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Research paper

Hydrogel-forming microneedle arrays: Potential for use in minimally-invasive lithium monitoring

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ABSTRACT

We describe, for the first time, hydrogel-forming microneedle (s) (MN) arrays for minimally-invasive extraction and quantification of lithium *in vitro* and *in vivo*. MN arrays, prepared from aqueous blends of hydrolysed poly(methyl-vinylether-co-maleic anhydride) and crosslinked by poly(ethyleneglycol), imbibed interstitial fluid (ISF) upon skin insertion. Such MN were always removed intact. *In vitro*, mean detected lithium concentrations showed no significant difference following 30 min MN application to excised neonatal porcine skin for lithium citrate concentrations of 0.9 and 2 mmol/l. However, after 1 h application, the mean lithium concentrations extracted were significantly different, being appropriately concentration-dependent. *In vivo*, rats were orally dosed with lithium citrate equivalent to 15 mg/kg and 30 mg/kg lithium carbonate, respectively. MN arrays were applied 1 h after dosing and removed 1 h later. The two groups, having received different doses, showed no significant difference between lithium concentrations in serum or MN. However, the higher dosed rats demonstrated a lithium concentration extracted from MN arrays equivalent to a mean increase of 22.5% compared to rats which received the lower dose. Hydrogel-forming MN clearly have potential as a minimally-invasive tool for lithium monitoring in outpatient settings. We will now focus on correlation between serum and MN lithium concentrations.

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1. Introduction

Despite the introduction of a wide range of mood stabilizing agents, lithium is still considered the 'gold standard' treatment for bipolar (BP) disorder [1,2]. As a pharmacological agent, lithium is a cornerstone of neuropsychopharmacology, primarily used to treat BP affective disorder, where it can improve both manic and depressive symptoms [3]. In addition, it also has many off-label uses, including treatment of alcoholism, hyperthyroidism, personality disorders, traumatic brain injury, tardive dyskinesia and postpartum affective psychosis [4]. Lithium, like all alkali metals, is highly reactive [5]. Therefore, it readily forms, and can be administered as, salts such as citrate, sulphate, chloride and, most commonly, carbonate. These salts are available in several different dosage forms, such as syrup and both conventional and sustained release tablets and capsules [4,6].

Early studies reported the effects of lithium on many neurotransmitter and neuromodulatory systems such as the cholinergic, monoaminergic and gamma-aminobutyric acid (GABA) systems [7]. Many theories speculate on the mechanism of lithium's mood stabilizing action. The initial accepted mechanism of action (MOA) of lithium in BP disorder suggested that lithium interfered with neuronal sodium–potassium electrogenic pumps and, in doing so, altered synaptic transmission [6,7]. However, recent evidence has indicated that lithium may have several MOA, including a direct effect on glutamatergic neural transmission, notably *via* neuronal excitability at hippocampal *cornu ammonis* (CA) 1 synapses, thereby improving the excitatory postsynaptic potentials [7].

Abbreviations: MN, microneedle (s); ISF, interstitial fluid; TDM, therapeutic drug monitoring; PMVE/MA (Gantrez® AN-139), poly(methylvinylether-co-maelic anhydride); PEG, poly(ethyleneglycol); N, Newtons; OCT, optical coherence tomography; PBS, phosphate buffered saline; FAAS, flame atomic absorption spectrometry; SD, Sprague–Dawley; RI, reverse iontophoresis.

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Following oral administration, lithium is rapidly absorbed from the gastrointestinal tract (GIT) with a peak plasma concentration (Cp_{max}) achieved after 1–5 h, and a half-life ($t_{½}$) of approximately 22 h [8]. In addition, lithium does not bind to plasma proteins, has a large volume of distribution (Vd) and can accumulate in many tissues [9]. Depending on its formulation, it has an 80–100% oral bioavailability and steady state concentration (Cp_{ss}) in blood is typically achieved within 4–5 days of starting treatment [8–10]. More than 95% of lithium is excreted unchanged through the kidneys. Over 80% of filtered lithium is reabsorbed in the proximal tubules and at Cp_{ss}, lithium clearance is directly proportional to the glomerular filtration rate (GFR) [9–11]. The clinically effective plasma concentration of lithium in human typically ranges from 0.4 to 1.2 mmol/l. This narrow therapeutic window can predispose patients to lithium toxicity with even minor changes in health status or co-prescribed medications. As such, continued lithium therapy requires regular therapeutic drug monitoring (TDM) to ensure optimum clinical benefits without the risk of toxicity [6]. Lithium toxicity in humans is a life threatening condition and typically occurs when serum concentrations exceed 1.5 mmol/l. Adverse effects include muscle weakness, coarse tremor, slurred speech, seizures and irreversible renal damage. Adverse effects of lithium on the kidney and thyroid gland have also been observed during long term use, even when a serum concentration is maintained within the recommended therapeutic window [12]. Moreover, the combination of a reduced Vd and reduced renal clearance of lithium in the elderly frequently leads to a lower tolerability with increasing age and, therefore, neurotoxicity may occur in the elderly at concentrations considered therapeutic in healthy adult populations [13]. Therefore, accurate, precise and regular TDM of lithium is crucial to ensure safe and beneficial treatment of patients. Typical regimes suggest that, upon commencement of lithium therapy, TDM should be performed on a weekly basis. However, once the patient is established on their required therapeutic dose, TDM is typically only performed monthly [14] (see Figs. 1 and 2).

