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Hemodialysis Prescription: Dose Adequacy by Continuous Monitoring of Fresh and Spent Dialysate Conductivity

A Thesis Presented
to the
Department of Kinesiology
Lakehead University

In Partial Fulfillment
of the Requirements for the
Degree of Masters of Science
in
Applied Sports Science and Coaching

by
Carl D. Goodwin ©

Abstract

Measurement of hemodialysis treatment adequacy is essential to monitor quality assurance for today's growing dialysis population. The universally accepted measure of hemodialysis dose is Kt/V. Kt/V above 1.2 has been shown to reduce patient morbidity and mortality. Currently, Kt/V is calculated from urea kinetic modelling using predialysis and postdialysis blood samples. This blood-based approach, as well as being costly and invasive, is typically performed once a month providing only periodic snapshots of dialysis adequacy. Methods to provide more frequent feedback to attending doctors have been developed based on urea concentration sensors in the spent dialysate stream. More recently, monitoring of dialysate conductivity in the spent dialysate stream has been proposed as an alternative to urea monitoring – ionic dialysance has been found to be highly correlated to urea clearance. The subject of this thesis is the kinetic modelling of spent dialysate conductivity.

The following single pool equation was developed to describe the kinetics of the spent dialysate conductivity during periods of constant inlet dialysate conductivity:

$$\ln\left| C_{di} - C_{do} \right| = \ln\left| C_{di}^{o} - C_{do}^{o} \right| - \frac{D}{V}\, t$$

where C_{di} and C_{do} are the inlet and outlet dialysate conductivities (mS/cm),

D is the ionic dialysance (ml/min),

V is the patient's effective distribution volume (ml), and

t is the session time (min)

This equation suggests a linear relationship between ln $|C_{di} - C_{do}|$ and dialysis time with slope

equal to -D/V. Evaluation of this slope permits direct calculation of Dt/V, an equivalent of urea Kt/V.

A clinical study to test this model was conducted with 14 patients treated by maintenance dialysis in the renal unit at Thunder Bay Regional Hospital, McKellar site. Dialysate conductivity data were collected from 85 dialysis sessions on an Integra hemodialysis machine (Hospal-Gambro Canada) equipped with conductivity sensors in both the inlet and outlet dialysate streams. When $\ln |C_{di} - C_{do}|$ was plotted versus dialysis time for each session, the data typically fell along a series of straight lines. However, the slope of the linear segments, rather than being relatively constant (= -D/V according to the proposed model), varied significantly with the inlet dialysate conductivity setting. The rate of ultrafiltration also influenced the $\ln |C_{di} - C_{do}|$ slopes. This was thought to be largely due to the convective component being improperly accounted for in the equation describing ionic mass transfer across the dialyzer. The impact of ultrafiltration rate on the patient's circulating blood volume may also have an effect on ionic mass transfer. Additional confounding factors were the periodic flow checks and the dialysate conductivity excursions associated with ionic dialysance measurements programmed into the Integra machine.

It was concluded that the currently proposed model was an oversimplification of intradialytic ionic mass transfer kinetics but that further studies with more sophisticated models, better accounting for the important role of convective mass transfer, were warranted. In this regard, a series of *in vitro* and *in vivo* studies have been suggested.

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Chapter 1. Introduction

The ability to instantaneously quantify a hemodialysis dose will have many benefits to patient care. Session to session quality assurance will be enhanced and patient lifestyles would more closely mimic quality of life with functioning kidneys. This study endeavours to verify the validity of a model by Dr. L.J. Garred (1998) to instantaneous measure Kt/V. Kt/V is the widely accepted measure of delivered dialysis dose (Garred, 1998; Depner, 1991).

More than 40,000 people nationally have end stage renal disease (ESRD) which has necessitated some form of renal replacement therapy (Prichard, 1997). The leading causes of ESRD in Canada are diabetes mellitus (25%), glomerulonephritis (21%) and vascular disease including hypertension (16%) (Prichard, 1997). The patient population requiring renal replacement therapy is increasing by 7.4 % per year (Prichard, 1997 & Schaudel et al, 1999). The leading form of renal replacement therapy is hemodialysis (Prichard, 1997). Currently, 30,000 people in Canada receive dialysis three times per week for 3-4 hours each session (Prichard, 1997). This places a high demand on resources in the renal unit, with costs of $30,000 per patient per year (Prichard, 1997). Goree et al (1995) cite costs of $88,585 for hospital hemodialysis.

The text of this study has been organized to give the reader a general overview of the motivation to complete the study in the introduction. The introduction is followed by a more detailed explanation of the relevant theory and background material needed to fully understand the calculated data resulting from this study and their importance for patients receiving hemodialysis.

Researchers have determined through the use of longitudinal and comparative studies

that small solutes resulting from normal body metabolism have a highly toxic effect on the body (Depner, 1991). There is some debate over the toxicity effects of large molecules but as yet the evidence does not fully support or dismiss large molecule toxicity (Depner, 1991). These small solutes are normally removed by the kidneys. Urea is produced in the body by the urea krebs cycle during protein catabolism. Urea is a small solute that is infinitely soluble in water (Depner, 1991). Urea is generally accepted as the characteristic solute to monitor when determining protein catabolism and monitoring renal replacement therapy (Garred, 1997; Depner, 1991). The Kt/V measure of delivered dialysis dose is a dimensionless number quantifying the amount of blood volume cleared of urea during the dialysis session (Garred, 1997; Depner, 1991). Therefore, Kt/V characterizes the amount of toxic small solutes cleared from the blood. Kt/V values of less than 0.8 cause a precipitous rise in patient deaths (Depner, 1991). Prichard (1997) has published figures which summarize Kt/V values of 1.2-1.4 in 64% of renal units in Canada.

Currently the most common method of Kt/V calculation is to determine pre&post-dialysis blood urea concentrations and apply an equation as published in Depner (1991) or Garred (1997). Most renal units routinely monitor Kt/V once per month (Prichard, 1997). This practice only effectively quantifies 1 in 12 dialysis sessions. The proposed method of calculating Kt/V will calculate Kt/V values every dialysis session improving quality assurance practices. Instantaneous measures of calculating Kt/V will allow future development of control system models that will enable the nephrologist to obtain repeatable Kt/V values. This is very important as there is some clinical data that suggests any exposure to toxic concentrations of small solutes have a chronic effect on patient health (Depner, 1991)

A previous study by Garred, Bottos & McCready (Hospal-Gambro internal report) had the unexpected finding that outlet dialysate conductivity and patient conductivity approach the

inlet dialysate conductivity in an exponential fashion. Dr. Garred has applied information from his hemodialysis kinetic modeling research (1997) to hypothesize that Kt/V can be calculated from the decay curve of outlet dialysate conductivity. This study will use clinical data obtained from current hemodialysis patients at Thunder Bay Regional Hospital (TBRH), McKellar site under the direction of the head nephrologist Dr. W. McCready.

Chapter 2. Section 1 Background Physiology

1.1 Introduction

In this study an investigation of instantaneous dialysis prescription dose is tendered. The following sections present some background information concerning the physiology of the kidney, physiology of water/waste movement in the body and the kinetics of dialysis. This generalized overview is presented to provide the reader with enough knowledge to grasp the complexities of the dialysis session.

1.1.1 Kidney Function

The human body carries two symmetrically placed kidneys located in the retroperitoneal space. The kidneys provide homeostasis (maintenance of metabolic equilbrium) of body composition. Proper functioning of the body systems depend on this maintenance. For example, fluid intake changes of plasma volume must be corrected to maintain optimum cardiac output and blood pressure. Most enzymes (controlling body metabolism) function best over rather narrow ranges of pH and/or ion concentration (Briggs & Schnermann, 1994). Thus, the kidneys recognize and adjust disturbances to homeostasis that occur as a consequence of food and fluid intake, body metabolism and exercise (sweating). The kidneys' urinary excretion of water and solutes regulate body fluid volume, osmolarity, electrolyte concentration (Na^+, K^+, Cl^-, Ca^+ Mg^{2+} and PO_4) and acidity. Of the number of products of metabolism excreted by the kidneys, urea is of prime interest in this study. As a note, the kidneys produce enzymes and hormones, notably renin, erythropoietin, and 1,25-dihydroxyvitamin D_3 (Greenberg, 1994).

1.1.2 End Stage Renal Disease (ESRD)

The human body can adapt to the loss of one kidney by increasing the size of the remaining kidney. Loss of functional kidney capacity (defined as ability to make corrections to body homeostasis) will result in the manifestation of symptomatic disorders (a disease state). End stage renal disease can be defined as any disorder that causes a reduction of functional capacity in the kidneys resulting in the need for replacement treatment. This functional capacity is typically measured by following the glomerular filtration rate (GFR). The formation of urinary excretion in the kidneys begins with a filtration process in the glomerulus. This filtration process is influenced by the pressure driving force across the capillary bed in the glomerulus and the permeability of the capillary bed. The filtrate continues to change composition through the remainder of the kidney before being excreted as urine. The GFR is expressed as a function of body surface area (normal values are approx. 125 ml/min/1.73m^2). For those solutes which are entirely eliminated by the kidneys, the rate of appearance in the urine is equal to the generation rate in the body. The concentration of these solutes is inversely related to GFR, and conversely GFR, can be assessed from these concentrations. In clinical terms GFR is usually estimated from urea and creatinine concentrations in urine over a specified collection period, typically 24 hrs. The creatinine clearance rate is used to indicate intervention of replacement treatment. Once this rate falls below 10 ml/minute/1.73m^2, intervention is required to prevent death (Greenberg, 1994).

1.1.3 Water/Na Physiology

The kidneys function to excrete urinary water to maintain body fluid volume and electrolyte balance such as Na (solute) concentration (expressed as osmolarity).

Water as fluid volume constitutes approximately 60% of body mass. Roughly two thirds of that water is contained in the cells as intercellular fluid (ICF) and the remaining one third outside of the cells as extracellular fluid (ECF). The following table illustrates the body composition for a typical 70 kg person.

	Water (L)	Protein (kg)	Na^+ (mmol)
ECF	15	0.3	2250
ICF	30	5.7	300
Total Body	45	6.0	2550

Table 1.1 Body Composition. (Halperin and Goldstein, 1999)

In calculating body water an assumption is made of the relative proportion of fat to lean body tissue. Females tend to have a lower body composition of water, 50% of body weight vs 60% for males due to the ratio of lean body tissue to fat content. Older people tend to have a lower water content due to their low lean body tissue (Halperin and Goldstien, 1999).

The ECF is made up of plasma water (20% of ECF), interstitial fluid (80% of ECF), and lymph circulation, which makes a negligible contribution (Halperin and Goldstien, 1999). Water is freely permeable across cell membranes. Changes in the extracellular sodium concentration result in shifts of water between the ECF and ICF compartments. For example, a decrease in the sodium concentration of the extracellular compartment results in a shift of water into the cells, increasing cell volume. Alternatively, an increase in extracellular sodium concentration

produces a shift of water from the intracellular to the extracellular compartment and decreasing cell volume (Sherwood, 1993). Of note, when there is an intake of electrolyte free water, this water distributes proportionately in the ICF and ECF compartments. This water expands both compartments. Conversely when there is an intake of isotonic saline only the ECF volume expands, there is no change in the ICF volume and sodium concentration (Halperin and Goldstein, 1999). Water movement between interstitial and intracellular spaces is governed primarily by osmotic concentration gradient. Under special circumstances water movement is governed by Starling's law. Starling's law of capillaries are governed by two factors: (i) hydrostatic pressure (blood pressure) and (ii) oncotic pressure. When blood pressure rises, water moves out of the blood vessels. Oncotic pressure, which is related to the concentration of the protein albumin, draws water through the capillary membrane against osmotic pressure(Halperin and Goldstien, 1999; Sherwood, 1993).

The body is provided with a thirst response which is governed by two mechanisms, the baroreceptors and the osmoreceptors. The baroreceptors respond to changes in blood pressure (which can manifest as changes in plasma volume for dialysis patients between sessions) and the osmoreceptors respond to plasma sodium concentration (osmolarity)(Rodriguez et al, 1981). Both systems are connected to the thalamus which controls the level of antidiuretic hormone (ADH). ADH levels in the kidneys have a water conserving role since water is freely permeable and will quickly cross into the urine if not checked by the ADH mechanisms(Briggs and Schnjermann, 1994). Reduction in blood volume reduces blood pressure creating an increase in the levels of ADH, similarly, an increase in sodium concentration (osmolarity) in the ECF increases ADH(Halperin and Goldstien,1999; Briggs and Schnjermann, 1994; Sherwood, 1993). Normal sodium concentrations(natremia)in the body are 140 mEq/L. Excursions from the norm

can be defined as hypo/hypernatremia. Hyponatremia is defined as serum (plasma) sodium concentrations of less than 135 mEq/L. Hyponatremia induces symptoms of nausea, vomiting, muscle cramps, malaise, headache, confusion and lethargy; seizures occur at sodium concentrations 120-125 mEq/L. Hypernatremia is defined as serum sodium concentrations greater than 146 mEq/L. Hypernatremia symptoms can manifest as dry mucous membranes, intense thirst, flushed skin, fever and oliguria (Sherwood, 1993). The kidneys control the concentration of electrolyte sodium. During incidents of hypo/hypernatremia, correction of adverse serum sodium concentration must be done slowly. If the correction is performed rapidly cerebral damage due to shrinkage or edema can result (Sherwood, 1993). There is some discussion whether this condition can occur during the short time of the dialysis session (McCready, 1998). The cerebral has mechanisms to control osmolarity which should be protective over the dialysis session. The brain barrier should protect the brain cells during hemodialysis (Ganong, 1987).

1.1.4 Protein Metabolism

The process of living for organisms such as humans can be called metabolism. Metabolism is the conversion, in a broad sense, of food stuffs into materials and energy that function to sustain life. Metabolism creates life-giving metabolites as well as waste metabolites (Sherwood, 1993). The end product of protein catabolism is urea produced through the Krebs ornithine-urea cycle. This pathway is illustrated in Figure 1.1 (Depner, 1991). Urea concentration is commonly expressed as mg urea nitrogen per decilitre of blood. The plasma concentration of urea nitrogen is termed blood urea nitrogen (BUN). Normal values for BUN are 8-12 mg/dl (Levey, 1994; Depner, 1991). The BUN is markedly elevated in ESRD patients.

In the dialysis patient BUN is directly related to dietary protein intake. The resulting accumulation of waste products normally secreted by the kidneys, is termed uremia (elevated urea levels). Although urea is not considered a toxic waste product, its presence is directly quantifiable to uremic waste products of protein metabolism through the Krebs ornithine-urea cycle (Figure 1.1)(Levey, 1994; Depner1991). Urea kinetics have been studied thoroughly and urea is the generally accepted solute used to monitor renal disease and dialysis treatment (Garred, 1998).

1.2 Choices of Therapy for End Stage Renal Disease

Patients with end stage renal disease require some form of renal replacement therapy to supplement or totally replace kidney function. The treatment is chosen by the nephrologist(kidney specialist) and the patient. The most common replacement therapies are discussed in the following section.

1.2.1 Transplant

The preferred treatment modality for end stage renal failure is kidney transplant. Although this treatment is limited primarily by the number of donors available(reference). As such, alternate renal replacement therapies are necessary both to make up the shortfall in transplantable kidneys and to provide care until a donor kidney is available.

1.2.2 Extracorporeal Therapies

Extracorporeal therapies use an artificial kidney placed outside the body. The artificial kidney is called a dialyzer. The typical dialyzer is a hollow fibre membrane filter. The

membrane is semipermeable, conceptually a thin sheet perforated by holes. There are approximately 10,000 hollow fibers, 2-3 km in total length providing 1-2 square metres of total surface area in the typical dialyzer (Garred, 1998; Daugirdas & Ing, 1994; Cheung, 1994). Blood is placed in intimate contact with dialysis solution (dialysate) during extracorporeal therapy. Blood pumped from an access site surgically placed in the patient, flows through the fibres of the artificial kidney with the dialysate passing around the outside of the fibres in counter-current fashion. The dialysate is a saline solution of similar composition to plasma water. The membrane's holes are of a small size that allow small solutes and molecules like water to freely pass through the membrane but larger molecules such as proteins cannot cross the membrane(Garred, 1998; Daugirdas & Ing, 1994; Cheung, 1994).

Extracorporeal therapies make use of counter-current mass transfer kinetics. The mechanisms for mass or solute transfer between the blood side and the dialysate side are convection and diffusion. Convective transfer occurs with solutes that are swept through the membrane with water. Diffusive transfer is the result of osmotic concentration gradients across the membrane. Figures 1.1 to 1.3 demonstrate how convection and diffusion methods are combined to give distinct advantages and disadvantages for the various forms of extracorporeal therapies (Garred, 1998).

The most common form of extracorporeal therapy is hemodialysis (Figure 2.1.1). Hemodialysis uses diffusion as the primary means of mass transfer. Convective transport occurs as a result of ultrafiltration but the volumes are small, 10-30 ml/min.

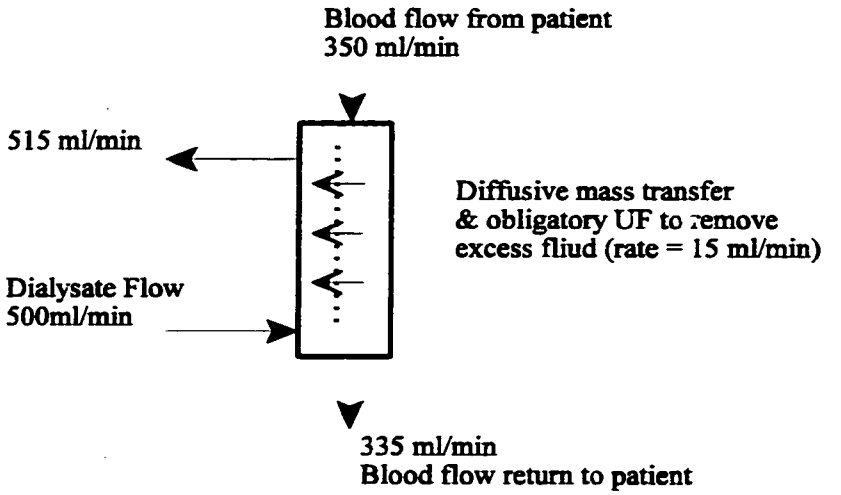


Figure 2.1.1 Hemodialysis Schematic. (Garred, 1998)

In hemofiltration all mass transfer is by convection. Hemofiltration is illustrated in Figure 2.1.2.

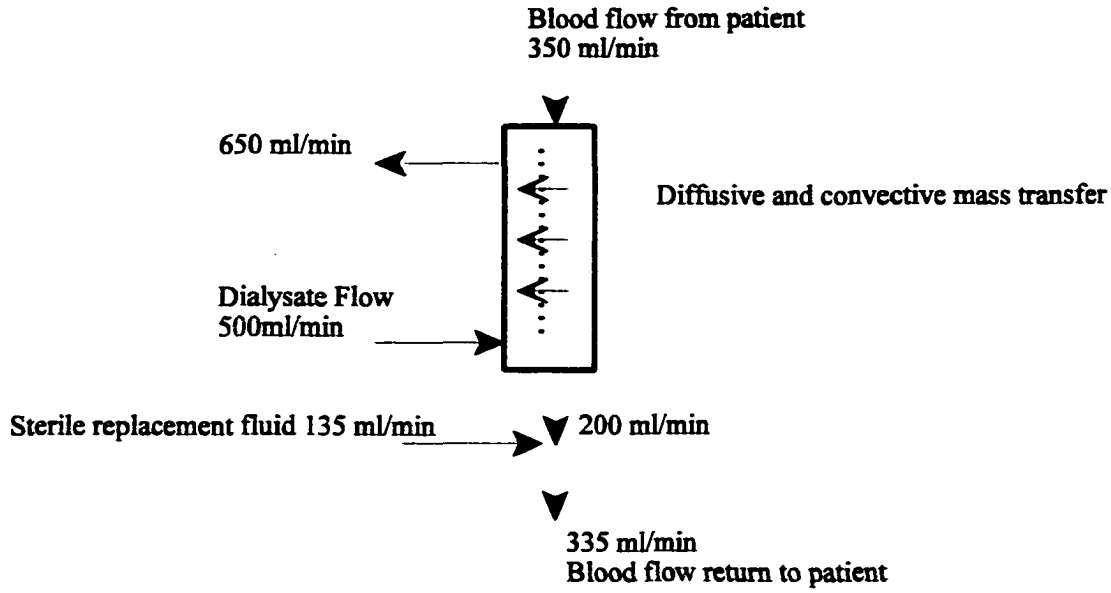


Figure 2.1.2 Hemofiltration Schematic. (Garred, 1998)

Hemodiafiltration combines both convective and diffusive mass transfer pathways (Figure 2.1.3).

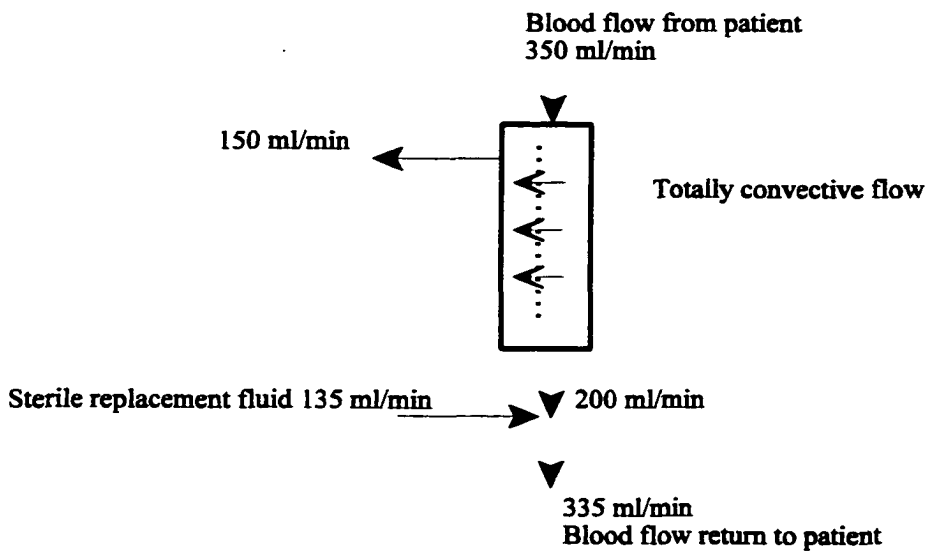


Figure 2.1.3 Hemodiafiltration Schematic. (Garred, 1998)

1.2.3 Peritoneal dialysis

Peritoneal dialysis can be thought of as analogous to hemodialysis. The peritoneal membrane is analogous to the membrane in the dialyzer providing a barrier to the large protein molecules while allowing the waste products and excess fluids to pass. "The peritoneal membrane is actually layering of tissue barriers beginning at the capillary endothelium through the capillary basement membrane to the mesothelial cell surface" (Daugirdas & Ing, 1994). An access (silastic catheter) is inserted into the abdominal cavity by either a surgeon or a nephrologist. A dialysate solution to restore acid/base and electrolyte balance and to remove the metabolic wastes and excess fluids is introduced into the peritoneal cavity. The effectiveness of the treatment depends on maintaining integrity of the peritoneal membrane.

The following table summarizes modes of peritoneal dialysis.

Manual procedures	
CAPD, continuous ambulatory peritoneal dialysis	three to four hour daytime dwells plus a long bedtime exchange
DPD, daytime peritoneal dialysis	four short day dwells, no night dwell
Automated procedures	
CCPD, continuous cycling peritoneal dialysis	long day dwell, multiple short night time exchanges
NIPD, nocturnal intermittent peritoneal dialysis	no day dwell, multiple short night time exchanges
TPD, tidal peritoneal dialysis	similar to NIPD, except abdomen not completely drained with each exchange
IPD, intermittent peritoneal dialysis	rapid cycling on an intermittent basis (usually three to four times per week), no dialysis between treatments

Table 1.2: Forms of Peritoneal Dialysis. (Piraino, 1994)

Section 2 Hemodialysis

The most prevalent renal replacement therapy in use currently is hemodialysis. Unit costs for hemodialysis range from $28,000 to $30,000 per patient depending on whether the dialysis is delivered in the home or in a renal unit at the hospital (Prichard, 1997).

2.1 Prescription

When hemodialysis is chosen as the treatment modality most appropriate for the circumstances of the ESRD patient, the optimum prescription is required. According to statistics provided by Prichard (1997) 74% of renal units use a 3hr treatment session with the maximum treatment time being 4hr in 52% of the units and 5hr in 41% of the units. This can be simplified to say that the majority of renal units use a 3 to 5hr treatment. Kt/V is used as prescription control in 60% of the renal units. Kt/V targets of 1.2-1.4 are achieved in 56% of the units, 1-1.2 in 21% and greater than 1.4 in 21% (Prichard, 1997)

2.1.1 Overview

The majority of end stage renal disease patients receive hemodialysis three times weekly for 3-5hrs. The goal of the dialysis session is to regain homeostasis for the patient. Therefore, many variables are monitored and many methods used to achieve adequate dialysis for the patients. The ESRD patient population is increasing at a rate of 7.4% per year (Prichard, 1997). The increased load on renal units has necessitated a shortening of the dialysis session. Ten years ago the three weekly sessions would typically be 8-10 hrs in length to ensure adequate delivered dialysis. The use of new high flow dialyzers with high mass transfer coefficients has increased waste removal rates (Daugirdas & Ing, 1994). As such the session times have been shortened

to 3-4 hours in a typical modern renal unit with 3 shifts per day (Garred, 1998;Daugirdas & Ing, 1994).

2.1.2 Goals of Hemodialysis

Dialysis efficiency must be high to meet the stringent time windows and the narrow window of delivered dialysis dose targets. Quality assurance must be maintained using timely, cost effective, standardized methods. This backdrop creates the desire to increase efficiency and lower costs while trying to improve dialysis dose. This is a competing process which will require closely monitered and controlled prescription results.

2.1.3 Hemodialysis Prescription

The hemodialysis prescription is designed to return the patient to homeostasis by removing water, waste metabolites, excess electrolytes and re-establishing the acid/base balance. The nephrologist approximates the patient's ideal weight and body water volume. From these calculations and typical blood flows a dialyzer can be chosen to give an appropriate dialysis dose. Kt/V, BUN, clearance, dialysance, plasma natremia and ideal weight figures are some of the current measures used for determining adequacy assurance(Daugirdas & Ing, 1994; Depner, 1991). For this study only Kt/V and natremia levels will be considered.

2.2 Dialysis Machine

The dialysis procedure can be separated into two parts for this discussion, the blood side and the dialysate side. Patient access to an artery and vein is typically in the lower arm or subclavian. Blood is pumped from the patient through the dialyzer and returned to the patient. The blood lines on the dialysis machine are provided with air detector and clamp to prevent air from being introduced into the blood. Highly purified water is supplied to the dialysis from a treatment plant. This water is heated to body temperature and run through a degassing chamber to remove air. The water is mixed with equal portions of concentrated bicarbonate and acid dialysate solutions and pumped through the dialyzer in counter-current fashion to the blood flow. The dialysate line is provided with a leak detector that will stop dialysis should a leak develop in the dialyzer. The dialysate line contains two pumps, one pump controls the dialysate flow rate and the other controls the ultrafiltration rate or water removal (patient weight loss). All flow rates are carefully monitered through redundant control systems. These safety features allow control of the dialysate solution sodium concentration, the dialysate flow rates, the blood flow rates and ultrafiltration (weight removal rate) rates (Daugirdas & Ing, 1994; Cheung, 1994).

Section 3 Urea Kinetics

Mass transfer relationships describe the movement of mass. These relationships are applied to hemodialysis to measure dialysis dose.

3.1 Quantification based on Urea Kinetics

This section outlines the most recent development of models to quantify delivered dialysis dose. This delivered dose can be thought of as the volume of blood cleared of waste. Urea has been selected as the marker used in the mass transfer relationships of kinetic modeling during dialysis (Garred, 1998; Daugirdas & Ing, 1994 Cheung, 1994).

3.1.1 Introduction to Urea Kinetics Modeling (UKM) in Dialysis

The discussion of urea kinetics is started with the assumption of single pool dynamics. The body water is considered to be a single well mixed volume due to the relatively quick transport mechanisms between compartments (Garred, 1998; Daugirdas & Ing, 1994; Depner, 1991). The mass balance characterizing urea concentration during dialysis is as follows (Garred, 1998):

$$\frac{dCV}{dt} = G - KC \qquad (1)$$

where
C is urea concentration
V is body water volume
G is urea generation rate
K is urea clearance rate

3.1.2 Dialysis Prescription and Kt/V

Dialysis prescription by the nephrologist involves water removal and waste removal. This study is concerned with waste removal prescription. Time on the dialysis machine, blood flow rate, dialysate flow rate and dialyzer membrane area and mass transfer characteristics are used to determine the delivered dialysis dose. A parameter called Kt/V is used to quantify dialysis dose and prescription. K is the dialyzer urea clearance rate and t is the time spent on dialysis. V is the body water volume of the patient (Garred, 1998; Daugirdas & Ing, 1994; Depner, 1991). For a complete description of the development of Kt/V refer to the reference Garred, 1998. Illustrated in equation 2 is the Garred formula for Kt/V (Garred, 1998).

$$\frac{Kt}{V} = \frac{\ln\left(\frac{C_{pre}}{C_{post}}\right) + 3\left(\frac{DBW}{BW}\right)}{1 - 0.0178t} \qquad (2)$$

where C_{pre}&C_{post} are the blood creatinine concentrations
BW is body weight

Results from the U.S. National Cooperative Dialysis Study (Gotch, 1985) and subsequent studies (Hakim et al,1994 & Parker et al,1994) have demonstrated a link between Kt/V and patient mortality and morbidity. These same studies have lead to the guideline values of a Kt/V prescription of 1.2 - 1.4 to minimize patient morality and morbidity rates. Ongoing studies funded by the National Institutes of Health will present whether this minimum should be changed to 1.6 - 1.7 (Petitclerc, 1999)

3.1.3 Limitations

Kt/V dialysis prescription and the use of Kt/V as a quality assurance monitor carries some

limitations. Kt/V numbers used for prescription are based on dialyzer clearance values determined from in vitro studies and estimates of the patient's body water volume. Both the dialyzer clearance and volume values are only an estimate of the values actually realized during the dialysis session. These values can vary significantly among individuals and sessions. From equation (2) to calculate Kt/V to validate the prescription, a pre dialysis blood sample and a post dialysis sample (preferably 30 mins after dialysis to correct for rebound[1]) are analyzed for urea concentration. As a result the session can only be assessed at some time after the patient has left the dialysis unit. Operationally, this means Kt/V monitoring is a periodic quality check. Blood sampling increases the risks of infection and contamination.

Currently urea monitors are in development to analyze the dialysate urea levels. These monitors will provide periodic measures of urea and calculate Kt/V, eliminating some of the current delay with blood samples. Although these monitors will only provide periodic measures.

The next section will present an alternate model of urea kinetics based on conductivity measured in the dialysate entering and leaving the dialyzer.

1. Rebound is an effect that describes how urea levels in the blood increase immediately after dialysis as urea from the body diffuses into the blood space. Typically after 30 minutes most of this re-adjustment has occurred.

Section 4 Quantification based on Conductivity Kinetics

An instantaneous measurement of metabolic waste transfer during dialysis would allow for improved quality assurance and enable automated control systems to be integrated with the dialysis machine. Conductivity technology is currently used to control the conductivity levels of the dialysate solution before entering the dialyzer. The conductivity of the dialysate solution is usually held constant for the dialysis session. There is some clinical experience with varied conductivity during the dialysate session from a high value (15.0 mS/cm) at the start to a low value (13.5-14 mS/cm) at the end of the session. This section details the development of a model to capitalize on this technology and directly calculate an instantaneous Kt/V.

4.1 Overview

Some studies have suggested that small uremic solutes contained in the blood contribute to toxic effects to a much larger extent than the larger solutes and waste metabolites (reference this). Therefore, a solute or molecule of similar properties or kinetics to urea will have the potential of obtaining the same results developed for urea (Depner, 1991). The following section will examine the use of conductivity to follow the ion behaviour of the dialysis solution as an indicator dialysis dose (Locatelli et al, 1995; Petitclerc et al; Steil et al, 1993).

4.2 Mixed Ion Dialysis Behaviour

There have been studies that have demonstrated the validity of sodium models to predict clearance values in dialyzers from sodium kinetics (Locatelli et al, 1995; Petitclerc et al; Steil et al, 1993). Along with this research there have been studies predicting sodium kinetics during a dialysis session (DiFilippo, 1997; Petitclerc, 1992, Locatelli, 1995). These studies provide

validity to the claim that sodium behaves like urea during a dialysis session and that conductivity values of dialysate can be used as direct measures of sodium concentration. Conductivity has been in use for quite some time to adjust and control dialysate in the dialysis machine (Bonomini et al, 1997; Ursino et al, 1996).

4.3 Machine Technology

In an earlier section (section 2.2) the dialysis machine was introduced. The latest release of dialysis machines by Hospal-Gambro (the Integra figure 4.1) contain conductivity meters that measure dialysate inlet and outlet conductivity. The Diascan feature of the Integra is used to make periodic estimates of Kt/V.

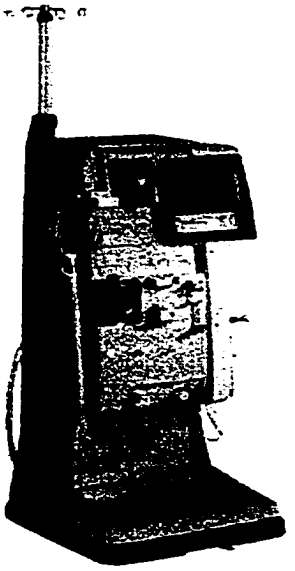


Figure 4.1 Hospal-Gambro Dialysis Machine.

4.3.1 Diascan

The Hospal-Gambro Integra dialysis machine has incorporated a dialysate out conductivity meter in the dialysate outlet line after the dialyzer. The placements of the conductivity meters are shown in figure 4.2.

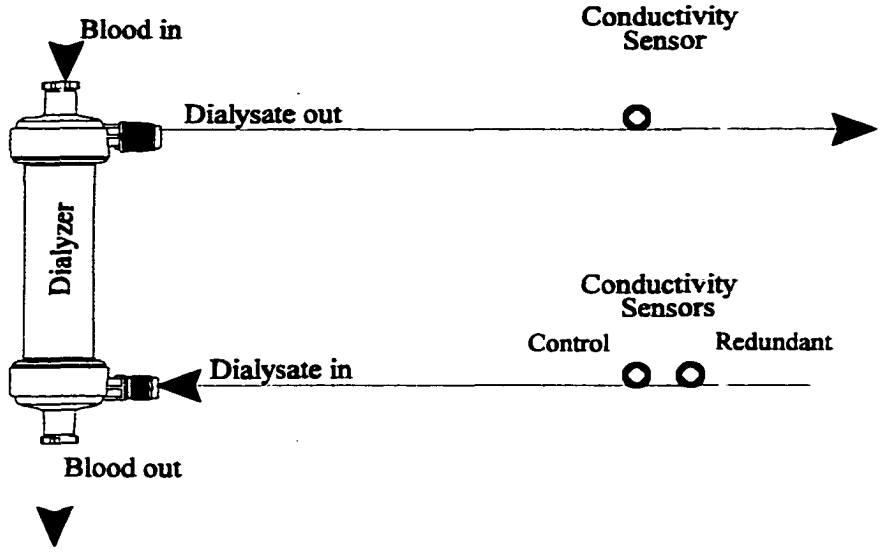


Figure 4.2 Placement of Conductivity Meters in Integra.

This dialysate out conductivity meter in the Integra is referred to by its' trade name Diascan. The Diascan feature is more than just the conductivity meter. Every 30 minutes the Diascan introduces a step change of dialysate inlet conductivity figure 4.3.

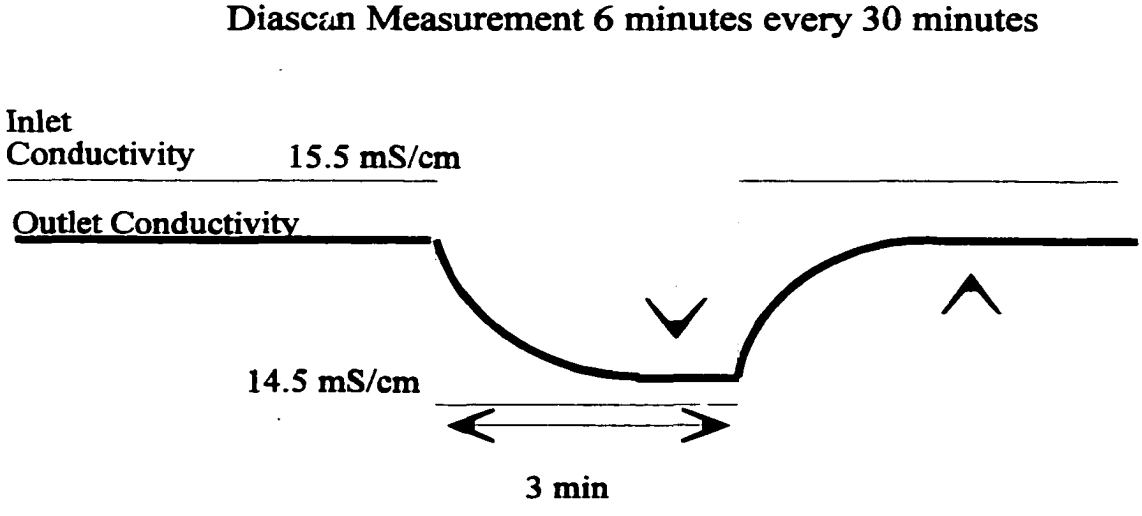


Figure 4.3 Diascan Measurement - Introduction of Step Change to Inlet Conductivity.

This is a step of 1.0 mS/cm up or down from the current inlet dialysate conductivity values. Measures of the outlet conductivity responses during the three minute step and step back to normal conductivity values allows the use of two sets of equations to be solved for Kt/V, clearance, ionic dialysance, ionic mass balance and patient plasma conductivity (Hospal-Gambro operating manual).

4.3.2 Diascan Kinetic modeling

The conductivity of the dialysate can be related to the total ion concentration of the solutions (Sancipriano et al, 1996; Locatelli et al, 1995). During a step change as shown in figure 4.3 the response of the outlet conductivity will provide a measure of concentration and mass transfer rates. Diascan relates this to an ionic dialysance by the following equation (Hospal-Gambro):

$$K_m = 1 - \frac{DC_o}{DC_i} \qquad (1)$$

where K is the ionic dialysance
ΔC_{oi} is the conductivity change of the inlet(i) and outlet(o)

Ionic Dialysance is a measure of the rate of clearance of ions from the blood and can be used as K for the Kt/V calculation (Petitclerc et al, 1993; Stiel et al, 1993). These results assume a patient volume based on Watson's formula (Depner, 1991) and only occur every 30 minutes. This measure improves the availability of Kt/V information in comparison to conventional blood sampling. Although, the Kt/V at the end of the session is not calculated unless the measure coincides with the end of the dialysis session. Therefore, the Kt/V measures are only periodic estimations of the delivered dialysis dose, an instantaneous measure would be preferable.

Section 5 Quantification based on Continuous Conductivity

This section presents the development of the instantaneous model of Kt/V using the continuous conductivity measures of both inlet and outlet dialysate. Modeling of sodium kinetics for the determination of sodium transfer between the dialysate and patient plasma has been used to control hemodynamic stability and patient natremia. The models use conductivity to follow sodium levels of the patient during the dialysis session (Petitcleric et al, 1993 & Ursino et al, 1996).

5.1 Sodium Kinetics (Garred, 1998)

The development of this model is the work of Dr. L.J. Garred, Chemical Engineering Department, Lakehead University, 1998.

5.1.1 Primary Model

For the development of the model the assumption is that patient conductivity(C_{pt}) will follow a single pool model

$$\frac{d(C_{pt}V)}{dt} = J \qquad (1)$$

where J is the rate of conductivity mass transfer from dialysate to patient

J can be expressed in terms of the diffusive dialysance and ultrafiltration rate.

$$J = D(C_{di} - C_{pt}) - K_{uf} C_{pt} \qquad (2)$$

where D is diffusive dialysance

K_{uf} is the mass transfer rate contributed by ultra filtration.

C_{di} is the inlet conductivity of the dialysate.

This expression while commonly used overestimates the contribution of convective mass transfer. However, key simplifications arise from using this expression and the error is not great at modest rates of ultrafiltration. The left hand side of equation (1) can be broken into parts.

$$\frac{d(C_{pt}V)}{dt} = \frac{VdC_{pt}}{dt} + \frac{C_{pt}dV}{dt}$$

$$\text{But} \quad \frac{dV}{dt} = -K_{uf}$$

if fluid removal by ultrafiltration comes entirely from the effective distribution for conductivity, K_{uf} is zero. Combining these two relationships with equations (1) and (2) gives:

$$V\frac{dC_{pt}}{dt} = D(C_{di} - C_{pt}) \tag{3}$$

Since Cpt cannot be directly measured equation (3) must be rewritten in terms of other variables. J can also be expressed in terms of conductivity disappearance from the dialysate stream.

$$J = Q_{di}C_{di} - Q_{do}C_{do} \tag{4}$$

Combining equations (2) and (4):

$$Q_{di}C_{di} - Q_{do}C_{do} = D(C_{di} - C_{pt}) - K_{uf}C_{pt} \tag{5}$$

or

$$(D + K_{uf})\, C_{pt} = Q_{do} C_{do} - (Q_{di} - D)\, C_{di}$$

Taking the derivative assuming constant Qdi, Qdo, D and Kuf:

$$(D + K_{uf}) \frac{dC_{pt}}{dt} = Q_{do} \frac{dC_{do}}{dt} - (Q_{di} - D) \frac{dC_{di}}{dt} \tag{6}$$

From (5)

$$(D + K_{uf}) \frac{dC_{pt}}{dt} = Q_{do} \frac{dC_{do}}{dt} - (Q_{di} - D) \frac{dC_{di}}{dt} \tag{7}$$

$$= Q_{do}(C_{di} - C_{do})$$

Substituting (6) and (7) into (3) in order to eliminate Cpt:

$$V \frac{dC_{do}}{dt} = D(C_{di} - C_{do}) + \frac{V(Q_{di} - D)}{Q_{do}} \times \frac{dC_{di}}{dt} \tag{8}$$

Re-arranging (8) to remove V from the Left hand side of the equation

$$\frac{d(C_{di} - C_{do})}{dt} = \frac{-D}{V}(C_{di} - C_{do}) + \frac{(D + K_{uf})}{(Q_{di} + K_{uf})} \times \frac{dC_{di}}{dt} \tag{9}$$

The situation to be analyzed is where dialysate conductivity (C_{di}) is constant or a series of

constant steps.

When Cdi is constant over a portion of the dialysis, the last term in equation (8) is zero. Both D and V likely vary as dialysis precedes generally decreasing in each case; consequently, the ratio, D/V, will be nearly constant. Equation (8) can be integrated for D/V constant to show:

$$\ln\left|(C_{di}-C_{do})\right| \quad {}_{vs}\ t \tag{10}$$

is a straight line with slope = -D/V. D/V is equivalent to K/V as both D and K are mass transfer clearance rates.

5.1.2 Potential Use in Dialysis

With validation of the model, instantaneous estimations of Kt/V will be provided during the dialysis session. This approach will allow comparisons of delivered dialysis dose for each session. Separate calculation of D/V will provide a direct indication of V (body water volume) as the clearance rates D or K are known for the dialyzers. V being the body water volume or the single pool area from which metabolic waste is removed. Instantaneous values of Kt/V being obtained, with ability to direct values for each dialysis session. Since conductivity values are followed closely and predictive, body response constants to sodium will be identified.

Chapter 3. Methodology

3.1 Study Variables

All data gathering of hemodialysis sessions for this study was performed on the Hospal-Gambro Integra model dialysis machine labeled H4, the first machine at the TBRH to be equipped with the Diascan option providing conductivity meters on both the fresh and spent dialysate streams. The entire set of Integra machine parameters available for capture is listed in tables A1-A3, Appendix A. A subset of 31 variables was chosen for capture in this study. These are listed in table 3.1.

3.2 Data Acquisition System

An ACER Extensa 368D laptop computer was used to capture relevant data from the Integra via its RS232 serial port. The commercial data acquisition software, ACQ, was used for data capture. The ACQ program listing developed for this study is provided in Appendix B. The ACQ program captures the 31 Integra study variable set (table 3.1) at a specified time interval throughout the dialysis session. In addition, at each data capture iteration, ACQ generates an additional parameter corresponding to the time, in minutes, since the start of data capture. The set of 32 values is written to an ASCII file. In a pilot study it was determined that the shortest possible interval between consecutive sets of data capture was approximately nine seconds. For convenience, the ACQ data capture interval was set at 10 seconds.

Parameter #	Integra Code		Integra Parameter Name	Study Name	Units
1	89, 3	4	Session Time	Prescribed Time	min
2	39	15	Dialysis Time	Dialysis Time	sec
3	89, 3	5	Inlet Conductivity Setting	Sodium Profile Setting	mS/cm
4	39	18	Inlet Conductivity	Sodium Profile Control	mS/cm
5	89, 1	42	Inlet Conductivity Protective	Inlet Conductivity Protective	mS/cm
6	89, 3	48	Inlet Conductivity	Inlet Conductivity Control	mS/cm
7	108, 4	34	Outlet Conductivity 3	Uncorrected Outlet Conductivity	mS/cm
8	89, 3	46	Outlet Conductivity 3	Corrected Outlet Conductivity	mS/cm
9	89, 3	47	Plasma Conductivity 3	Plasma Conductivity	mS/cm
10	89, 3	40	Gain	Diascan Gain	
11	89, 3	41	Offset	Diascan Offset	uS/cm
12	89, 1	52	P2	Dialysate & Ultrafiltrate Flow	ml/min
13	89, 1	7	Dialysate Flow	Dialysate Flow	ml/min
14	39	22	Dialysate Flow	Dialysate Flow Setting	ml/min
15	89, 1	12	Temperature	Temperature	C
16	89, 1	25	Blood Flow	Blood Flow	ml/min
17	89, 3	6	Weight Loss	Weight Loss	g
18	89, 1	11	Weight Loss	Weight Loss	kg
19	89, 1	10	Weight Loss Rate	Weight Loss Rate	kg/h
20	89, 3	7	Weight Loss Rate	Weight Loss Rate	g/h
21	39	30	Kt	Kt	
22	39	50	Hemoglobin	Hemoglobin Filtered	g/dl
23	89, 3	28	Hemoglobin	Hemoglobin Unfiltered	g/dl
24	89, 3	29	Hemoglobin TO	Hemoglobin BV Initial Value	g/dl
25	39	51	Blood Volume	Blood Volume	%
26	39	53	Ionic Mass Balance	Ionic Mass Balance	
27	39	54	Dialysance	Dialysance	
28	39	59	Kt/V	Kt/V	
29	89, 3	35	Rising Hydraulic Delay	Time Delay	sec
30	39	44	Diastolic Pressure	Diastolic Pressure	mmHg
31	39	45	Systolic Pressure	Systolic Pressure	mmHg

Table 3.1 Integra Dialysis Machine Variables Captured by the Data Acquisition System.

3.3 Data Acquisition for a Dialysis Session

The laptop was connected to the Integra via the RS232 port 15-30 minutes before the patient to be studied was connected to the machine. The data acquisition program was started immediately and ACQ sample time (parameter 32) began at this point. Data acquisition was terminated approximately 15-30 minutes following patient disconnection from the Integra. The data captured by the ACQ program are written to an ASCII file during the dialysis session. Following the dialysis session the data were saved to an EXCEL file in which the data captured before and after the actual period of dialysis were removed and headers added to label the data columns. Data removal was facilitated by inspection of the Integra dialysis time (parameter 2). This parameter is set to the prescribed dialysis time in seconds at the start of dialysis (the moment when the start button on the Integra is pressed) and counts down to zero corresponding to the end of dialysis. The data for each study session were stored in the original ASCII format on a single floppy disk. The EXCEL files generated for all study sessions were stored on a single zip disk. A copy of this zip disk may be found in the back cover of this report

3.4 Study Patients

Only stable patients with a lower arm AV fistula capable of blood flow rates of 300-400 ml/min were considered for this study. Patients participating in the study were informed of the nature of the study and the computer data acquisition system to be attached to the RS232 port of the dialysis machine. The patients were assured that the computer could in no way affect the operation of the dialysis machine. The study patients were then asked to sign a consent form. During this study no changes were made to the patients' dialysis treatment.

A total of 14 patients, 7 females and 7 males, participated in the study. Patient parameters are listed in table 3.2. Patients ranged in age from 13 to 88 and weighed between 44.3 kg and 159.2 kg. Patients had undergone an average of 331 dialyses or about 2.1 years of hemodialysis before entering the study. The number of study dialysis sessions per patient ranged from 1 to 23. Complete data were acquired for 85 dialysis sessions with these patients over the study period of October to December 1998.

Patient	Sex	Age (years)	Ideal Weight (kg)	Dialyzer	# of Dialyses prior to study	# of Study Sessions
CL	F	13	44.3	B31.6	92	23
MJ	F	57	46	B31.6	94	8
WP	M	52	94.5	F80A	300	1
HF	M	49	159.2	F80A	360	7
DS	M	37	69.5	F80A	796	9
SM	M	22	74.5	F60A	297	9
MA	F	78	83.5	BK1.6	223	5
JB	M	44	91.5	F80A	370	5
BG	M	52	64	F8	249	5
KS	M	62	89	BK1.6	690	8
NF	F	52	85	F80A	780	2
DC	F	54	70.5	F60A	20	1
IK	F	78	80	F80A	140	1
LA	F	88	47.3	B31.6	230	1
Mean		52.7±20.5	78.5±28.7		331±252	6.5±5.8
Range		13-88	44.3-159.2		92-796	36547

Table 3.2. Patient Statistics and Treatment Summary.

