Optical analysis of Lithium Carbonate: Towards the development of a Portable Lithium Blood Level analyzer for Bipolar Disorder Patients

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***Abstract*— Lithium medication is the gold standard of treatment in Bipolar Disorder patients, preventing and reducing mood swings and suicidality. However, despite its effectiveness, it is a potentially hazardous drug requiring regular monitoring of blood levels to ensure toxic levels are not reached. This paper describes the first steps towards developing a new portable device that can be used by Bipolar Disorder patients to facilitate the analysis of lithium blood levels at home. Solutions of lithium carbonate have been optically fingerprinted using a high-end spectrophotometer. Preliminary measurements indicate that while the visible to near infrared region of the absorption spectra fall heavily within the water band, measurements in the Ultraviolet region show a strong distinction between different lithium concentrations. The optical spectra of Lithium in the 220 nm to 230 nm region demonstrated the ability to differentiate between concentrations representing those found in patients.**

I. Introduction

Bipolar disorder is a serious life-long condition, characterized by recurrent episodes of depressed and manic mood states which cause major impairment in the lives of those affected [1]. Bipolar disorders affects up to 2.4 million people in the UK, 12 million in the US and 254 million worldwide [2]. In the UK, it is estimated that the annual societal cost of bipolar disorder is about £2 billion [3].

Lithium is the most widely used medication for treating bipolar disorder [4] and, although, it is highly effective at reducing the frequency and intensity of mood swings, it can be potentially dangerous. Lithium prescribed in the form of carbonate (Li_2CO_3) or citrate has a very narrow therapeutic range (concentrations ranging from 0.4 to 1.0 mM) with the upper limit being uncomfortably close to toxic levels [5]. The use of lithium salts can affect thyroid and kidney function [6]. Toxic lithium levels can cause circulatory collapse, kidney failure, neurological abnormalities, seizures, coma and even death [5, 7]. While in health lithium concentrations are reasonably stable, they can rapidly reach toxic levels during intercurrent illness such as febrile conditions and dehydration or the addition of some drugs [8].

As a result, lithium requires regular on-going monitoring to maintain therapeutic levels and avoid toxicity. Determination of blood lithium levels involves relatively complex laboratory methods, such as flame photometry or ion-selective electrode analysis, which require withdrawal of blood samples and transport of samples to the laboratory [9]. It is recognised that in the UK lithium monitoring falls short of recommended standards. Furthermore, bipolar patient adherence to lithium therapy is "erratic" [10]. Reasons include frequent blood tests, which contributes to patients defaulting from treatment. This is associated with unacceptably high levels of relapse.

Currently, there is no available blood lithium level analyser for bipolar patients. This research proposes the development of a new portable non-invasive device to facilitate detection of changes in lithium concentrations. Such a device will be painless, user-friendly and could be used as frequently as necessary in the patients' home. Also, it would put more control into the hands of the patient while also providing an early warning that lithium concentrations are drifting outside therapeutic ranges. The device will incorporate optical and electrical sensing technologies. In an attempt to develop such a technology, this paper outlines the first steps in optically fingerprinting lithium carbonate in order to determine the optical window of interest and the capability of optical techniques to identify the concentrations of lithium found in blood.

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II. METHOD

As a precursor to optically identifying lithium in blood plasma, the optical characteristics of lithium carbonate in solution were investigated in order to identify the appropriate wavelengths and optical window on which to focus measurements. Therefore, solutions of lithium carbonate in distilled water were analyzed in the laboratory, including solutions whose concentrations reflect those typically found in blood.

In order to observe any absorption bands unique to Li_2CO_3 in solution, a reference spectrum of pure distilled water was taken across the effective operational range of the spectrophotometer (200 – 3200 nm) (Lambda1050, Perkin Elmer, USA). The spectral measurements were repeated three times at a resolution of 1 nm, and the results averaged, and smoothed in UV WinLab Data Processor and Viewer software (Perkin Elmer Inc, USA).