Clinical laboratories employ several methods for the measurement of lithium in serum. These include flame atomic absorption spectrometry (FAAS), flame emission spectrometry (FES), inductively-coupled plasma mass spectrometry (MS) and ion-selective electrodes (ISE) [15,16]. Colorimetric, photometric and enzymatic methods have also been used for TDM purposes [16]. Of these methods, FAAS is the most commonly used technique, due to its sensitivity and simplicity [15–17]. Despite the valuable clinical data provided by TDM, its practical application in clinical settings can be greatly limited by the high cost and time-consuming nature of analytical procedures, as TDM requires repetitive withdrawal of blood samples by nursing or medically-trained personnel using hypodermic needles [18]. Sampling is, therefore, invasive and often painful, especially in patients with difficult venous access [19,20]. In addition to the need for trained personnel, the use of conventional needles is often associated with a risk of infection or transmission of blood-borne diseases, due to accidental needle-stick injuries and/or improper needle disposal [20]. Notably, previous attempts to monitor lithium using either saliva or urine, as alternatives to TDM using blood, have not proven to be successful [20,21]. Therefore, developing a minimally-invasive method would be a major advance in lithium TDM, allowing non-medically trained personnel, or the patient themselves, to monitor their lithium levels, thus ensuring patients are receiving the optimum dose.

ISF has previously been proposed as a viable alternative to plasma or serum as a source for TDM [22]. The composition of

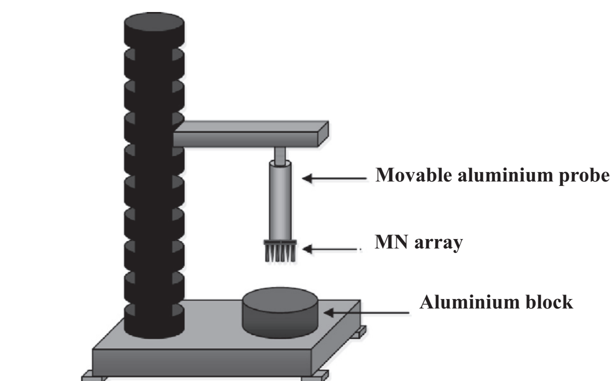

Fig. 2. Texture Analyser set-up for application of compressional forces to MN array.

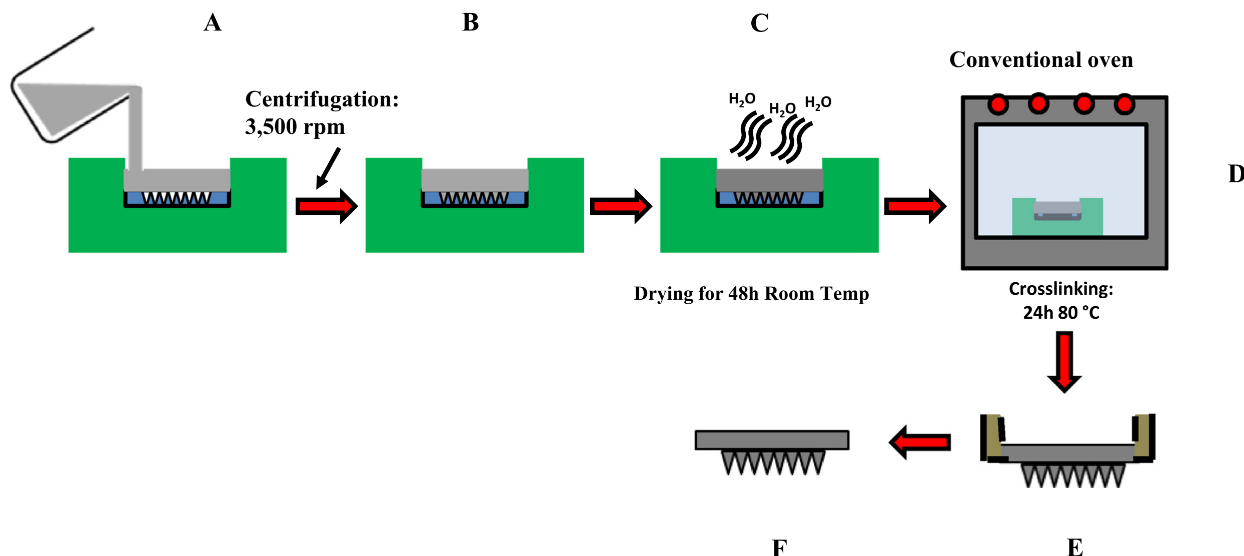

Fig. 1. Diagrammatic representation of steps involved in the preparation of polymeric MN. (A) Polymer matrix was transferred to the silicone mould and (B) centrifuged at 3500 rpm for 15 min. Upon drying for 48 h (C) and heating for 24 h at 80 °C (D) to induce crosslinking *via* esterification, the silicone mould was carefully peeled away from the polymeric MN array (E) and side walls removed using a hot scalpel blade (F).

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