3.5 Study Dialysis Sessions

The dialysate flow rate was 500 ml/min for all 85 dialysis sessions of the study. Blood flow rates between 300 and 400 ml/min were required for the study. Blood flow rate was maintained at 400 ml/min for 70 %, at 350 ml/min for 20% and at 300 ml/min for 10% of the sessions. Study dialysis sessions were between 3.5 and 4 hours in length. Eight of the study patients had a treatment length of four hours and the remainder of the patients were dialyzed for 3.5 hours. Normal treatment prescription for all study patients included inlet dialysate conductivity profiling and ultrafiltration profiling. Profiling of the inlet dialysate consisted of a descending series of constant conductivity steps. A typical profile is shown in the upper frame of figure 3.1. For the session illustrated the inlet dialysate conductivity is fixed at 15.0 mS/cm for the first hour of dialysis, at 14.5 mS/cm for the following 2 hours and reduced to 14.0 mS/cm for the final treatment hour. As a result of this descending step profile the direction of sodium transfer is from the dialysate to the patient early in the treatment and from the patient into the dialysate towards the end of the treatment. The purpose of the high sodium in the early stages of the session is to diminish extracellular to intracellular fluid movement. The ultrafiltration profile typically employed a descending series of constant ultrafiltration rate steps of varying lengths separated by 10 minute rest periods. During the rest period ultrafiltration was reduced to the minimum value of 0.1 kg/h to facilitate vascular space refilling. A typical ultrafiltration profile is shown in the lower frame of figure 3.1.

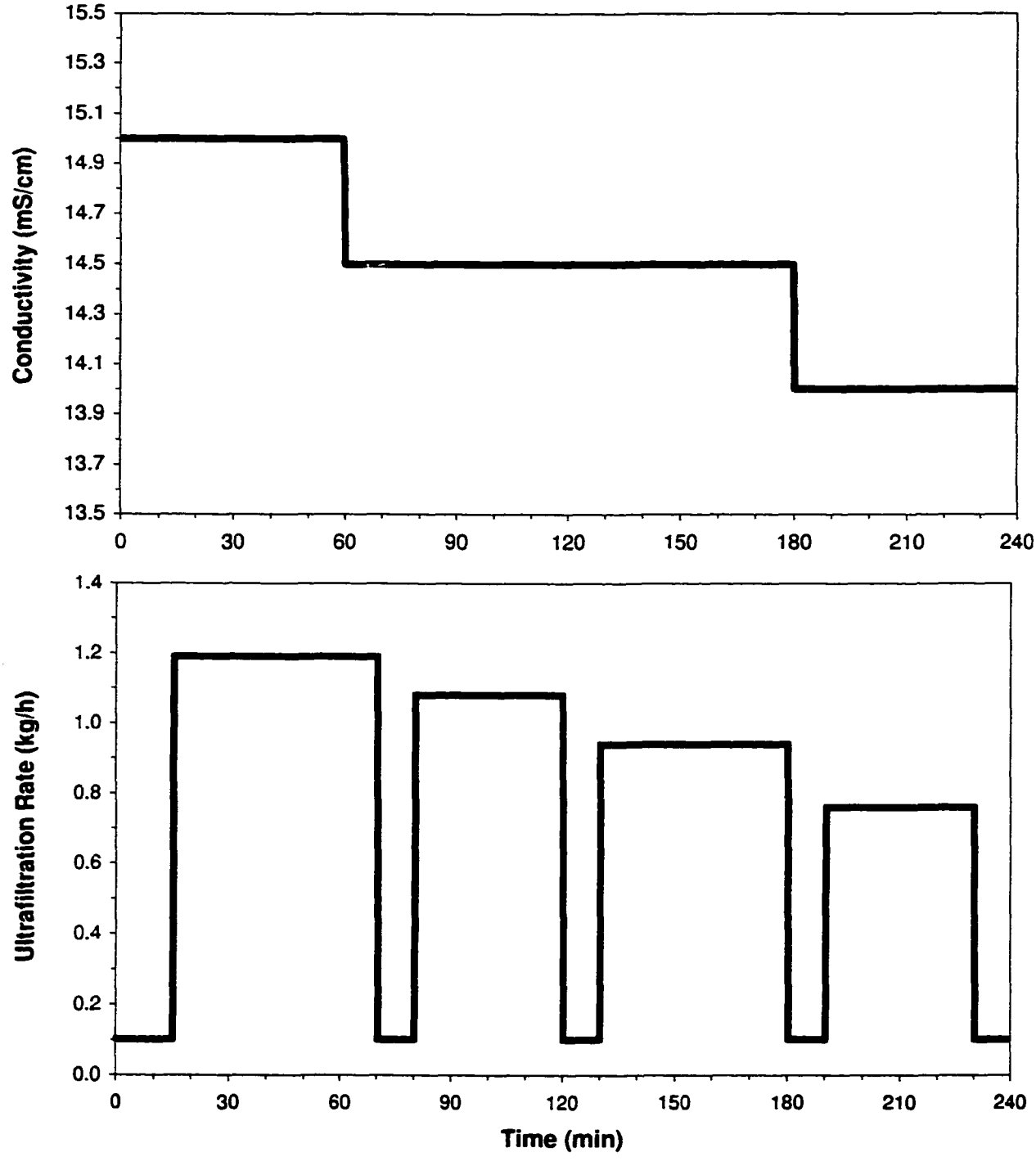


Figure 3.1. Typical inlet dialysate conductivity profile (upper frame) and ultrafiltration profile (lower frame) as employed by the Thunder Bay Regional Hospital Renal Unit.

Chapter 4. Results

4.1 Treatment of Study Data

A total of 85 dialysis sessions were studied between October and December, 1998. There were 13 patients in the study group, 6 females and 7 males, ranging in age from 13 to 88. The data acquisition system, ACQ, captured 32 parameters at 10 second intervals for each of the dialysis sessions studied. The complete data set is stored on the zip disk attached to the back cover.

The most relevant parameters to this study are fresh or inlet dialysate conductivity (C_{di}) and spent or outlet dialysate conductivity (C_{do}). The data acquisition program captured four different inlet conductivity values (parameters 3-6). Sodium Profile Setting (parameter 3) is the dialysate conductivity profile prescribed for the dialysis session and entered into the Integra by the nephrologist or renal nurse prior to the start of the treatment. Sodium Profile Control (parameter 4) is the set value for the inlet dialysate conductivity control system of the Integra. The Sodium Profile Setting and the Sodium Profile Control conductivity values are identical except the control value generates a brief ramp signal when the Sodium Profile Setting has prescribed a step change in inlet dialysate conductivity. There are two conductivity meters in the inlet dialysate line of the Integra dialysis machine; they are identified as 41 and 42 on the Integra flow sheet, figure 4.1. The redundant meters are a necessary safety feature to guard against an inappropriate inlet dialysate conductivity being generated by the dialysis machine. Inlet Conductivity Control (parameter 6) corresponds to the dialysate conductivity measured by the first meter (labelled as 41 on figure 4.1). This is the sensor feedback value used for inlet dialysate conductivity control. Inlet Conductivity Protective (parameter 5), the conductivity

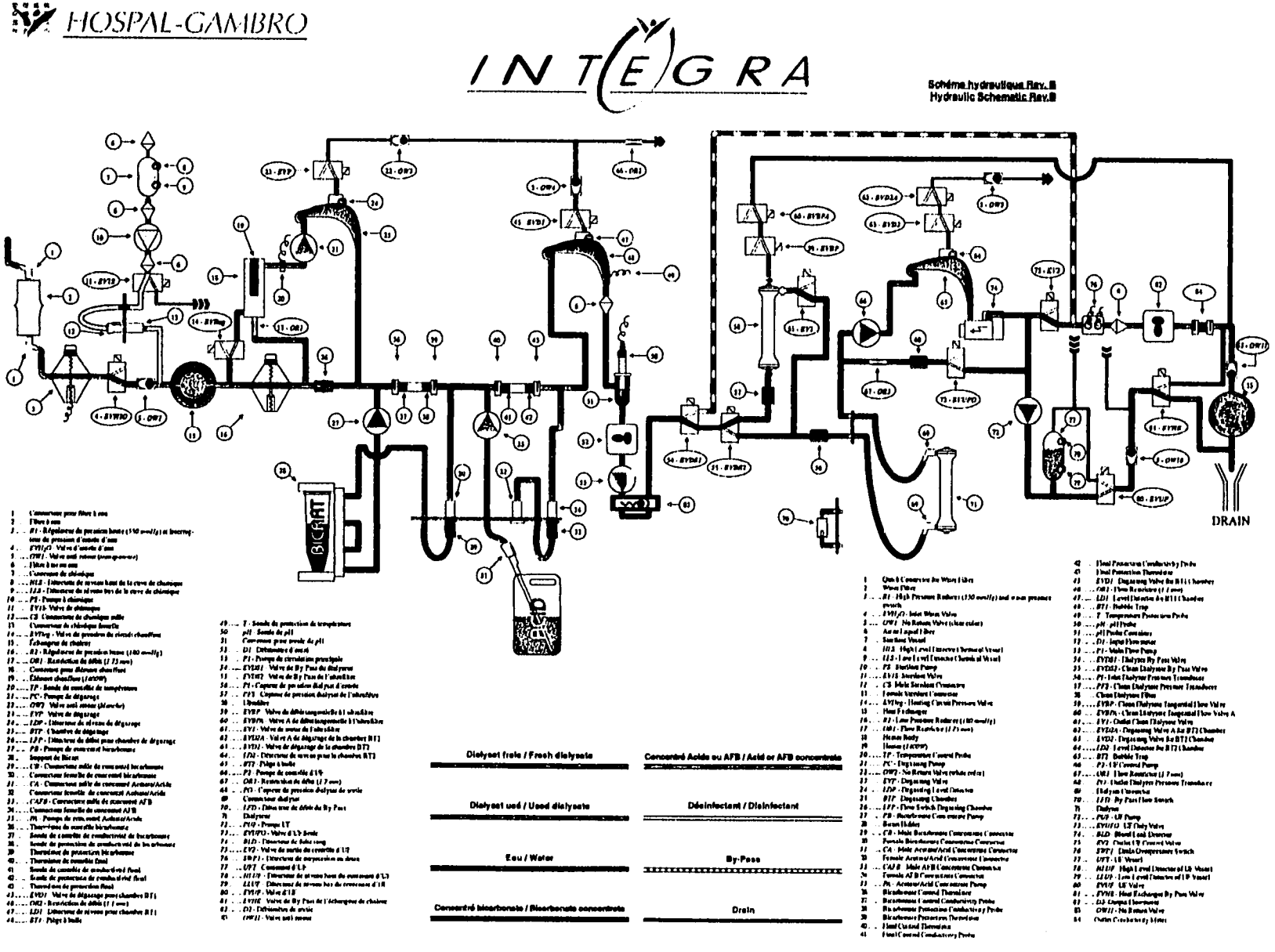


Figure 4.1. Integra Hydraulic Flow Schematic

measured by the second meter (42 on figure 4.1), provides a redundant measure of inlet dialysate conductivity. When the two values differ by more than 0.1 mS/cm, an alarm sounds on the dialysis machine. Sodium Profile Setting (parameter 3) and Inlet Conductivity Control (parameter 6) have been plotted on figure 4.2 for the first 120 minutes of dialysis session CL051198. This figure illustrates the noise in the Inlet Conductivity Control (parameter 6) measurement (green triangles in figure 4.2) relative to the constant Sodium Profile Setting (black line in figure 4.2) of 15.5 mS/cm. Given the fluctuations in the conductivity meter values, it was decided to use the Sodium Profile Setting (parameter 3) as the C_{di} value for validating the mathematical model. The downward steps in conductivity of 1 mS/cm noted at 10 minutes and each 30 minutes thereafter correspond to Diascan measurements of ionic dialysance and patient conductivity.

Two different outlet conductivity values (parameters 7 & 8) were captured by the data acquisition system. The Uncorrected Outlet Conductivity (parameter 7) is the conductivity measured by the spent dialysate conductivity meter (labelled 84 on figure 4.1). For a period during the start-up procedure, fresh dialysate is shunted to the spent dialysate conductivity meter bypassing the dialyzer. The outputs of the control inlet conductivity meter (parameter 6) and spent dialysate conductivity meter (parameter 7) are compared and the offset used to generate a Corrected Outlet Conductivity (parameter 8). The offset between the Uncorrected Outlet Conductivity (parameter 7) and Corrected Outlet Conductivity (parameter 8) is illustrated in figure 4.3, for the first 120 minutes of dialysis session CL051198. The downward spikes at approximately 10, 40, 70 and 100 minutes reflect the outlet dialysate conductivity response to the step change in inlet conductivity during Diascan measurements. The upward and downward spikes between Diascan readings (indicated by the upper arrows in figure 4.1) occur every 15

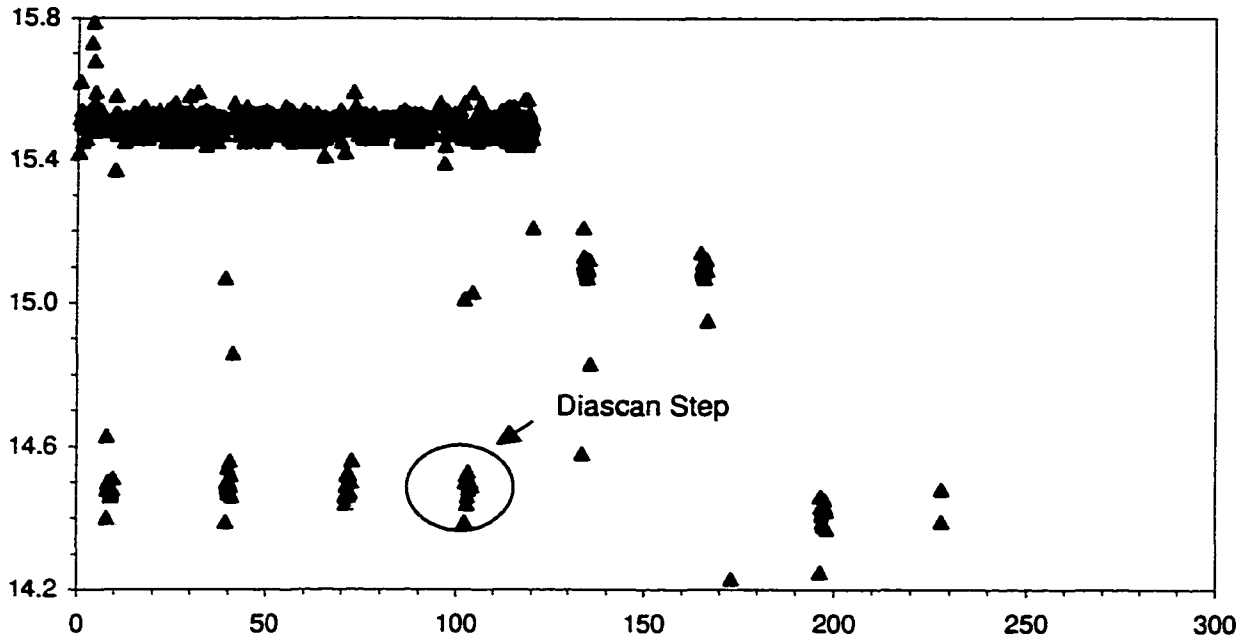


Figure 4.2. Illustration of the measurement noise of the inlet dialysate conductivity sensor. Study session CL051198

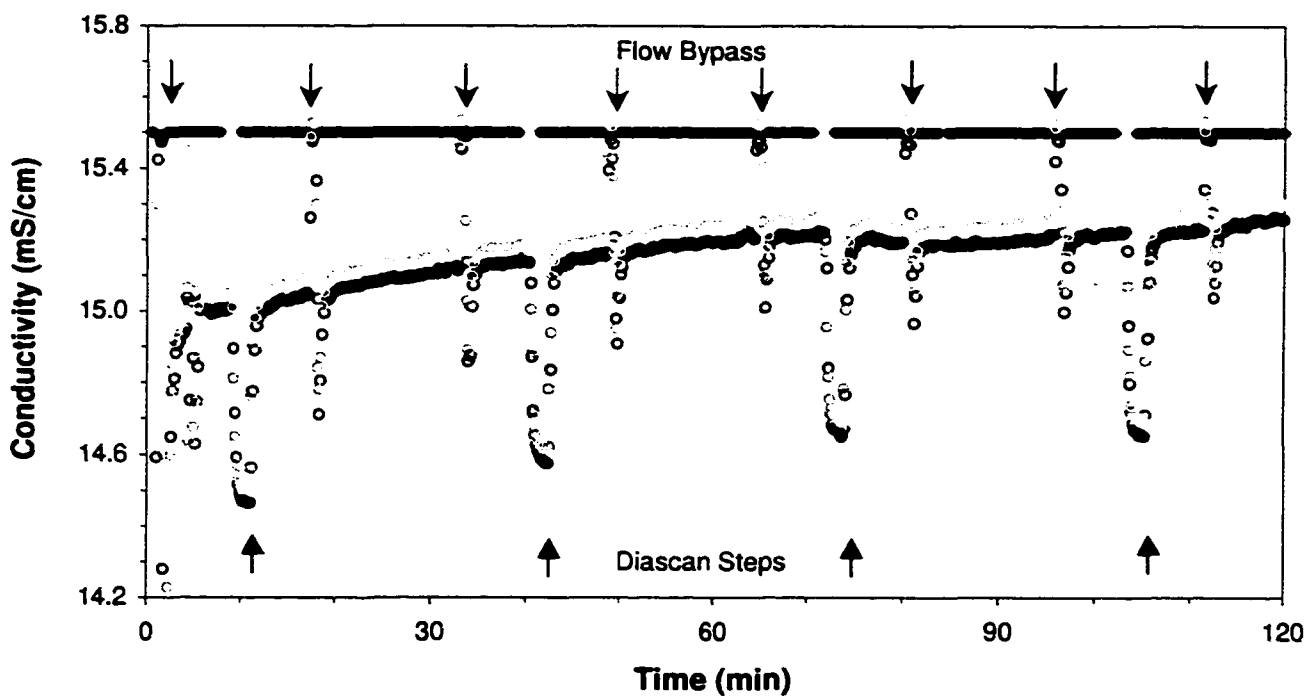


Figure 4.3. Outlet dialysate conductivity sensor readings without offset (yellow) and with offset (green). Inlet dialysate conductivity shown as black line. Study session CLL051198.

minutes when the Integra performs a calibration of the inlet and outlet dialysate flow meters (52 and 82 on figure 4.1). During the one minute dialyzer bypass, the outlet conductivity rises to equal the inlet value. The abrupt fall after this rise is due to the lower conductivity of the dialysate trapped in the dialyzer during the bypass period. For study model validation, it was necessary to remove both of these excursions from the outlet conductivity data set. Further reduction in signal noise was obtained by using a centrally located seven point moving average. In this data smoothing technique, the conductivity value at each time point was averaged with the three proceeding and the three following conductivity values. The filtered, smoothed outlet conductivity data (green circles on figure 4.5) were the values of C_{do} used for study model validation.

A further problem arose from the physical placement of the inlet conductivity sensor (41 on figure 4.1) and the outlet conductivity sensor (84 on figure 4.1) in the Integra machine. The location of the two sensors results in an appreciable time lag between the moment dialysate passes by the inlet conductivity sensor and when the same dialysate reaches the outlet conductivity sensor. This hydraulic delay is illustrated in figure 4.4 which shows the delay in the outlet dialysate conductivity sensor response to the step change in conductivity registered at the inlet sensor when a Diascan measurement is initiated. The hydraulic delay is inversely proportional to dialysate flow rate and varies with dialyzer size. This hydraulic time lag, termed Rising Hydraulic Delay (parameter 29), is captured by the Integra machine for each Diascan measurement performed. The Rising Hydraulic Delay (RHD) values provided a means of compensating the data set samplings for the hydraulic time delay between the two sensors. For use in the study, the average Rising Hydraulic Delay was rounded to the nearest 10 seconds. For

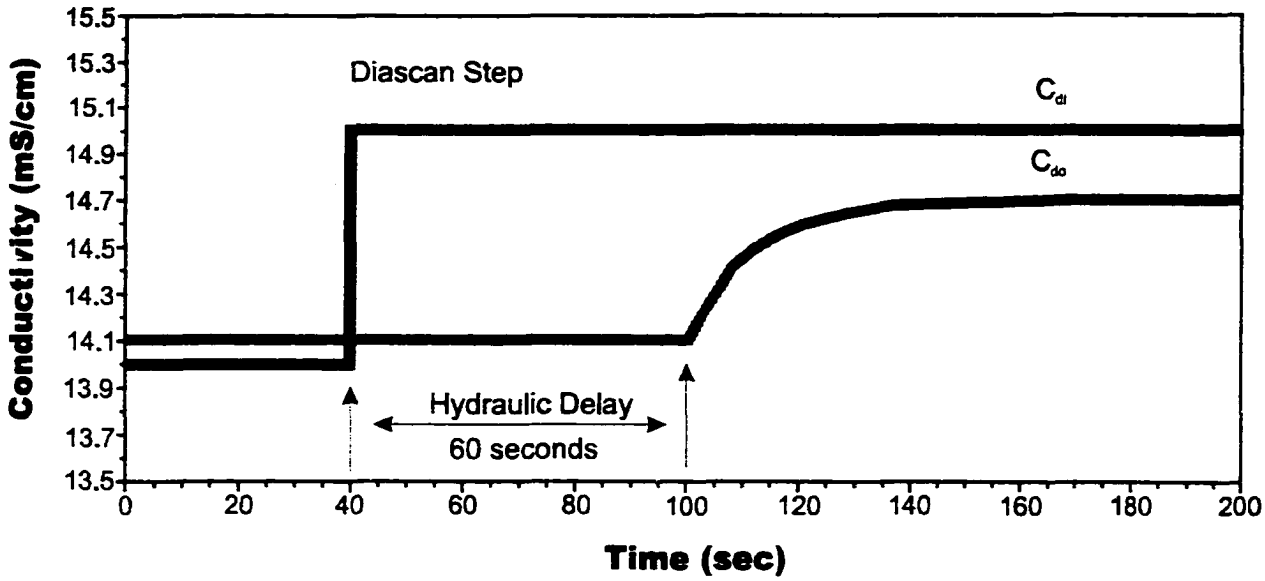


Figure 4.4. Measurement of hydraulic time delay between conductivity sensors during a Diascan step.

the study session illustrated in figure 4.4, the RHD is 60 seconds and the data set sampling interval is 10 seconds; therefore, the outlet dialysate conductivity recorded with a particular data set corresponds to the inlet conductivity value recorded 6 data sets (or 60 seconds) earlier. Figure 4.5 shows the filtered Outlet Conductivity data (green circles) where the spikes associated with flow bypass and Diascan procedures have been removed and the data sets have been time-shifted to compensate for the hydraulic time delay between the inlet and outlet conductivity sensors. The red diamonds in figure 4.5 correspond to the patient conductivity determined from each Diascan measurement.

4.2 Model Study Validation

According to the model developed in Chapter 2 Section 5.1 the outlet dialysate conductivity change with time during a period of constant inlet dialysate conductivity is expected

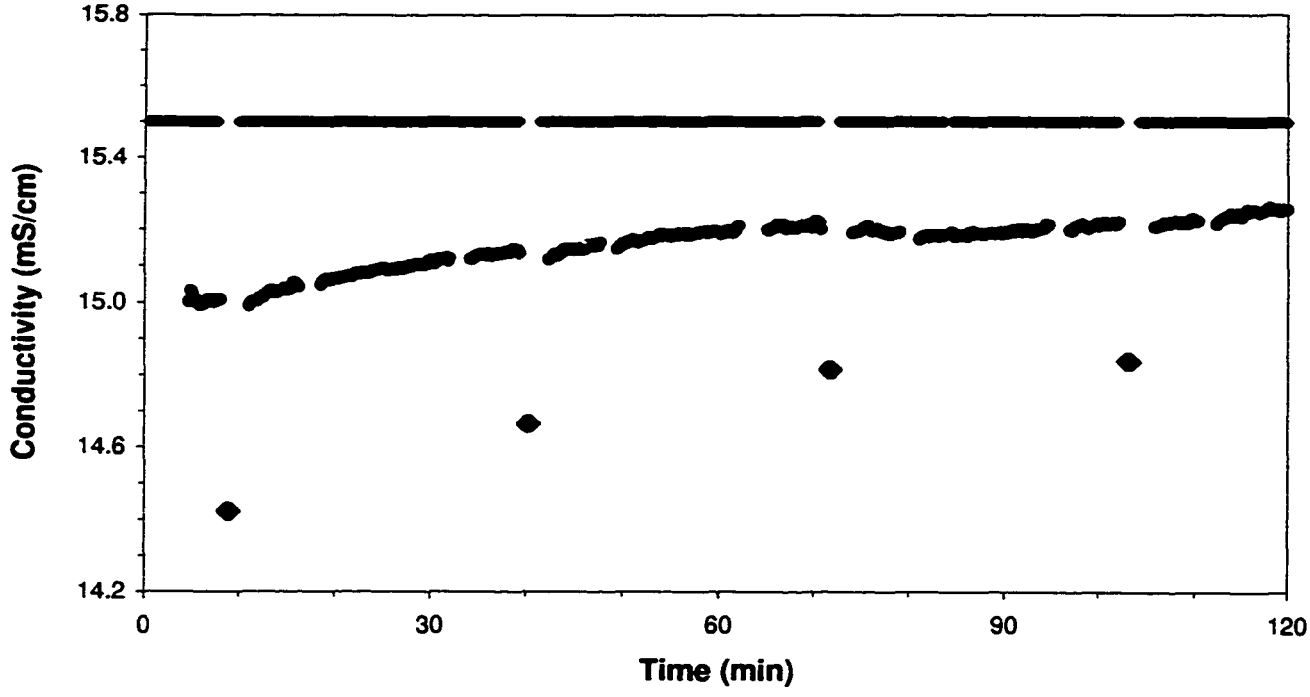


Figure 4.5. C_{di} (black line), C_{do} (green circles), and Diascan measured patient conductivity C_{pt} (red diamond). Study session CL051198.

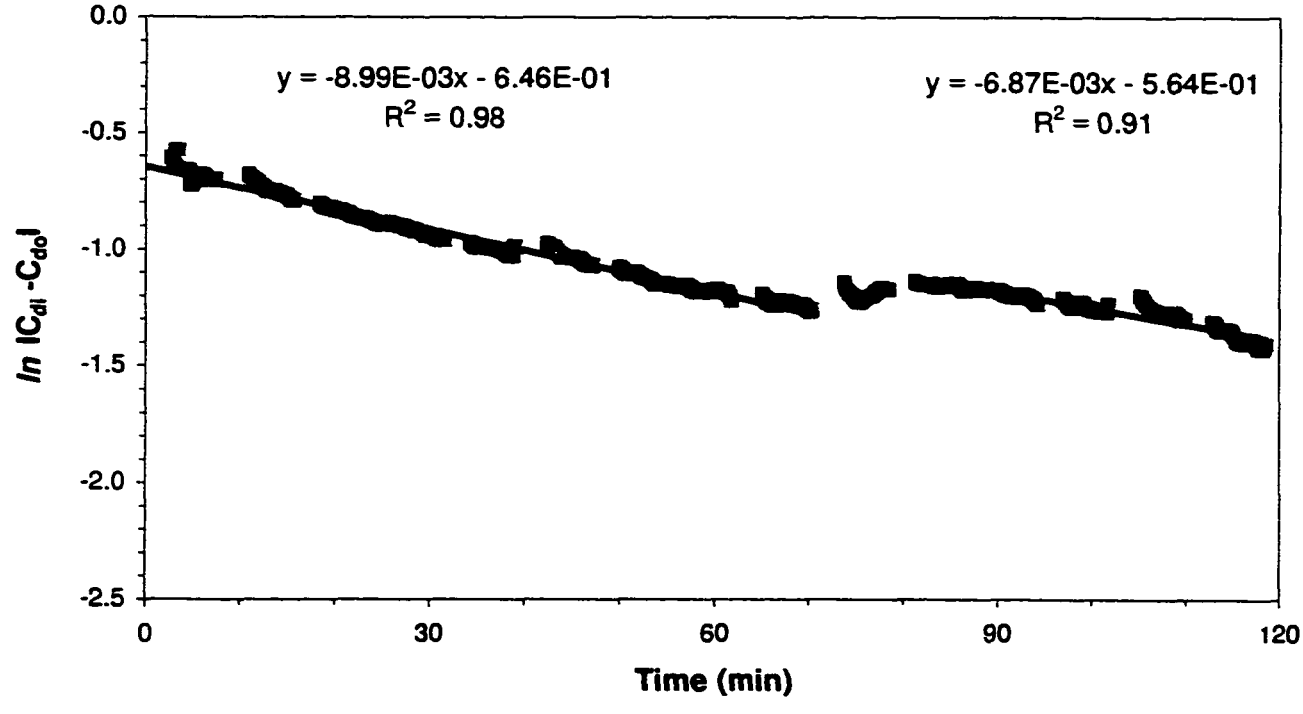


Figure 4.6. Validation of the study model for the first period of constant inlet dialysate conductivity. Study session CL051198.

to obey the following equation,

$$\ln\left| C_{di} - C_{do} \right| = \ln\left| C_{di}^{o} - C_{do}^{o} \right| - \frac{D}{V}\, t \qquad (10)$$

where C_{di}^{o}, C_{do}^{o} represent the inlet and outlet dialysate conductivities at the start of the period of constant C_{di} and t represents the time elapsed in this period.

Therefore, a plot of $\ln|C_{di} - C_{do}|$ versus time is expected to exhibit straight line behaviour. Figure 4.6 is such a plot for the C_{di}, C_{do} data shown in figure 4.5. Linear regression analysis was used to appraise the hypothesis of straight line behaviour during each period of constant C_{di}. The $\ln|C_{di} - C_{do}|$ data for the first 120 minutes of session CL051198 (figure 4.6) appear to follow a straight line for the first 70 minutes, followed by a transition period between 70 and 80 minutes to a second straight line from 80 to 120 minutes. Linear regression was performed on each straight line segment and the corresponding linear equations and R^2 values are shown on figure 4.6. Both R^2 values exceed 0.9 indicating strong linear fit of the $\ln|C_{di} - C_{do}|$ data for each period; however, the slope of the line segments between 0 and 70 (-0.00899 min^{-1}) is significantly different from the best fit line slope between 80 and 120 minutes (-0.00687 min^{-1}). While the close to linear fit over an extended time period is an encouraging finding, the significant difference in slope between the two straight line segments was not anticipated and would appear to invalidate the proposed model. Change in linear regression line slopes are thought to be related to changes in ultrafiltration and vascular refilling rates. This will be considered further in the Discussion section.

For most study sessions dialysate conductivity profiling resulted in three periods of constant C_{di} and therefore, three opportunities to test the linear relationship between $\ln|C_{di} - C_{do}|$ and session time. Figure 4.7 shows the recorded inlet and outlet conductivity data for the entire

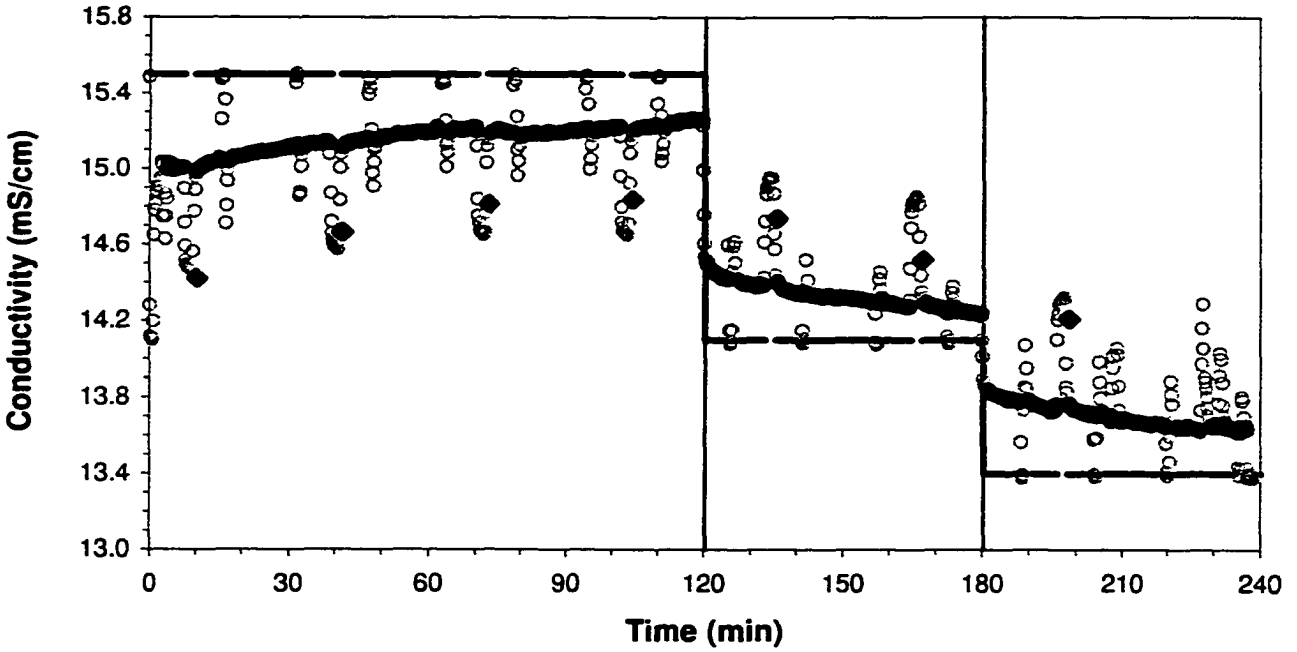


Figure 4.7. C_{di} (black line), C_{do} raw (open gold circles) C_{do} study (solid dark green circles), including Diascan patient conductivity C_{pt} (red diamonds). Study session CL051198

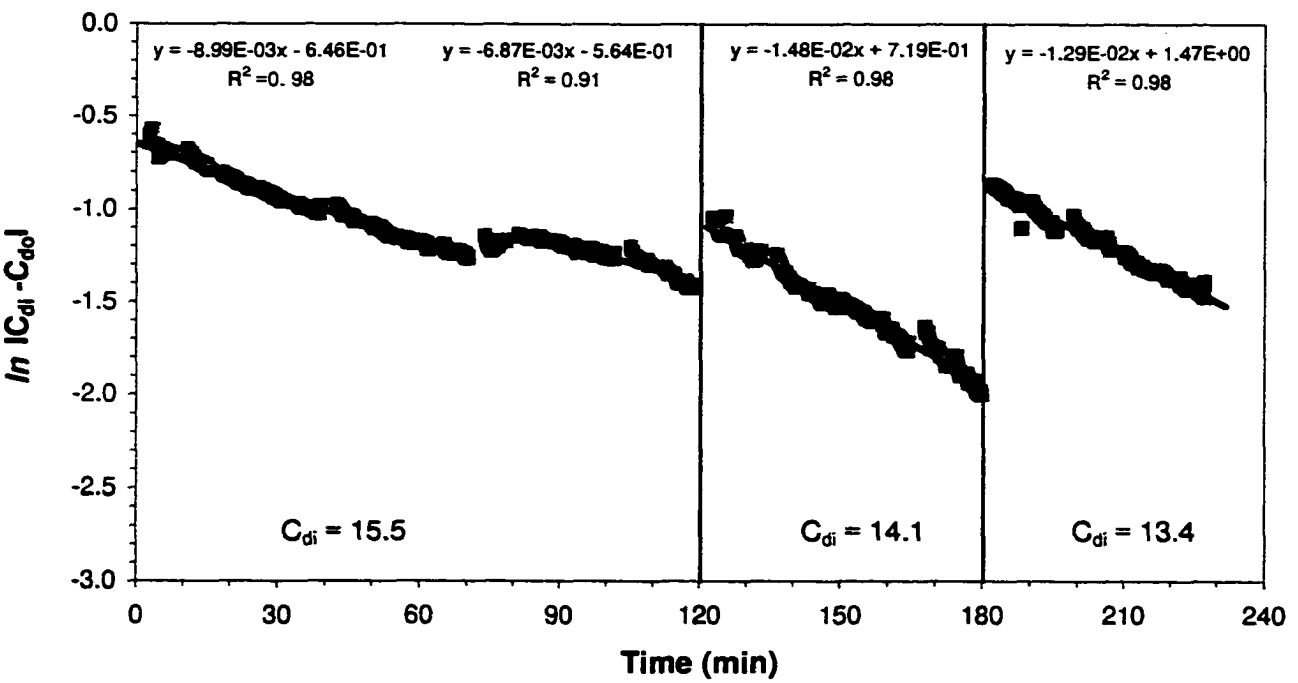


Figure 4.8. Plot of ln $|C_{di} - C_{do}|$ data for the entire study session CL051198.

240 minutes of study session CL051198 and figure 4.8 shows the corresponding $\ln|C_{di} - C_{do}|$ versus time plot. For the session depicted, sodium is transferring to the patient for the first 120 minutes (C_{di} exceeds C_{do}) and from the patient to the dialysate for the last 120 minutes (C_{do} exceeds C_{di}). As a consequence, the Diascan measure of patient conductivity (red diamonds on figure 4.7) is seen to rise for the first 2 hours of the dialysis session and to fall during the final 2 hours. The $\ln|C_{di} - C_{do}|$ data of figure 4.8 are seen to follow straight line behaviour for the period of constant $C_{di} = 14.1$ mS/cm (120-180 minutes) as well as for $C_{di} = 13.4$ mS/cm (180-240 minutes). The linear regression coefficient is 0.98 for both periods of constant C_{di}. However, once again the regression line slope differs significantly between the two line segments (-0.0148 min^{-1} versus -0.0129 min^{-1}) and from the regression line slopes found in the first 120 minutes of the study session. Plots similar to figures 4.7 and 4.8 (C_{di}, C_{do} and C_{pt} versus session time and $\ln|C_{di} - C_{do}|$ versus session time) may be found for all 84 sessions in Appendix C. For most sessions, the $\ln|C_{di} - C_{do}|$ data were found to fall along one or more straight line segments for each period of constant C_{di}. A notable exception occurred when the inlet conductivity was set very close to the patient conductivity as in the example of the 65-130 minute period of study session NF231298 shown in figure 4.9. This results in little difference between the inlet and outlet dialysate conductivities and therefore too much scatter to establish straight line behaviour when the $\ln|C_{di} - C_{do}|$ data are plotted versus time (figure 4.10). There was typically considerable variability among slopes of the regression line segments for each session, similar to the variability noted for the study session CL051198, shown in figure 4.8. This variability in straight line segment slopes was not expected from the proposed mathematical model which predicted a constant slope equal to -D/V, independent of C_{di}. The factors related to this variability in segment slope will be explored further in the Discussion section of this report.

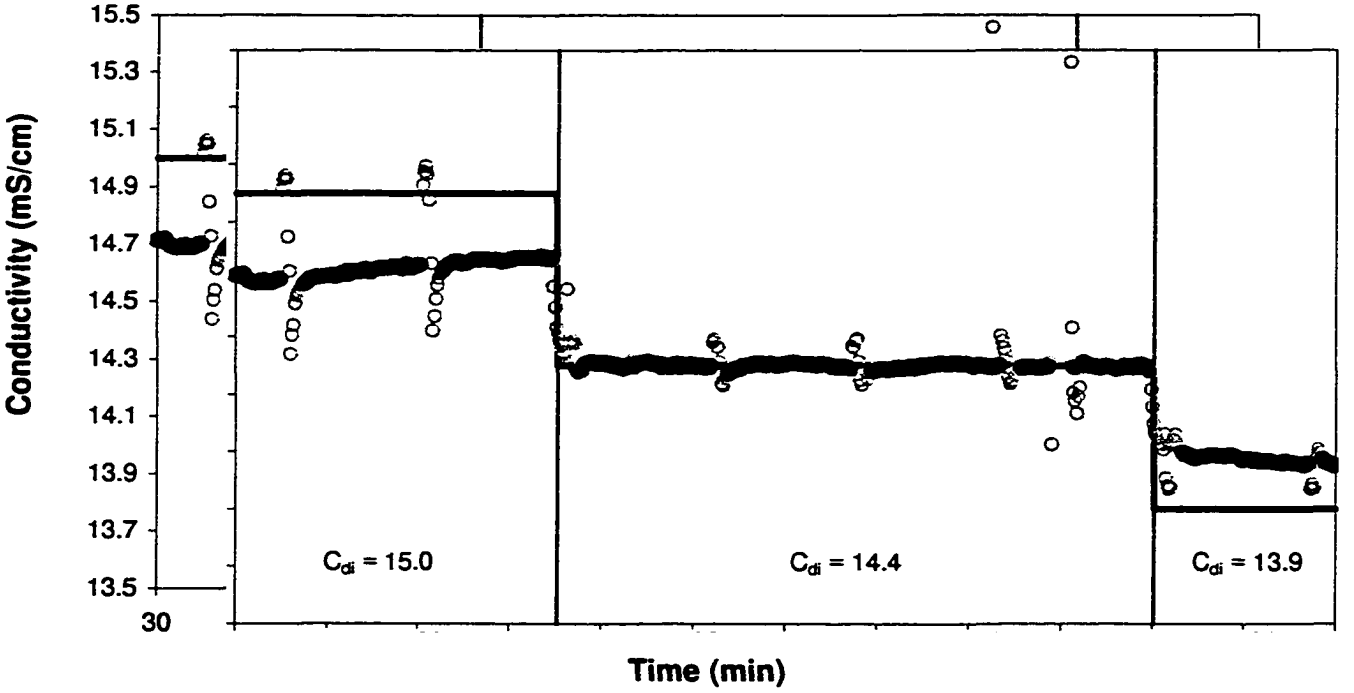


Figure 4.9. C_{di} (black line) and C_{do} (green circles) during period when dialysate conductivity approaches patient conductivity

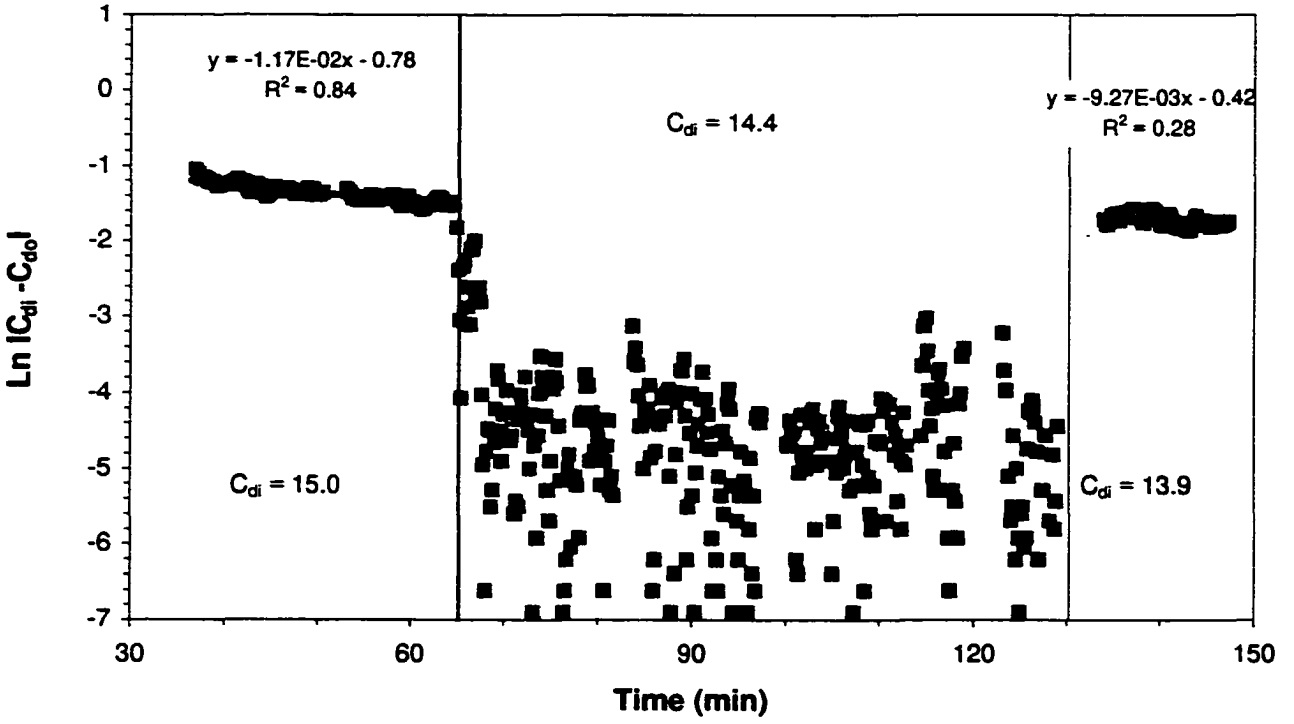


Figure 4.10. Study data when meter accuracy is insufficient. Study session NF231298.

As noted above, the $\ln|C_{di} - C_{do}|$ versus time plot for an individual test session was typically characterized by a series of straight line segments with each segment having a different slope. There was no identifiable trend in the sequence of straight line segment slopes for a session (such as for example, the series of slopes rising or falling); however, the pattern of straight line segments for an individual patient appeared to be repeated in subsequent sessions with the same treatment prescription. This is illustrated in figures 4.11- 4.13 for three consecutive dialysis sessions for patient CL. A break in the line segment is evident in each of the three consecutive sessions at approximately 70 minutes of the first constant C_{di} step. The ratio of the slopes before and after this break is similar in each of the three sessions. Similar trends are evident through the final 2 hours of each session. The linear segments for the second and third C_{di} steps are similar in slope and significantly steeper than the line segments for the first C_{di} step.

4.3 Treatment Dose Quantification

According to the proposed model, $\ln|C_{di} - C_{do}|$ plotted versus dialysis time was expected to yield a single straight line for each period of constant C_{di}, with the line slope being equal to -D/V and independent of C_{di}. This would then allow direct calculation of Dt/V by multiplication of this slope by the dialysis session time. As described above the measured $\ln|C_{di} - C_{do}|$ data generally fell along a sequence of straight line segments of varying slope. The proposed model and its use to obtain Dt/V as a direct quantification of dialysis dose was therefore not validated by the study results. Nevertheless, it was thought worthwhile to attempt a determination of Dt/V based on the slopes of the piecewise linear fit of the $\ln|C_{di} - C_{do}|$ versus dialysis time data. The technique for this is illustrated in Figure 4.14. The linear regression line for each period in which

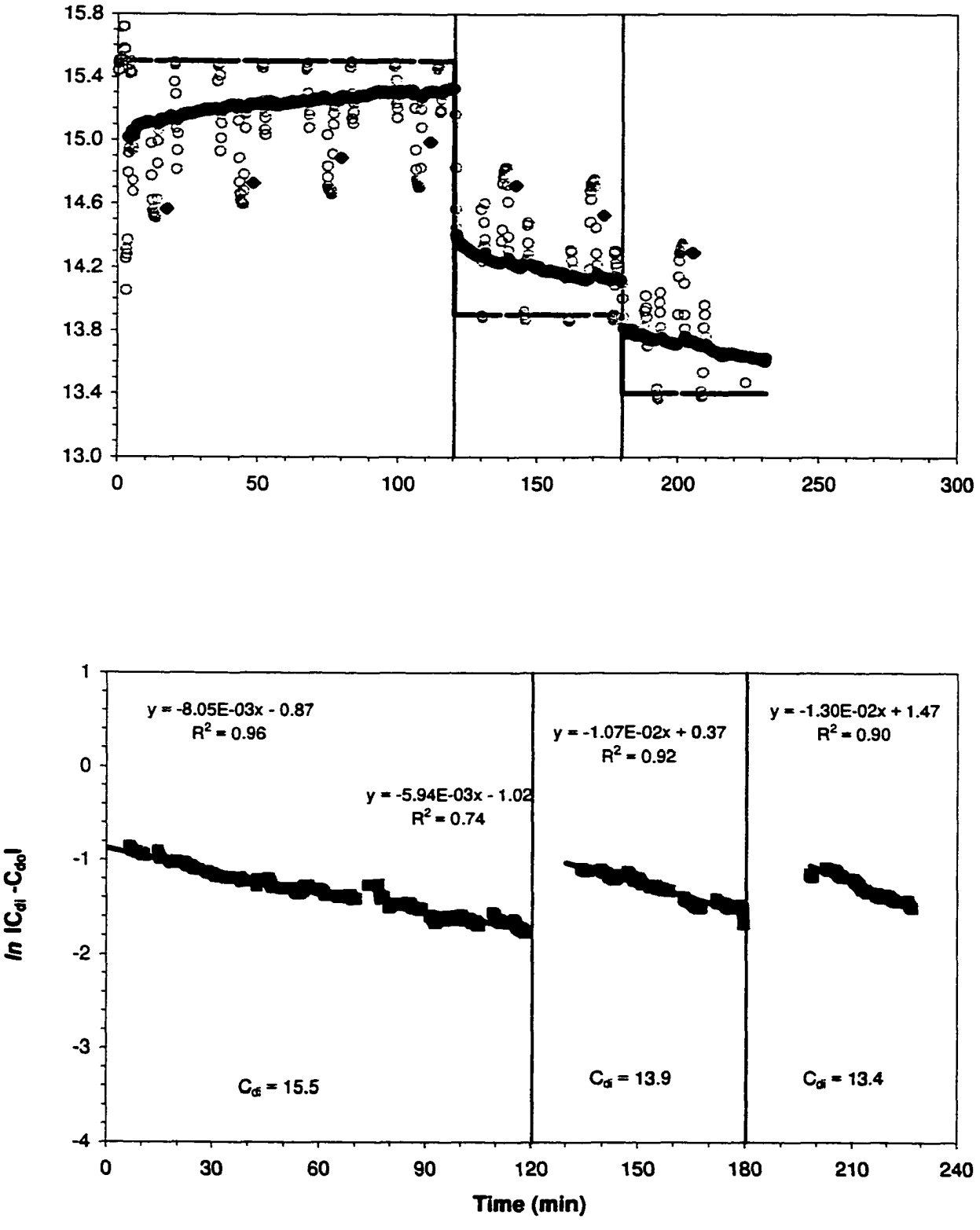


Figure 4.11. First of three consecutive sessions for patient CL.