Two batches of Li_2CO_3 solutions were prepared in pure distilled water by diluting a concentrated solution down. The concentrated solution was prepared using a solid pure (99.999%) form of Li2CO3 from Acros Organics (NJ, USA). As there are two Lithium ions (Li^+) in one molecule of Li_2CO_3, it was only necessary to prepare the whole solution to half the desired concentration to achieve the therapeutic doses of lithium. Unlike other lithium salts Li_2CO_3 has negative water solubility, i.e. as temperature increases the amount able to dissolve into the water decreases. All samples were prepared and tested at ambient temperature (21°C), where the maximum concentration achievable is approximately 175 mmol/L. The batches were prepared and classified thus:

- Batch 1 – Fingerprinting concentrations.
- Batch 2 – Therapeutic concentrations.

The concentrations prepared are shown in table 1.

Table 1: Li_2CO_3 concentrations

Batch 1 (mmol/L) [effective Li^+]	**Batch 2 (mmol/L) [effective Li^+]**
5.3 [10.6]	0.1 [0.2]
10.7 [21.4]	0.2 [0.4]
21.3 [42.6]	0.3 [0.6]
42.5 [85.0]	0.4 [0.8]
-	0.5 [1.0]
-	0.6 [1.2]

Batch 1 was processed in the same way as the reference water spectrum (3 repeat scans, averaged and smoothed). A region of interest was identified from the spectrum of batch 1, and by applying the 2nd derivative of this region, using an inbuilt Savitzky-Golay algorithm, a unique absorption band was identified. Batch 2 was similarly treated and the area under the curve of the second derivative was calculated.

These results were then used to build a calibration function in MATLAB® (The MathWorks, USA). This was done by computing the area under the absorption curve of the second derivative in the band of interested for all three scans in each therapeutic concentration, and for pure water, which was given a lithium concentration value of 0.0 mmol/L for referencing purposes and zero point calibration.

Lastly the samples from batch 2 were re-run in the spectrophotometer and their concentrations calculated using the calibration function.

III. RESULTS

A full spectrum of distilled water and the Li_2CO_3 concentrations of batch 1 were obtained, see figure 1. It was easily observed that the primary water absorption bands in the infrared regions dominate, however the UV

