent of the PVC membrane, the EMIS sensors have been stored under dry conditions for 48 h. Fig. 3 depicts a scanning electron microscopy picture of the Ca^{2+} -sensitive PVC membrane onto the Ta₂O₅ layer. Before testing, the sensors have been preconditioned in a 0.1 M CaCl₂ standard solution (Fluka) for at least 48 h.

The modified EMIS sensors have been characterised in both CaCl₂ solutions with different concentrations from 0.01 to 100 mM

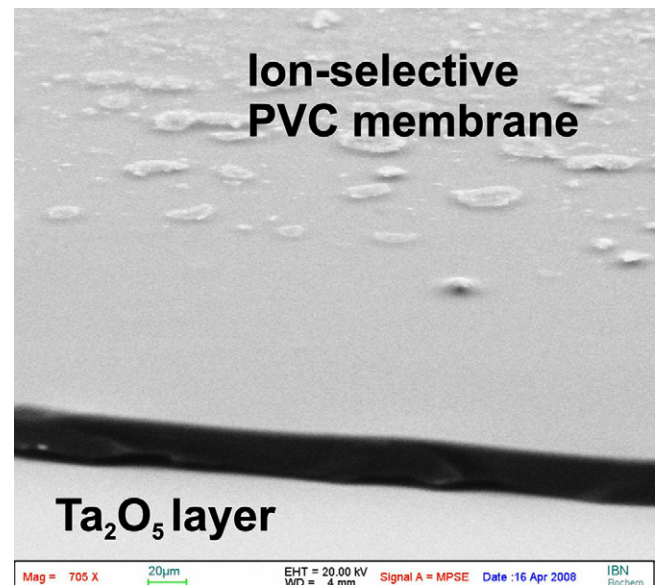


Fig. 3. Scanning electron microscopy picture of the Ca^{2+} -sensitive PVC membrane on the Ta₂O₅ layer.

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