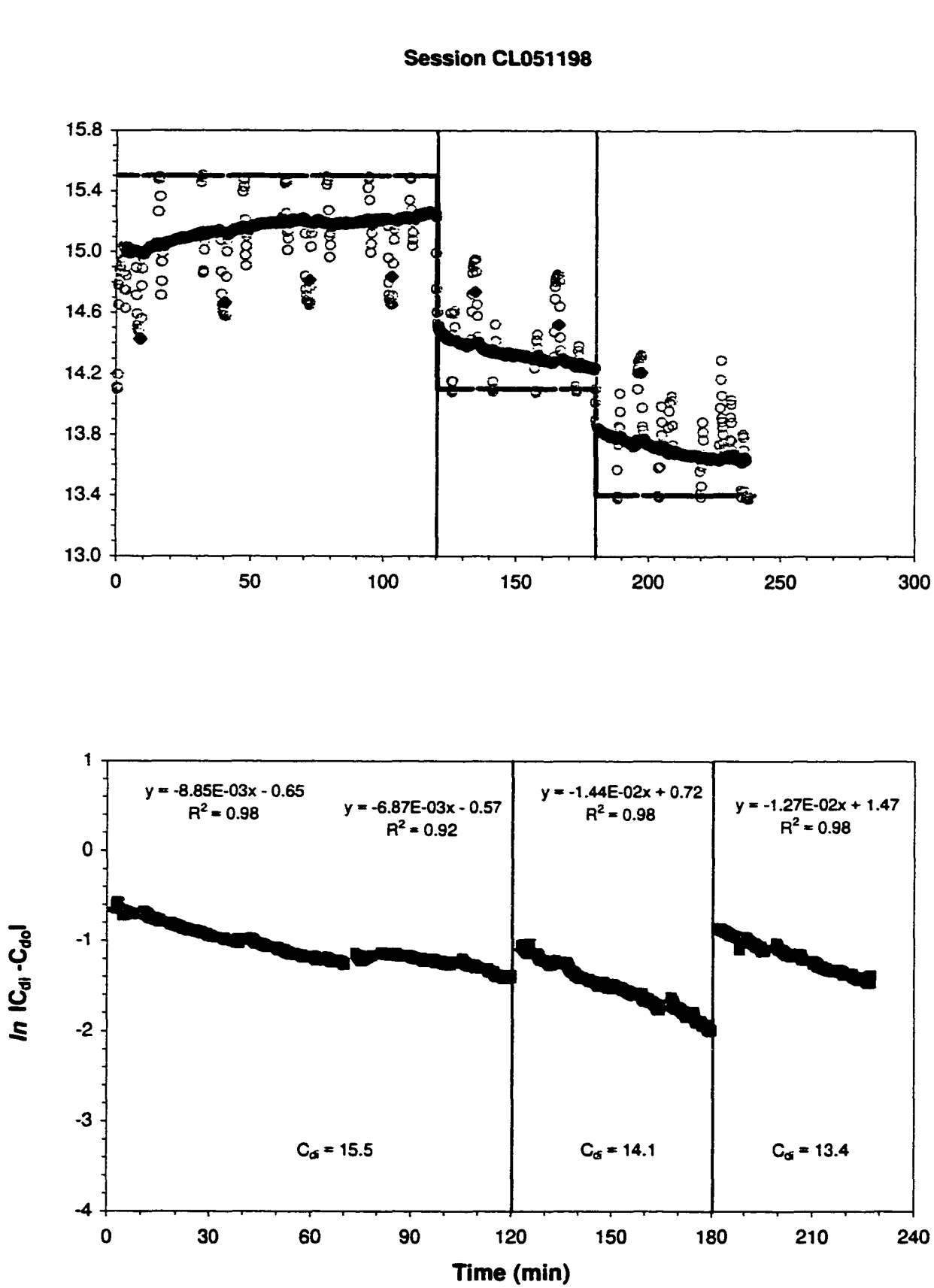


Figure 4.12. Second of three consecutive sessions for patient CL.

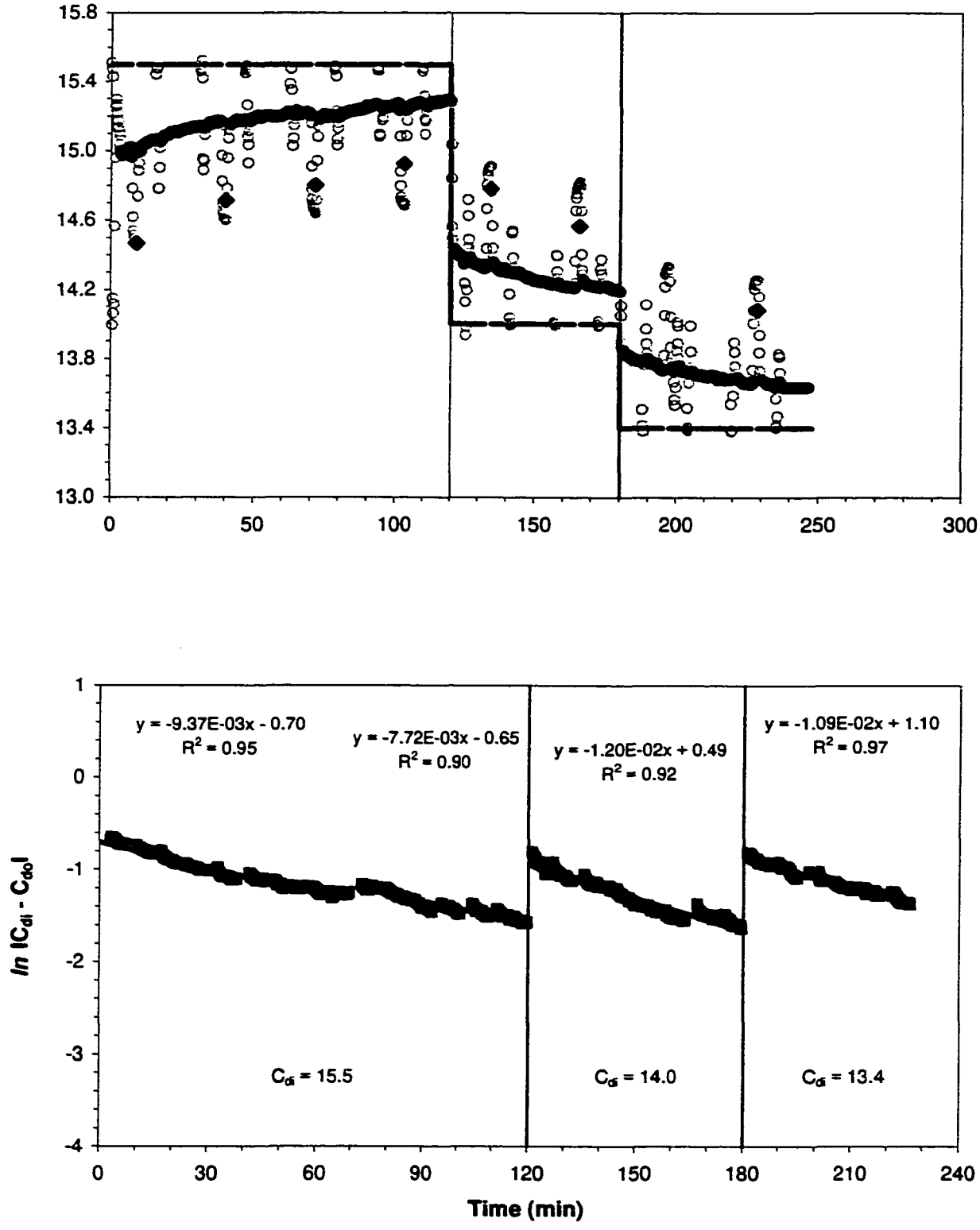


Figure 4.13. Third of three consecutive sessions for patient CL.

the $\ln|C_{di} - C_{do}|$ versus time data fell along as straight line was extended to obtain a sequence of straight lines that covered the entire session time. The Dt/V contribution for each of these periods was calculated as the product of the line slope (taken as a positive) and the dialysis time associated with this line segment. For the session illustrated in Figure 4.14, the first line segment spans the first 81.3 minutes of this dialysis session and has a slope of -8.99×10^{-3} min^{-1}. The Dt/V for the first 81.3 min of this dialysis session is therefore 0.71. The Dt/V contributions of the subsequent 3 periods of linearity are 0.27, 0.86 and 0.75, respectively, for a total Dt/V = 2.59. The Dt/V calculated by the Integra machine based on periodic measurements of conductivity dialysance and an assumed distribution volume of 25.3 L, was 2.17. Pre and postdialysis values of blood urea concentration were available for this session permitting calculation of a urea Kt/V using equation 2. The urea Kt/V was 2.23. The three Kt/V values are in modest agreement; however, Dt/V is approximately 18% greater than the other two Kt/V values.

Dt/V values calculated as described above together with the corresponding Diascan Dt/V are listed in Table 4.1 for 65 study sessions. Urea Kt/V values are also listed in this table for the 10 sessions which coincided with monthly blood work.

The study values of Dt/V are plotted against the Diascan calculated Dt/V in Figure 4.15. Not surprisingly, the correlation is poor ($R^2 = 0.20$), with considerable scatter about the line of identity (broken line). The study Dt/V values tend to somewhat lower (mean = 1.39) than the Diascan calculated values (mean = 1.48). The study Dt/V values are plotted against urea Kt/V for the 10 sessions where it could be calculated in Figure 4.16. The correlation between the two values is unexpectedly close ($R^2 = 0.78$). The good agreement between Kt/V urea and Dt/V calculated from the $\ln|C_{di} - C_{do}|$ versus time data is encouraging but may only be fortuitous.

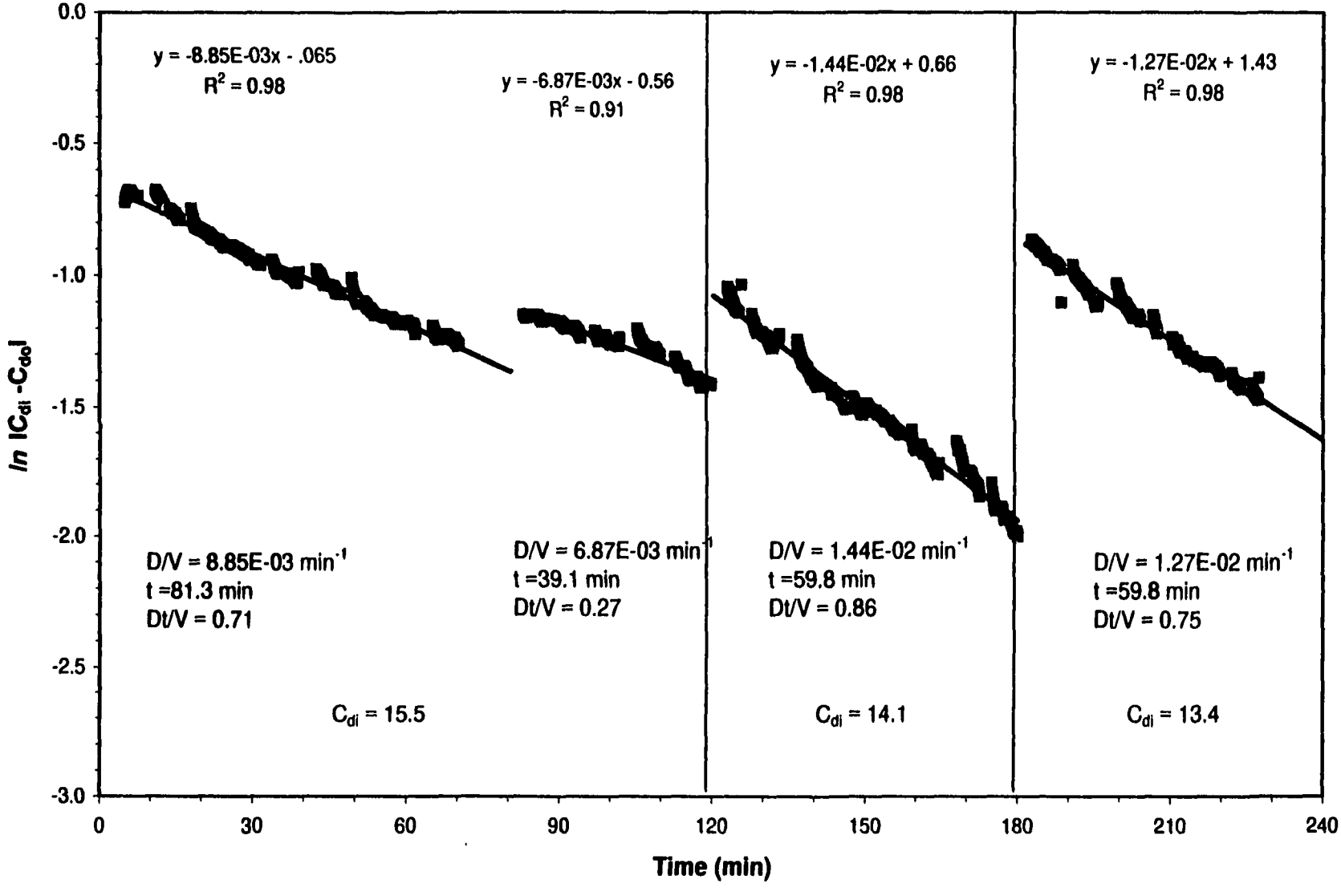


Figure 4.14. Treatment dose Dt/V calculation for study session CL051198.

Study Session	Dt/V study	Dt/V Diascan	Kt/V urea
CL241298	1.01	2.07	
CL221298	0.91	1.83	
CL191298	3.34	1.91	
CL171298	2.56	1.93	2.04
CL081298	1.41	2.02	
CL051298	1.64	2.10	
CL031298	1.79	2.01	2.1
CL011298	2.45	2.02	2.11
CL281198	1.26	2.14	
CL261198	1.73	2.09	
CL241198	2.25	2.13	2.11
CL211198	2.14	2.09	
CL191198	2.20	2.17	
CL141198	2.27	1.88	
CL121198	2.19	1.46	
CL071198	2.83	1.53	
CL051198	2.59	2.17	2.23
CL291098	2.13	2.21	
CL271098	2.13	1.55	2.3
NO161298	1.09	1.23	
MA181298	1.63	1.70	
MA141298	1.39	1.57	
MA041298	1.85	1.56	
MA061198	1.13	1.43	
MA021198	1.91	1.50	
KS231298	0.78	1.03	
KS181298	1.17	0.92	
KS161298	0.87	0.92	
KS141298	1.26	0.98	
KS091298	1.06	1.00	1.16
KS021298	1.11	0.94	
IR151298	1.11	1.50	
LI091298	1.03	0.69	
JB091298	1.48	1.12	1.31
JB161198	1.27	1.86	
JB131198	0.95	1.15	
JB111198	1.12	1.11	
JB091198	1.01	1.39	
MA071298	1.09	0.73	
MA111198	1.14	0.91	
MA091198	0.74	1.23	
DS071298	0.92	1.13	
DS271198	0.86	1.18	
DS251198	0.80	1.12	
DS231198	1.14	1.22	
DS201198	0.93	1.18	
DS041198	1.35	1.36	1.22
SM041298	1.25	0.97	
SM301198	1.19	0.89	
SM271198	1.16	0.74	
SM251198	1.58	1.02	
SM201198	1.10	0.98	
SM041198	1.43	0.94	1.48
SM181098	1.30	2.24	
DS041298	1.40	0.98	
BG251198	0.64	1.52	
BG231198	0.57	1.58	
BG201198	1.39	1.62	
BG181198	1.44	1.54	
BG161198	0.53	1.59	
HW131198	1.55	2.00	
HW111198	0.46	1.70	
HW091198	0.97	1.90	
HW061198	0.50	1.80	
HW141098	0.90	1.48	
Mean	1.4	1.48	1.84
Standard Deviation	0.59	0.45	0.45

Table 4.1 Treatment dose for study dialysis sessions.

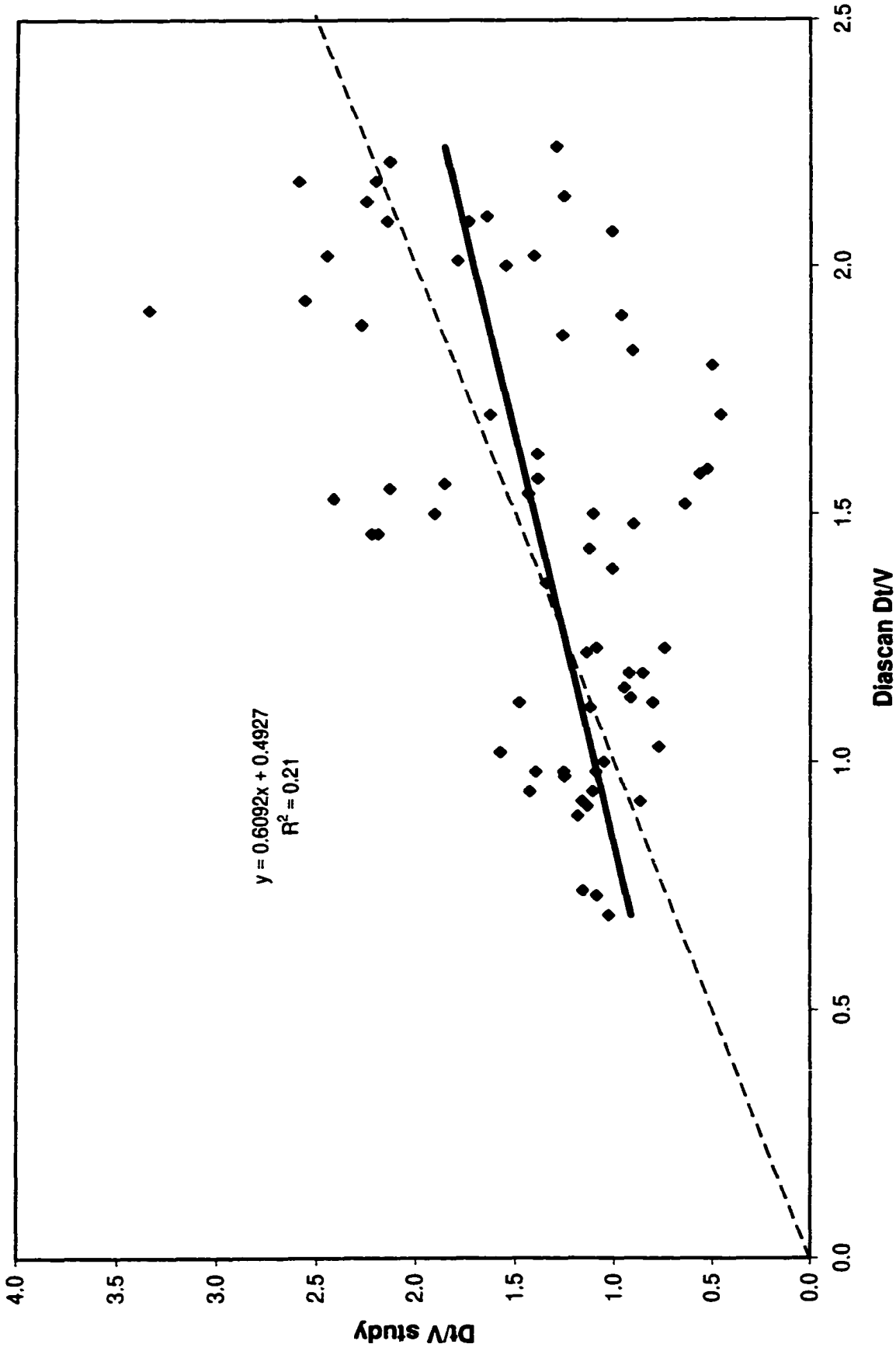


Figure 4.15. Comparison of Dt/V calculated from the study data with Diascan Dt/V.

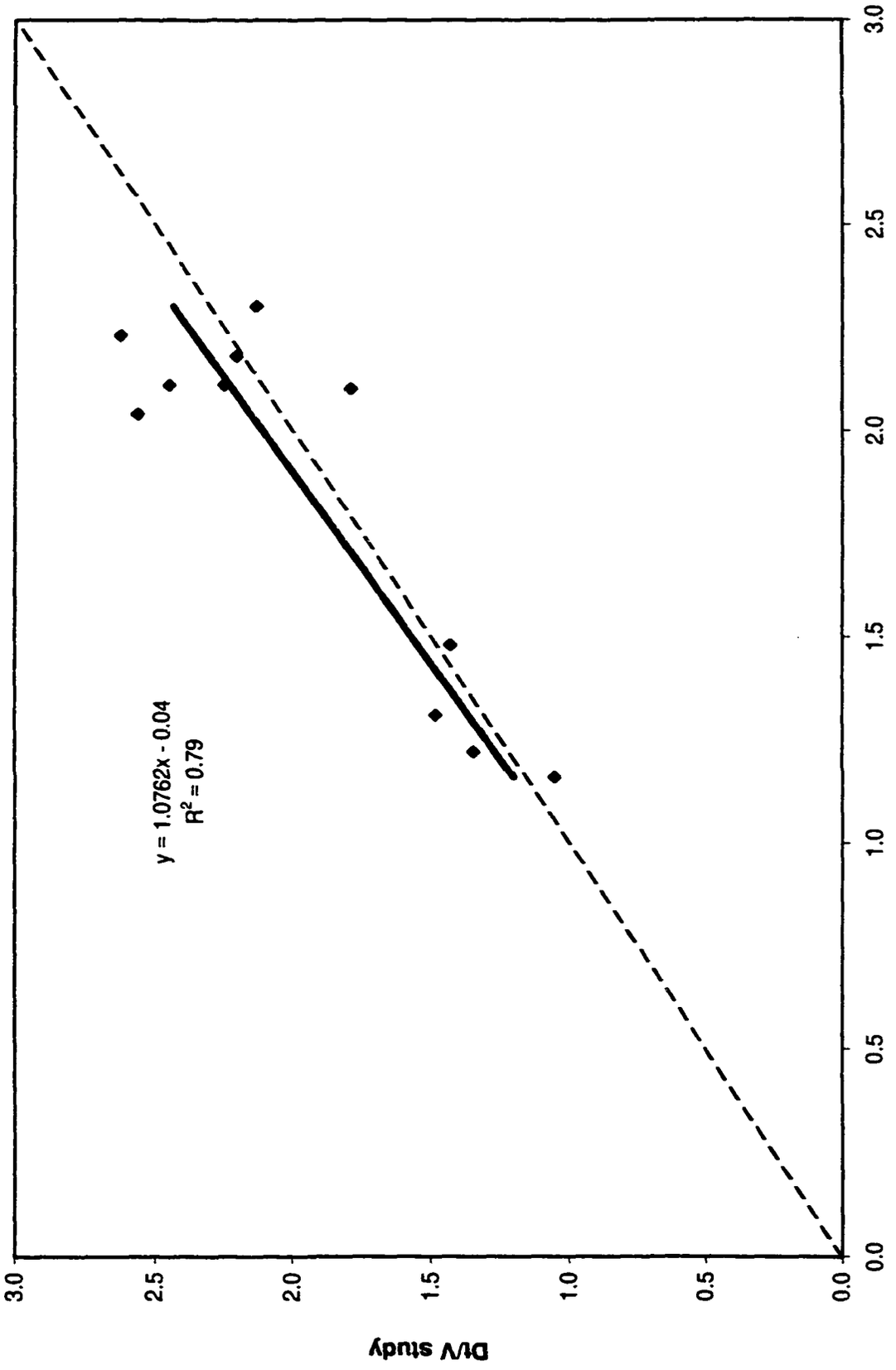


Figure 4.16. Comparison of Dt/V calculated from the study data with Kt/V urea for 10 sessions with monthly blood work.

Chapter 5. Discussion

5.1 Study Model and Its Validation

A key element of a quality assurance program for hemodialysis adequacy in the treatment of end stage renal failure is a convenient and accurate measurement of delivered dose. The current standard for treatment dose assessment is Kt/V based on urea concentration in predialysis and postdialysis blood samples; however, this blood based approach has many shortcomings. There has, therefore, been considerable interest in finding an alternate method of dialysis dose determination which is accurate and capable of automation, such that it can be performed routinely at minimal cost and without the need for blood sampling. The central objective of the study reported here is the evaluation of an alternate method of quantifying dialysis dose meeting these criteria and based on measurement of ionic conductivity in the dialysate streams entering and leaving the dialyzer.

A single body pool model governing the kinetics of ionic conductivity was developed. This model gave rise to equation (10) for periods when the conductivity of dialysate entering the dialyzer is constant:

$$\ln\left| C_{di} - C_{do} \right| = \ln\left| C_{di}^{o} - C_{do}^{o} \right| - \frac{D}{V}\, t \qquad (11)$$

The implication of this simple algebraic equation is that the natural logarithm of the absolute value difference between the inlet and outlet dialysate conductivities should fall linearly with dialysis treatment time. The slope of this line should equal -D/V from which Dt/V, an equivalent to Kt/V urea, may be calculated.

This proposed approach to quantifying dialysis treatment adequacy was evaluated in a clinical study in which inlet and outlet dialysate conductivities were monitored at 10 second intervals for 85 dialysis sessions in 14 patients treated on the Integra dialysis machine. The collected data, which are presented graphically in Appendix C, were analyzed in the context of the proposed model in the Results chapter. According to the model equation, the $\ln|C_{di} - C_{do}|$ data were expected to fall along a series of straight lines, one for each period of constant C_{di}, with a common slope equal to -D/V. The data did generally fall along a series of straight line segments as predicted by the study model equation. However, it was commonly found that the slopes of the line segments for different periods of constant C_{di} varied significantly. Furthermore, it was often the case that the $\ln|C_{di} - C_{do}|$ data, for a period of constant C_{di}, fit a sequence of two or more line segments of different slope. These trends suggest that, in contradiction to the study model, the $\ln|C_{di} - C_{do}|$ versus session time slope may depend on C_{di} and other factors. Some of the possible confounding factors include ultrafiltration rate, changes in circulation blood volume, and programmed interventions of the Integra dialysis machine, such as periodic flow meter checks and Diascan measurements. The impact of these factors will be discussed in this chapter.

5.2 Diascan and Flow Meter Disturbances

In the Results chapter, spikes were noted at regular intervals in the C_{do} data (see Figure 4.3). These spikes were caused by the flow meter check performed by the Integra machine every 15 minutes and by the step change in inlet dialysate conductivity at 30 minute intervals that is part of the Diascan test when that option is active. The C_{do} data spikes were removed from the data used to test the study model (see Figures 4.5 and 4.6); however, the impact of these C_{do}

excursions appears to extend beyond the short "spike" period. The upper panel of Figure 5.1 shows the C_{do} data for the first 60 minutes of session CL101198 during which C_{di} was fixed at 15.5 mS/cm. Diascan was disabled for this dialysis, so only C_{do} disturbances due to the 60 second flow meter checks performed every 15 minutes are present. The corresponding C_{do} spikes are shown as open gold circles. These data were removed for the model validation, leaving the gaps observed in the lower panel of Figure 5.1. The $\ln|C_{di} - C_{do}|$ data between the flow checks appear to follow a linear decline except for a 1-2 minute period following each C_{do} spike (denoted by blue arrows) that is characterized by a transient of the $\ln|C_{di} - C_{do}|$ curve towards the line of linear fall. The result, when the transients are ignored, is a sequence of straight lines of similar slope but with a slight upward displacement of each line relative to the previous one. This is equivalent to a decreased rate of clearance associated with each flow check period. The net effect of this phenomenon is that a single linear regression line fitted to the $\ln|C_{di} - C_{do}|$ for the entire 60 minute period of constant C_{di} has a less steep slope (smaller D/V) than the slope of the regression lines fitted to the data sets between pairs of flow checks.

The step in C_{di} of a Diascan measurement provokes a similar yet more pronounced transient. This is illustrated for study session CL051198 in Figure 5.2. The blue arrows indicate the 15 minute flow meter check. The red arrows indicate the Diascan measurements at 10, 40, 70 and 100 minutes; the red diamonds in the upper frame indicate the Diascan calculated patient blood conductivity. Immediately following each of the Diascan gaps, where C_{do} data have been removed, there is a clear 1-2 minute transient in the $\ln|C_{di} - C_{do}|$ curve. This transient disrupts the nearly linear fall of $\ln|C_{di} - C_{do}|$ between flow checks. The transients following the Diascan measurements at 10, 40 and 100 minutes have very similar shapes; however the $\ln|C_{di} - C_{do}|$ transient at 70 minutes is much more pronounced, suggesting that some other factor must have

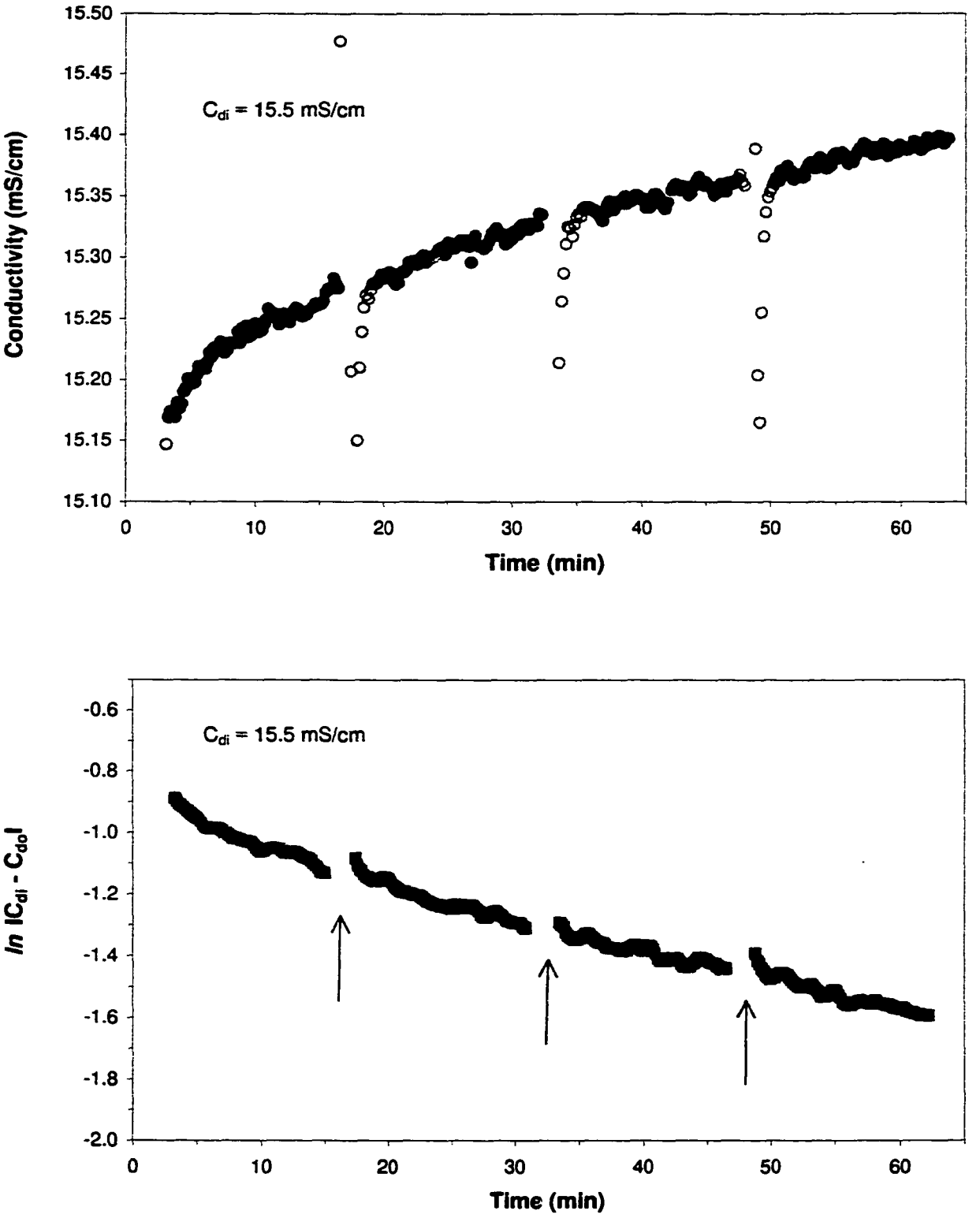


Figure 5.1 The impact of dialysate flow meter checks on the study data for session CL101198.

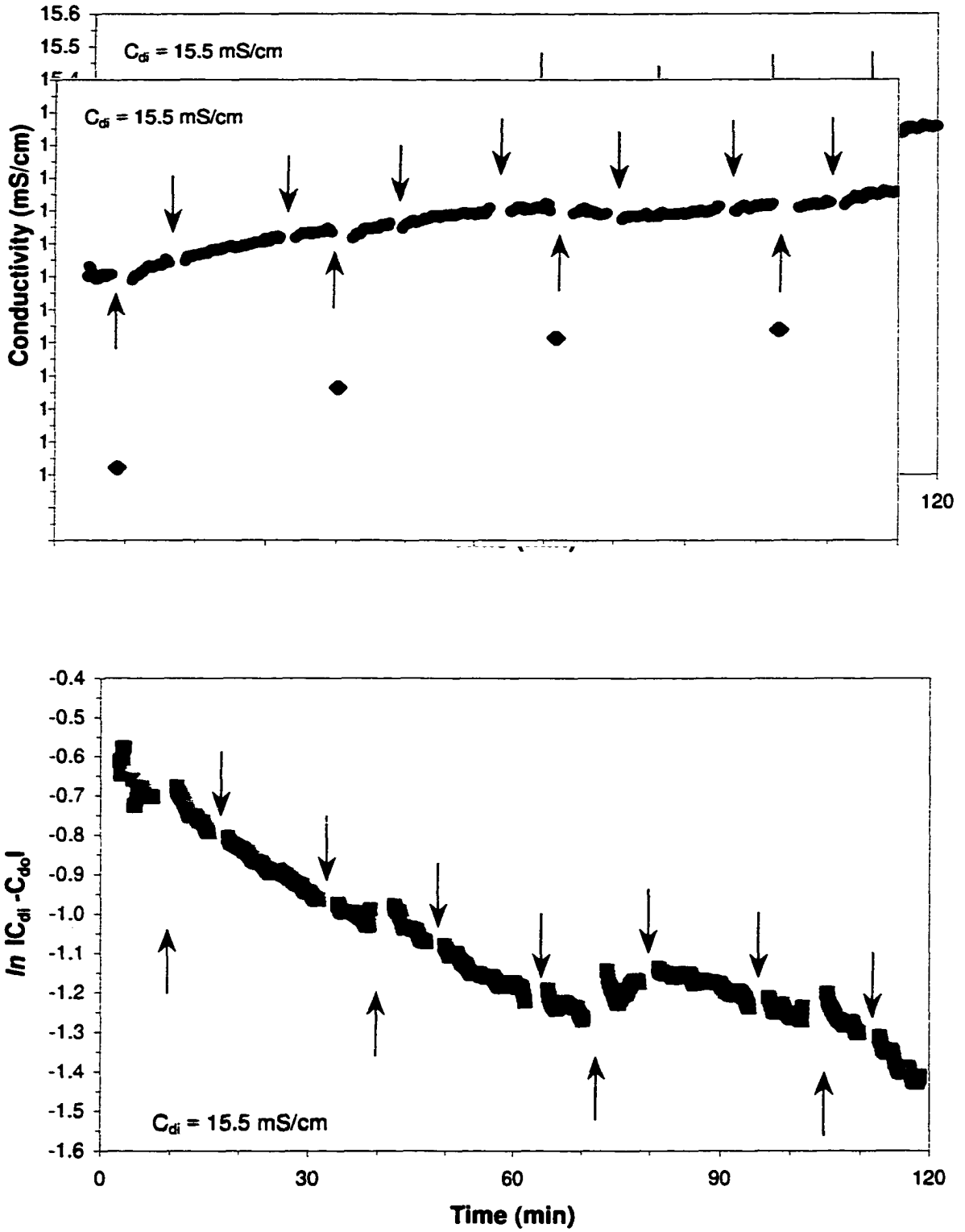


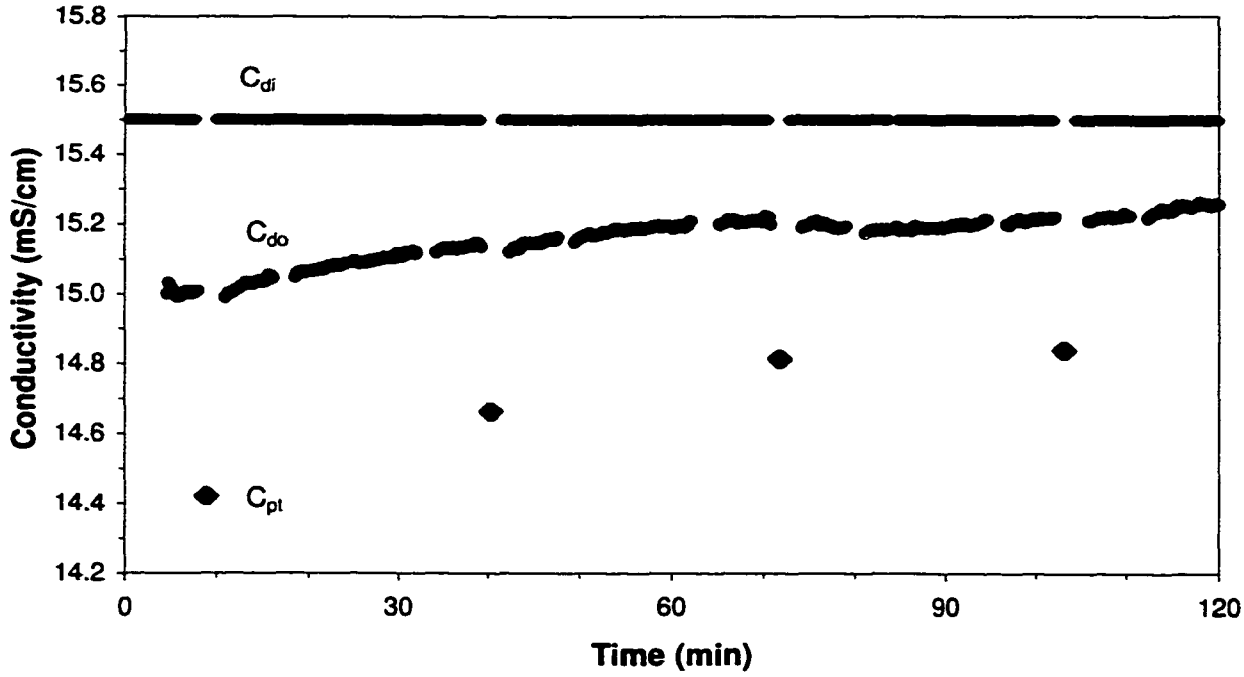
Figure 5.2. Effects of Diascan measurement and dialysate flow meter checks for study session CL051198.

also impacted C_{do} at this time. In this instance, it is the change in the ultrafiltration rate at 70 minutes which has caused much of the shift of the C_{do} profile.

5.3 Ultrafiltration and Vascular Refilling Effects

Ultrafiltration profiling was employed in almost all of the study dialysis sessions. Typically, the ultrafiltration profiles were comprised of periods of constant ultrafiltration rate separated by short periods of minimal ultrafiltration (0.1L/h, the minimal rate permitted by the Integra machine). The purpose of these "rest periods" was to allow for refilling of the patients' vascular compartment from the interstitial space. This profiling approach was illustrated in Figure3.1.

Step changes in ultrafiltration rate were observed to have a significant impact on the C_{do} profile. This is illustrated in Figure 5.3 for session CL051198. The solid green line in the lower panel of Figure 5.3 shows the ultrafiltration profile programmed for the first 2 hours of this session. After an initial 15 minutes of minimal ultrafiltration, the rate was set to 1.4 L/h for the following 55 minutes. Ultrafiltration was then turned down for a 13 minute refilling period, after which ultrafiltration was reset to 1.33 L/h. During the first period of constant ultrafiltration, the $\ln|C_{di} - C_{do}|$ data follow a linear decline except for the periodic offsets associated with flow meter checks and the Diascan measurement at 40 minutes. At the 70 minute point, the ultrafiltration rate was abruptly decreased to 0.1 L/h; a Diascan measurement occurred at about the same time. These events coincide with a marked alteration in the C_{do} profile. Prior to the 70 minute ultrafiltration step, C_{do} rises progressively towards C_{di}. Between 70 and 80 minutes there is an abrupt downturn in C_{do}. When the ultrafiltration was reset to 1.33 L/h at about the 83 minute mark, the C_{do} profile is observed to again rise in a steady fashion towards C_{di}. $\text{Ln}|C_{di}$ -



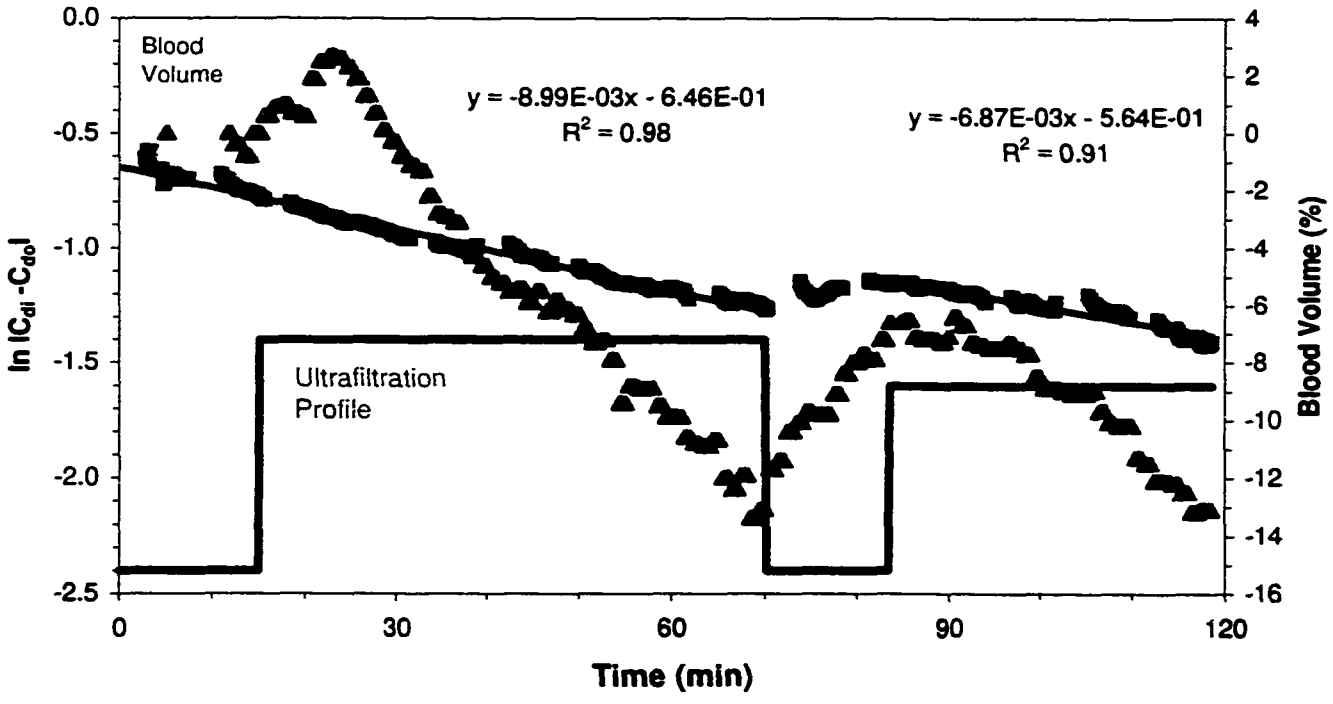


Figure 5.3. Validation data during first constant conductivity step with ultrafiltration rates and blood volume. Study session CL051198

$C_{do}|$ once again falls linearly; however, the line is displaced upwards from the previous line and is less steep.

There are two ways in which ultrafiltration may impact on the C_{do} profile. Firstly, there is the direct effect of ultrafiltration on dialysis clearance. Mass transfer of NaCl in conventional hemodialysis is predominately by convection. Diffusive mass transfer is only significant when dialysate conductivity differs significantly from effective patient conductivity; this generally only occurs when dialysate conductivity profiling is employed. Therefore, significant changes in ultrafiltration rate should have a dramatic impact on dialysance which will be reflected in the C_{do} and $\ln|C_{di} - C_{do}|$ profiles. It is, therefore, important in any effort to model the kinetics of dialysate conductivity that the influence of ultrafiltration be accurately accounted for in the mass transfer equation used. This may not be the case in the model developed here, wherein conductivity mass transfer was expressed as a simple sum of convective and diffusive components. In reality, there is a complex interaction between diffusive and convective mass transfer and thus a more sophisticated mass transfer model may be required than the one tested in this study.

An additional indirect effect of ultrafiltration on solute mass transfer occurs through its impact on the circulating vascular volume of the patient. During dialysis, fluid is ultrafiltered from blood as it passes through the extracorporeal circuit. Unless this fluid is replaced at an equivalent rate from the interstitial space, blood volume falls. This commonly occurs when the ultrafiltration rate is high. This is illustrated in Figure 5.3.

The red triangles in Figure 5.3 show the changes that occur in this patient's blood volume (expressed as a percent change from the start of the session) over the first 120 minutes of dialysis. Relative blood volume is computed by the Integra machine from the reciprocal of the

relative change in hemoglobin concentration detected by an infrared sensor (Hemoscan option) located in the arterial blood line of the machine. In the dialysis session shown in Figure 5.3, the patient's blood volume falls steadily over most of the first period of high ultrafiltration (about a 15 % decrease between 22 and 69 minutes). A 7% expansion of blood volume occurs over the 13 minute period of minimal ultrafiltration (70-83 minutes). The vascular volume remains fairly stable for the first 15 minutes of the second high ultrafiltration period and then mostly declines over the final 20 minutes shown.

Variations in circulating blood volume and vascular refilling may impact dialysate conductivity kinetics in two ways. The increase in concentration of plasma protein and formed cells when blood volume contracts results in a decreased blood water flow to the dialyzer (for the same blood pump flow) which in turn can lead to a decrease in dialysance. Increased concentration polarization of plasma protein adjacent to the dialyzer membrane may also cause a decrease in dialysance as well as reduced convective mass transfer.

In addition, if the electrolytic composition of the refilling fluid entering the vascular compartment from the interstitial space is different from the plasma electrolyte composition, this would result in a transient shift of the latter the magnitude of which would depend on the rate of refilling relative to the current plasma volume.

These are complex phenomena and it is difficult to predict their impact on the C_{do} and $\ln|C_{di} - C_{do}|$ profiles. It may be possible to gain some insight from an examination of study data. In study session CL051198 (Figure 5.3), ultrafiltration was held constant at 1.4 L/h between the 15^{th} and 70^{th} minute of dialysis. For the first few minutes of this period, the rate of refilling exceeds ultrafiltration and the patient's blood volume is expanding. At about the 22 minute point, there is an abrupt drop in refilling rate and blood volume begins to contract. This sudden

change in refilling rate does not appear to have an impact on the C_{do} and $\ln|C_{di} - C_{do}|$ profiles at the 22 minute mark. The patient's blood volume continues to contract during the rest of this ultrafiltration period with a total decrease in blood volume of about 15%. There is no apparent change in the $\ln|C_{di} - C_{do}|$ slope over this interval. Thus significant changes in both refilling rate and patient blood volume appear to have had negligible impact on dialysate conductivity kinetics in this instance.

On the other hand the data collected in study session MA061198 may indicate an impact of vascular refilling on dialysate conductivity kinetics (see Figure 5.4). During the second period of constant ultrafiltration (0.81 L/h between 65 and 105 minutes) C_{do} is seen to fall until about the 90 minute mark and then rise towards the C_{di} value of 14.5 mS/cm. This would suggest a parallel fall and rise in the effective blood conductivity of the patient. This C_{do} trend appears to parallel an inverse trend of the patient's relative blood volume. That is, the patient's blood volume was mostly rising to the 90 minute point, indicating that the rate of vascular refilling exceeded ultrafiltration during this period. There was then an abrupt decrease in vascular refilling leading to a contracting blood volume until the ultrafiltration rate was turned down at 105 minutes. These observations could be explained by a difference in the sodium content of plasma and the vascular refilling fluid crossing from the interstitial space. If the interstitial fluid has a lower sodium content, plasma sodium could fall when the refilling rate is high. When the refilling rate is low and both ultrafiltration rate and C_{di} are high, the plasma sodium would be expected to rise. Further studies will be needed to clarify the impact of vascular refilling on dialysate conductivity kinetics.