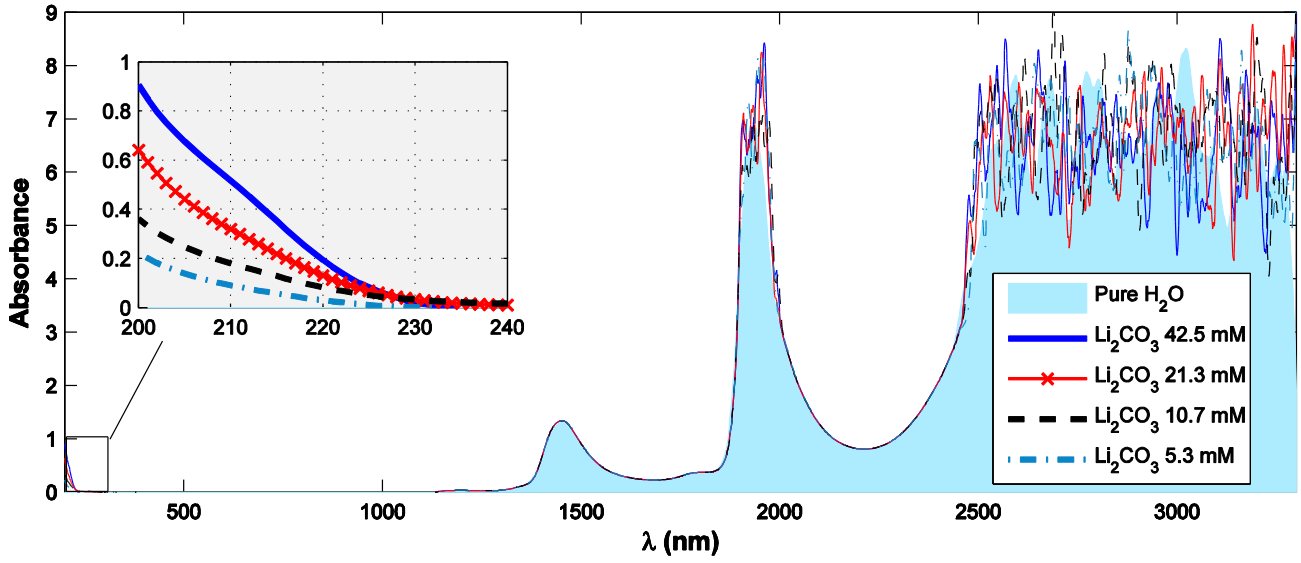

Figure 1: Full pure water spectrum with various concentrations of Li_2CO_3

band of approximately 200 – 240 nm demonstrated a characteristic slope, increasing as the concentrations got higher.

In the UV region of interest the 2nd derivative of batch 1 revealed two distinct peak regions, one with a peak value approximately 205 – 206 nm, the second with a peak value at approximately 225 nm. The first band demonstrated a non-linear relationship of concentration vs. the peak absorbance value, whereas the second band steadily increased with increasing concentrations. The band was labeled γ, see figure 2A.

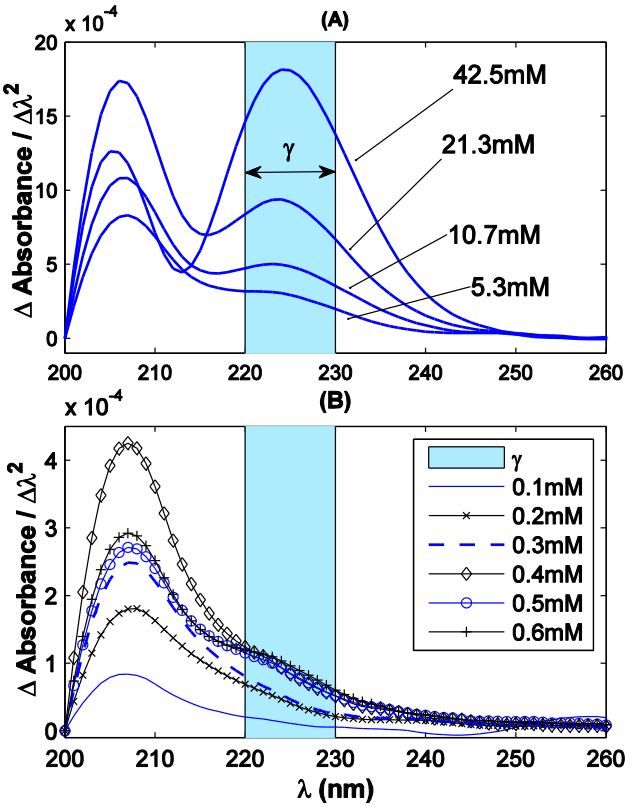

Figure 2: Second derivative absorption curves (200 – 260 nm), Batch 1 (A), Batch 2 (B)

The second derivative of the absorption curves for the therapeutic concentrations were observed to have less of a distinct peak in the γ-band, but the general trend of the absorbance at the peak value was still observed to increase with increasing concentrations, see figure 2B.

A calibration curve with a cubic function was computed from the 21 data points from the scans, see figure 3. The curve is given in equation 1, and has an R^2 value of 0.9758.

$$[Li_2CO_3] = 0.071z^3 + 0.051z^2 + 0.107z + 0.266 \quad (1)$$

$$where\ z = \{((x - 0.00019))/(0.00012)\}$$

and where x is the area under the curve of the 2nd derivative of the spectrum at each concentration of Li_2CO_3 between 220 nm and 230 nm depicted in figure 2B.