Blood volume monitoring with the Integra's Hemoscan option was conducted in almost all study sessions. The relative blood volume was commonly found to fall in a linear fashion

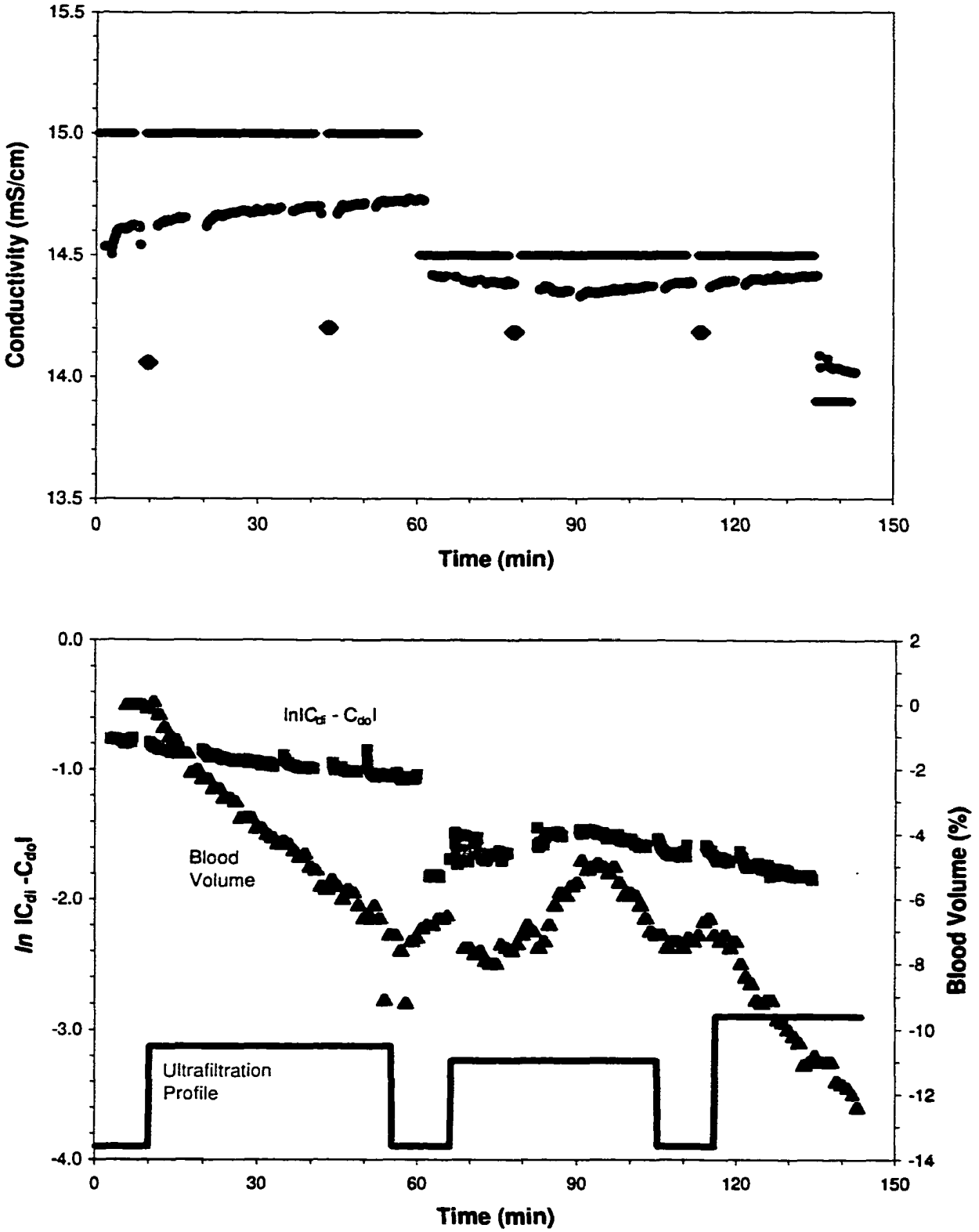


Figure 5.4. The impact of vascular refilling on dialysate conductivity kinetics. Study session MA061198.

during periods of constant ultrafiltration. The slope (S) of the linearly decreasing relative blood volume is directly related to the difference between ultrafiltration rate (Q_{uf}) and vascular refilling rate (Q_r):

$$Q_{uf} - Q_r = -S*V_{bo} \tag{12}$$

where V_{bo} is the (unknown) patient's blood volume at the start of the dialysis session. A correlation was noted in many sessions between the slope of these lines of linearly falling blood volume and the slope of the $\ln|C_{di} - C_{do}|$ data for the same period of constant C_{di} and Q_{uf}. This is illustrated for session MA131198 in Figure 5.5.

During the first period (15-32 minutes) of constant C_{di} (15.0 mS/cm) and constant Q_{uf} (0.989 L/h), the $\ln|C_{di} - C_{do}|$ slope (-0.0101 min^{-1}) and relative blood volume slope (-0.00252 min^{-1}) are in a ratio of 4.02:1. During the second period of constant C_{di} (14.4 mS/cm) and constant Q_{uf} (0.989 L/h), between 75 and 108 minutes, both slopes are considerably smaller (-0.00441 and -0.0011 min^{-1}, respectively) however the ratio is unchanged, 4.00:1. The final period of constant C_{di} (13.9 mS/cm) and constant Q_{uf} (0.839 L/h) occurs between 135 and 180 minutes. The slopes of $\ln|C_{di} - C_{do}|$ and relative blood volume during this period are -0.00367 and -0.00094 min^{-1}, respectively, for a ratio of 3.89:1. Thus, for this study session, there is a close relationship between the $\ln|C_{di} - C_{do}|$ slope and the difference between ultrafiltration and vascular refilling rates as characterized by the slope of the relative blood volume curve, despite a large variation in the slopes of both curves. The implication of this relationship is unclear; however, it may be another indication that the rate of vascular refilling from the interstitial space has a direct impact on dialysate conductivity kinetics. Once again, further study to clarify these relationships is indicated.

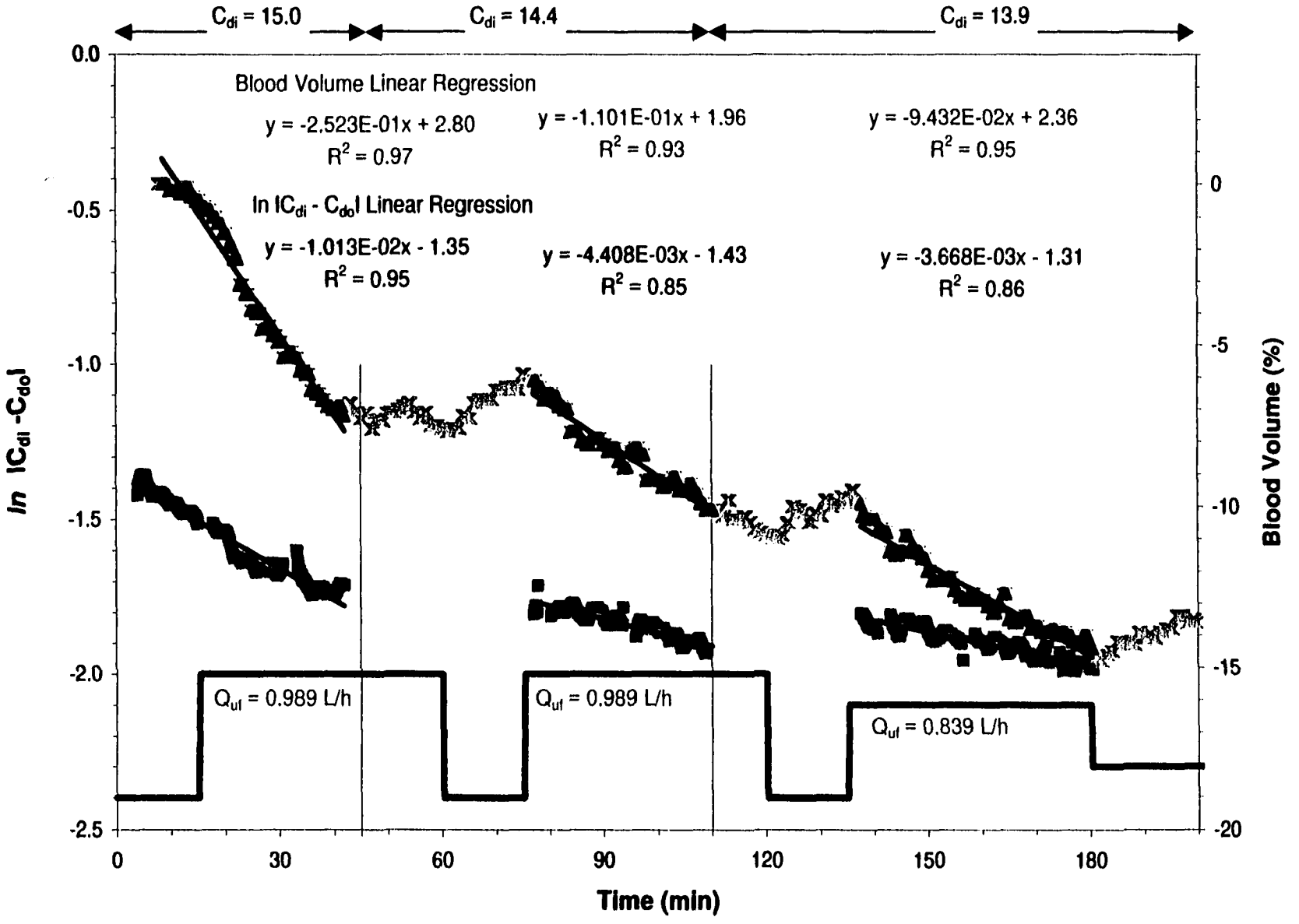


Figure 5.5. Comparison of ln $|C_{di} - C_{do}|$ slope to ultrafiltration induced blood volume slope. Study session MA131198

Chapter 6. Conclusions and Recommendations

6.1 Conclusions

In this study, a simple model of dialysate conductivity kinetics was developed and expressed as equation 11. It was proposed that this model might allow direct assessment of dialysis dose, Kt/V, from the outlet dialysate conductivity - time profile during a period of constant inlet dialysate conductivity. The model predicted that plotting $\ln|C_{di} - C_{do}|$ against dialysis time would yield a series of straight lines, each corresponding to a period of constant C_{di}, with a common slope equal to -D/V from which Dt/V, an equivalent of Kt/V, could be calculated. This proposition was not confirmed by the results of the clinical validation study. Several extraneous factors impacted upon or caused deviations to the outlet dialysate conductivity - time curve. These include: changes in ultrafiltration rate, varying circulating blood volume and vascular refilling rate and the periodic flow checks and Diascan interventions programmed into the Integra dialysis machine. In particular, it was concluded that a more sophisticated model to describe dialysate kinetics is needed, more specifically, one that accurately reflects the interactions between diffusive and convective mass transfer. Future efforts, therefore, should be directed towards this end. In this regard, the following *in vitro* and *in vivo* studies are recommended.

6.2 Recommendations for Future Studies

An *in vitro* single pool study is proposed in which a tank would be filled with either a high conductivity (16.5 mS/cm) or a low conductivity (13.0 mS/cm) dialysate. The tank volume would be dialyzed against a constant conductivity dialysate of sufficiently different conductivity

to provide a large gradient for diffusive mass transfer. Flow-through conductivity cells would monitor the conductivity in all streams, permitting mass balance closure and accurate determination of conductivity dialysance throughout the mock dialysis session duration. Runs would be conducted at various constant rates of ultrafiltration, including no ultrafiltration. These controlled studies should permit development of a more precise equation of coupled convective and diffusive mass transfer for incorporation in a model of dialysate conductivity kinetics. The proposed study would be complemented by the steady state *in vitro* experiments currently being conducted to examine the impact of ultrafiltration rate on dialyzer clearance.

Additional clinical studies should be conducted with more frequent data sampling of the parameters most relevant to dialysate conductivity kinetic modelling. In particular, the conductivity levels in the inlet and outlet dialysate streams should be captured approximately once per second in order to provide a richer data base for evaluating proposed models.

A clinical study is currently being organized in which a second dialyzer will be inserted into the extracorporeal blood circuit upstream to the principal dialyzer. The dialysate-side fluid in the added dialyzer will be pumped in a closed loop and therefore should be in near diffusive equilibrium with the arterial blood. A flow-through electrode in the re-cycle loop will provide a continuous measure of this equilibrated plasma conductivity. This additional parameter will permit a more direct evaluation of dialysate conductivity kinetic models.

It is hoped that the work reported here and the additional studies described above will lead to a better understanding of the kinetics of electrolyte mass transfer in dialysis and that the gained knowledge will lead to new automated methods to accurately measure the dialysis dose delivered during a treatment session.

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Appendix A. Integra Data Configuration

A.1 Integra Machine Variables

The data acquisition cards installed in the Integra dialysis machine are configured for availability to a serial port. The variables available for capture by data acquisition software from the Integra machine are listed in Tables A.1-A.3.

CHANNEL.	PARAMETER	Type	Units	MAX	MIN	dec	Notes
1	Digital Channel 1	Digital					
2	Digital Channel 2	Digital					
3	Digital Channel 3	Digital					
4	Alarm 1	Alarm					
5	Alarm 2	Alarm					
6	Alarm 3	Alarm					
7	Alarm 4	Alarm					
8	Operating Phase/Acq. Status	Analog					
9	Machine Configuration	Analog					
10	Integra Internal Phase	Analog		3	0	0	
11	Dialysis Mode (Blood Module)	Analog		2	0	0	
12	Reserved	Analog					
13	Reserved	Analog					
14	Reserved	Analog					
15	Actual Time	Analog	h:min	600	10	0	
16	Actual Total Weight Loss	Analog	kg	8000	100	3	
17	Actual Weight Loss Rate	Analog	kg/h	3000	100	3	
18	Final Conductivity	Analog	mS/cm	170	130	1	
19	BIC 84% Conductivity	Analog	mS/cm	35	27	1	
20	Blood Flow	Analog	ml/min	700	0	0	
21	Dialysate Temperature	Analog	C	395	360	1	
22	Dialysate Flow Rate #	Analog	ml/min	4	1	0	
23	Infusion Pump Setting	Analog	l/h	2000	0	3	
24	Heparin Pump Rate	Analog	ml/h	99	5	1	
25	Total Blood	Analog	l	995	5	1	
26	TM Pression	Analog	mmHg	350	0	0	
27	Venous Pressure(VPS)	Analog	mmHg	300	50	0	
28	Arterial Pressure sensor (APS)	Analog	mmHg	150	-350	0	
29	PH	Analog		900	300	1	
30	Depurated Blood Volume (KT)	Analog	l	995	0	1	
31	Single Needle Max Press	Analog	mmHg	300	0	0	
32	Single Needle Min Press	Analog	mmHg	300	0	0	
33	Sasmpler Partial Collection	Analog	ml	2000	0	0	
34	Sampler Effective Time	Analog	min	600	0	0	
35	Dioascan Effective QB	Analog	ml/min	300	0	0	
36	Effective Dialysis Time	Analog	min	600	0	0	
37	Total Heparin Infused	Analog	ml	300	50	1	
38	BIC 66% Conductivity	Analog	mS/cm	60	46	1	
39	Total Infused Quantity (BIO)	Analog	l	10000	100	3	
40	APS	Analog		100	0	0	
41	Arterial Pump Setting	Analog	ml/min	700	0	0	
42	Venous Pump Setting	Analog	ml/min	700	0	0	
43	Stroke Volume	Analog	ml	100	5	0	
44	Diastolic Pressure	Analog	mmHg	235	30	0	
45	Systolic Pressure	Analog	mmHg	255	50	0	
46	Heart Rate	Analog		175	40	0	
47	Scale	Analog	kg	5000	0	3	
48	Bed Scale	Analog	kg	150	0	0	0=0kg/1000=150kg
49	Ultrafiltration Pressure	Analog	mmHg	500	0	0	
50	Hemoglobin	Analog	g/dl	180	40	1	
51	Actual Blood Volume	Analog	%	400	-400	1	
52	Outlet Conductivity	Analog	mS/cm	1300	1700	2	
53	Inoic Mass Balance	Analog	mM/l	800	-500	0	
54	Ionic Effective Dialysance	Analog	ml/min	300	0	0	
55	Urea Concentration	Analog	mg/dl	1000	0	1	
56	Plasma Conductivity	Analog	mS/cm	1700	1300	2	
57	Pressione Uscita Emodial	Analog	mmHg				
58	Total Urea Removed	Analog	g	5000	0	2	
59	Kt/V	Analog		300	0	2	
60	Urea Reduction Ratio	Analog	%	1000	0	1	

Table A.1. Parameter Page 39 Access Code for Data Acquisition

CHANNEL	PARAMETER	Position	UdM	MAX	MIN	dec.	Notes
1	Digital						
2	Digital						
3	Digital						
	Master Variables						
4	Type BICA	1 W					
60	Field	1 W					
	Hydraulic						
5	Status	1 W	busta(lsb)				
6	Phase Number	W0 HY					
7	Dialysate Flow	W1 HY	ml/min	4	1	0	[FLUSSO_D]
8	Light Feedback	W14 HY	ml/min				
9	K	W7 HY					
10	Weight Loss Rate	W13 HY	kg/h	3000	100	3	[PESO_H]
11	Total Weight Loss	W16 HY	kg	8000	100	3	[PRED_TOT]
12	Temperature	W19 HY	C	395	360	1	[TEMPERAT]
13	Conductivity	W23 HY	mS/cm	170	130	1	[CONDA]
14	Bic 8.4% Conductivity	W27 HY	mS/cm	35	27	1	[CONDB]
15	PC (Actual Value)	W32 HY					
16	VALV1	W34 HY					
17	VALV2	W35 HY					
18	SEN1	W36 HY					
19	SEN1	W37 HY					
20	Pressione PFS	W38 HY	mmHg				
21	PI	W45 HY	mmHg				
22	PO	W46 HY	mmHg				
23	PS (FLAGS)	W48 HY					
	Blood						
24	Blood Phase	W0 BL					
25	Blood Flow (Actual Value)	W1 BL					
26	Venous Flow (Actual Value)	W5 BL					
27	Infusion Pump (Actual Flow)	W9 BL					
28	Auxillary FLow	W18 BL					
29	Arterial Pressure (APS)	W20 BL	mmHg	380	50	0	[PRE_VEN]
30	Venous Pressure (VPS)	W23 BL	mmHg	150	-350	0	[PRE_ART]
31	S/N Pressure	W26 BL	mmHg	300	0	0	[PMIN_SN]
32	SENS1	W29 BL					
33	SENS2	W30 BL					
34	Valves	W31 BL					
	Protective						
35	End INF Optical	W1 P					
36	End INF Level	W2 P					
37	Patient SENS	W4 P					
38	PI Pressure	W5 P	mmHg				
39	PO Pressure	W6 P	mmHg				
40	PFS Pressure	W7 P	mmHg				
41	VEN Pressure	W8 P	mmHg				
42	COND A	W9 P	mS/cm				
43	CCND B	W10 P	mS/cm				
44	Temperature	W11 P	C				
45	Pump A	W12 P					
46	Pump B	W13 P					
47	UF Vessel	W15 P					
48	UF Pump	W16 P	ml/min				
49	Infusion Pump	W17 P					
50	Dial Flow	W18 P	ml/min				
51	D2 Flow	W19 P	ml/min				
52	P2 Pump Flow	W20 P	ml/min				
53	ART P. Flow	W23 P					
54	VEN P. Flow	W24 P					
55	ART P. Teeth	W25 P					
56	VEN P. Teeth	W26 P					
57	BIO P. Teeth	W27 P					
58	Jumpers	W28 P					
59	Sensors	W32 P					

Table A.2. Parameter Page 89, 1 Access Code for Data Acquisition

CHANNEL	PARAMETER		UdM	MAX	MIN	dec.	Notes
1	Digital						
2	Digital						
3	Digital						
4	Session Time Setting	SET	min	600	10	0	
5	ACE Conductivity Setting	SET	mS/cm	170	130	1	
6	Total Weight Loss Setting	SET	g	8000	100	0	
7	Weight Loss Rate Setting	SET	g/h	3000	100	0	
8	Final Blood Volume Setting	SET	%	0	-400	1	
9	Final Conductivity Setting	SET	mS/cm	170	130	1	
10							
11	TWL Tol. Setting	BVT	g	1000	-1000	0	
12	BV Tol. Setting	BVT	%	10	-10	0	
13	CD Tol. Setting	BVT	mS/cm	10	-10	1	
14	WLR MAX INI Setting	BVT	g	3000	100		
15	CD MAX INI Setting	BVT	mS/cm	170	130	1	
16	CD MIN FIN Setting	BVT	mS/cm	170	130	1	
17	BV Desired	BVT	%	400	-400	1	
18	TWL Desired	BVT	g	8000	0	0	
19	CD Desired	BVT	mS/cm	1700	1300	2	
20	BV Error	BVT	%	400	-400	1	
21	TWL Error	BVT	g	2000	-2000	0	
22	CD Error	BVT	mS/cm	100	-100	1	
23	WLR MIN	BVT	g	3000	100	0	
24	WLR MAX	BVT	g	3000	100	0	
25	CD MIN	BVT		170	130	1	
26	CD MAX	BVT		170	130	1	
27	EQUIVALENT CD	BVT	mS/cm	1700	1300	2	
28	HGB Unfiltered	HEMO	g/dl				
29	TO HGB	HEMO	min	30	0		
30							
31	Diascan Meas. Time	DIAS	min	600	0	0	
32	Diascan CPY1	DIAS	uS/cm	17000	12000	0	
33	Diascan CPY2	DIAS	uS/cm	17000	12000	0	
34	Diascan CPY3	DIAS	uS/cm	17000	12000	0	
35	Rising Hydr. Delay	DIAS	sec	150	0	0	
36	Falling Hydr. Delay	DIAS	sec	150	0	0	
37	Rising Time Constant	DIAS	sec	150	0	0	
38	Falling Time Contant	DIAS	sec	150	0	0	
39	Diascan Calb	DIAS					
40	Diascan Gain	DIAS					
41	Diascan Offset	DIAS					
42	Diascan Phase	DIAS					
43	Diascan CP_DY_DATA_FLAG	DIAS					
44	CALIB and MEAS AVAILABLE FLAG	DIAS					
45	Diascan Effective QB	DIAS	ml/min	700	0	0	
46	Outlet Conductivity	DIAS	mS/cm	13000	17000	3	
47	Plasma Conductivity	DIAS	mS/cm	17000	13000	3	
48	Inlet Conductivity	DIAS	mS/cm	1700	1300	2	
49							
50	Actual Dialysate Flow Rate	ACT	ml/min				
51	Actual S/N Pressure	ACT	mmHg				
52	Actual PI Pressure	ACT	mmHg				

Table A.3. Parameter Page 89, 3 Access Code for Data Acquisition

Appendix B. Data Acquisition Program

B.1 Data Acquisition Study Configuration Program

The 31 variables chosen for capture are listed in Table 3.1 in Chapter 3. The ACQ program written to capture these variables during the dialysis session at 10 second intervals is listed in figure A.1.

Figure B.1 ACQ Program. Study Parameter Capture Variables

```
# file Canada.ini          date 01/12/98
#
#-----------------------------------------------------------------
# BEFORE TO START:
# 1) you have to set the right serial port connenct to your Integra;
#    - set SerialPort parameter in the [Custom] paragraph
#    - change the name of the paragraph related to the configuration
#      of the port (now [com1])
# 2) than you have to set the right machine identifier that you have
#    on Integra; change the MachineId parameter in the [Custom] paragraph
# 3) to use the data acquisition board you have to put the PCLDRV.SYS
#    in your CONFIG.SYS and restart the computer
#
# Note on actual setup:
# 1) the acquisition program save data in directory named DATA (parameter
#    Directory in the [Main] paragraph)
# 2) the filename is made with 4 digit from data and 4 from the patient name
# 3) the maximum duration of the acquisition is 10 h (parameter MinDurata
#    in the [Main] paragraph)
# 4) the sampling rate is 10 sec (parameter SecAcq in the [Main] paragraph)
#-----------------------------------------------------------------

[Custom]
SerialPort = 0    # 0 for com1, 1 for com2, ...
MachineId = 2     # identification number set on the integra

[Com1]
Presente? = Si
BaudRate = 9600
NumBit = 8
NumBitStop = 1
Parita' = N

#-----------------------------------------------------------------
[Main]
Nome = Hospal - Plasma Conductivity Measurement
SecAcq = 10
MinDurata = 300
MinSvuota = 0.0
Directory = DATA
Prefisso = Date
Bell = 0
```

WhatSave = V.Istantaneo
WhatGraf = V.Istantaneo
ShortSignal = Time, Time2, ICndInS, ICndIn, ICndInP, ICndS, ICndOut3, ICndOut3A, ICndPl3, Gain, Offset, IQd1, IQd2, IQd3, Temp, IQb, TotWtL1, TotWtL2, WtRate1, WtRate2, KT, HG, HG2, HG3, BV, Ionic, Dial, KT/V, RDel, DP, SP

[Color]
TextColor = 14
RectColor = 11
ChartColor = 4
DataColor = 0

#----------
Signal
#----------

[Time]
Nome = Time
ValoreMin = 10
ValoreMax = 600
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 4

[Time2]
Nome = Time
ValoreMin = 10
ValoreMax = 600
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 15

[ICndInS]
Nome = Inlet Conductivity Setting
ValoreMin = 13
ValoreMax = 17
ParConversione = 0.1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 5

[ICndIn]
Nome = Inlet Conductivity
ValoreMin = 13
ValoreMax = 17
ParConversione = 0.1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 18

[ICndInP]
Nome = Inlet Conductivity Protective Value
ValoreMin = 13
ValoreMax = 17
ParConversione = 0.01, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 42

```
[ICndS]
Nome          = Inlet Conductivity
ValoreMin     = 13
ValoreMax     = 17
ParConversione  = 0.01, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 48

[ICndOut3]
Nome          = Outlet Conductivity 3
ValoreMin     = 13
ValoreMax     = 17
ParConversione  = 0.001, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 108, 4
Offset = 15
Address = 34

[ICndOut3A]
Nome          = Outlet Conductivity 3
ValoreMin     = 13
ValoreMax     = 17
ParConversione  = 0.001, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 46
```

```
[ICndPl3]
Nome          = Pl Cond Thr
ValoreMin     = 13
ValoreMax     = 17
ParConversione = 0.001, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 47

[Gain]
Nome          = Gain
ValoreMin     = 13
ValoreMax     = 17
ParConversione = 0.1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 40

[Offset]
Nome          = Offset
ValoreMin     = 13
ValoreMax     = 17
ParConversione = 0.1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 41
```

```
[IQd1]
Nome          = Dialysate Flow rate
ValoreMin     = 1
ValoreMax     = 4
ParConversione  = 1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 52

[IQd2]
Nome          = Dial Flow
ValoreMin     = 1
ValoreMax     = 4
ParConversione  = 1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 7

[IQd3]
Nome          = Dial Flow
ValoreMin     = 1
ValoreMax     = 4
ParConversione  = 1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 22
```

```
[Temp]
Nome          = Temp
ValoreMin     = 36
ValoreMax     = 39.5
ParConversione = 0.1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 12

[IQb]
Nome          = Blood Flow
ValoreMin     = 0
ValoreMax     = 700
ParConversione = 1, 0
# Procedura ReadCCM
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 25

[TotWtL1]
Nome          = Wt Loss
ValoreMin     = 100
ValoreMax     = 8000
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 6
```

```
[TotWtL2]
Nome          = Wt Loss
ValoreMin     = 0.1
ValoreMax     = 8.000
ParConversione  = 0.001, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 11

[WtRate1]
Nome          = Wt Loss Rate
ValoreMin     = 0.1
ValoreMax     = 3
ParConversione  = 0.001, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 1
Address = 10

[WtRate2]
Nome          = Wt Loss Rate
ValoreMin     = 100
ValoreMax     = 3000
ParConversione  = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 7
```

```
[KT]
Nome          = KT
ValoreMin     = 0
ValoreMax     = 99.5
ParConversione  = 0.1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 30

[HG]
Nome          = HG
ValoreMin     = 4.0
ValoreMax     = 18.0
ParConversione  = 0.1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 50

[HG2]
Nome          = HG2
ValoreMin     = 4.0
ValoreMax     = 18.0
ParConversione  = 0.01, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 28
```

[HG3]
Nome = HG2
ValoreMin = 0
ValoreMax = 30
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 29

[BV]
Nome = BV
ValoreMin = -40.0
ValoreMax = 40.0
ParConversione = 0.1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 51

[Ionic]
Nome = Ionic
ValoreMin = -500
ValoreMax = 800
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 53

[Dial]
Nome = Dialysance
ValoreMin = 0
ValoreMax = 300
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 54

[KT/V]
Nome = KT/V
ValoreMin = 0
ValoreMax = 3.00
ParConversione = 0.01, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 59

[RDel]
Nome = RDel
ValoreMin = 0
ValoreMax = 150
ParConversione = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 89, 3
Address = 35

```
[DP]
Nome          = Dia Pres
ValoreMin     = 30
ValoreMax     = 235
ParConversione  = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 44

[SP]
Nome          = Sys Pres
ValoreMin     = 50
ValoreMax     = 255
ParConversione  = 1, 0
# Procedura ReadCCMcnd
Tipo = Seriale
Analogic/Digital? = CCM
Input/Output? = Input
Porta = &Custom.SerialPort&
CCMid = &Custom.MachineId&
Message = 39
Address = 45


# End of File ----------------------------------------------------
```

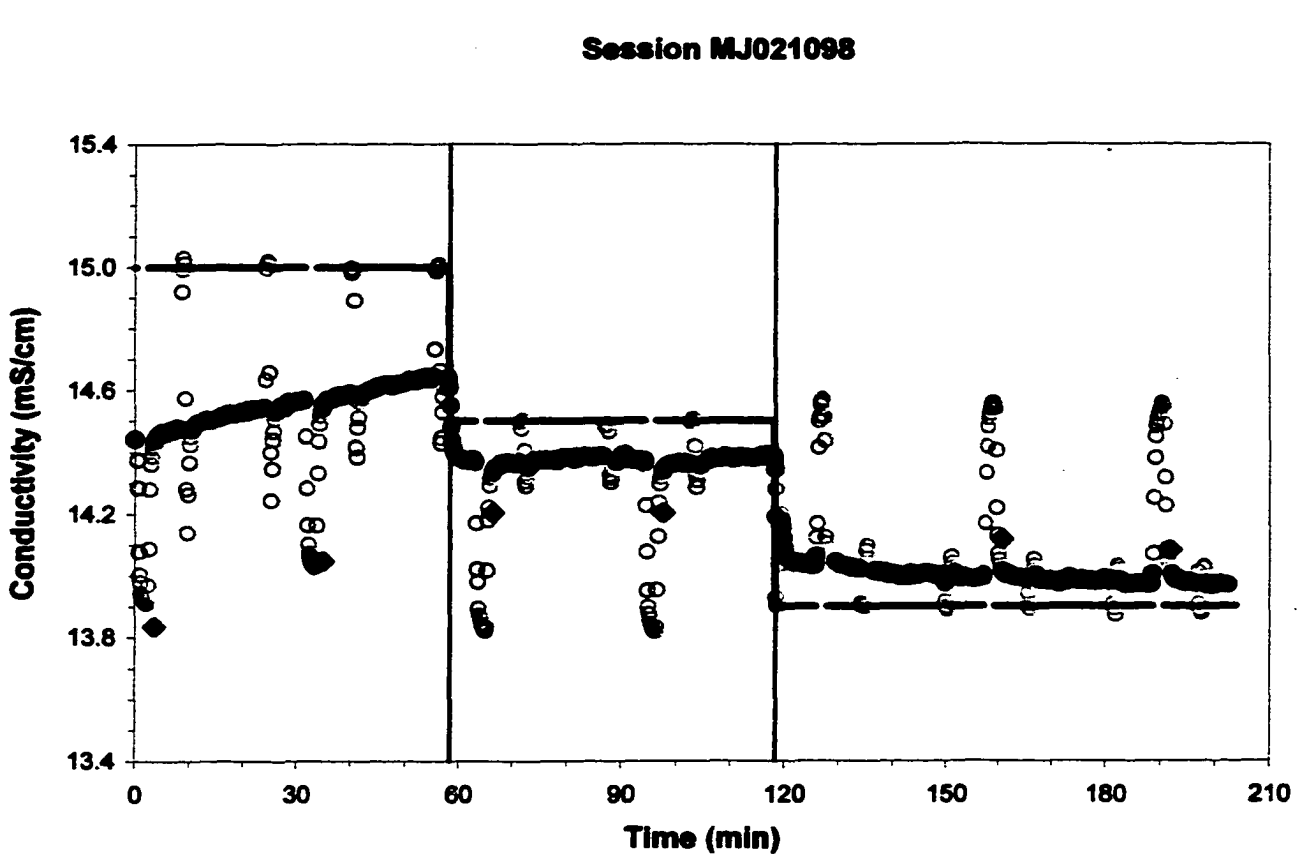
Appendix C. Study Validation Data

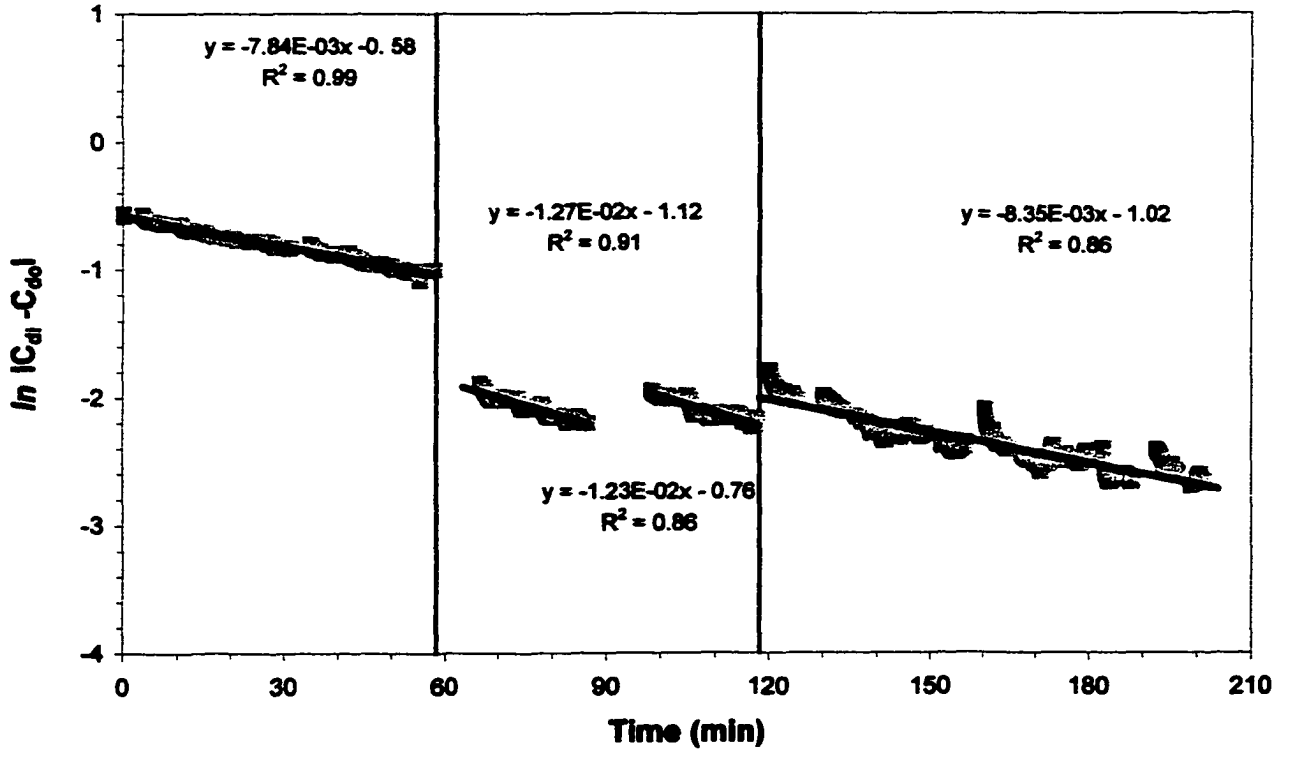
C.1 Study session dialysate conductivity data

In this appendix, the data for each of the 85 study sessions performed in the 14 patients are graphically displayed in chronological order. Each page corresponds to one study session and contains two frames. The upper frame shows the dialysate conductivity values measured by the Integra dialysis machine. The black line represents the inlet dialysate conductivity (C_{di}) profile programmed by the renal unit staff. The open gold circles and solid green circles are the outlet dialysate conductivity (C_{do}) values measured by the Diascan outlet conductivity meter. The solid green circles represent the subset of outlet conductivity values used for the study model validation; the open gold circles are outlet conductivities corresponding to calibration procedures of the Integra machine. The red diamonds represent the patient plasma conductivity calculated by the Integra machine at 30 minute intervals when the Diascan option is active.

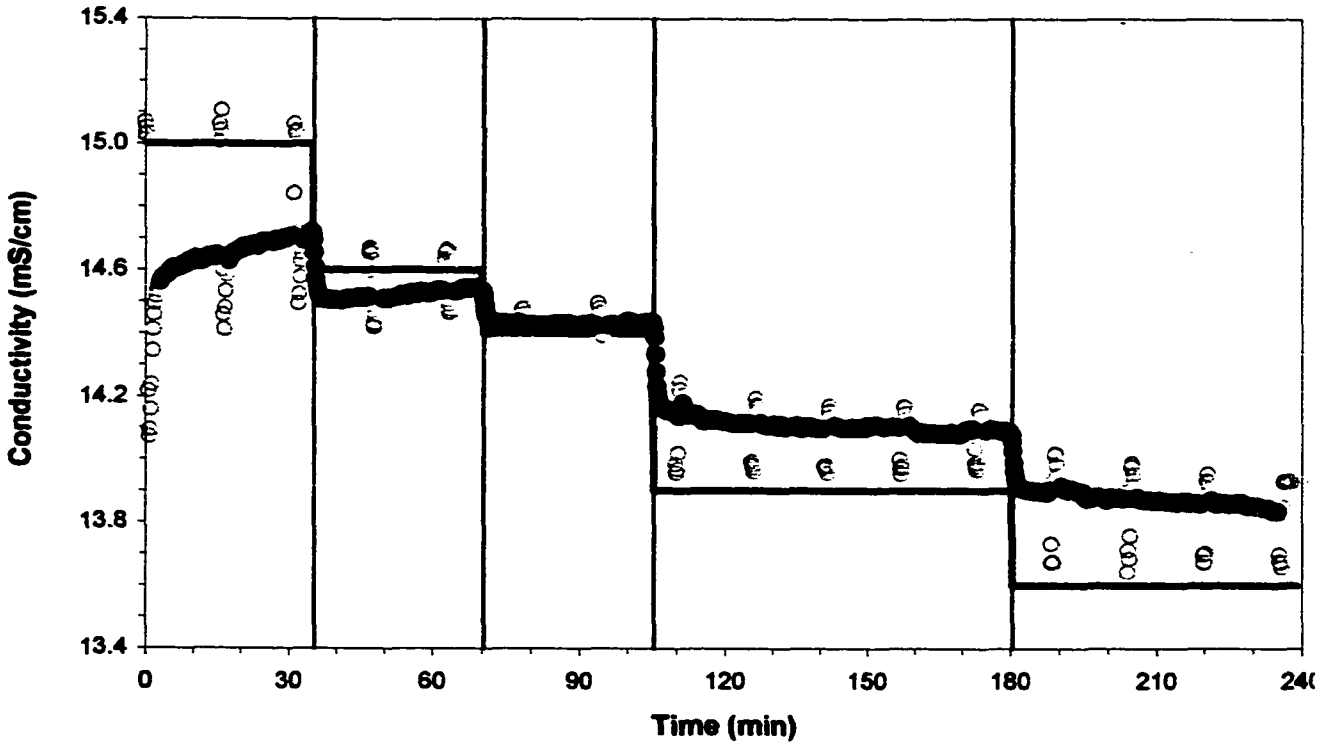
In the lower frame, $\ln|C_{di} - C_{do}|$ (based on the solid black line C_{di} values and solid green circle C_{do} values in the upper frame) is plotted versus dialysis time. Linear regression lines and equations are displayed, as appropriate, for each period of constant C_{di}.

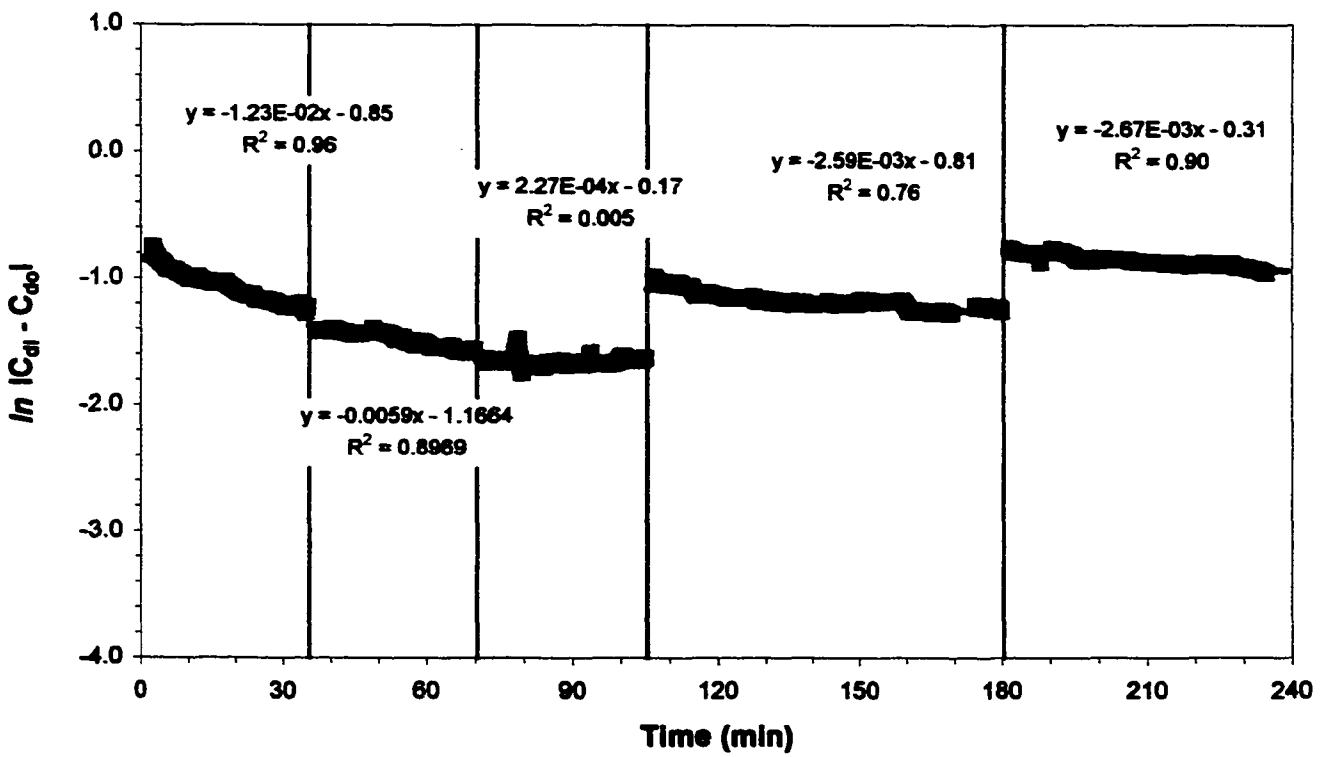
The study sessions in this appendix are presented in chronological order.