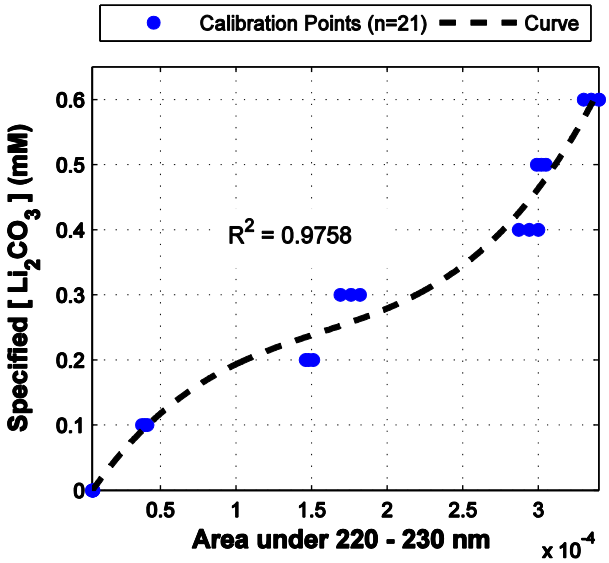

Figure 3: Calibration curve for Li_2CO_3 in pure water.

The batch 2 was re-run, and concentration calculation results are shown in table 2. The ability of the spectroscopic method in conjunction with the calibration curve to determine the lithium carbonate concentration of solutions decreases with decreasing concentration. However, it can sufficiently identify the range of concentration.

Table 2: Li_2CO_3 concentration calculation from derived calibration function.

Specified [Li_2CO_3] (mM)	Area under 2nd Derivative	Calculated [Li_2CO_3] (mM)	Difference (%)
0.10	0.00004	0.08	23
0.20	0.00015	0.23	15
0.30	0.00018	0.25	15
0.40	0.00029	0.44	11
0.50	0.00030	0.47	6
0.60	0.00033	0.59	1

IV. Conclusion

It has been determined that the addition of Li_2CO_3 to pure water does have a measureable contribution in the deep-UV absorption spectra.

In the therapeutic range, Li_2CO_3 has been shown to have a determinable absorption band, which we have labelled the γ-band, as seen when the second derivative is calculated, and from this a calibration function was constructed that had a very high correlation coefficient.

Using the calibration function to calculate the concentration on a re-run of batch 2, it was revealed that the higher concentrations could be calculated more reliably, with higher accuracy. It has to be taken into account that a [Li_2CO_3] of 0.5 mM is equal to a therapeutic dose of 1.0 mM, due to the double-lithium ion in the Li_2CO_3 molecule.

It is therefore reasonable to conclude that with the method of measuring Li_2CO_3 reported here it can be determined to within a 1 – 6% accuracy whether an unknown solution of Li_2CO_3 is either inside or outside the high-end of the therapeutic limit.

Observations of the 2nd derivative spectra reveal an interesting behavior at the 200 – 220 nm region, especially visible when looking at the 0.4 mM curve, absorbance seems to jump high then fall low again at 0.5 mM. This may be the result of contaminants in the solution or an actual optical phenomena that has been overlooked, however as this curve is the result of averaging it seems unlikely until the experiment can be re-run.

The 210 – 220 nm region shows the possible presence of an isobestic point that may indicate a point where careful observation and computational analyses may provide a reference point where therapeutic concentrations of Li_2CO_3 have a common absorbance value. Further experiments are needed to determine if this is the case or what is being seen is the result of noise or smoothing errors. Further investigations are planned to make an attempt at measuring other common medicinal lithium compounds in solution to help identify any characteristic in the absorption spectra that is solely unique to the lithium ions. Different mixtures with other common salts that appear in blood and other bodily fluids, such as saliva or urine, will also be conducted to investigate the effect that these have on the observed absorption curves.

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