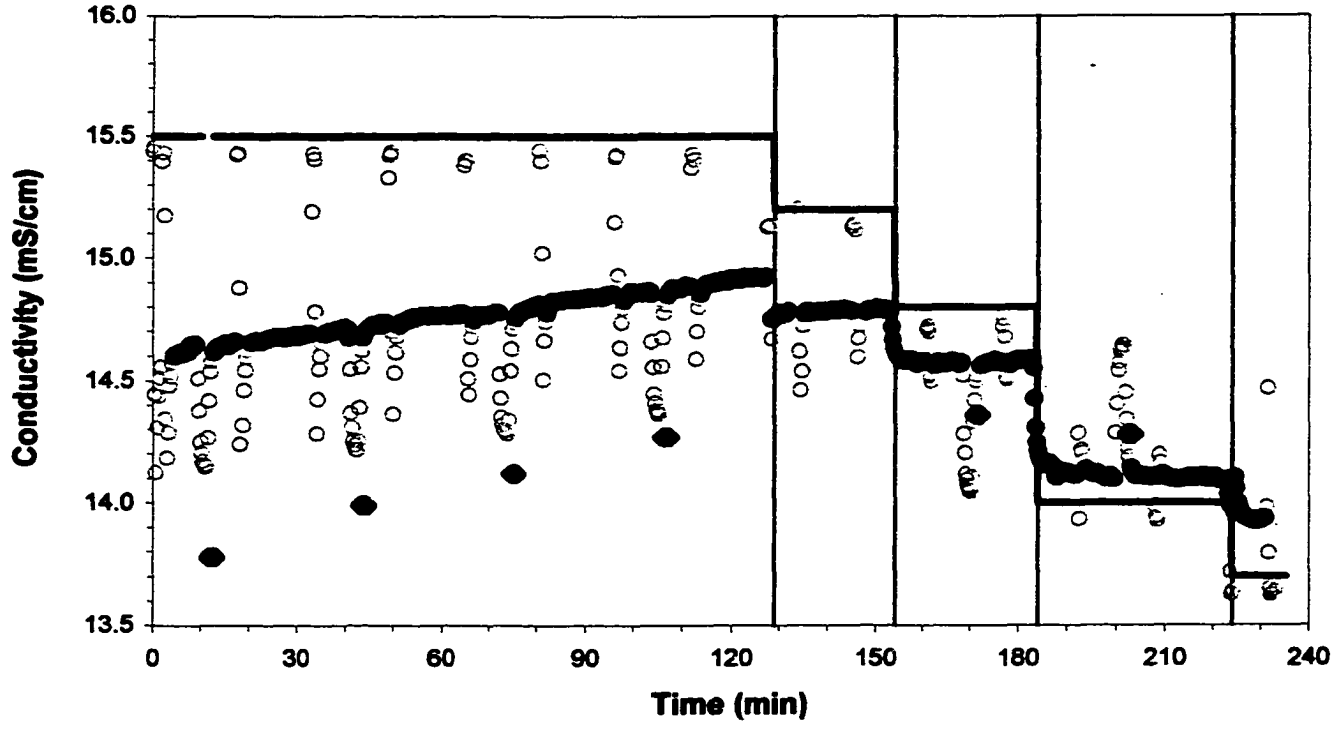


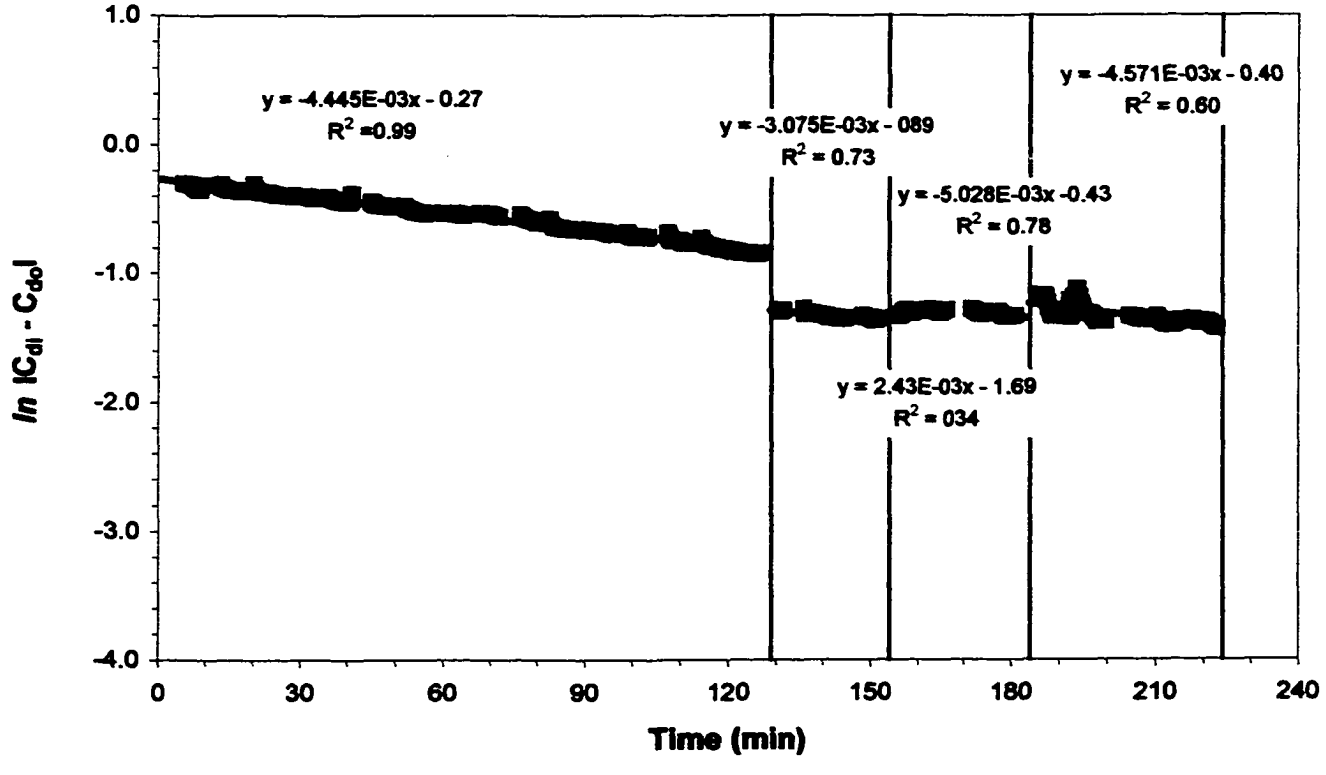


C2



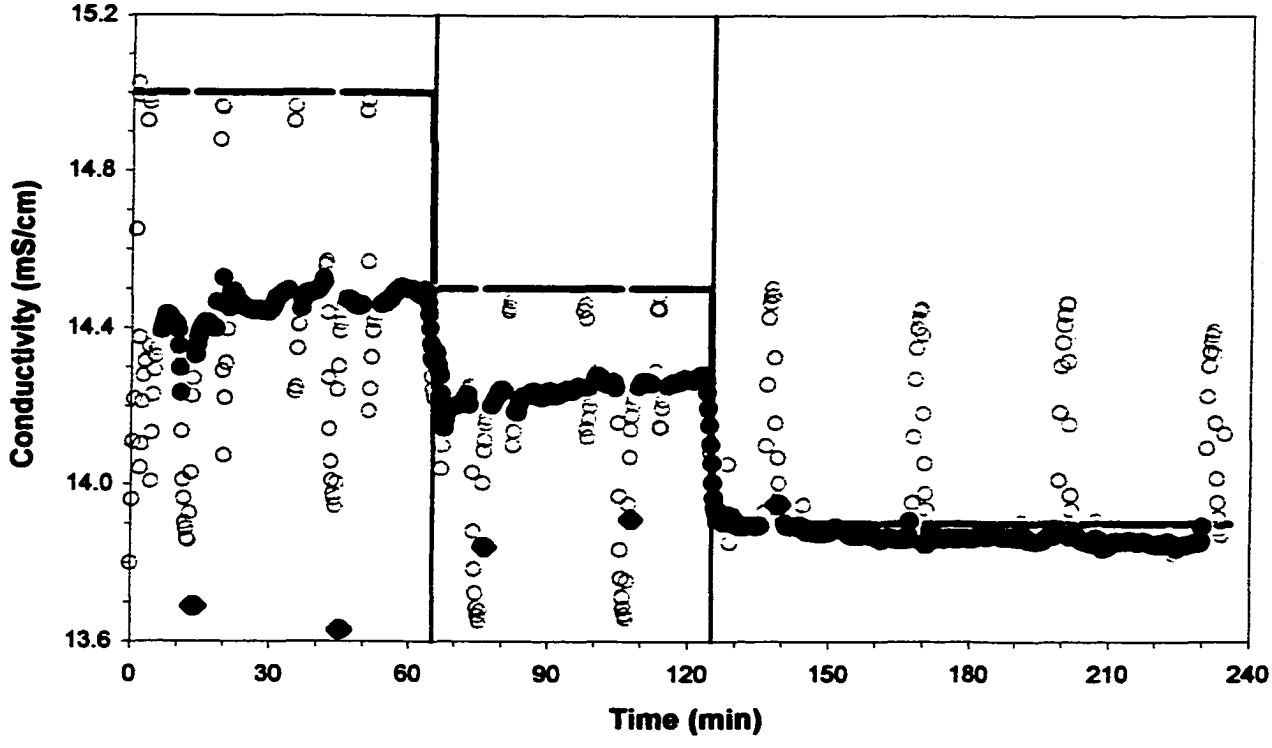


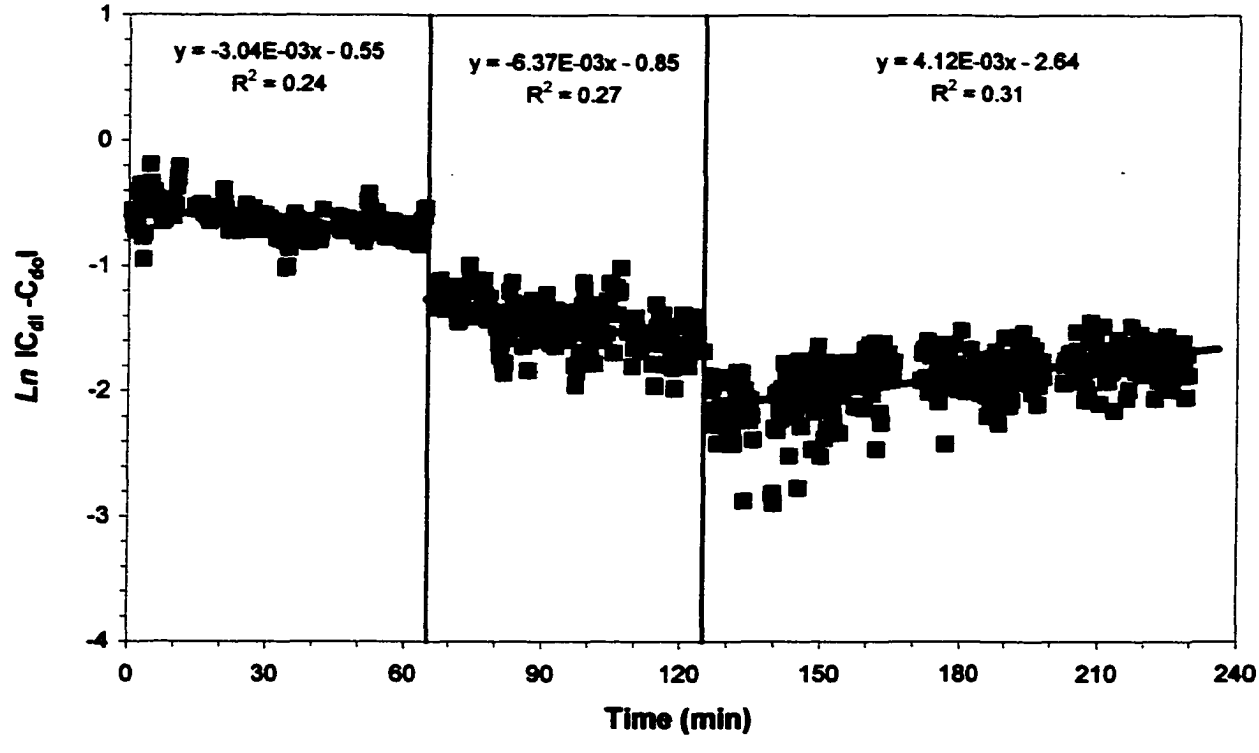


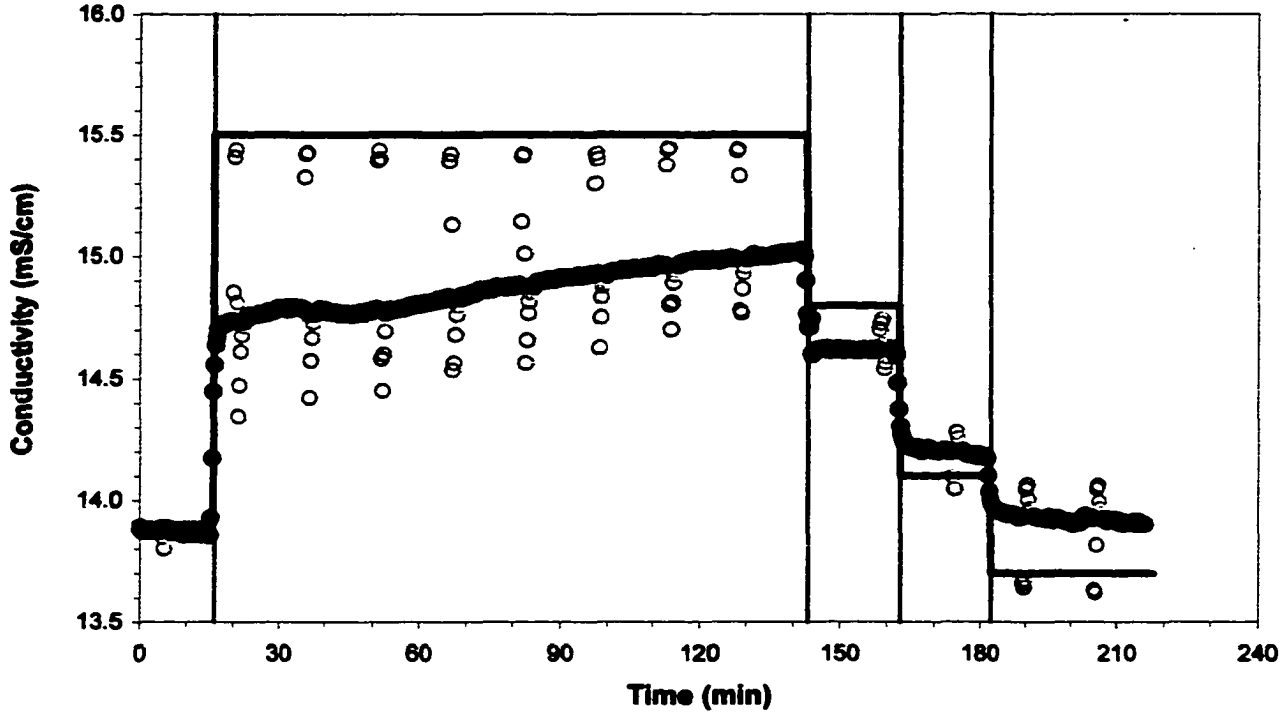


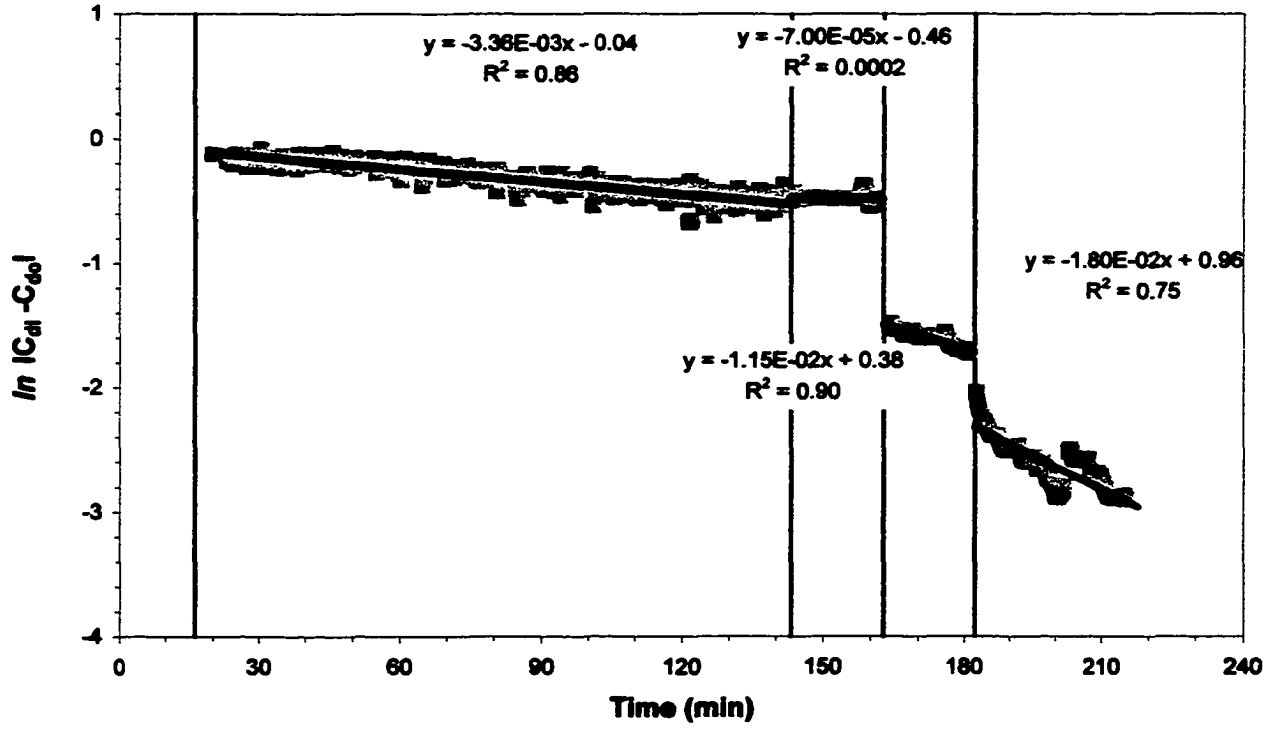
C4

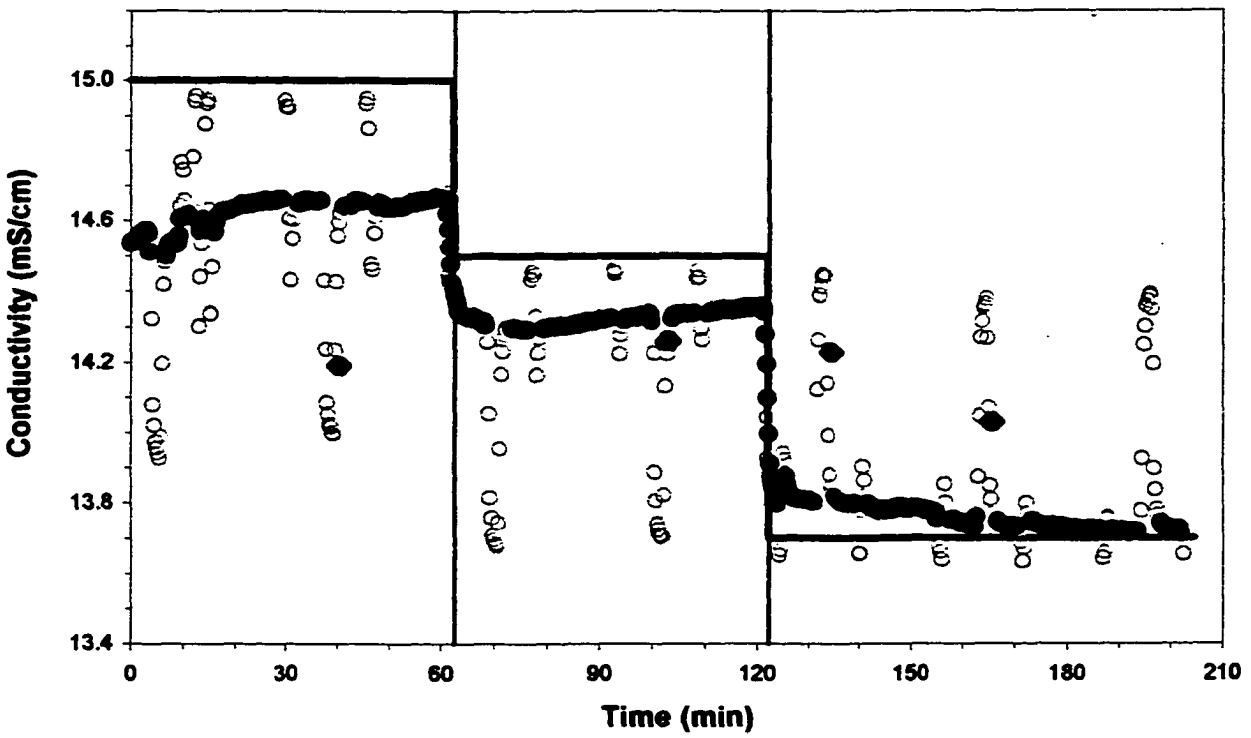
Session DS161098

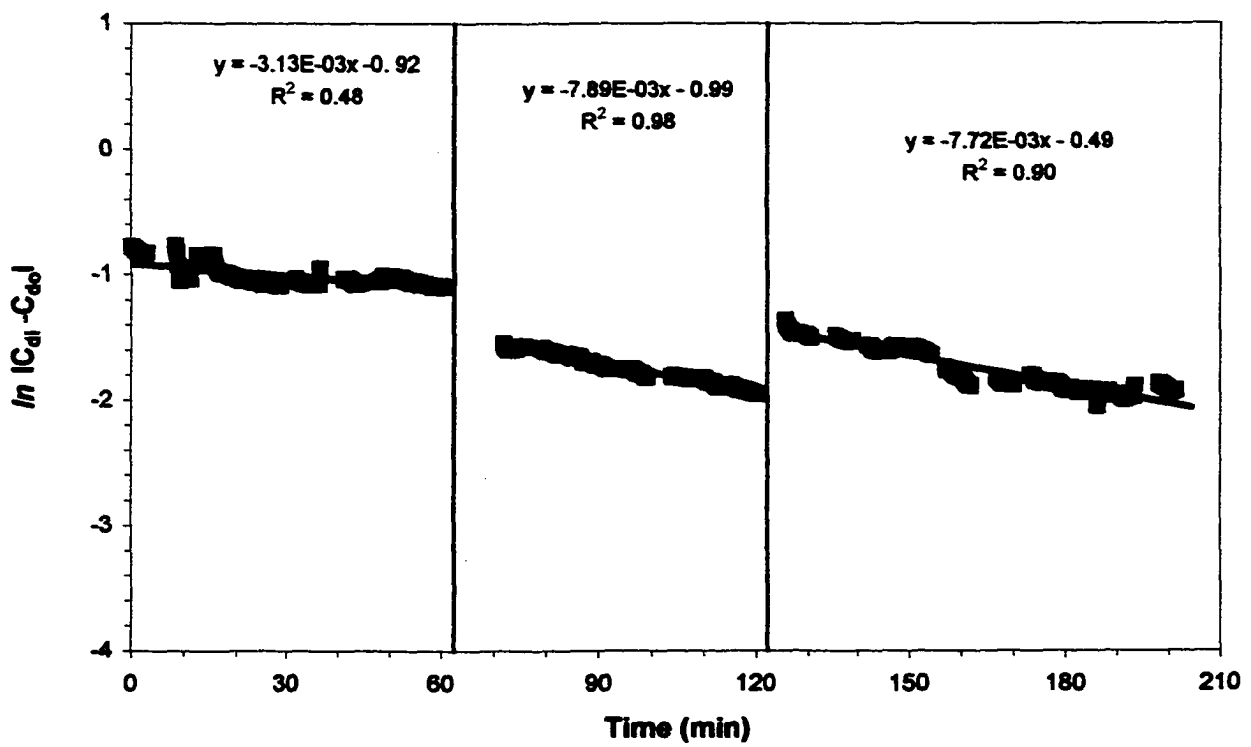




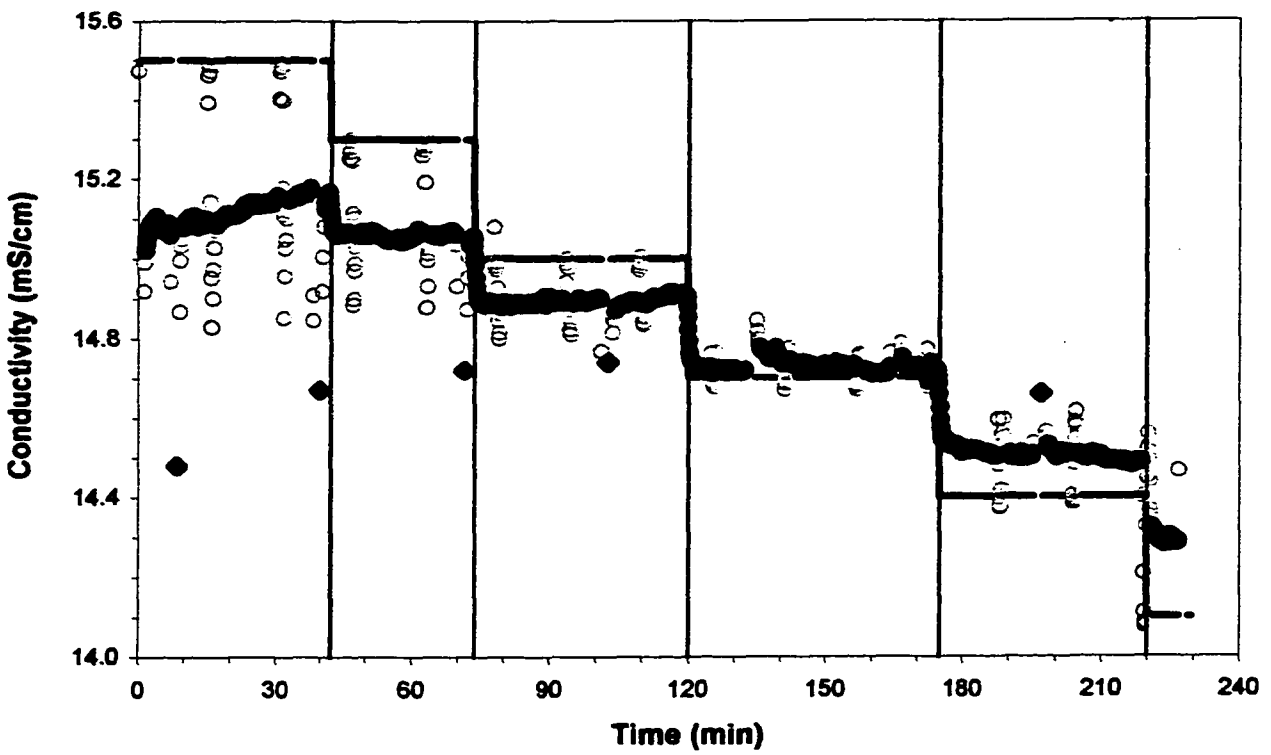


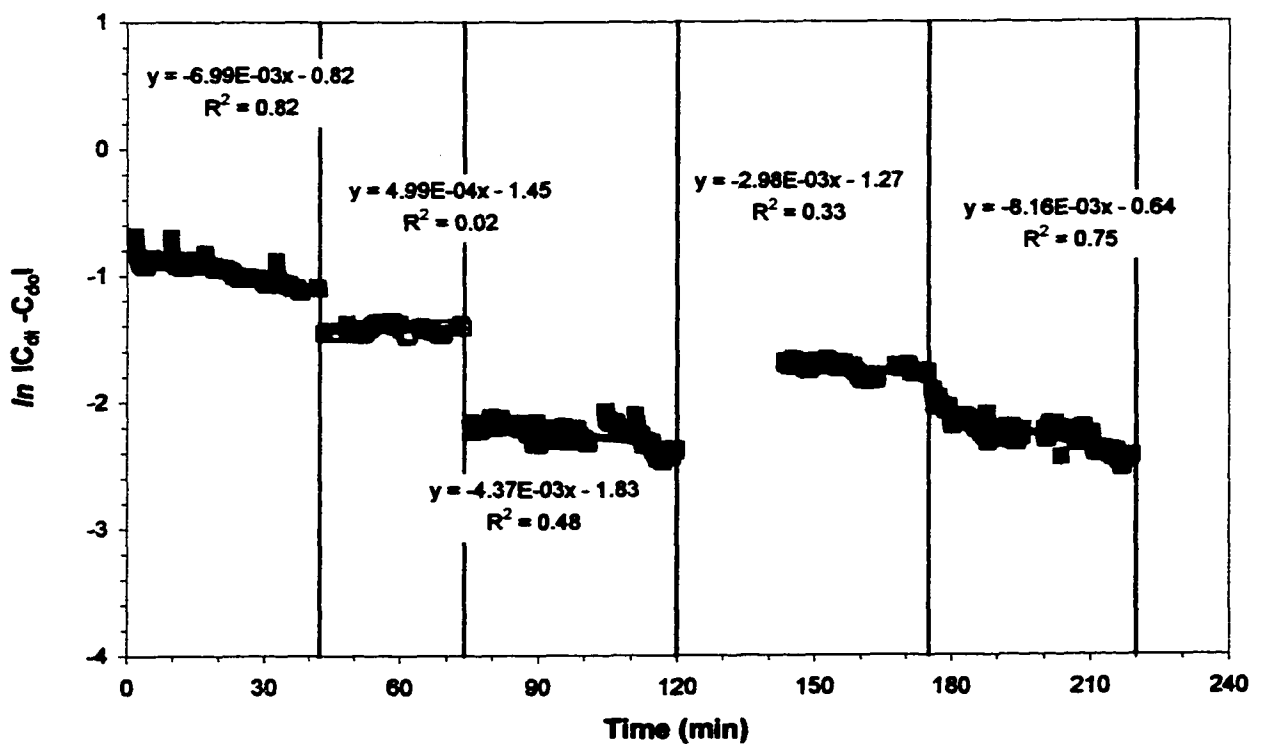


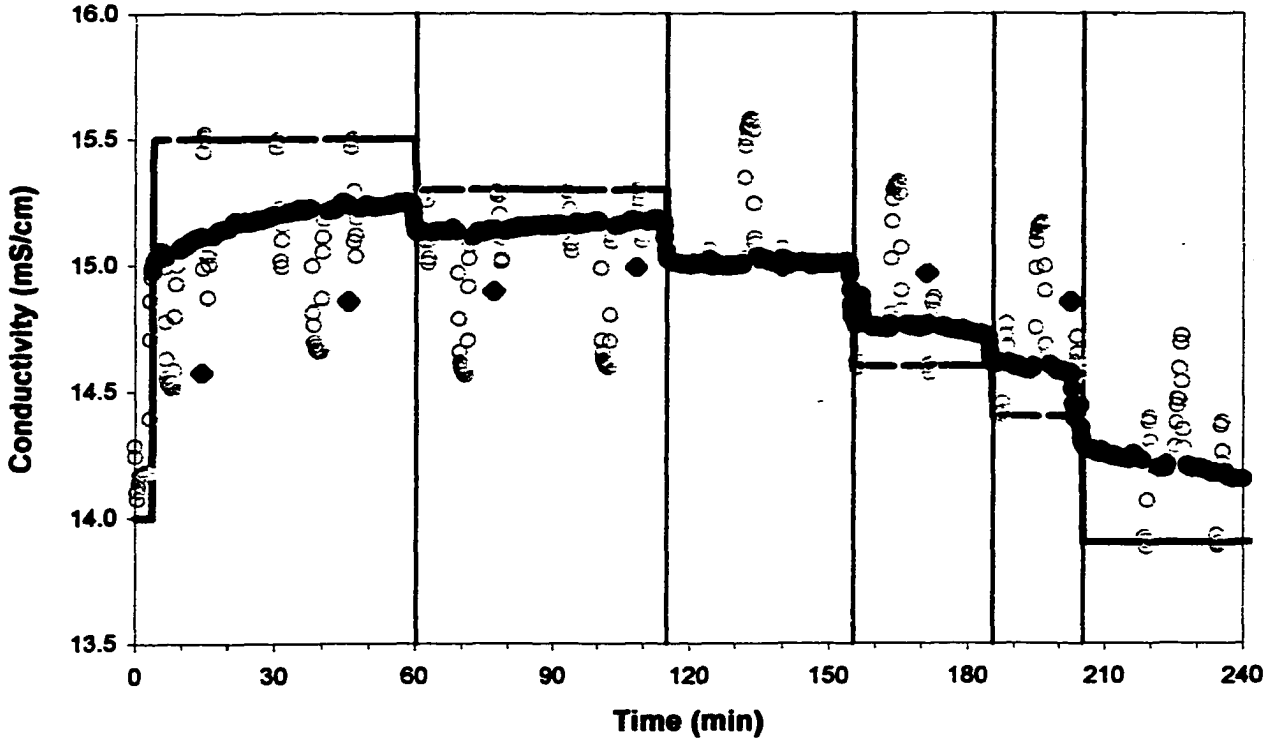


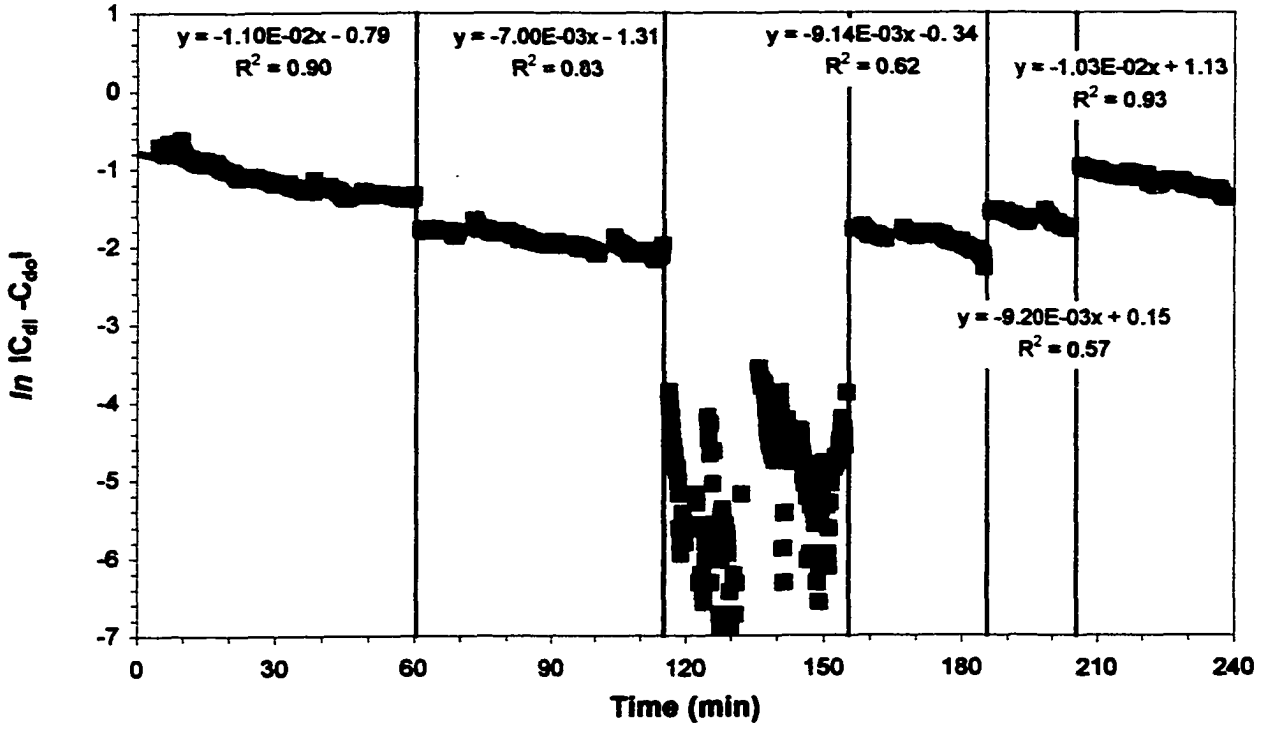


C7

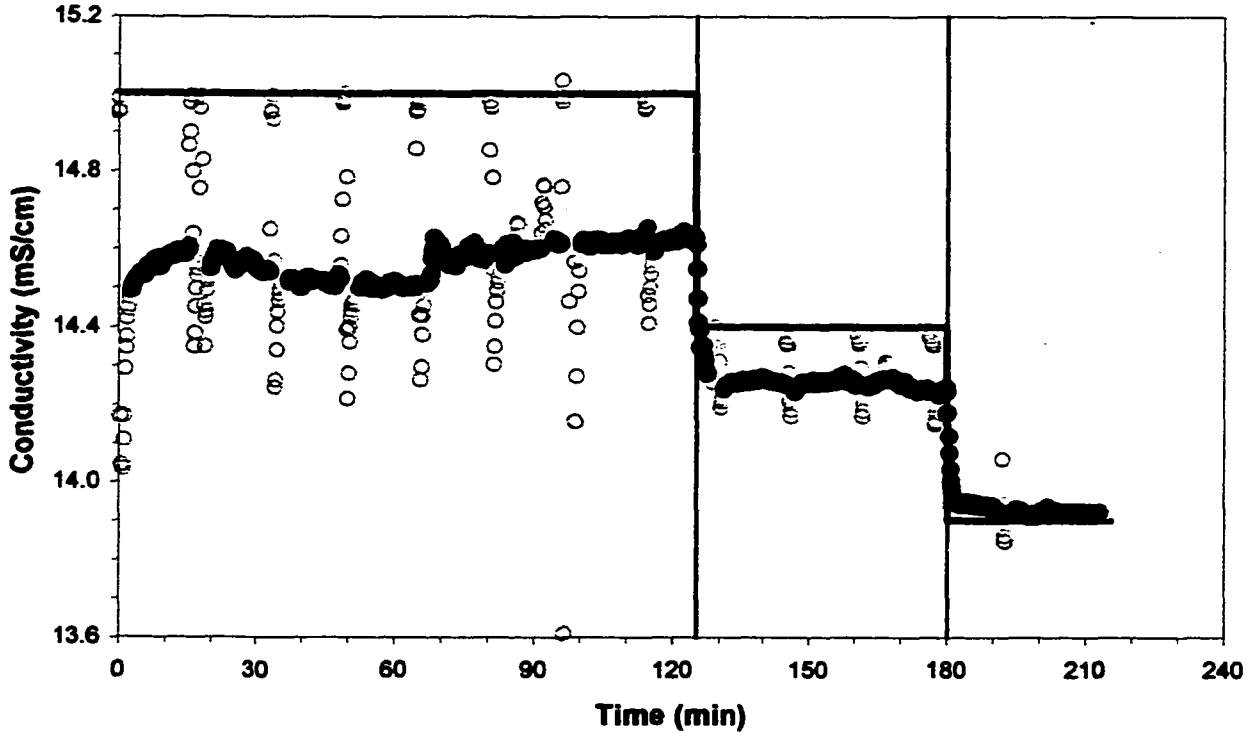


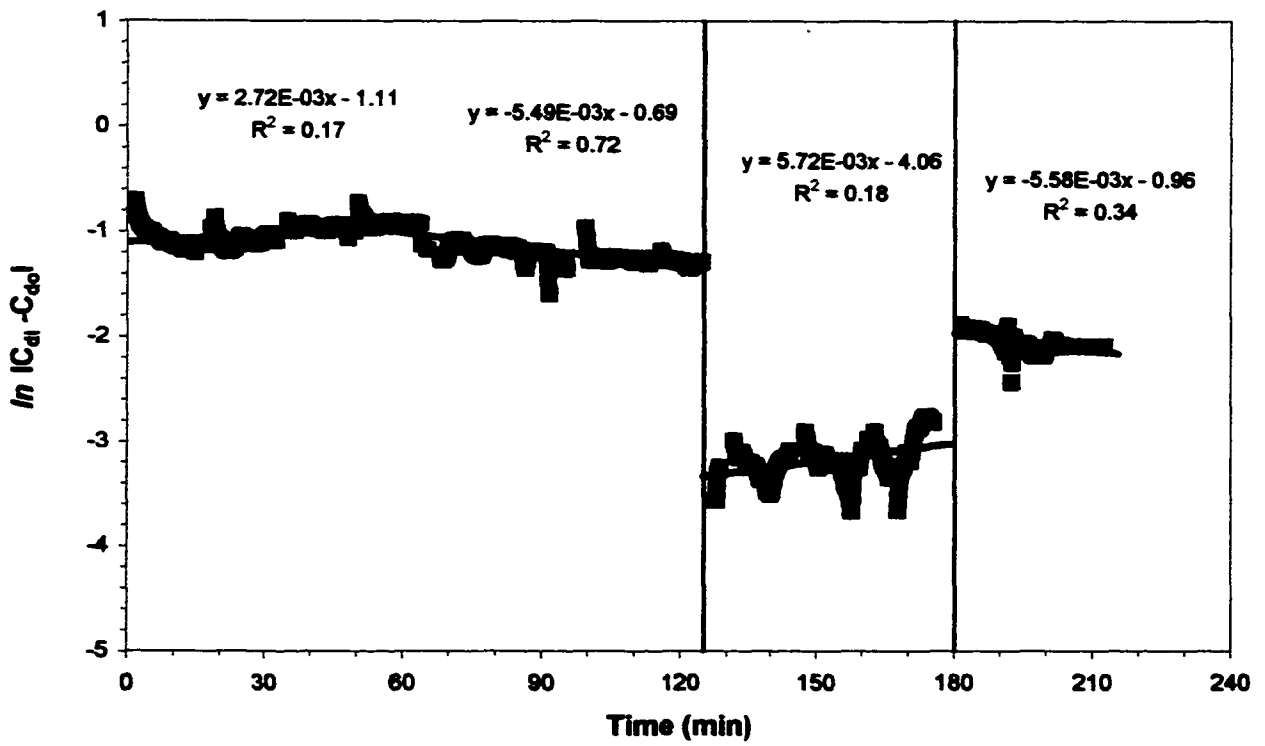






Session DS021198





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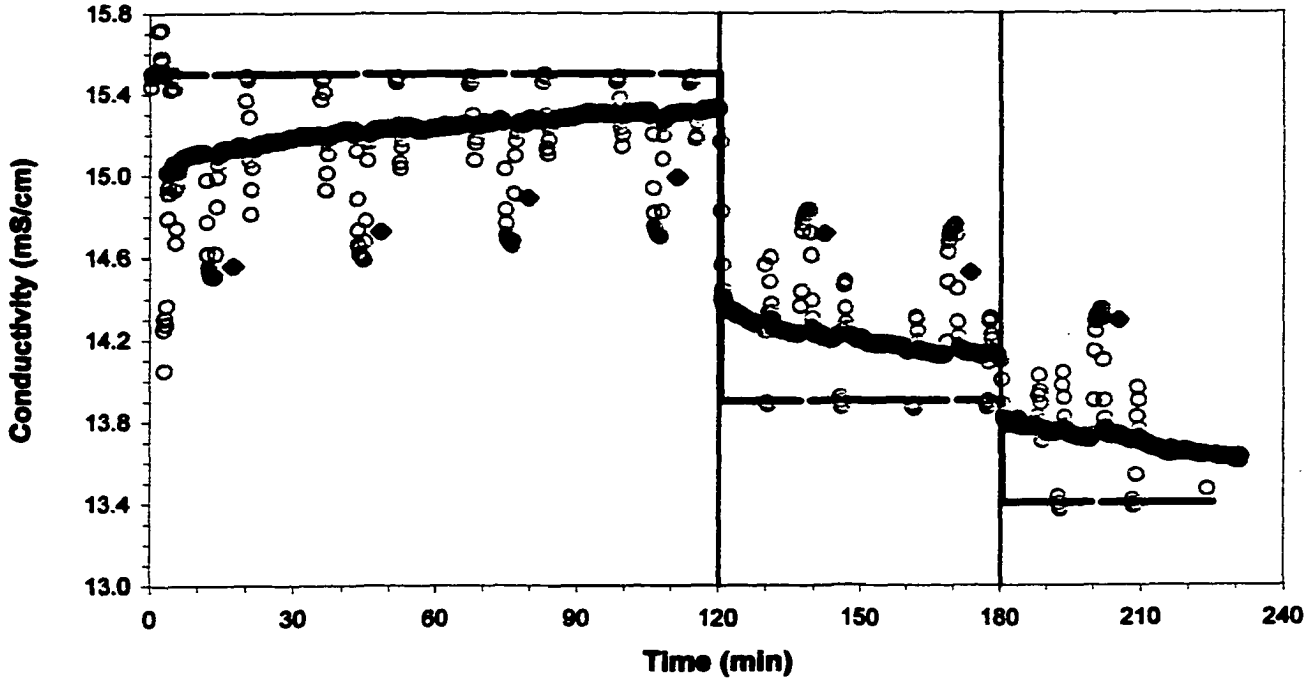
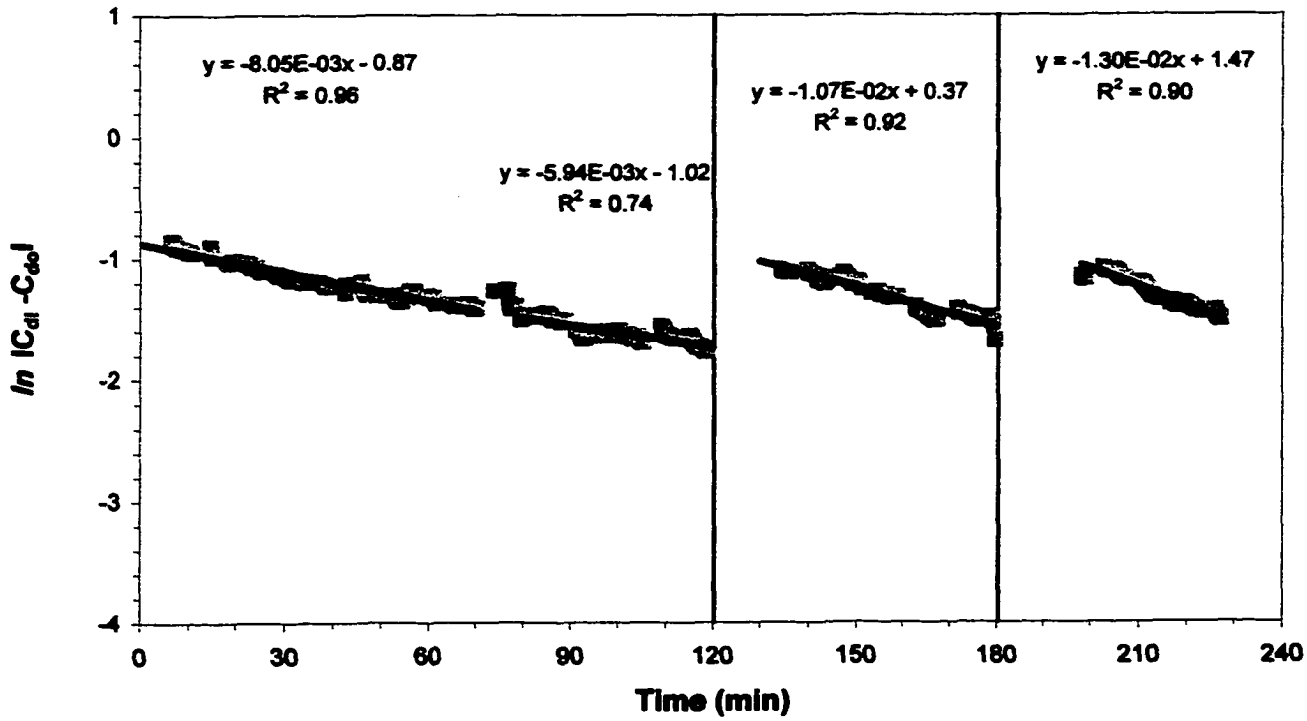
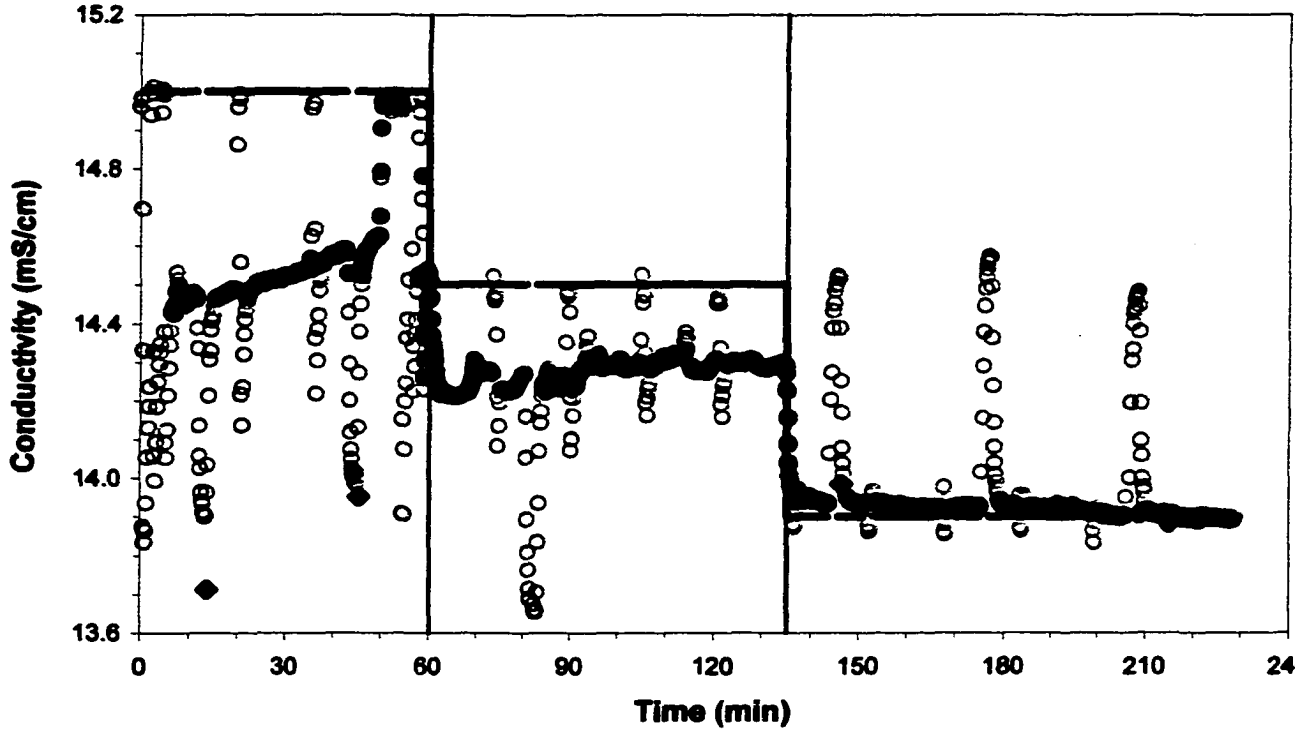
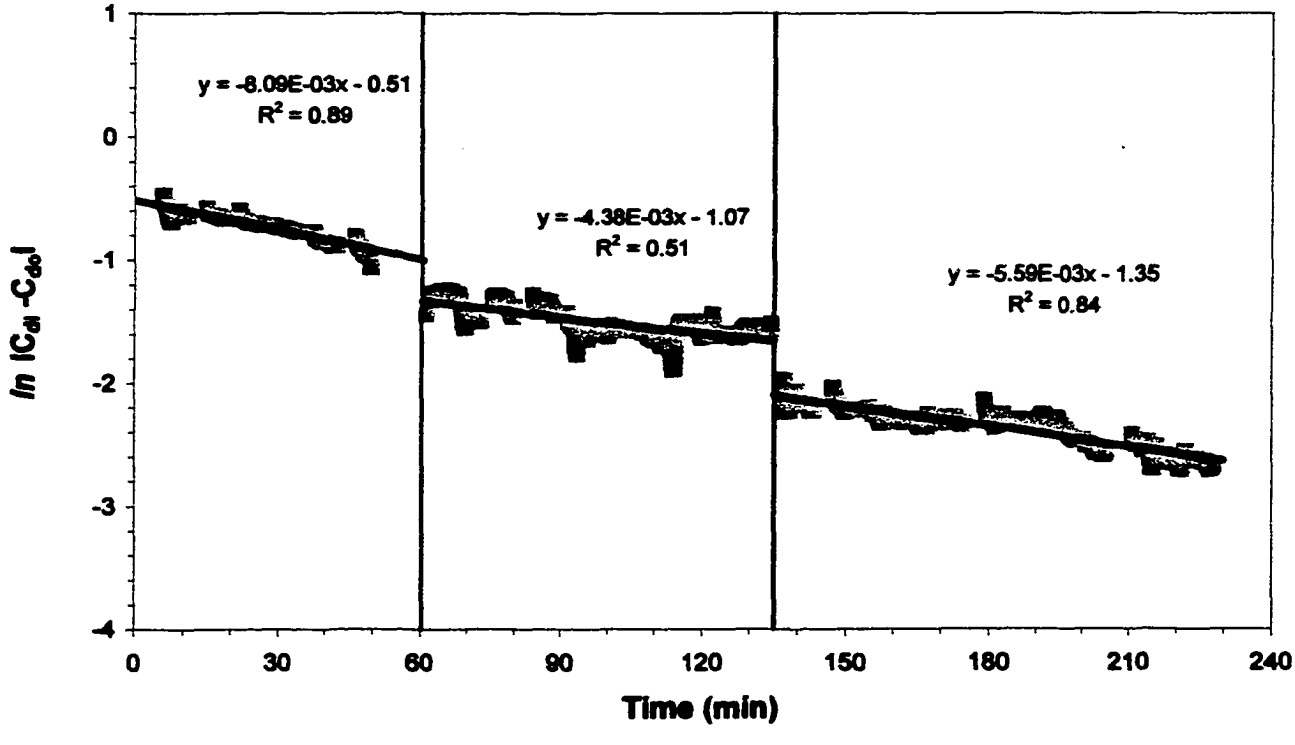
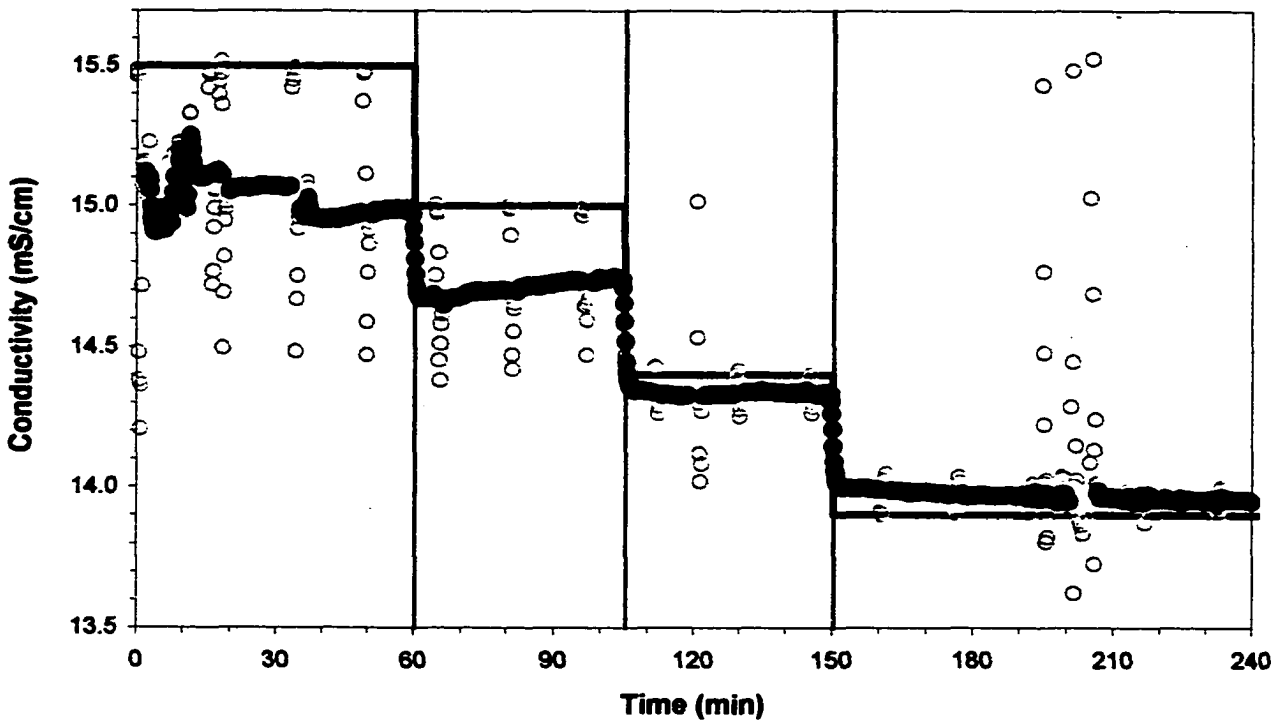
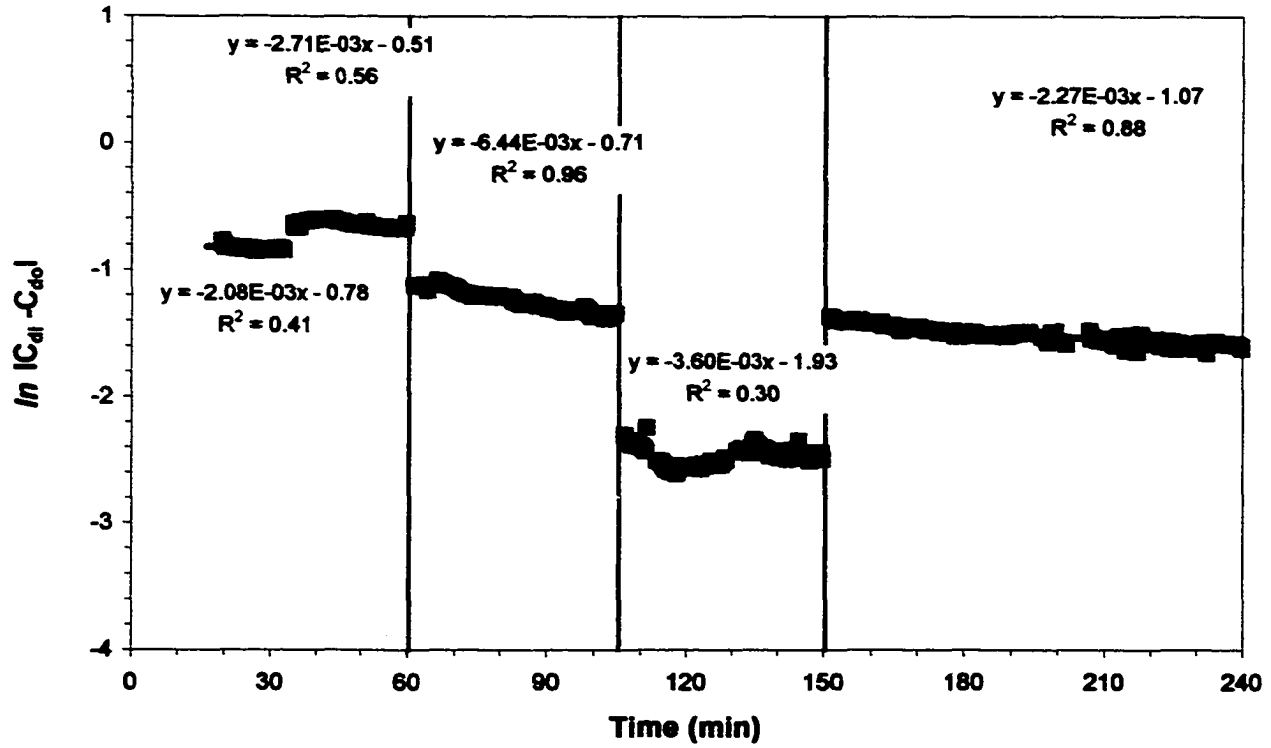




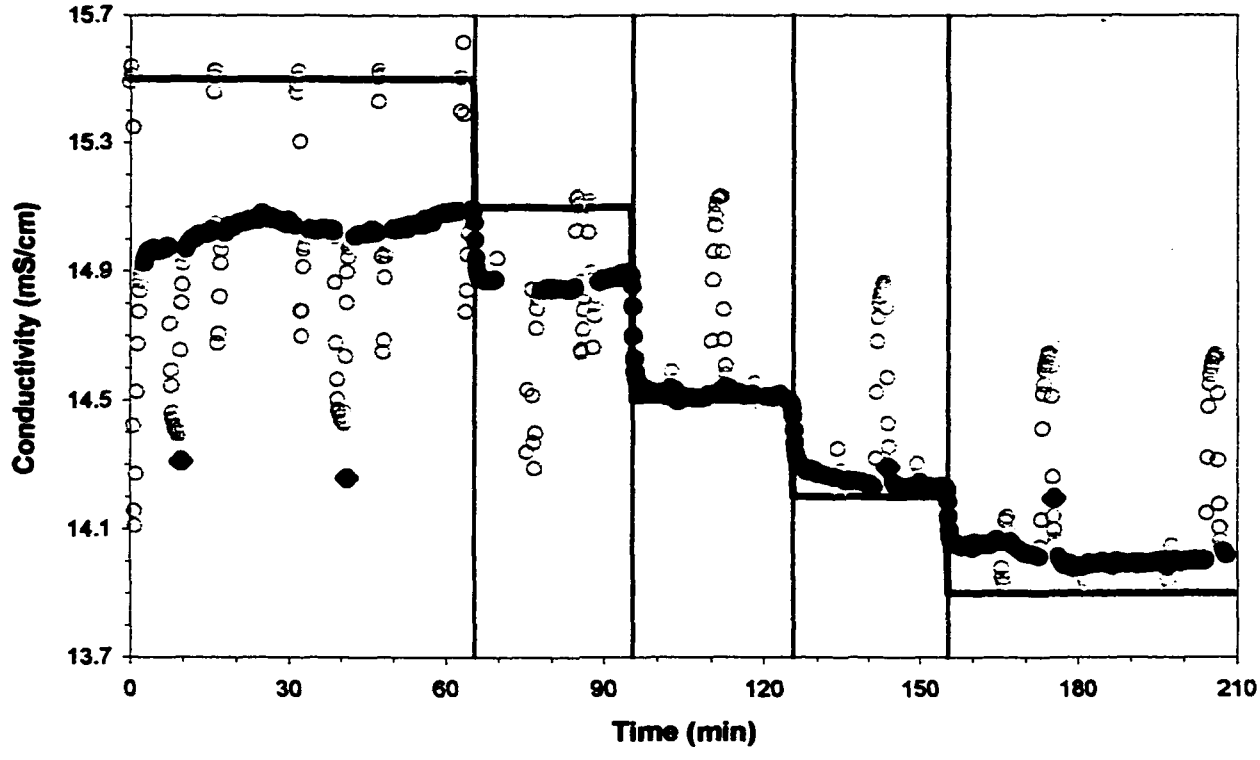


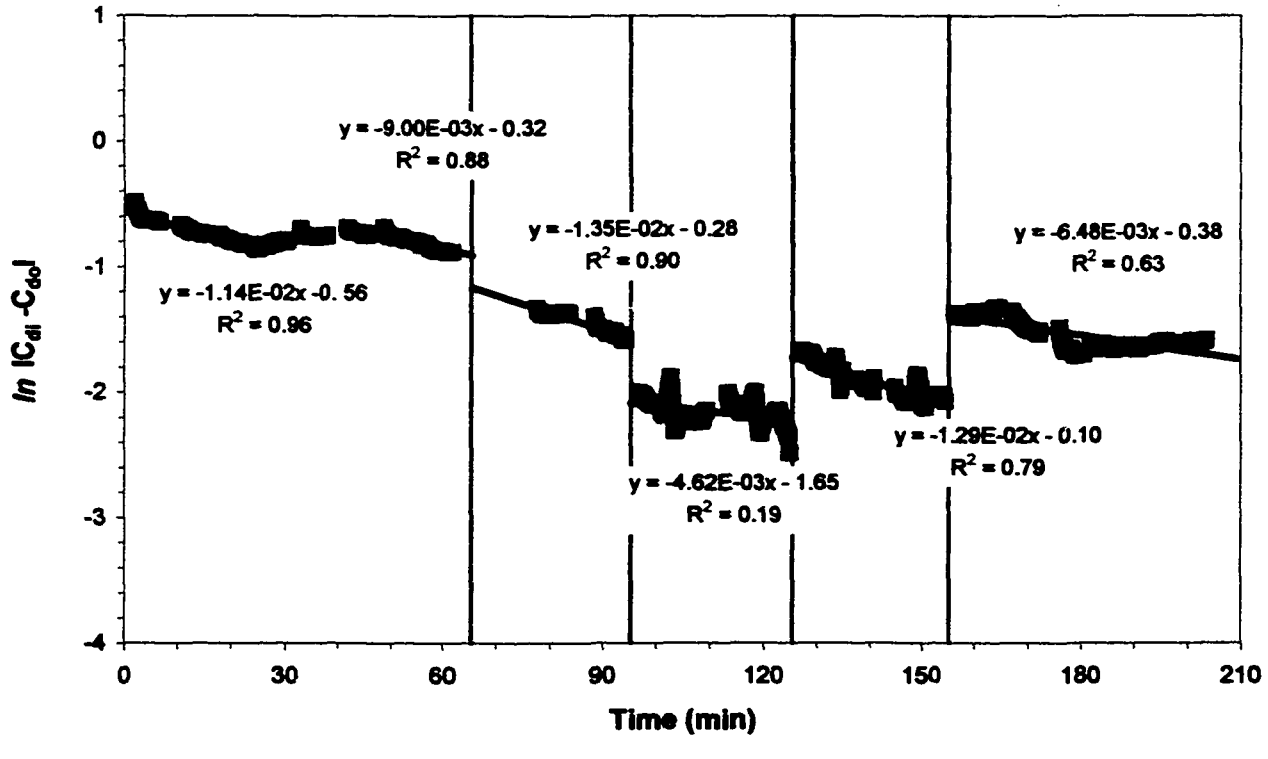




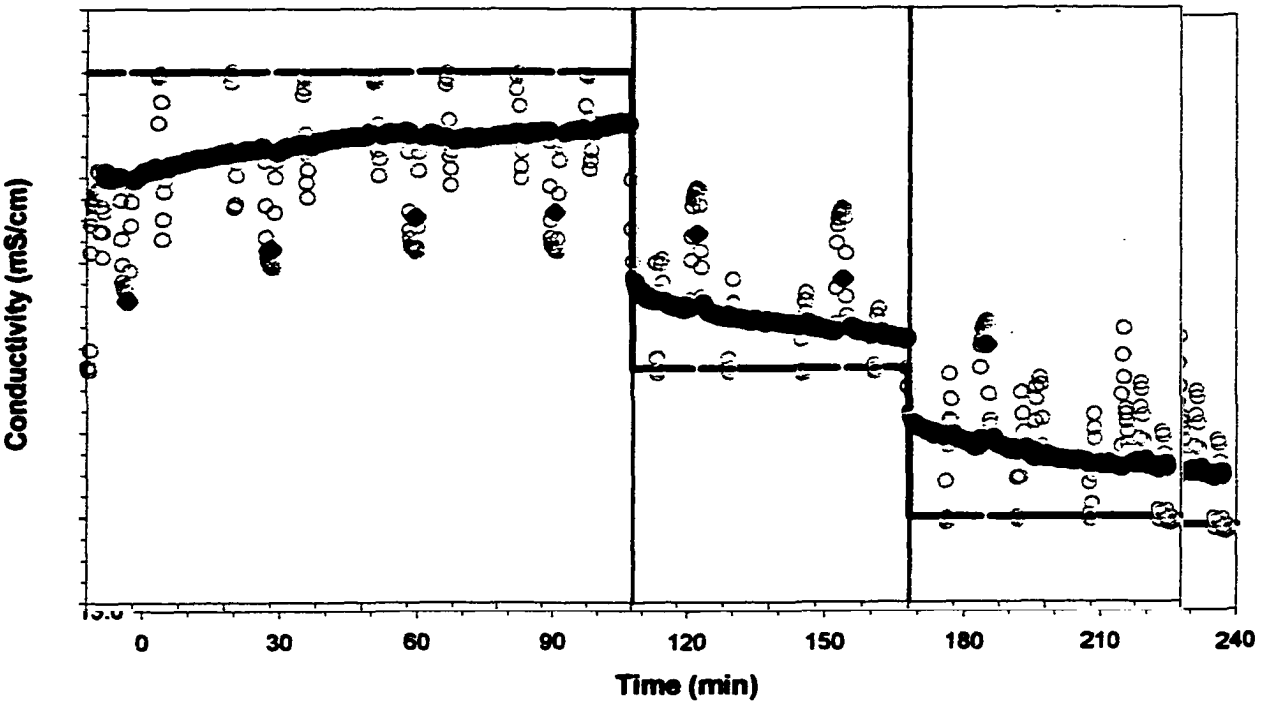


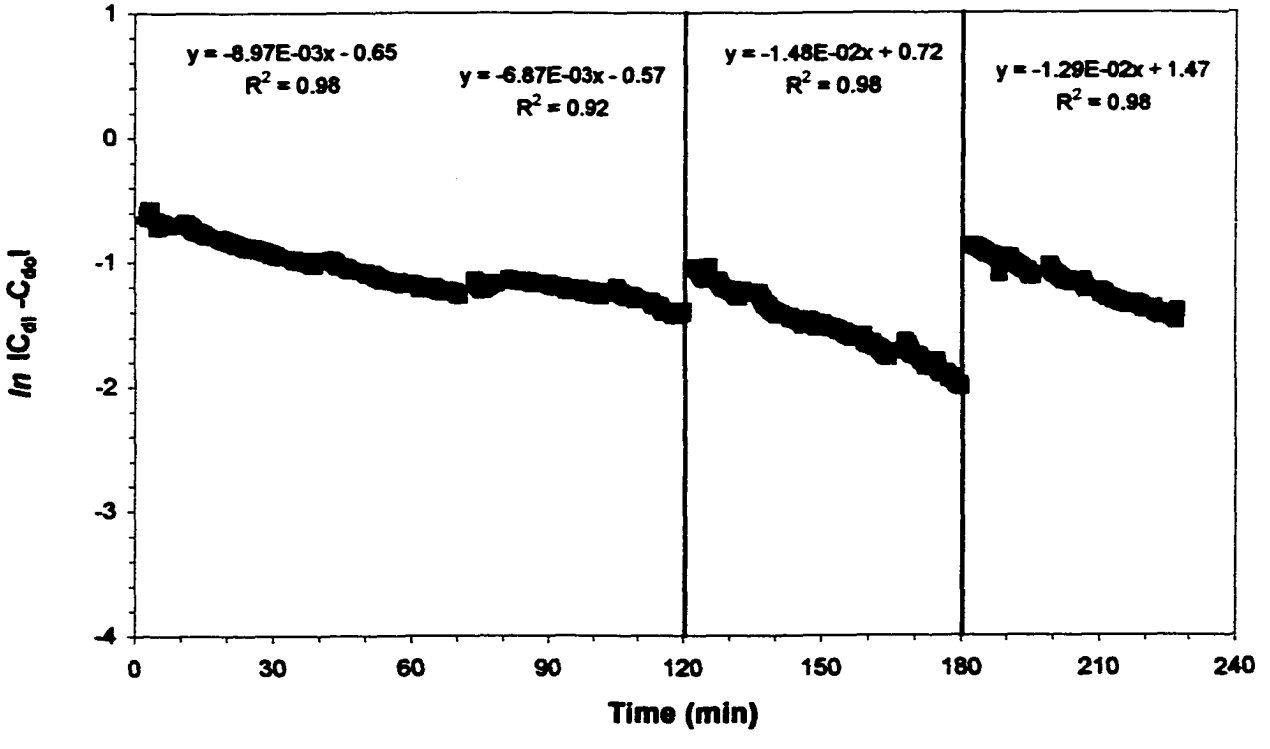
Session SM041198

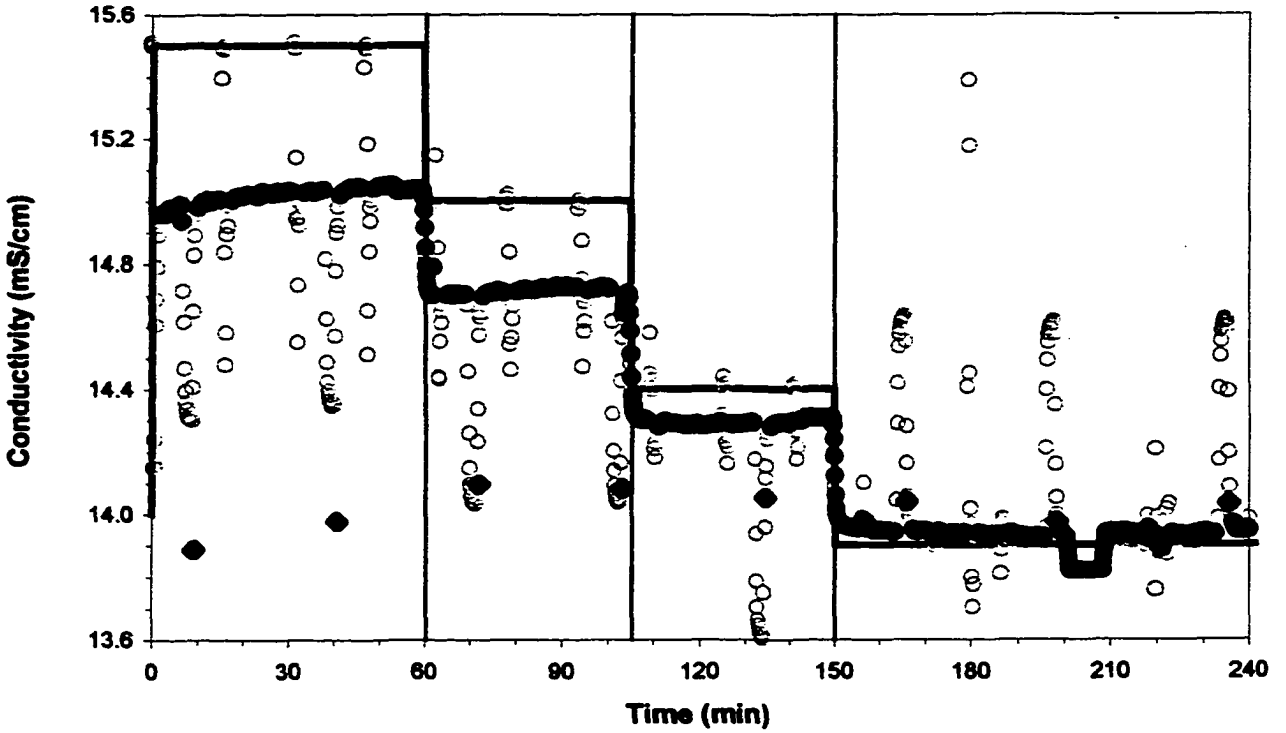


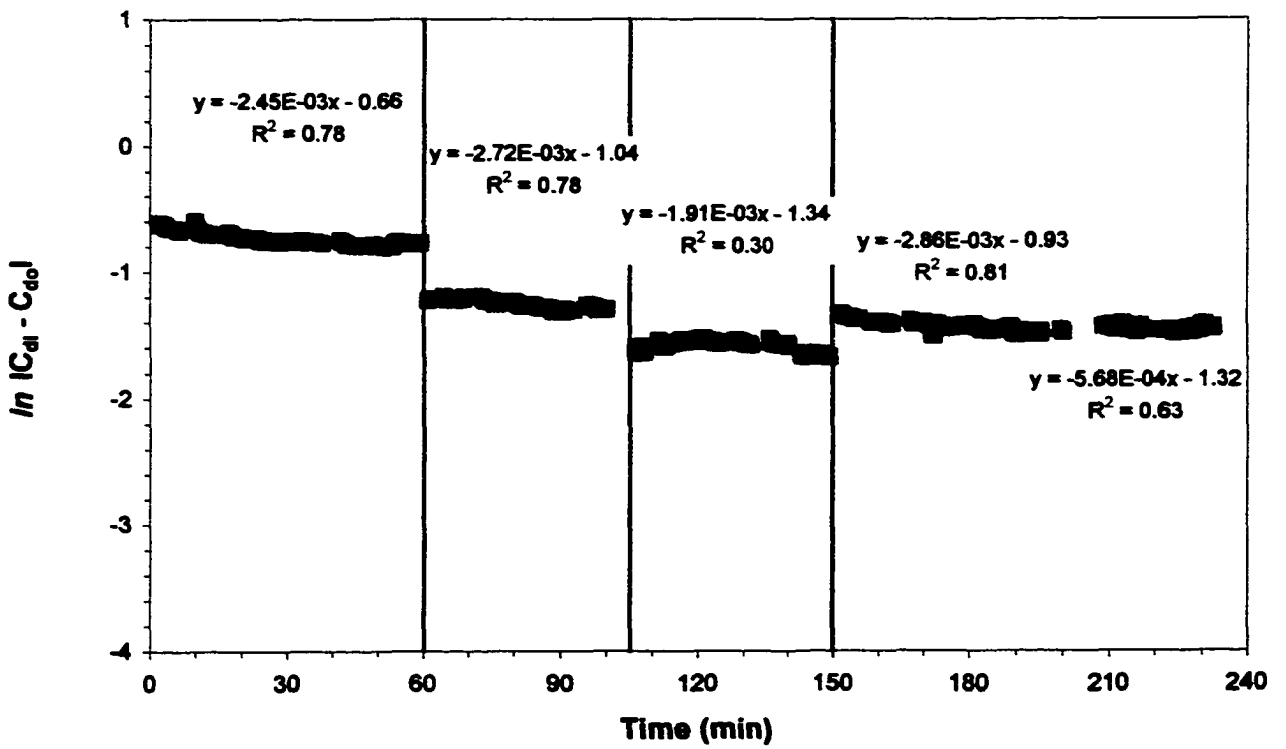


Session CL051198

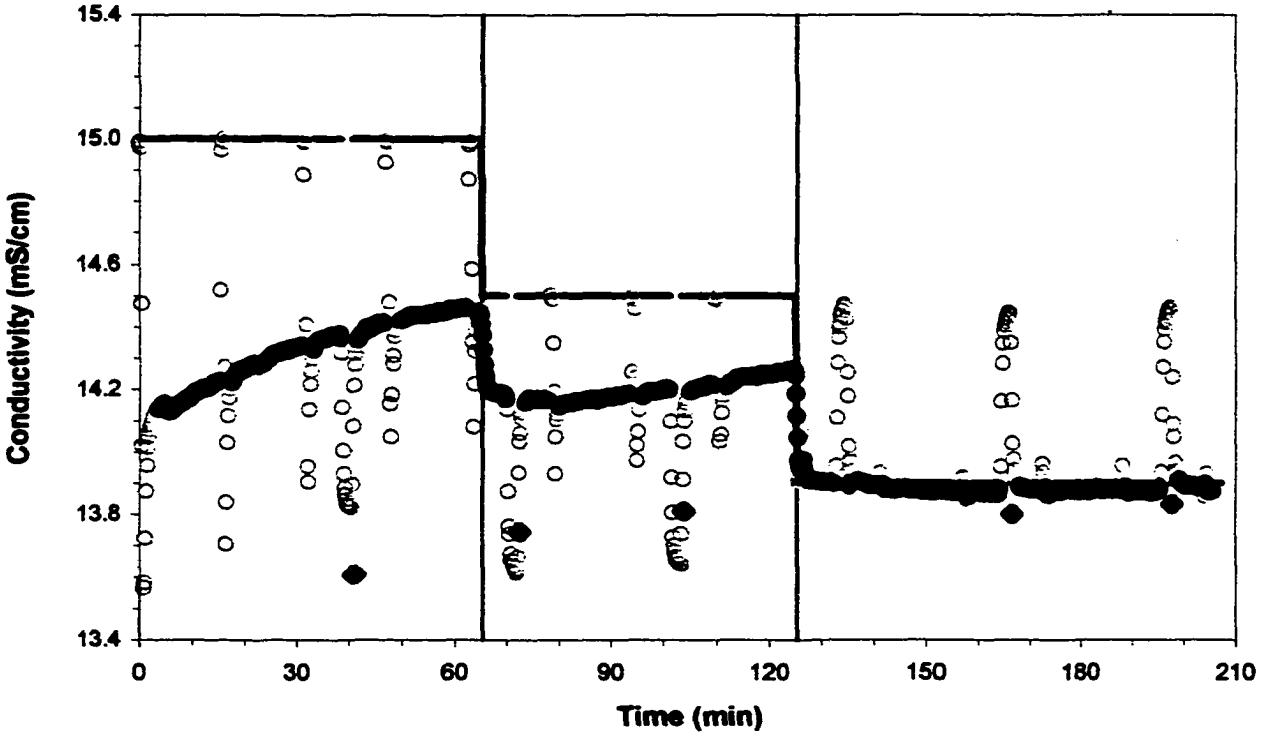


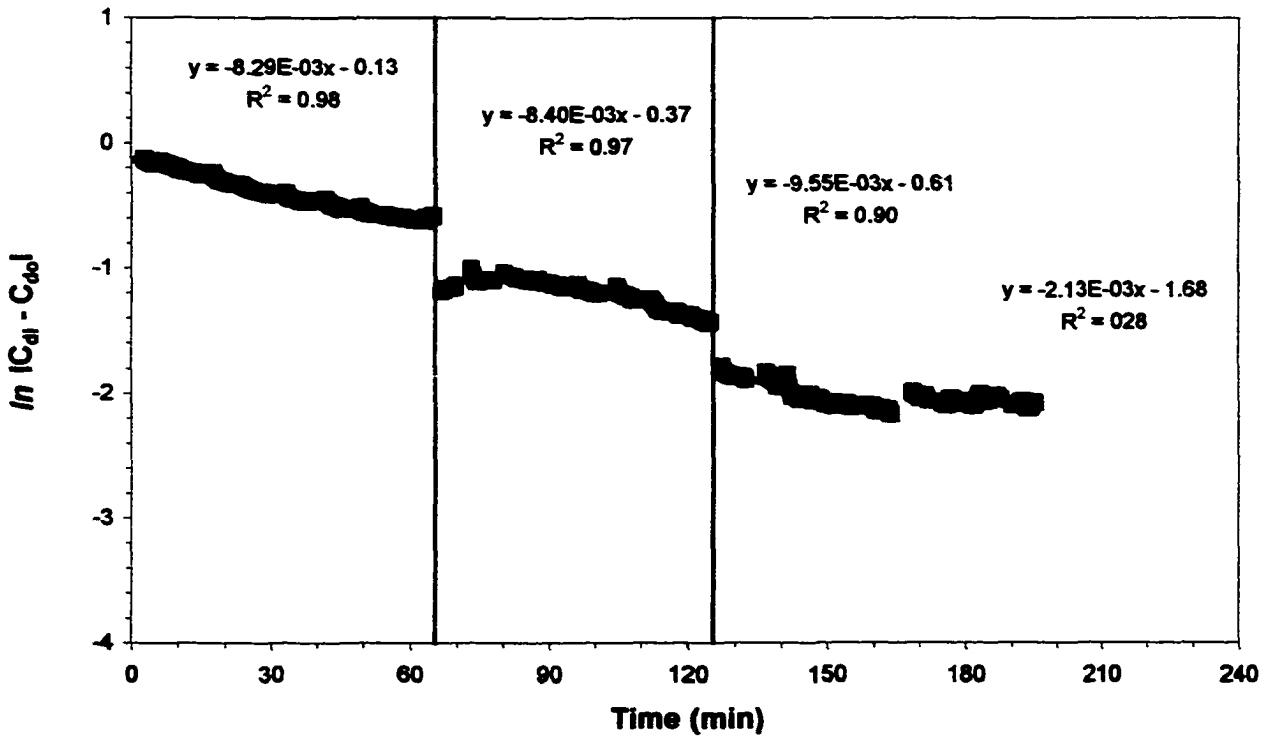


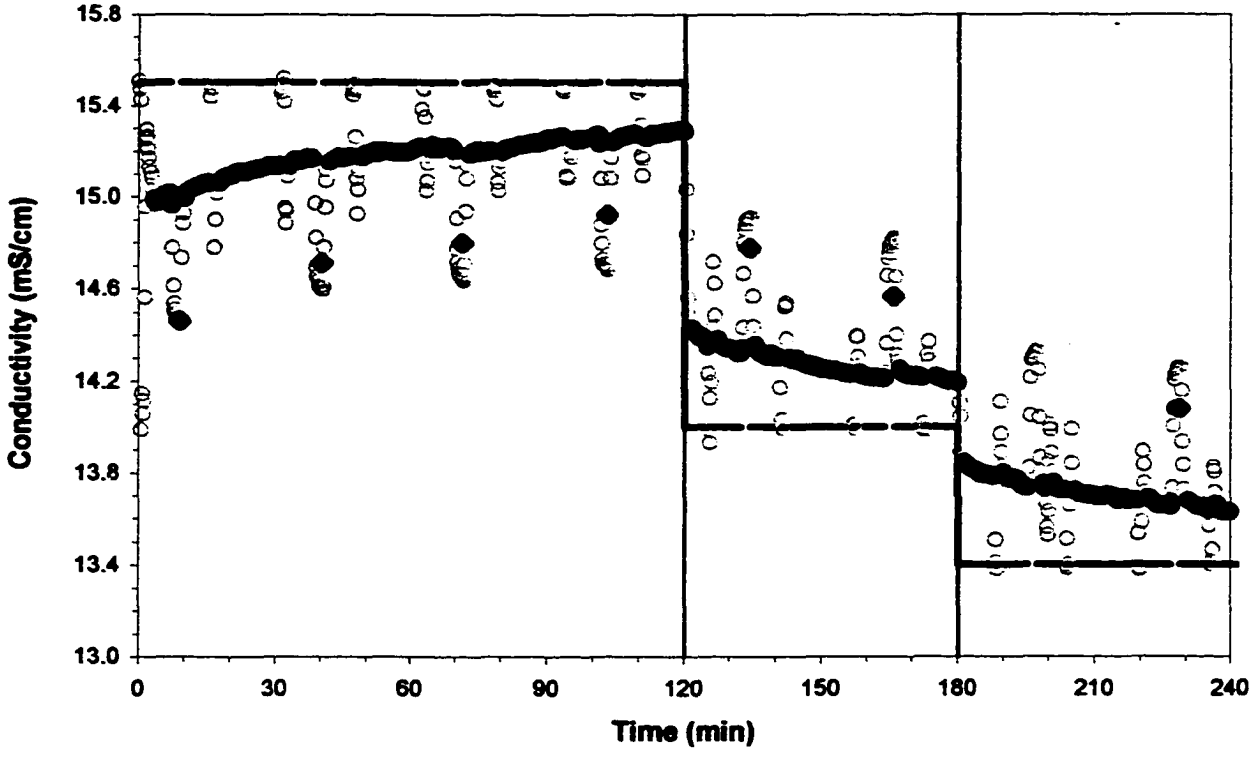


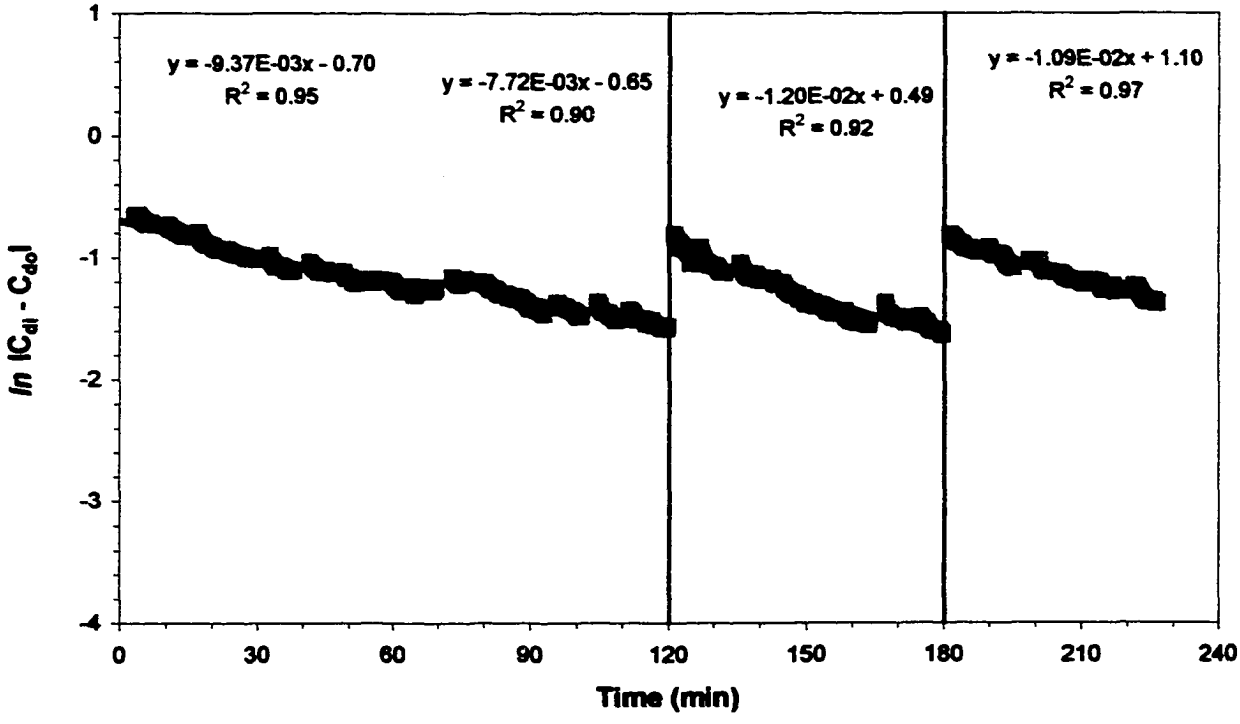


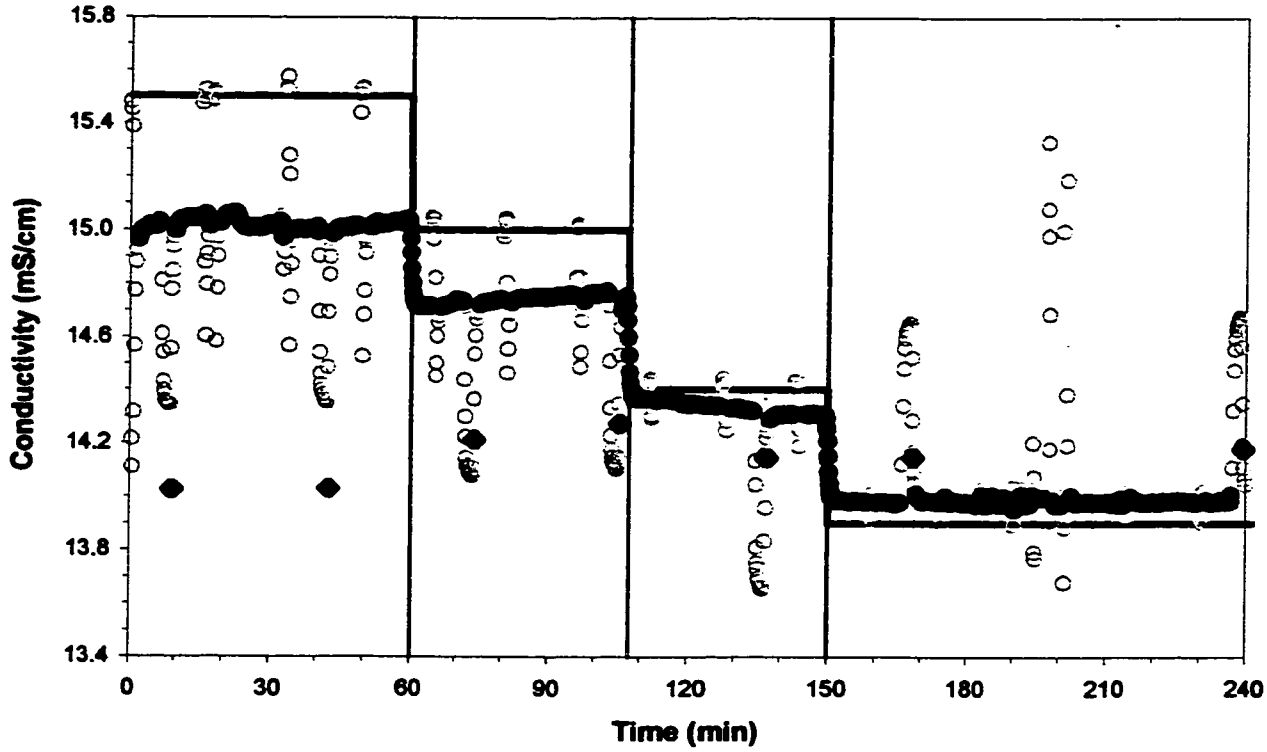
Session MJ061198

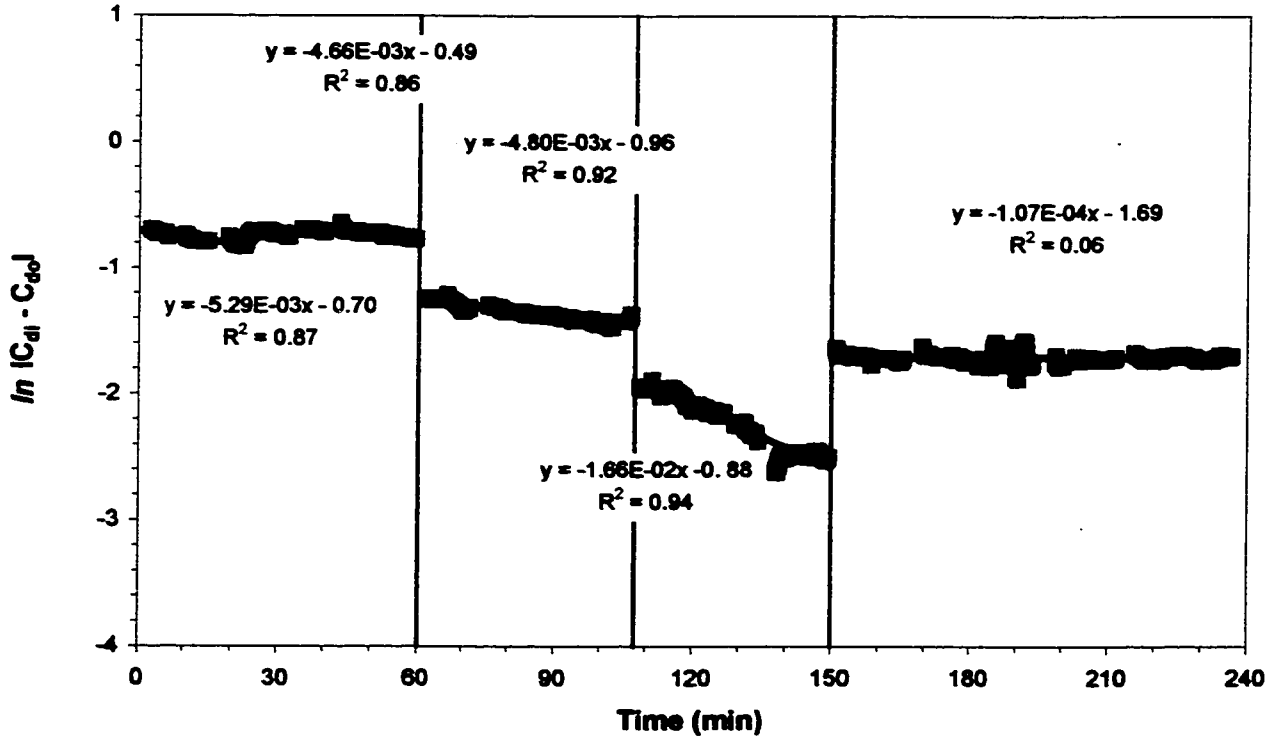


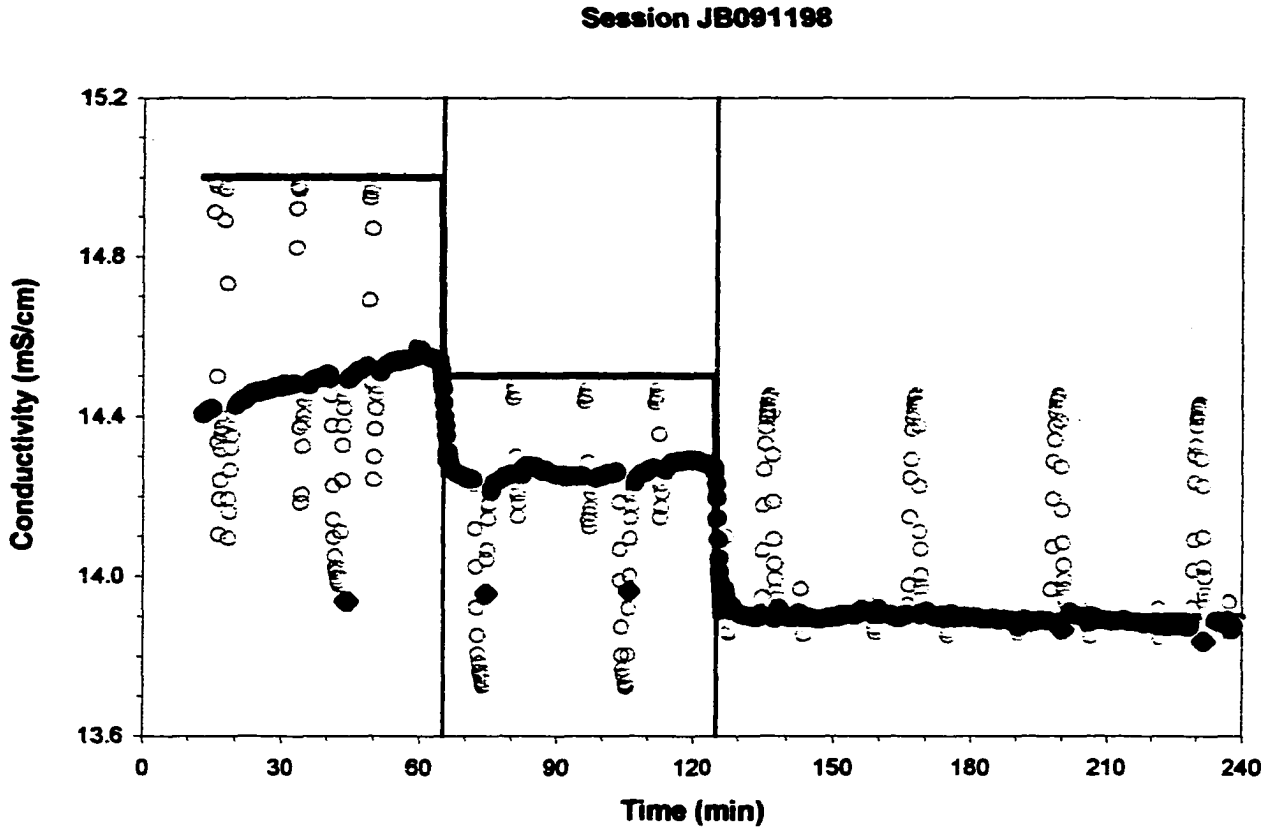


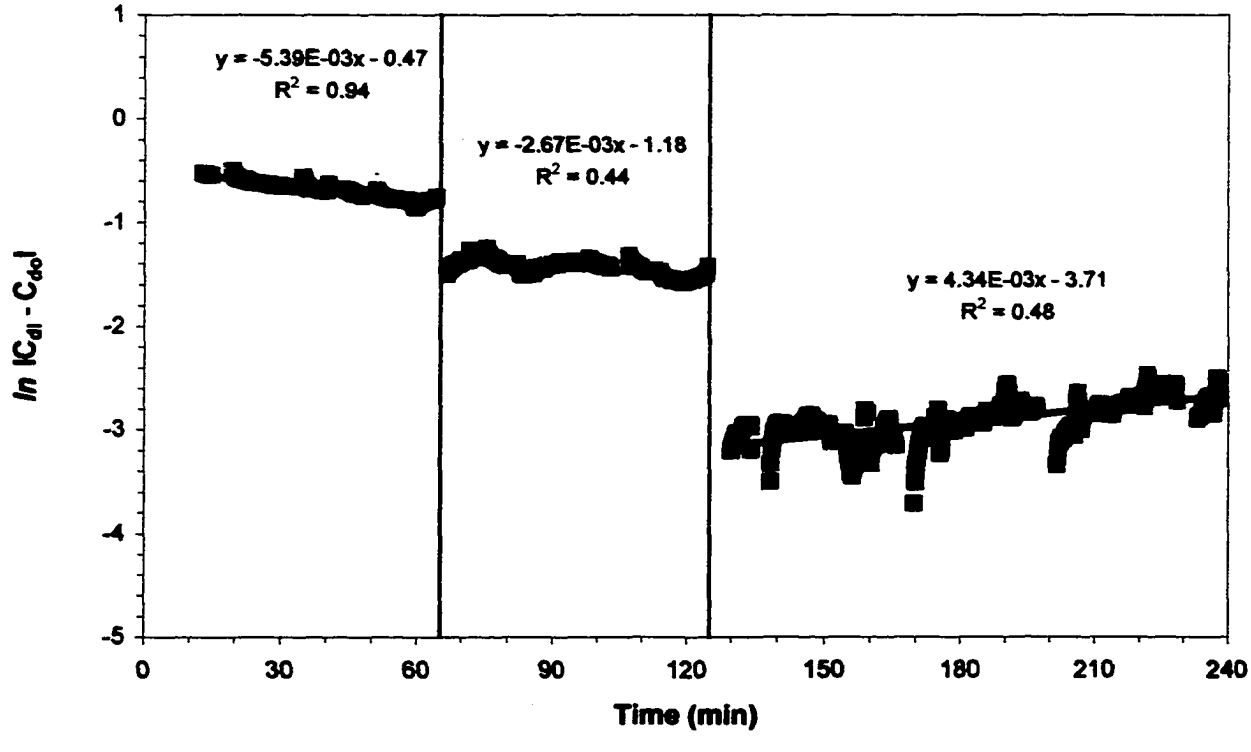




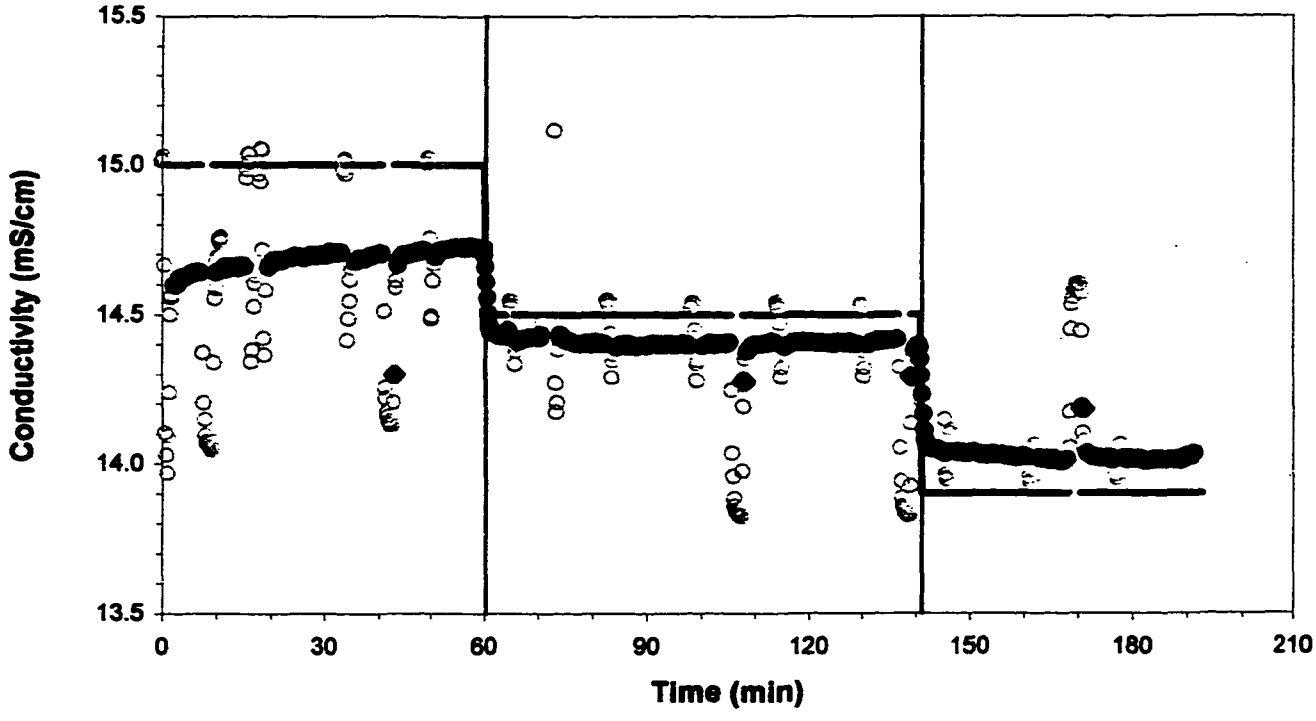


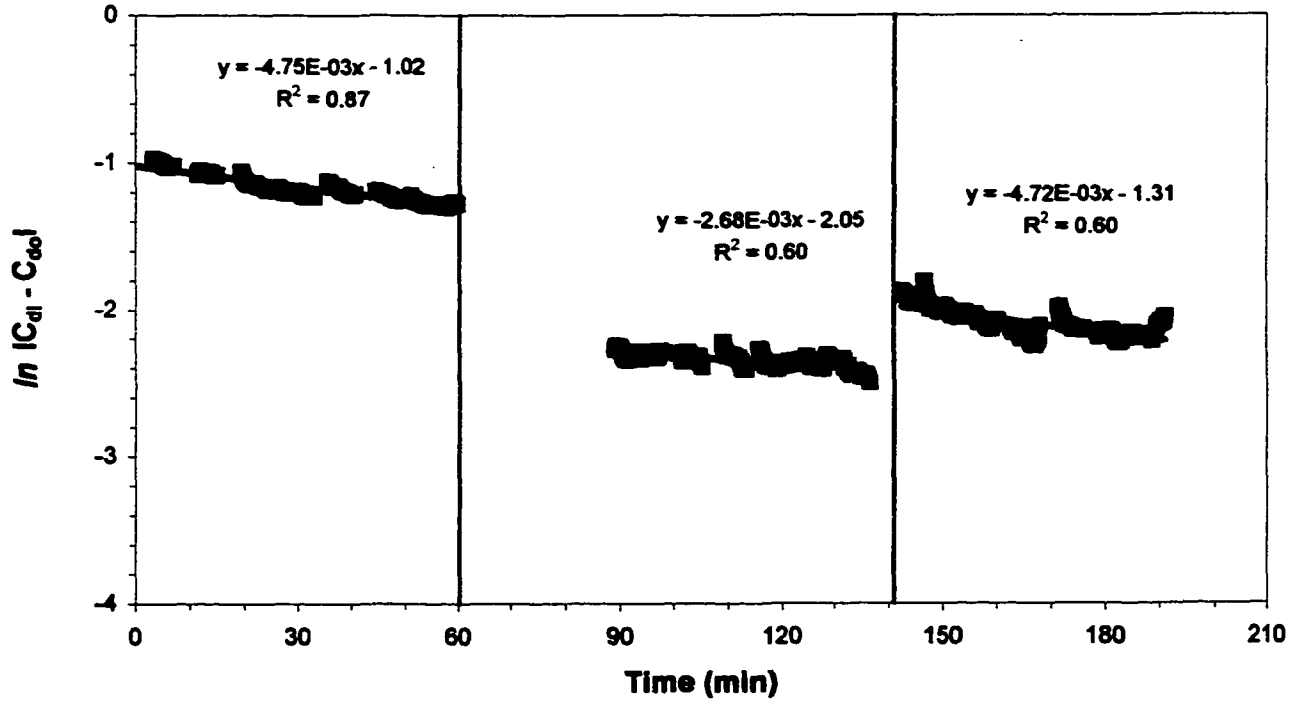




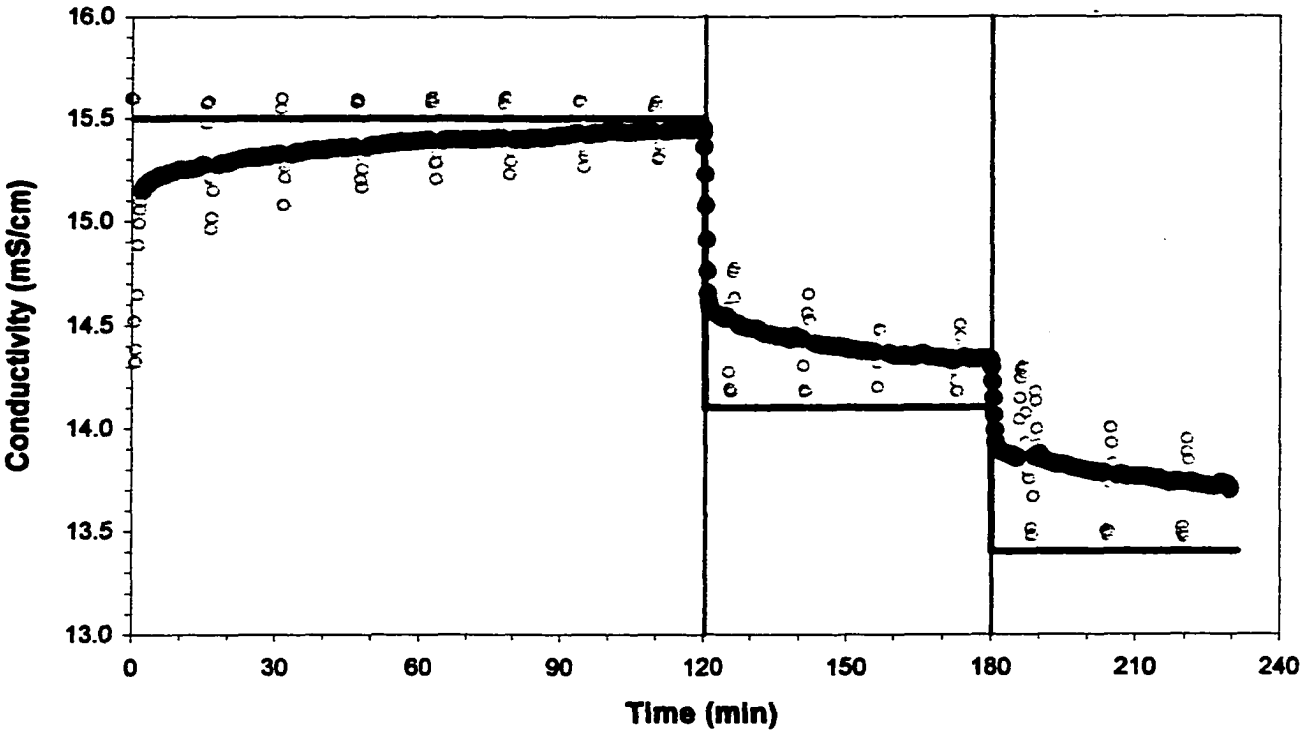


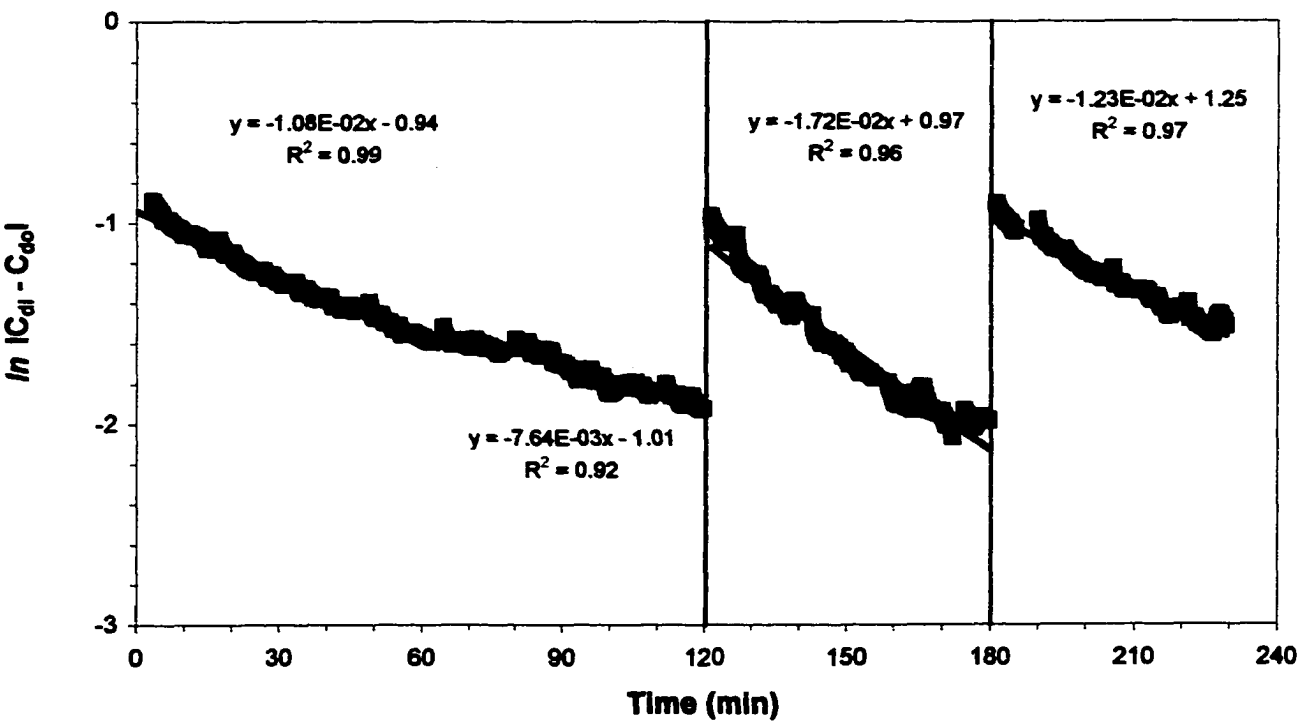
Session MA091198





Session CL101198





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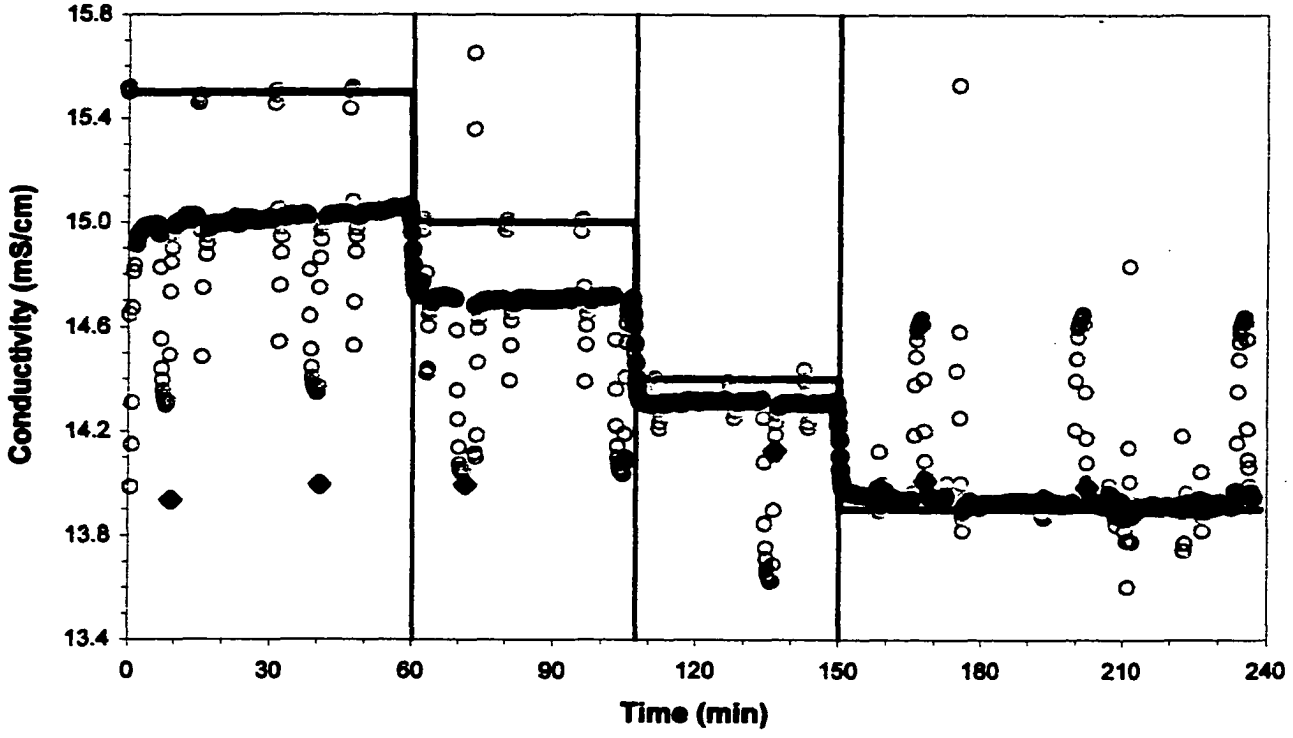

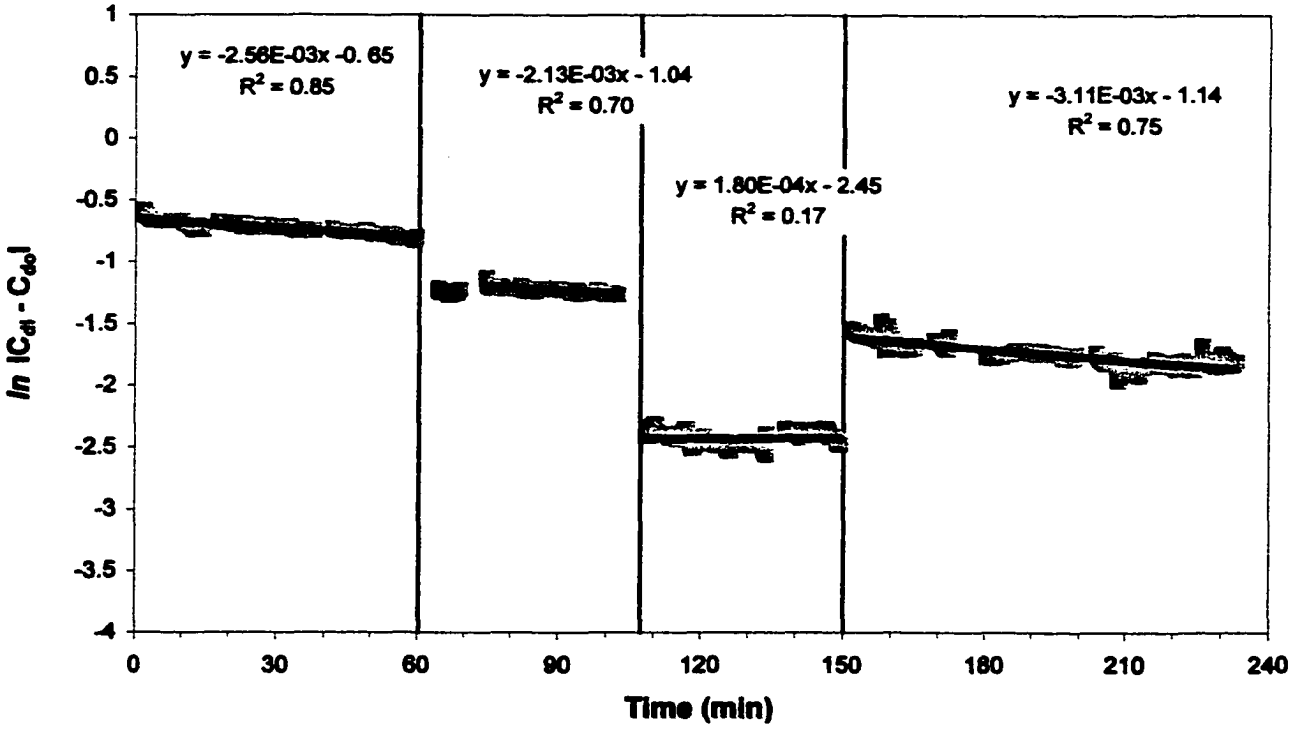

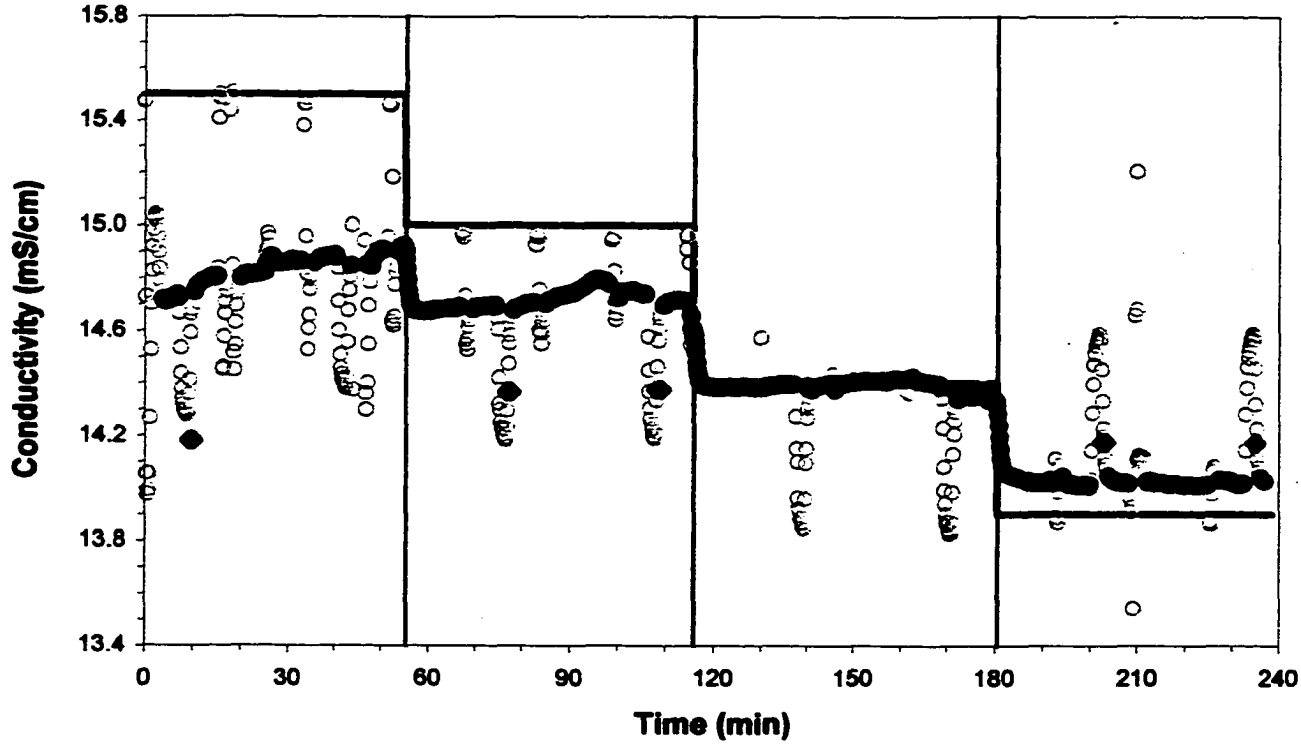

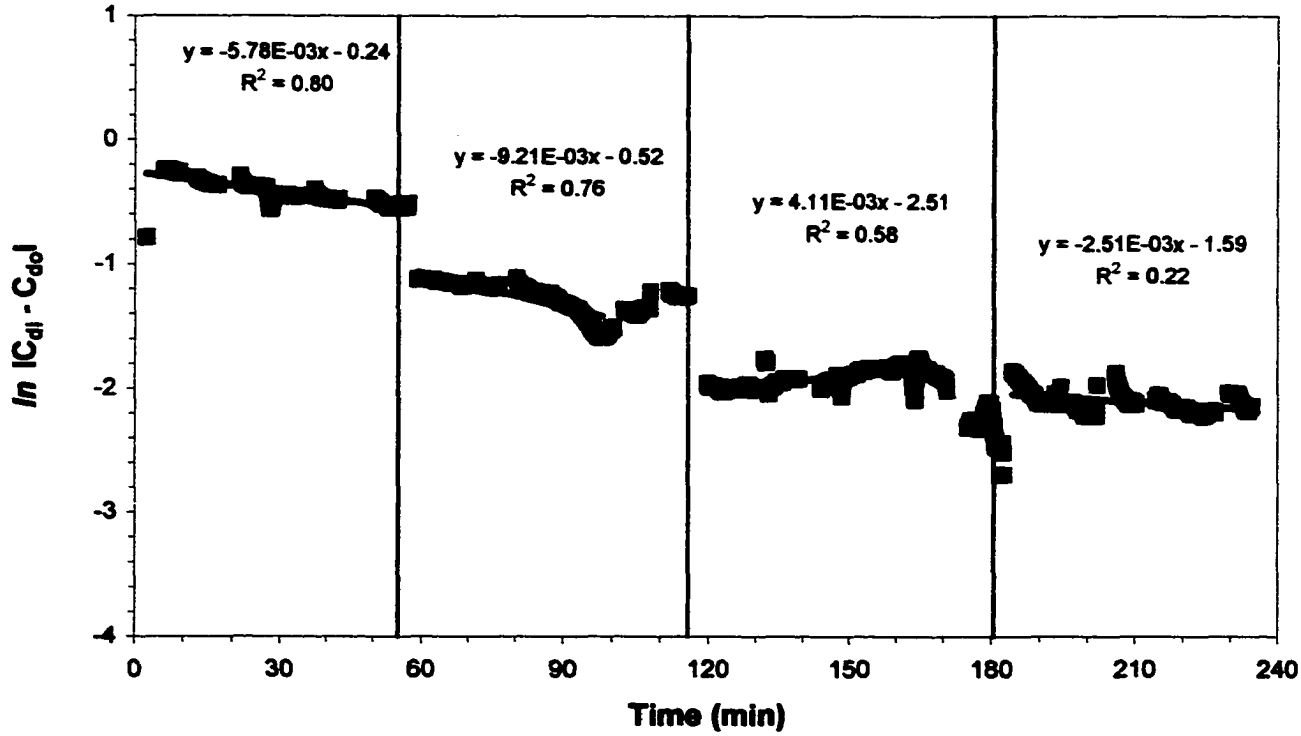

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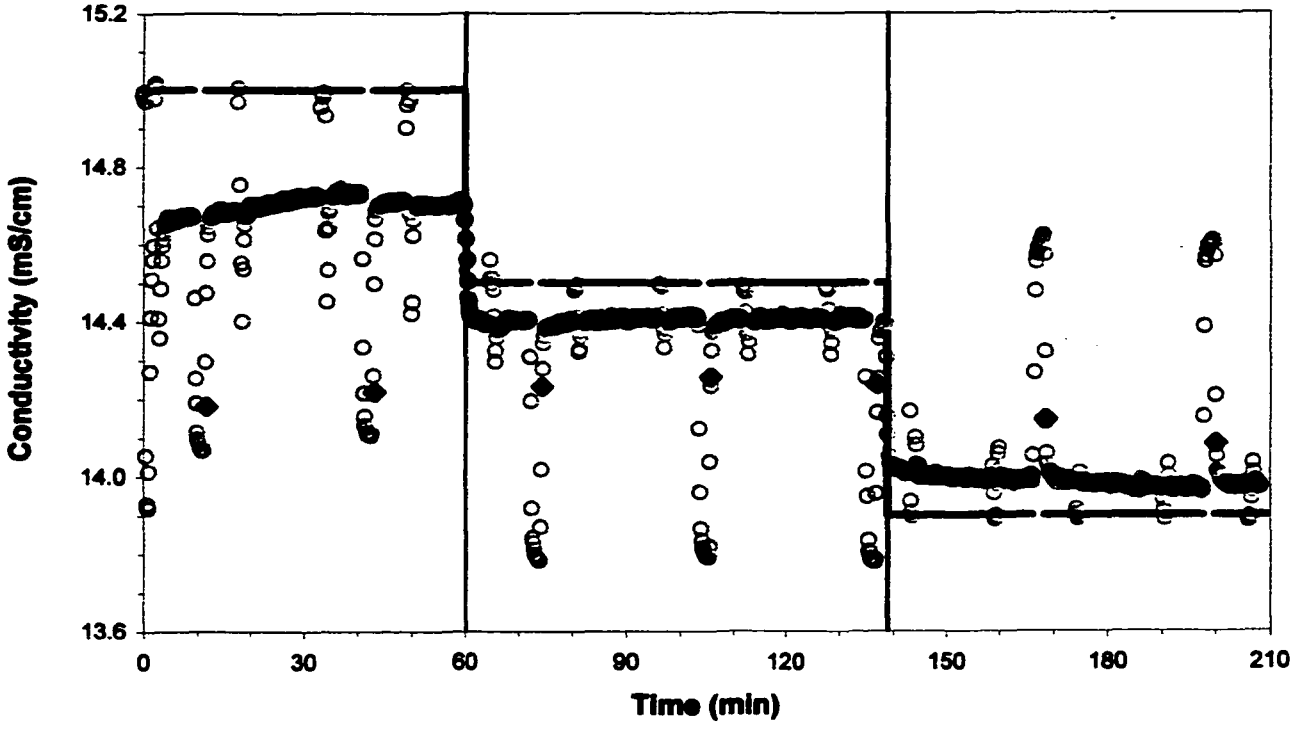

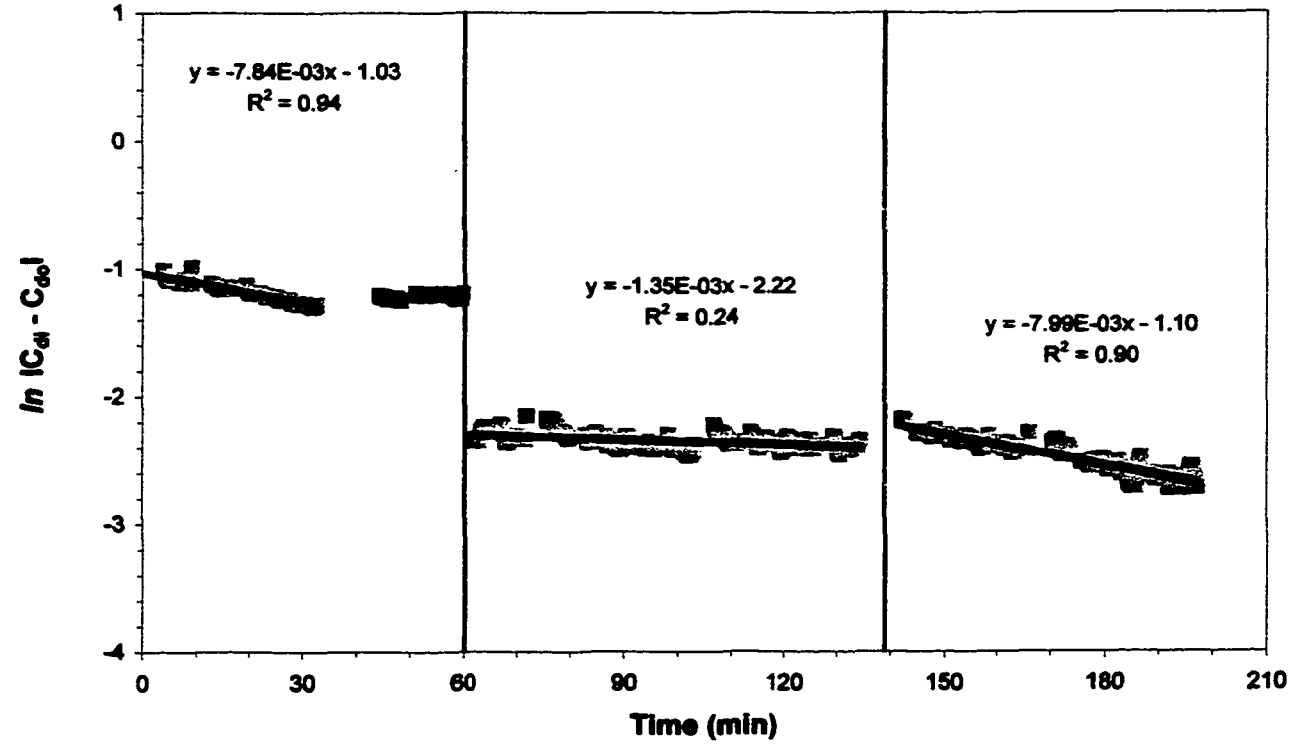

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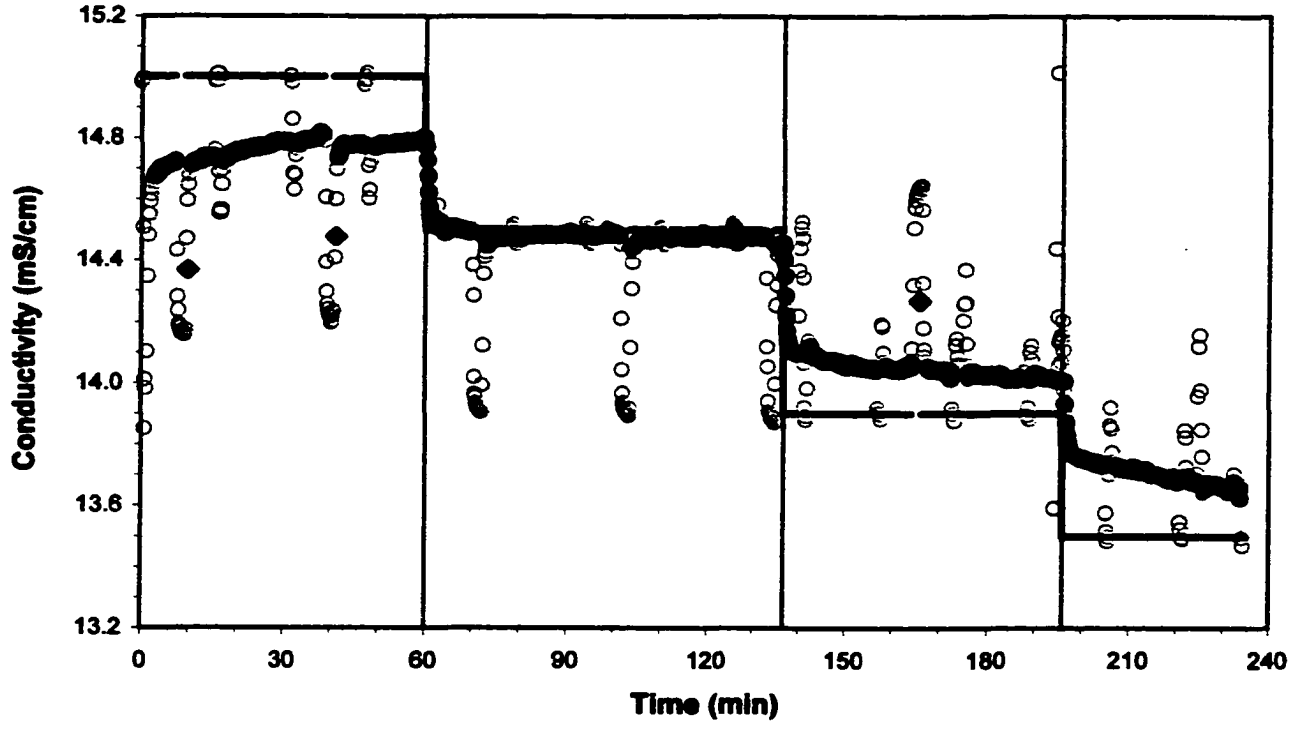

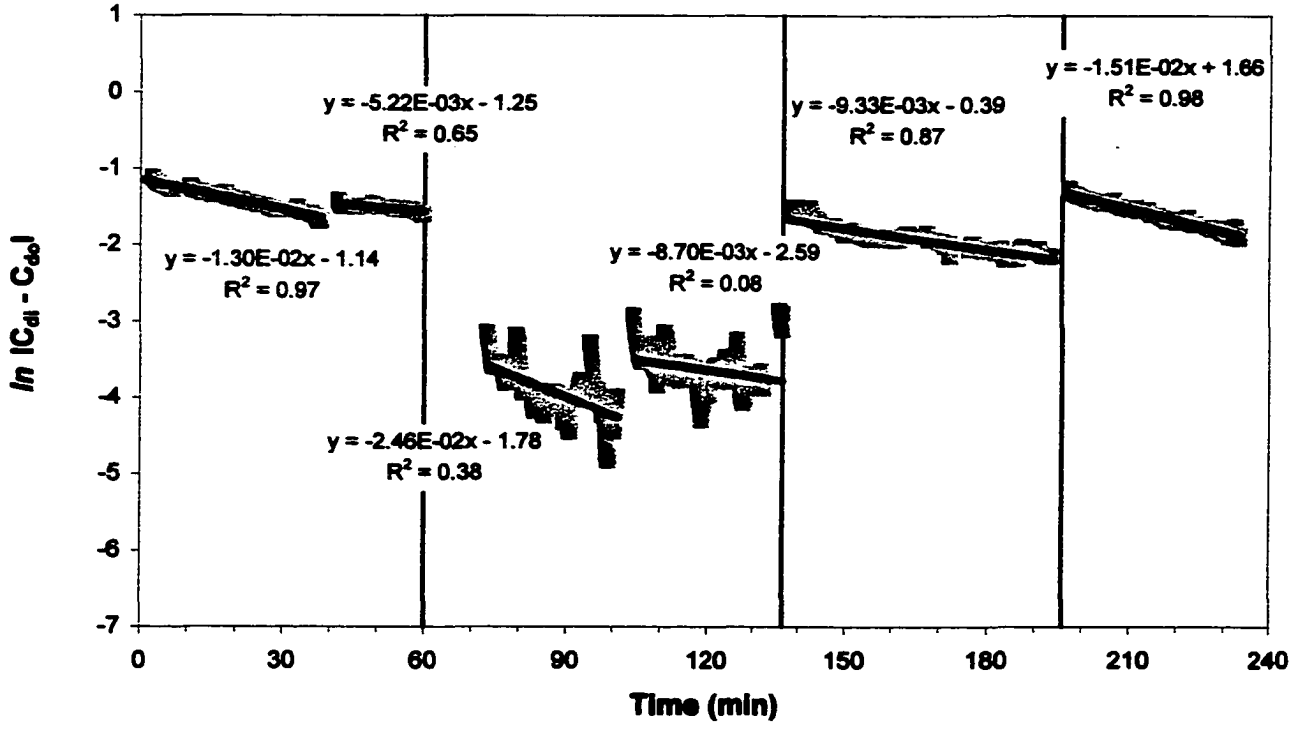

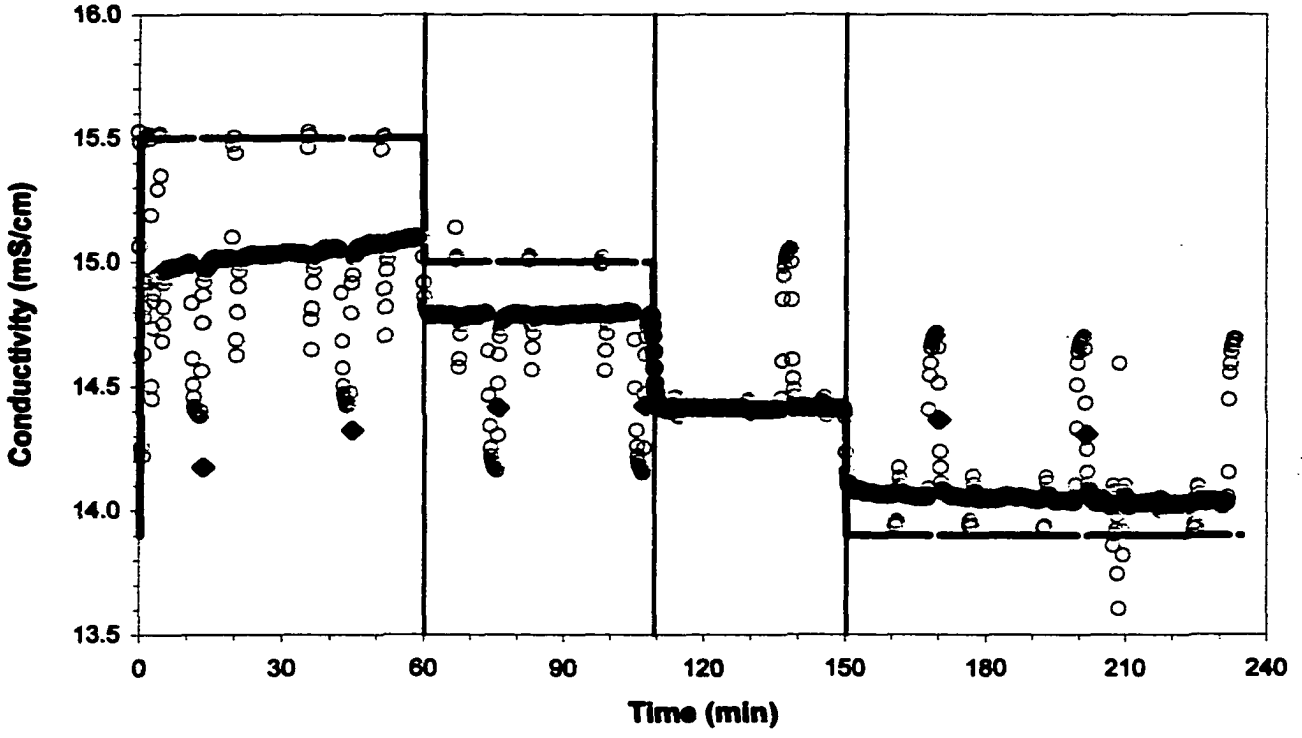

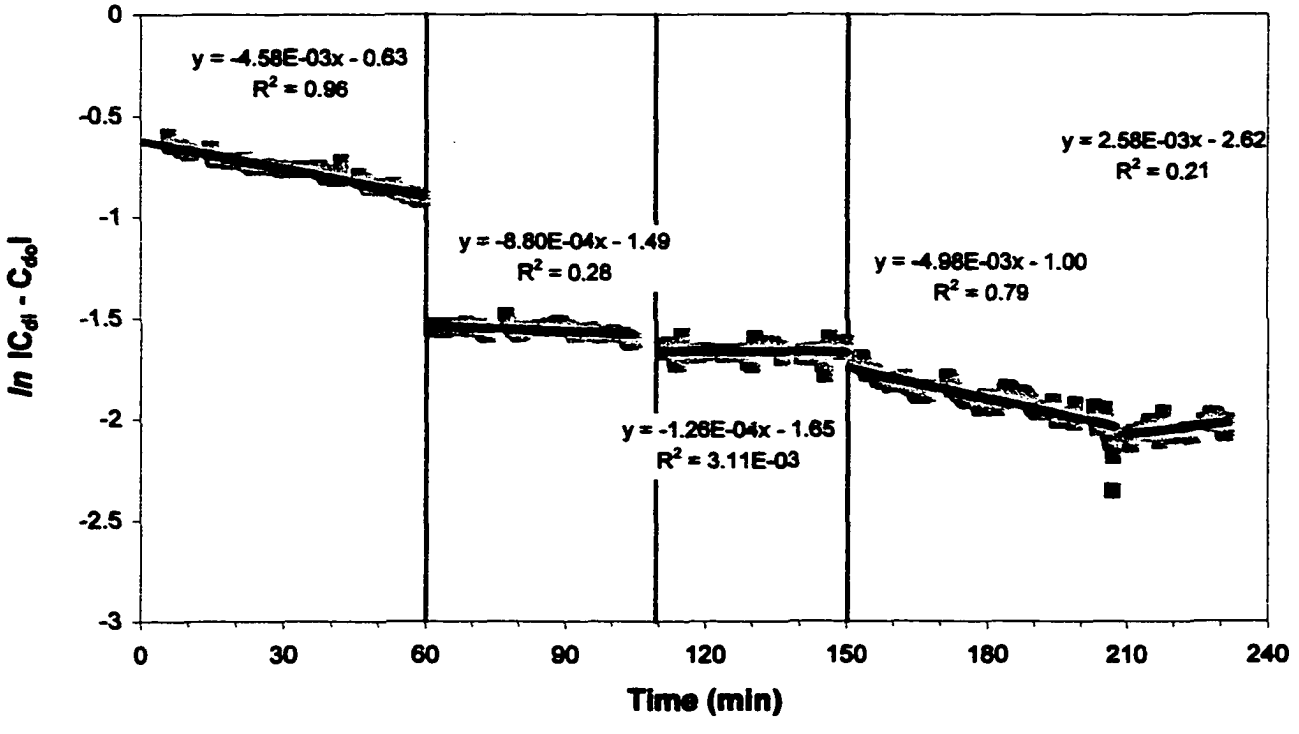

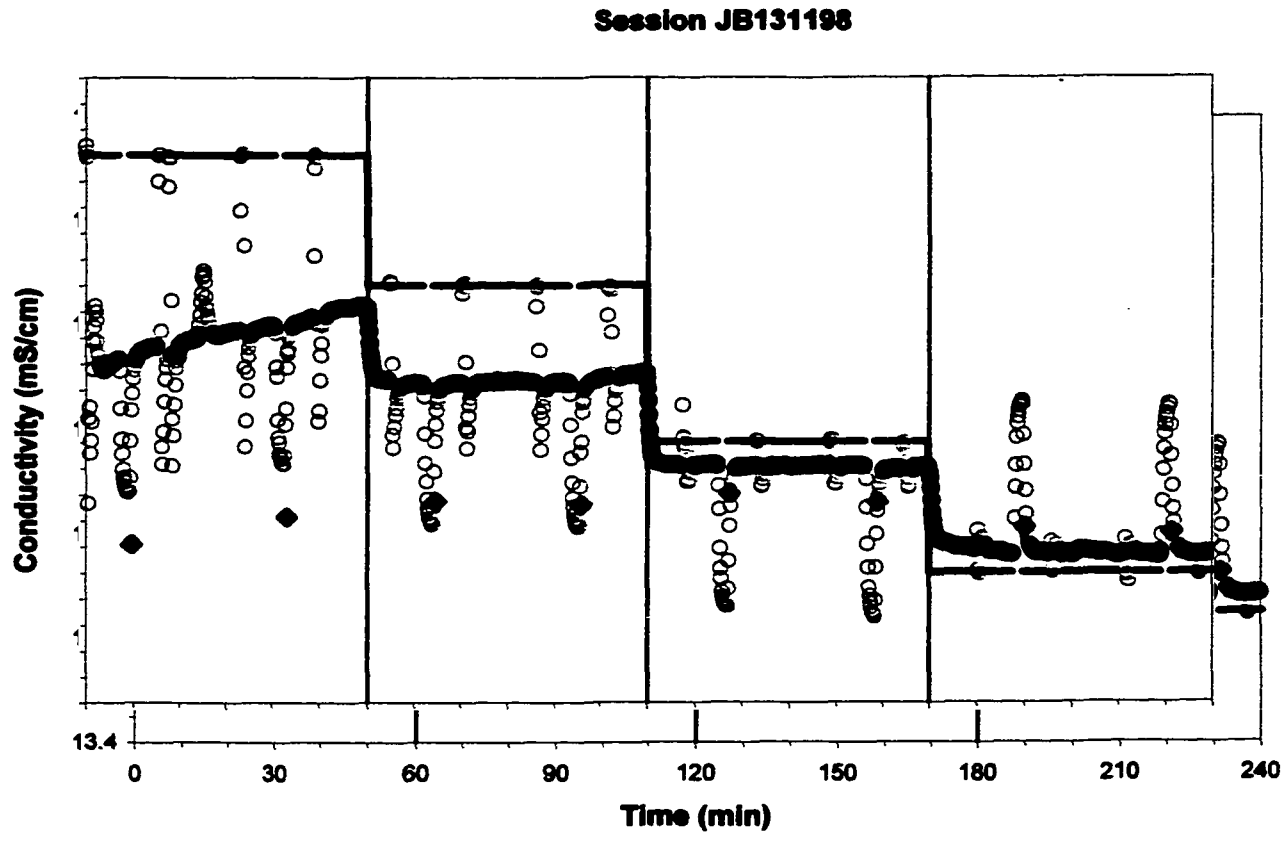

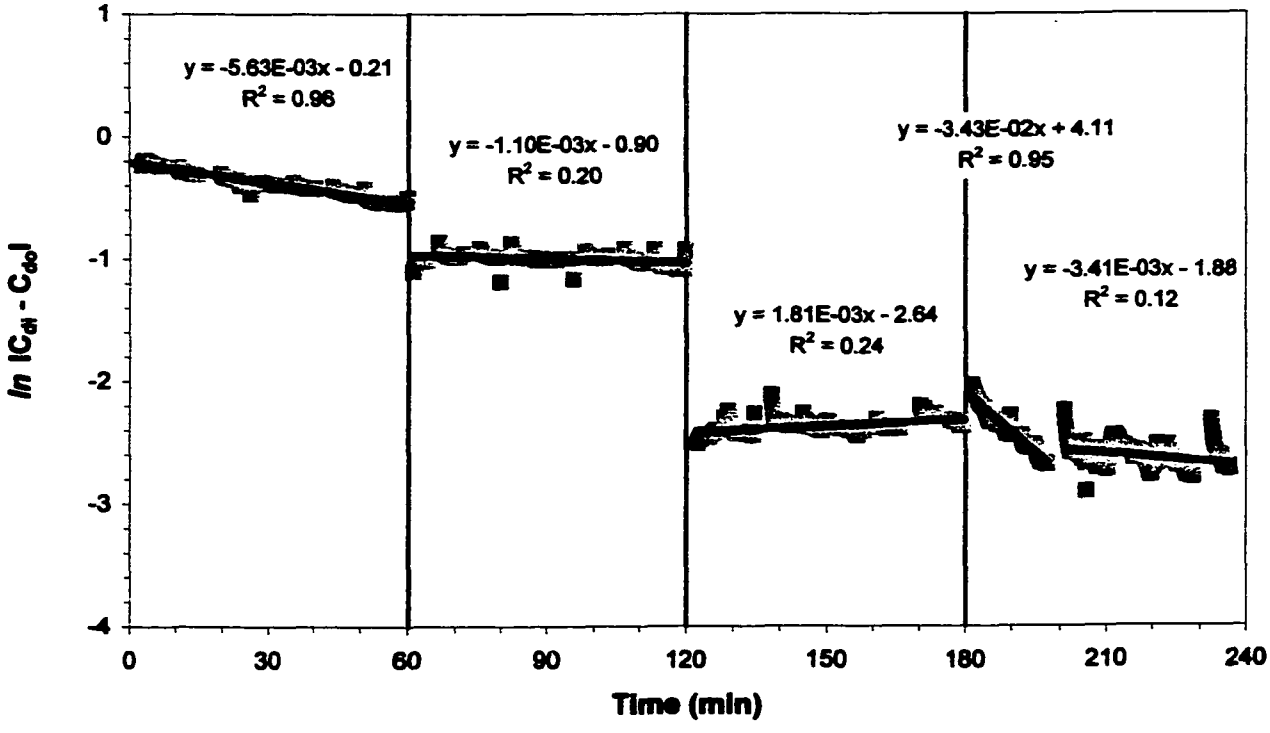

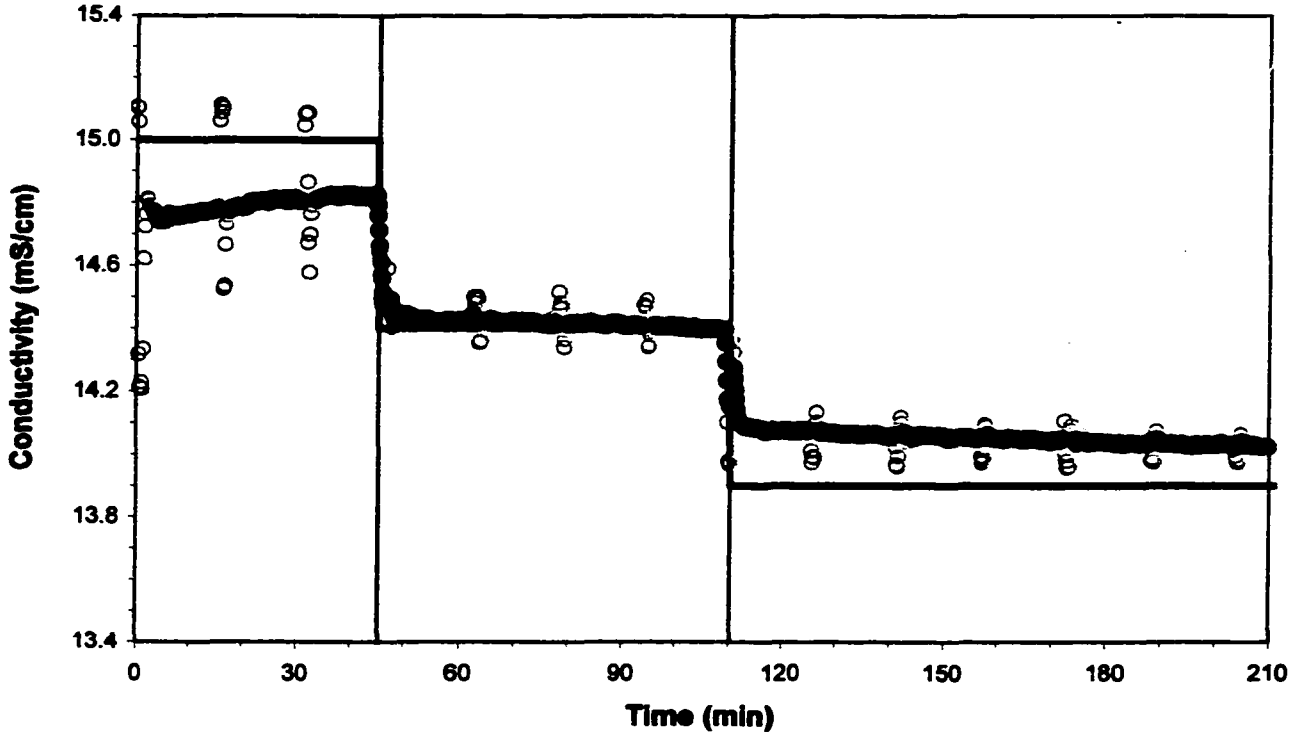

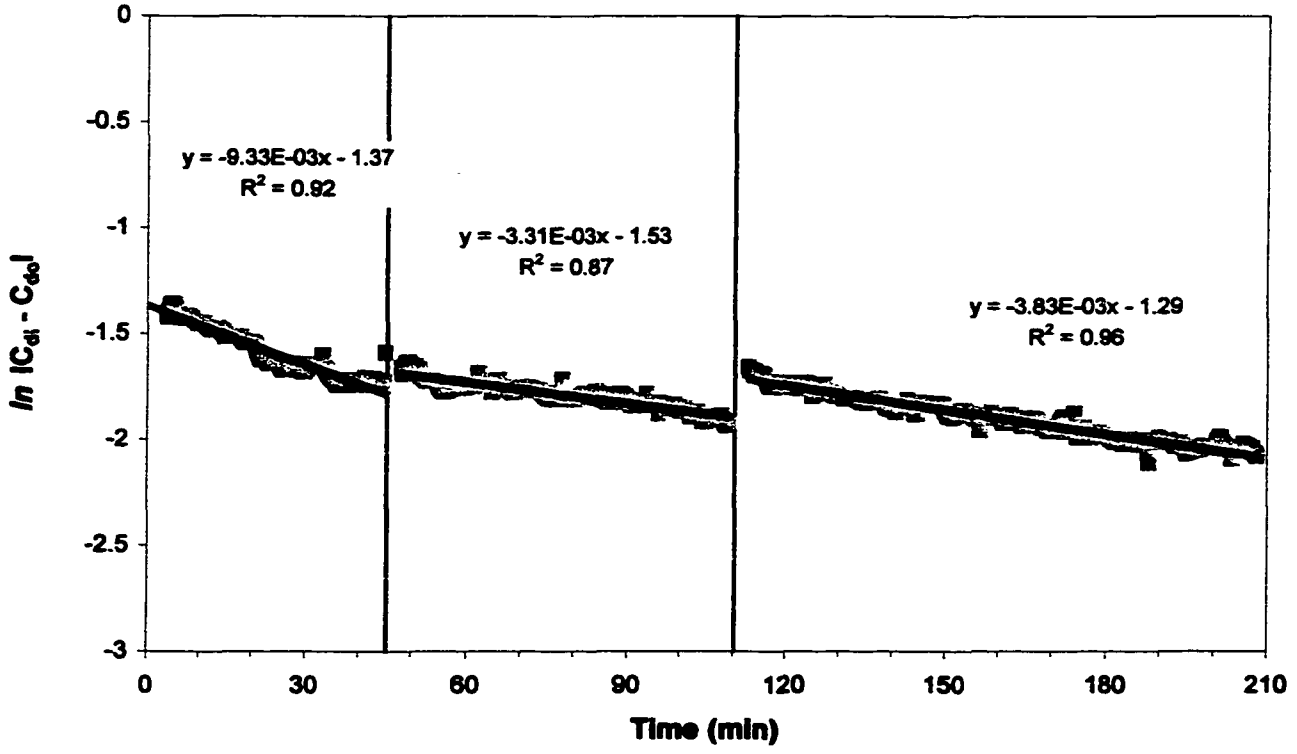

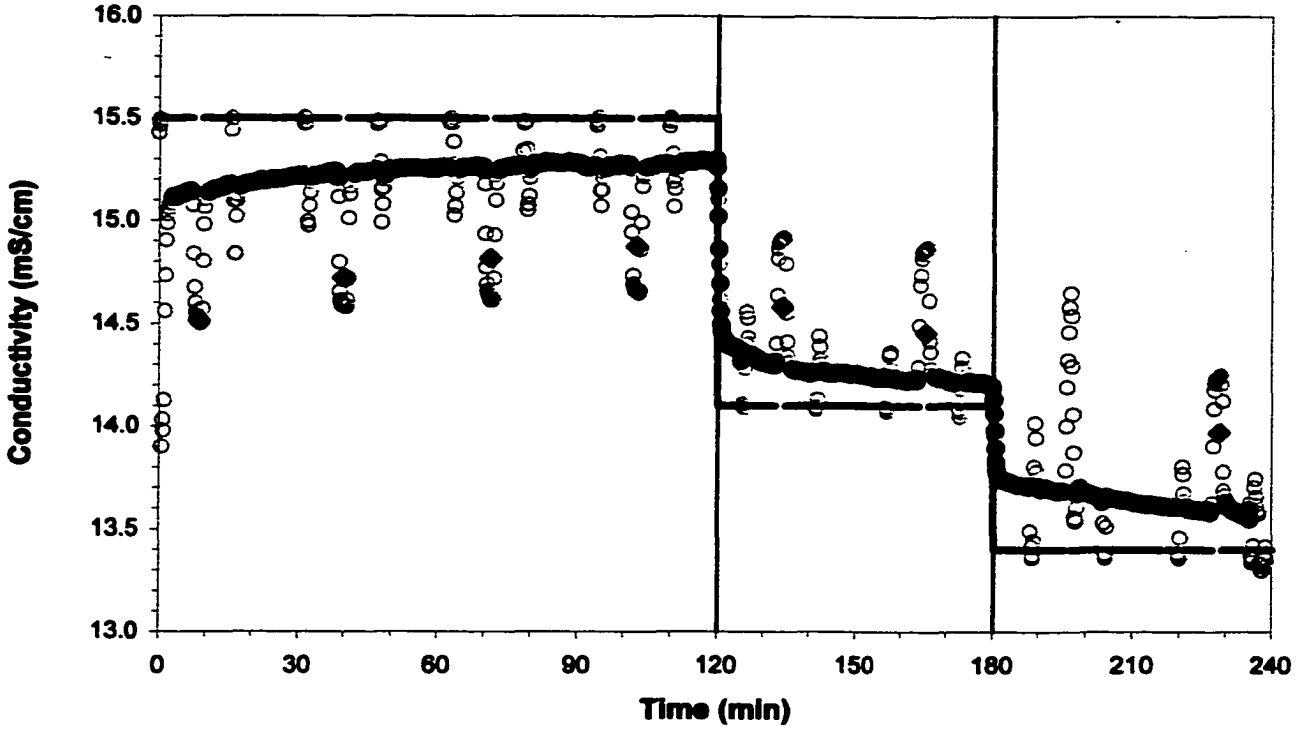

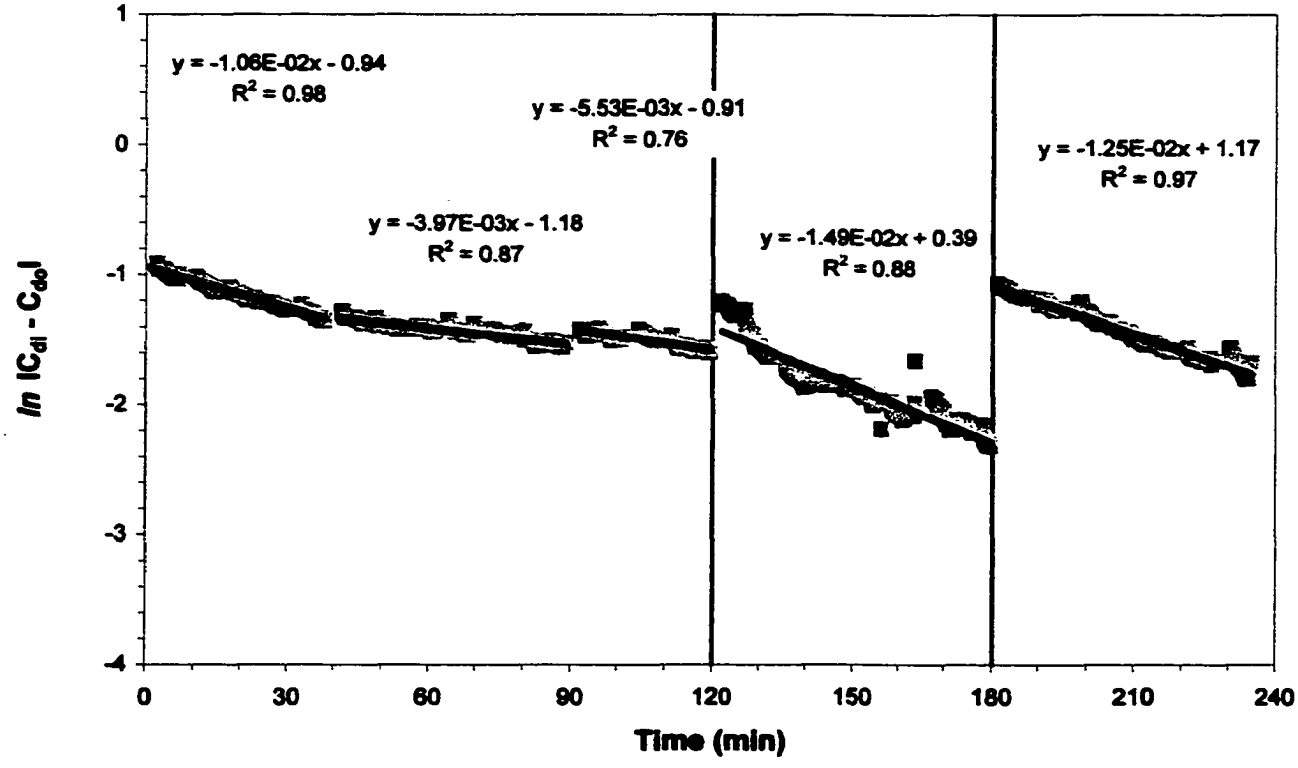

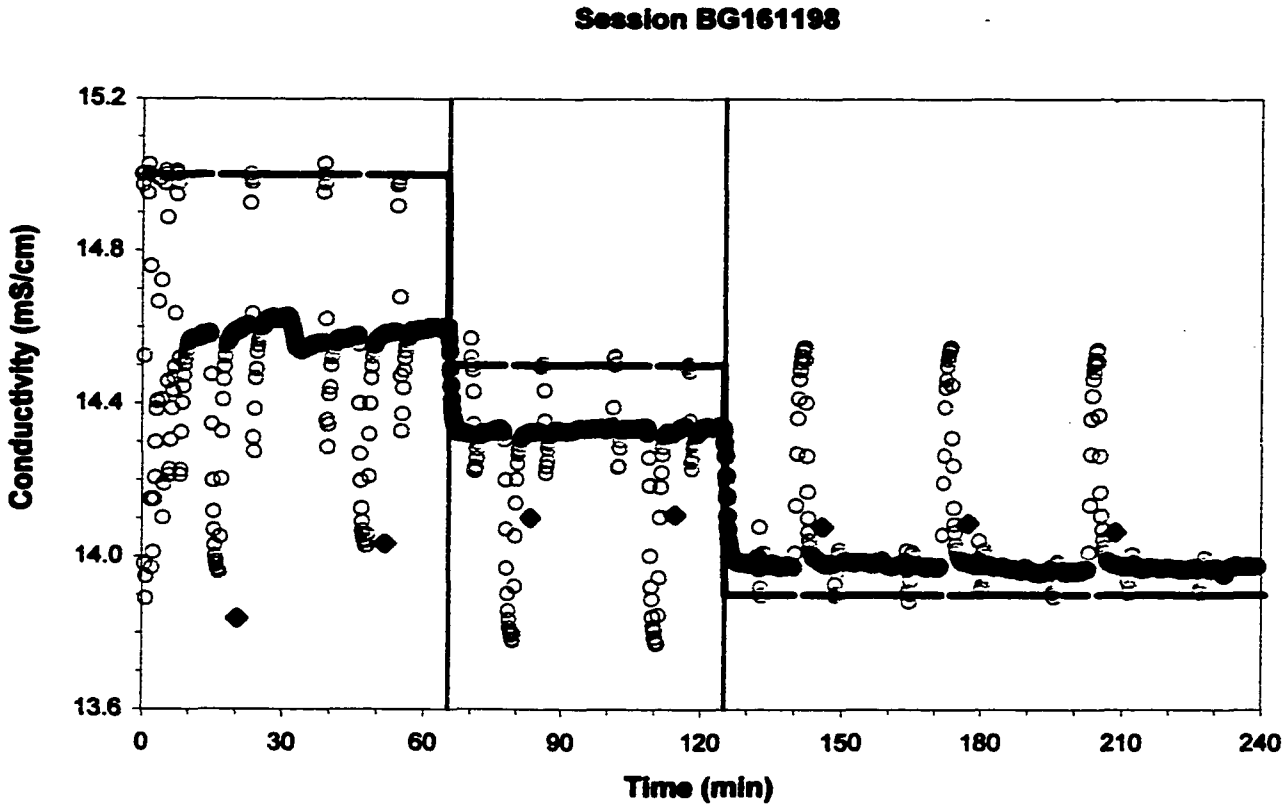

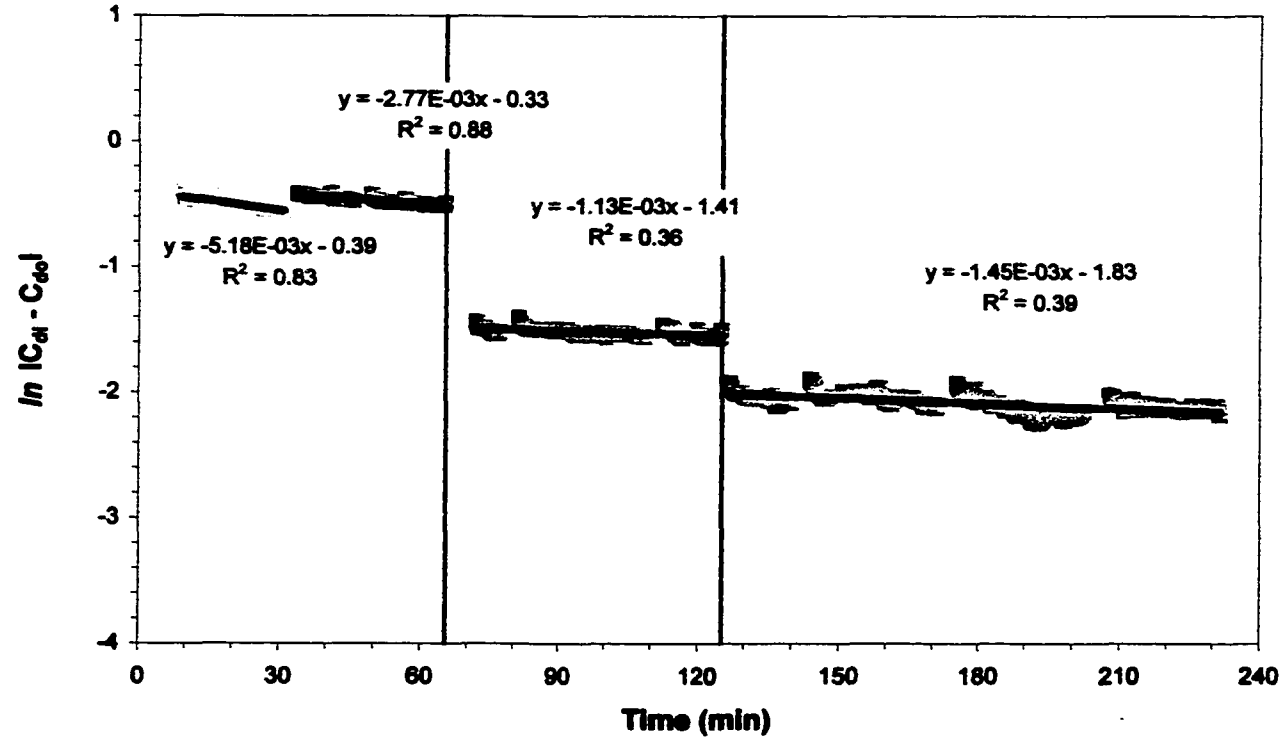

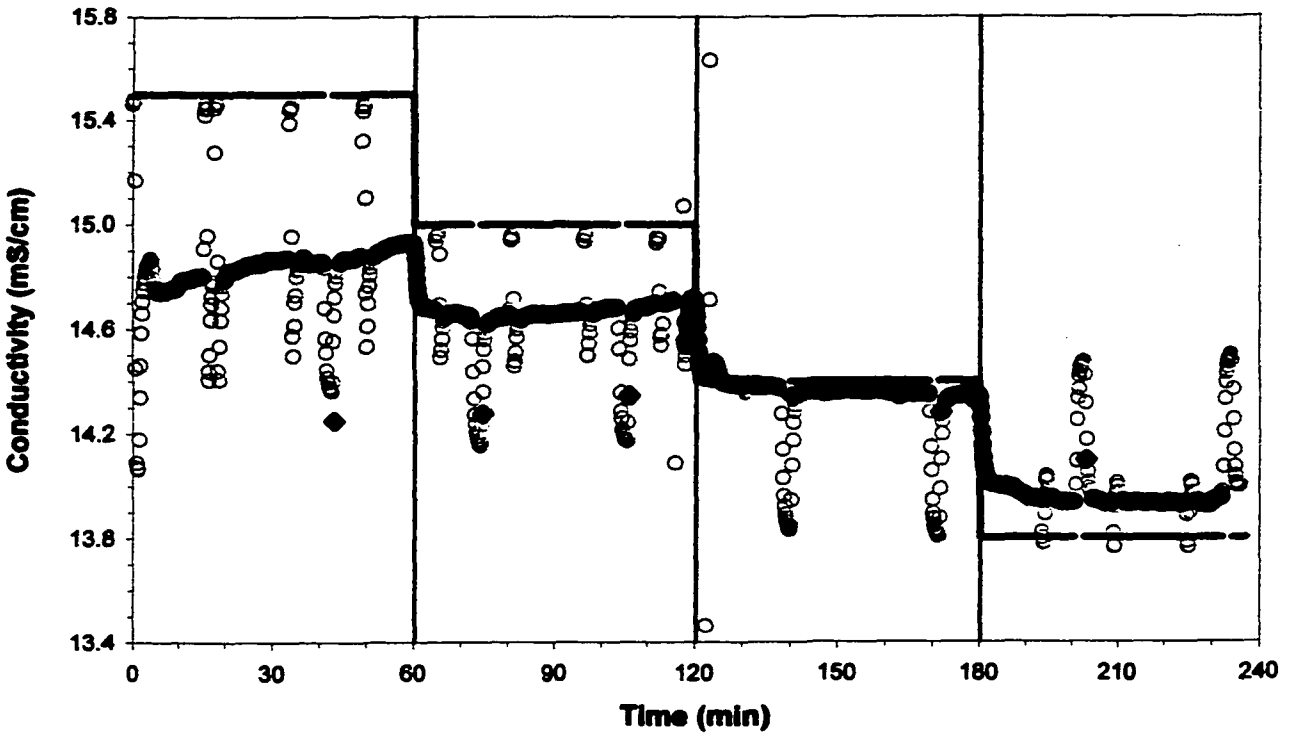

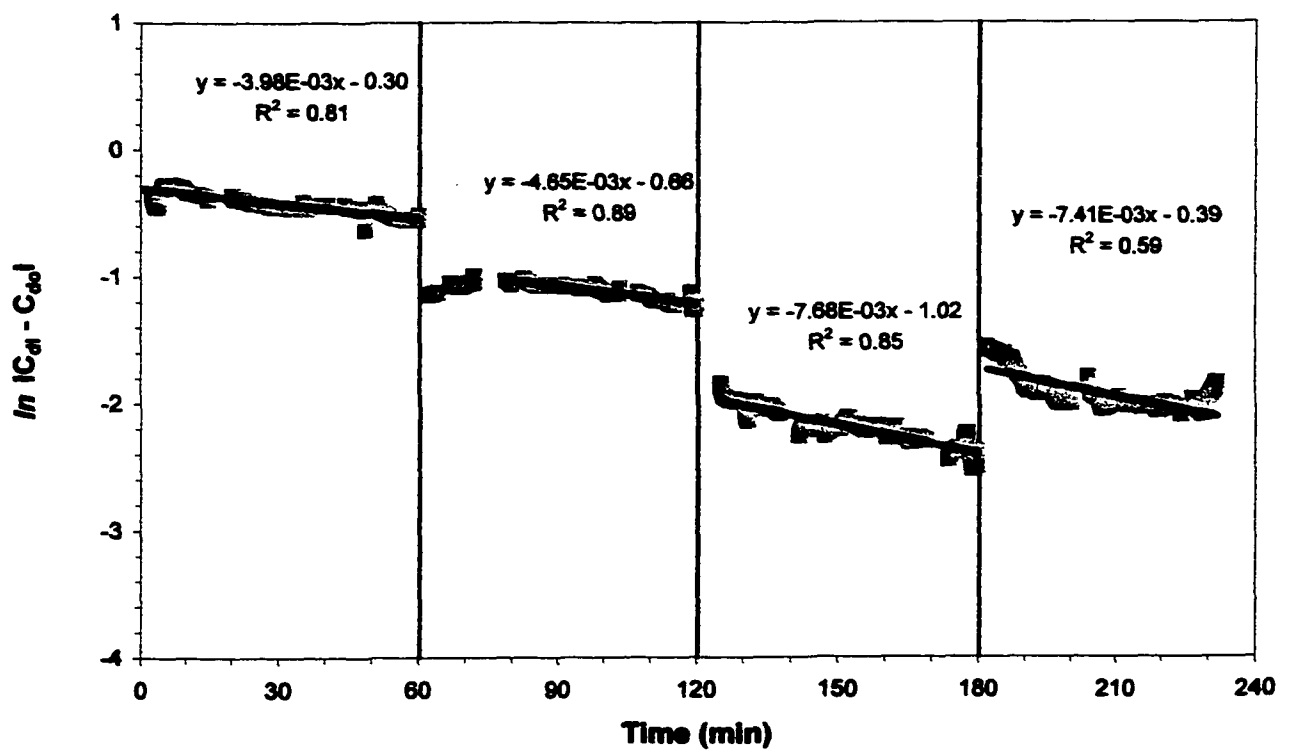

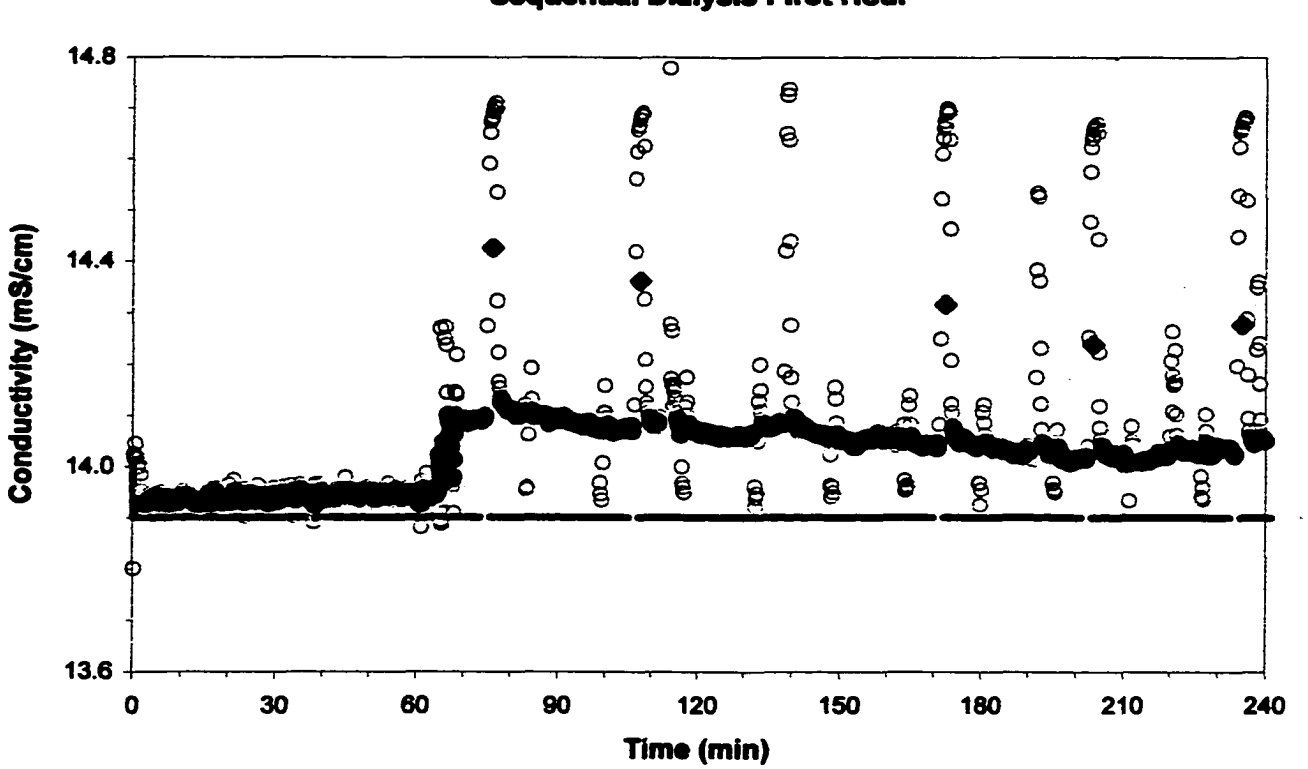

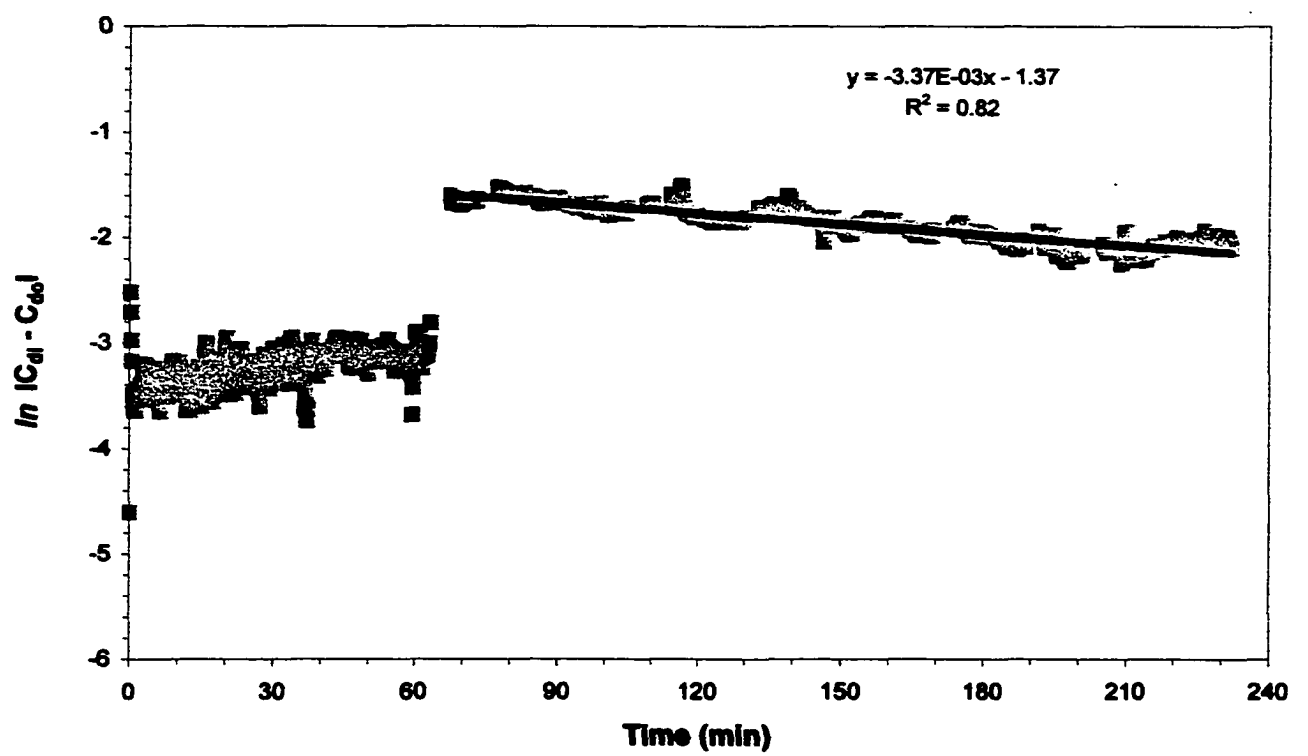

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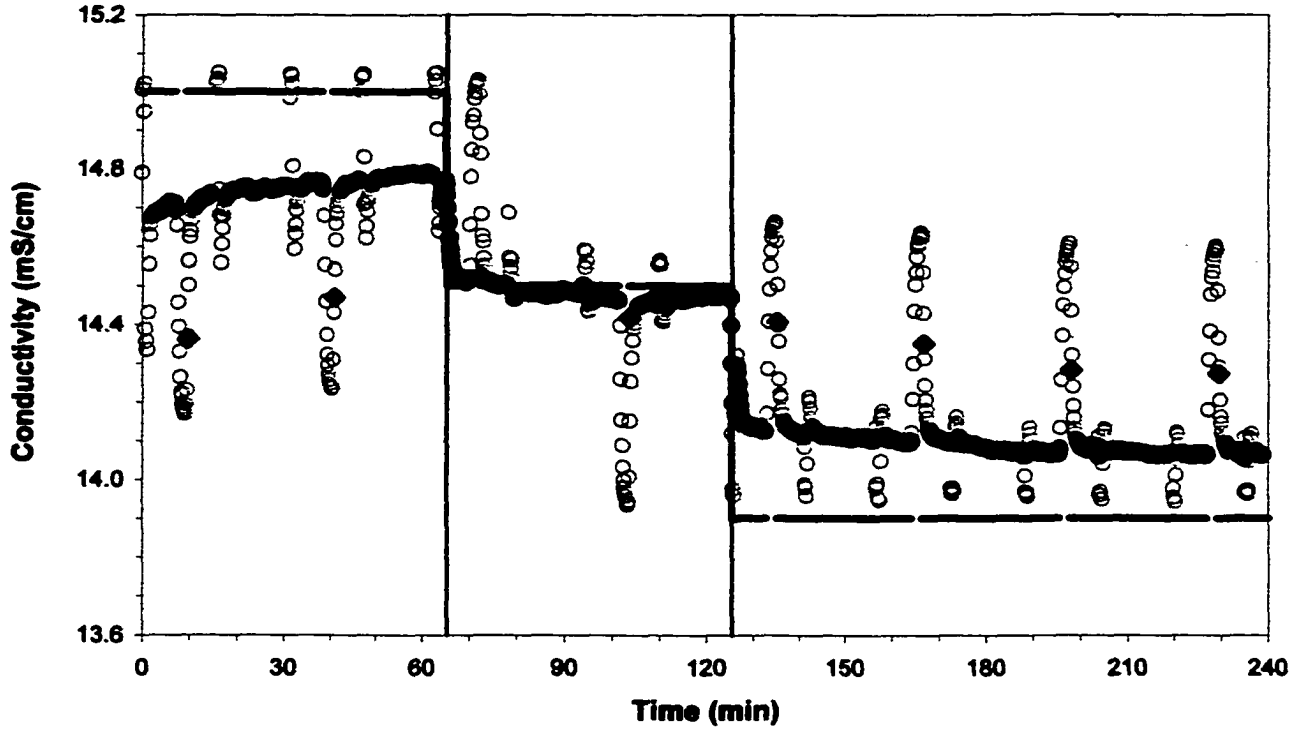

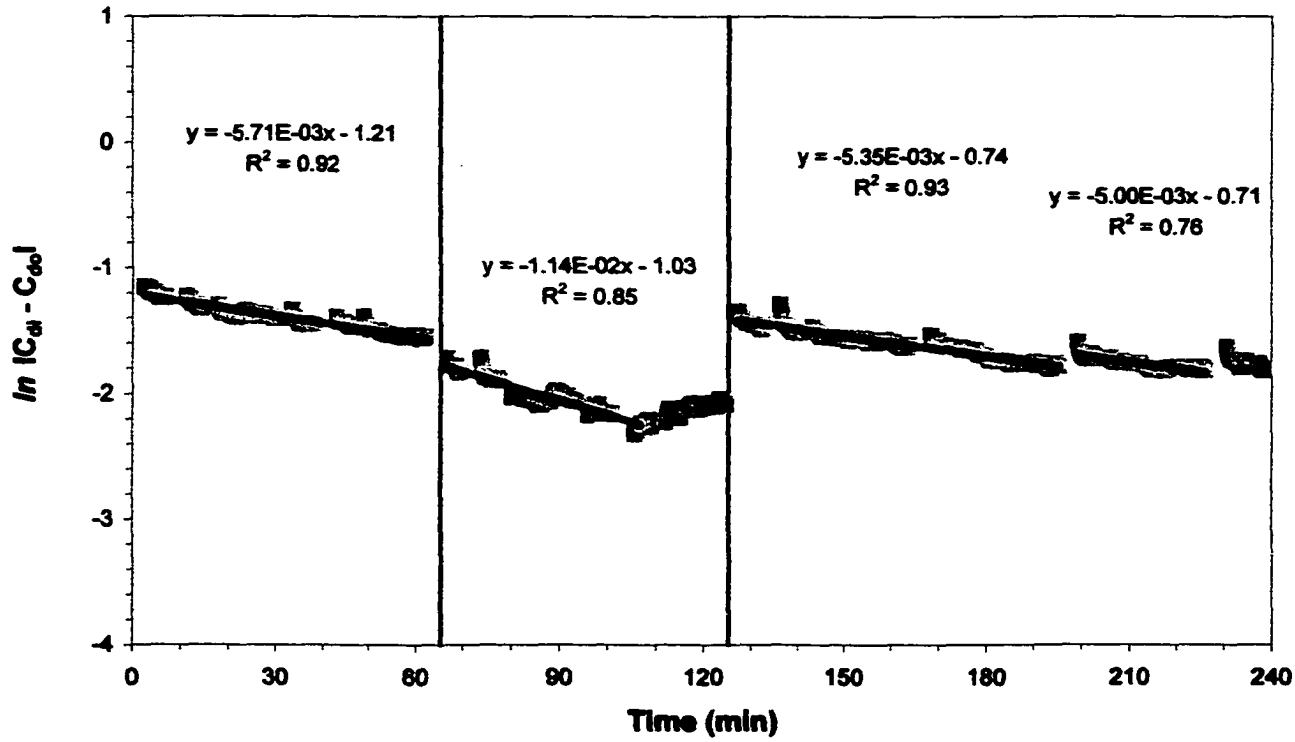

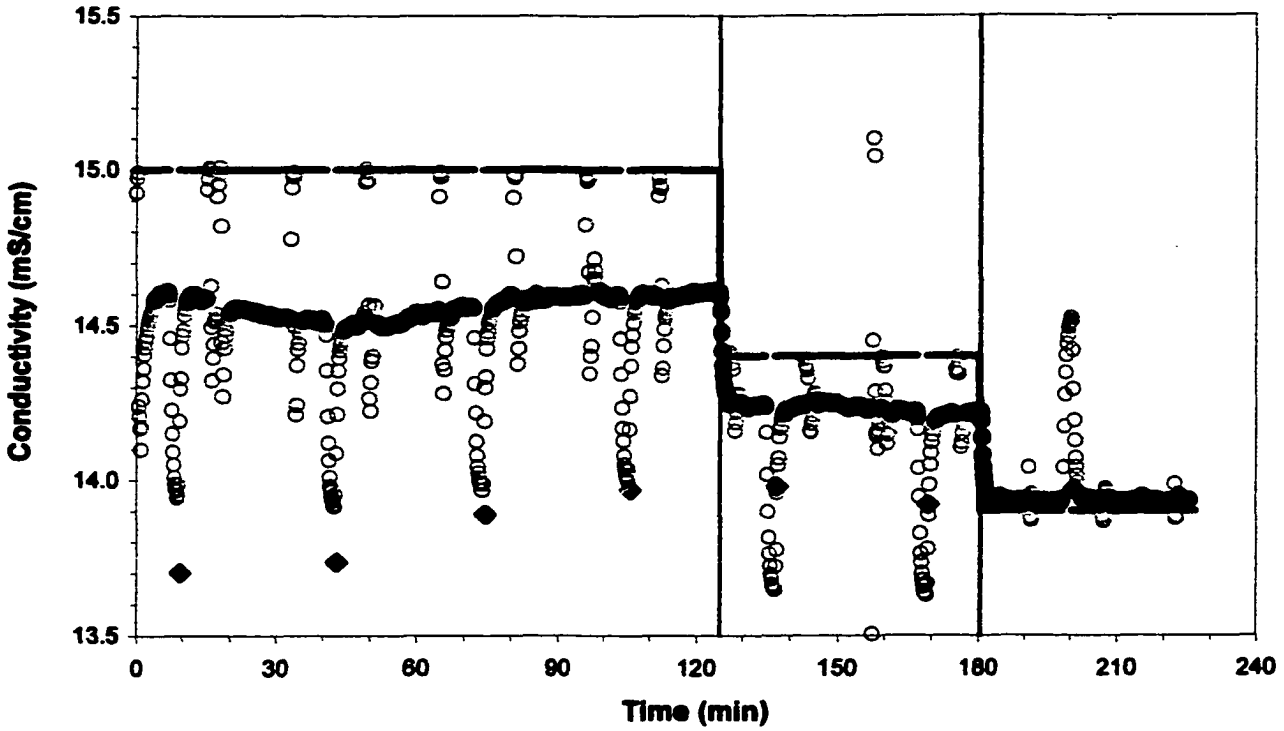

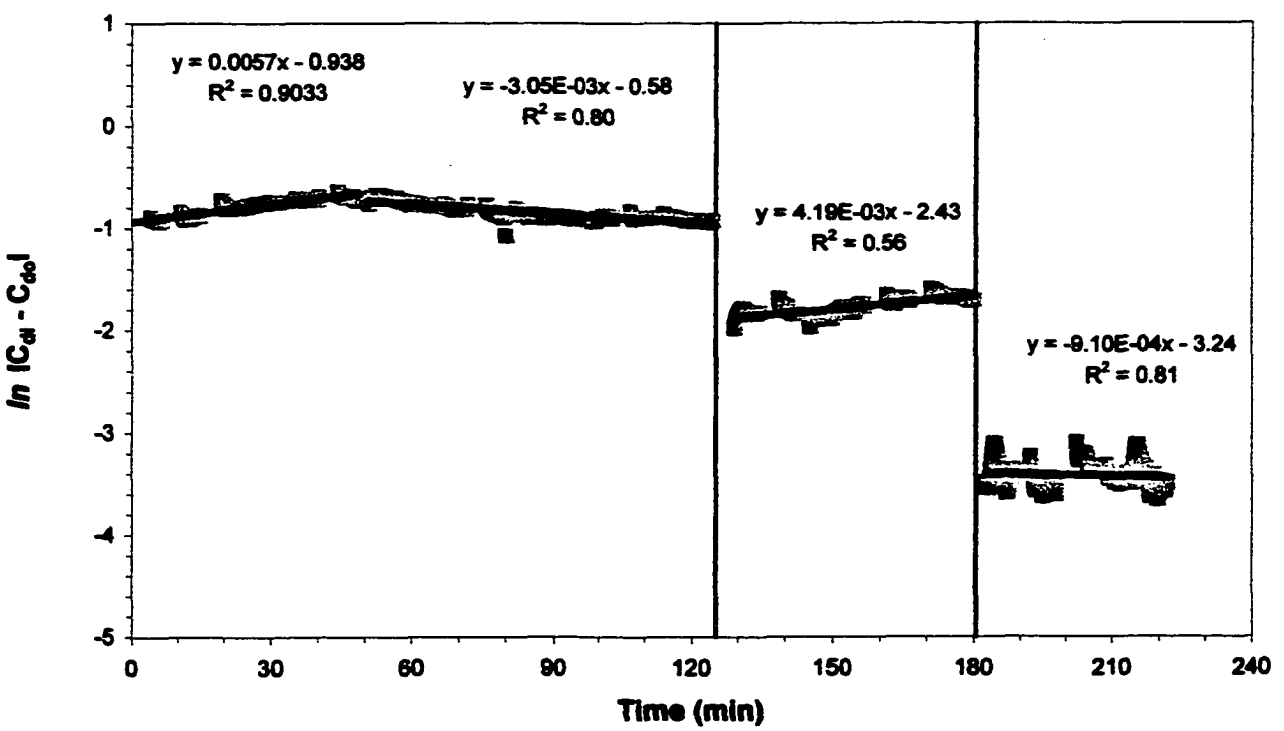

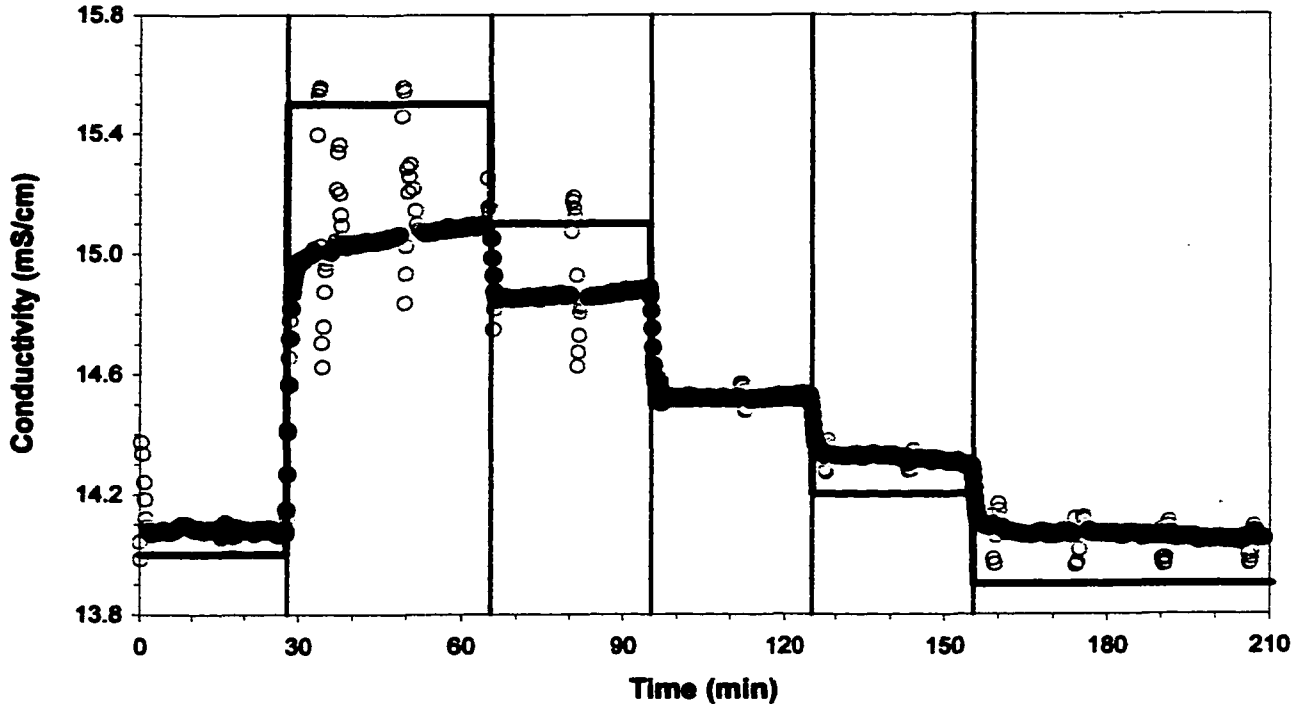

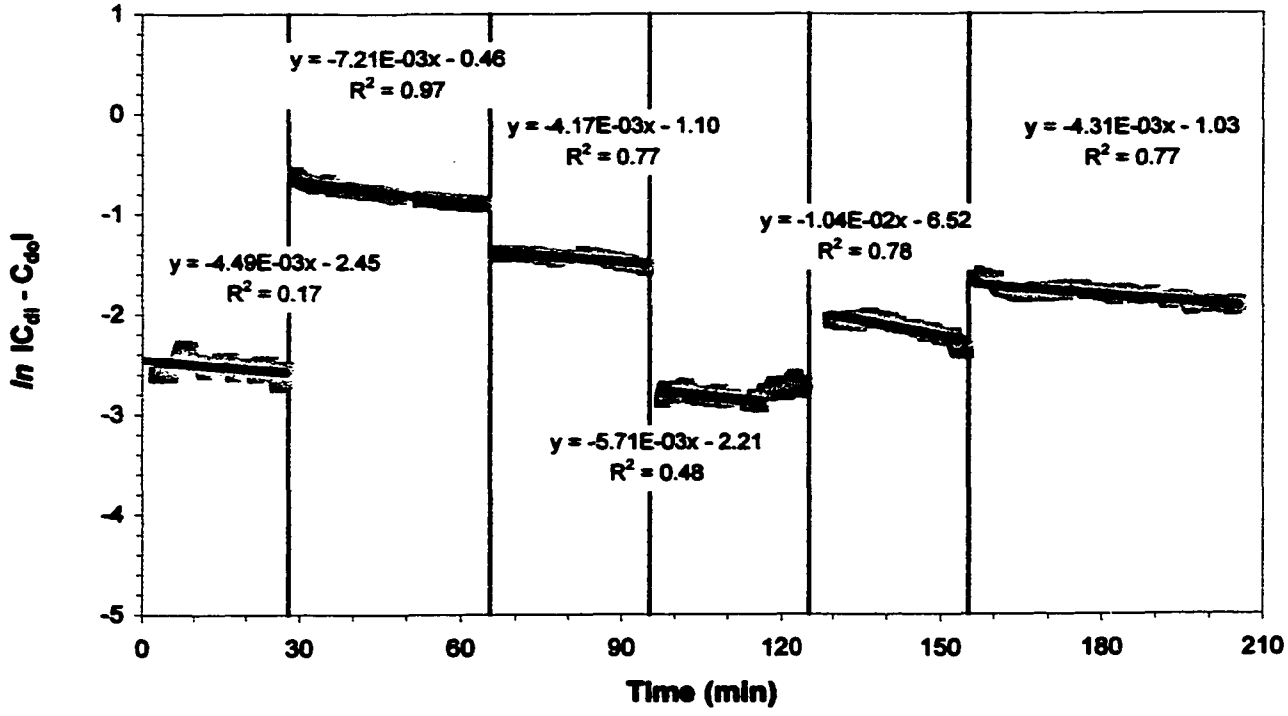

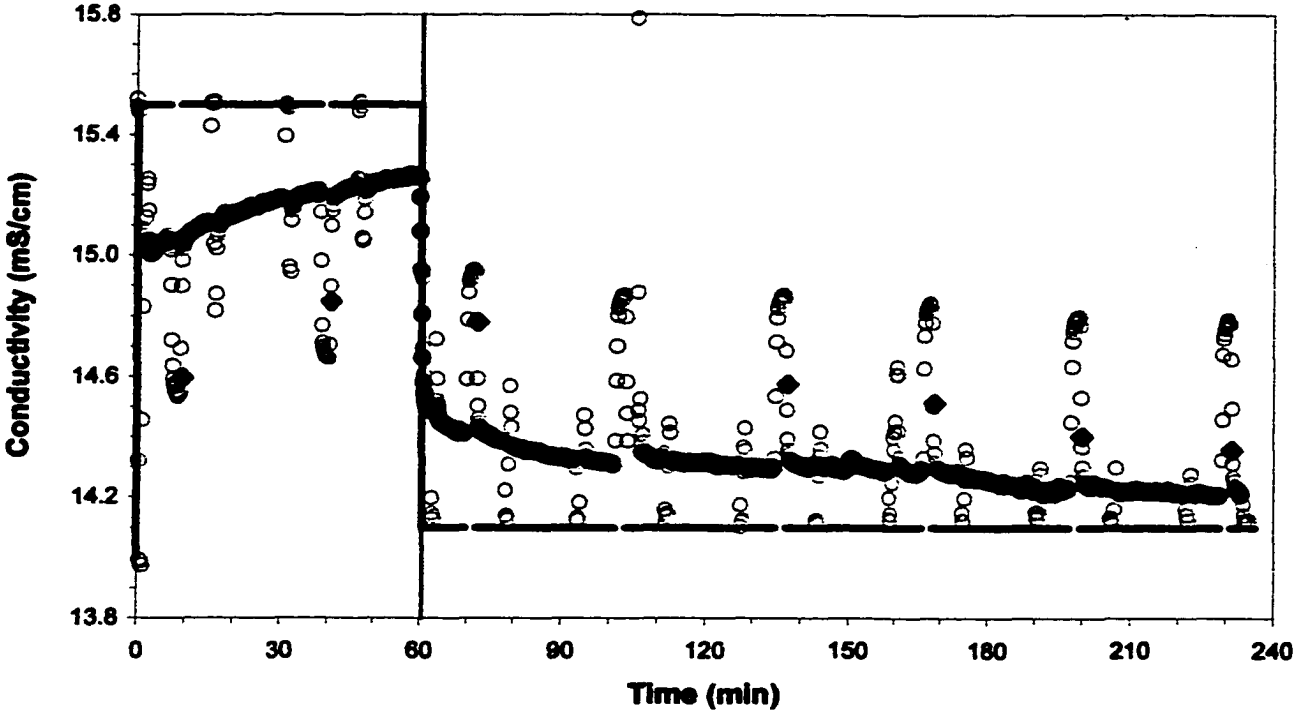

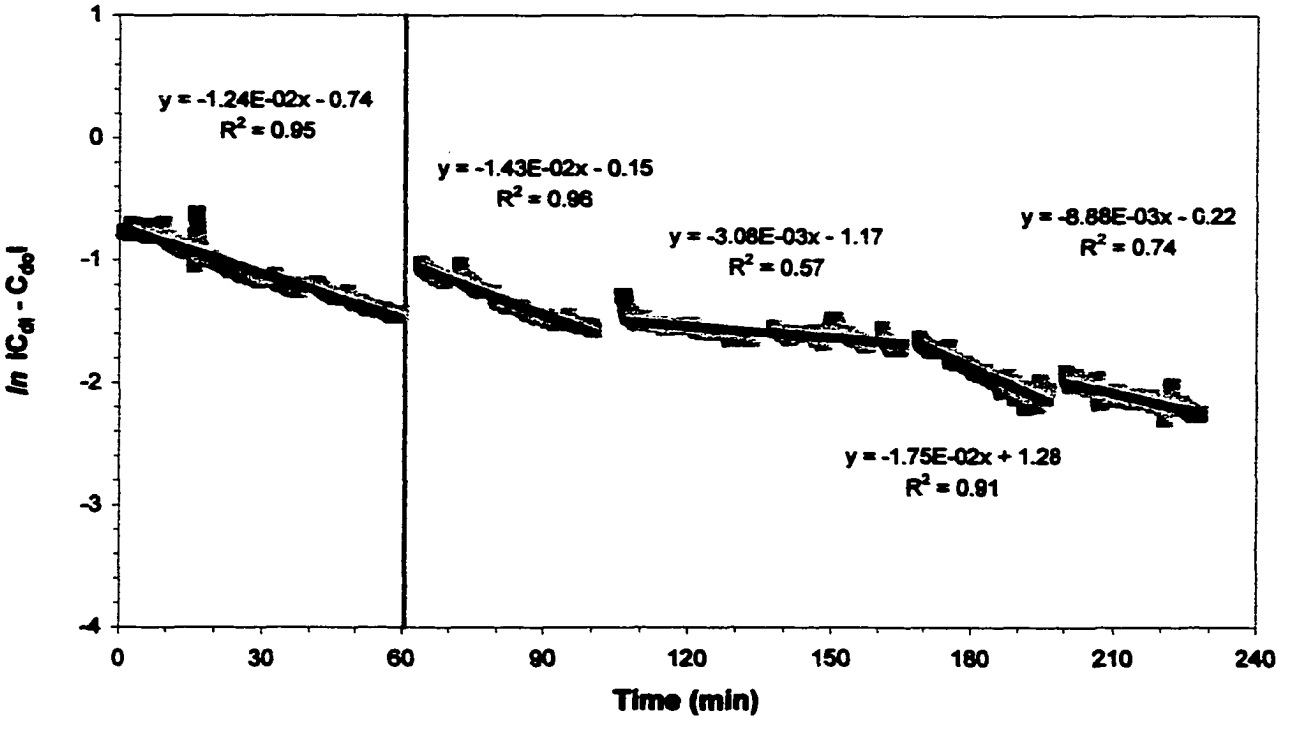

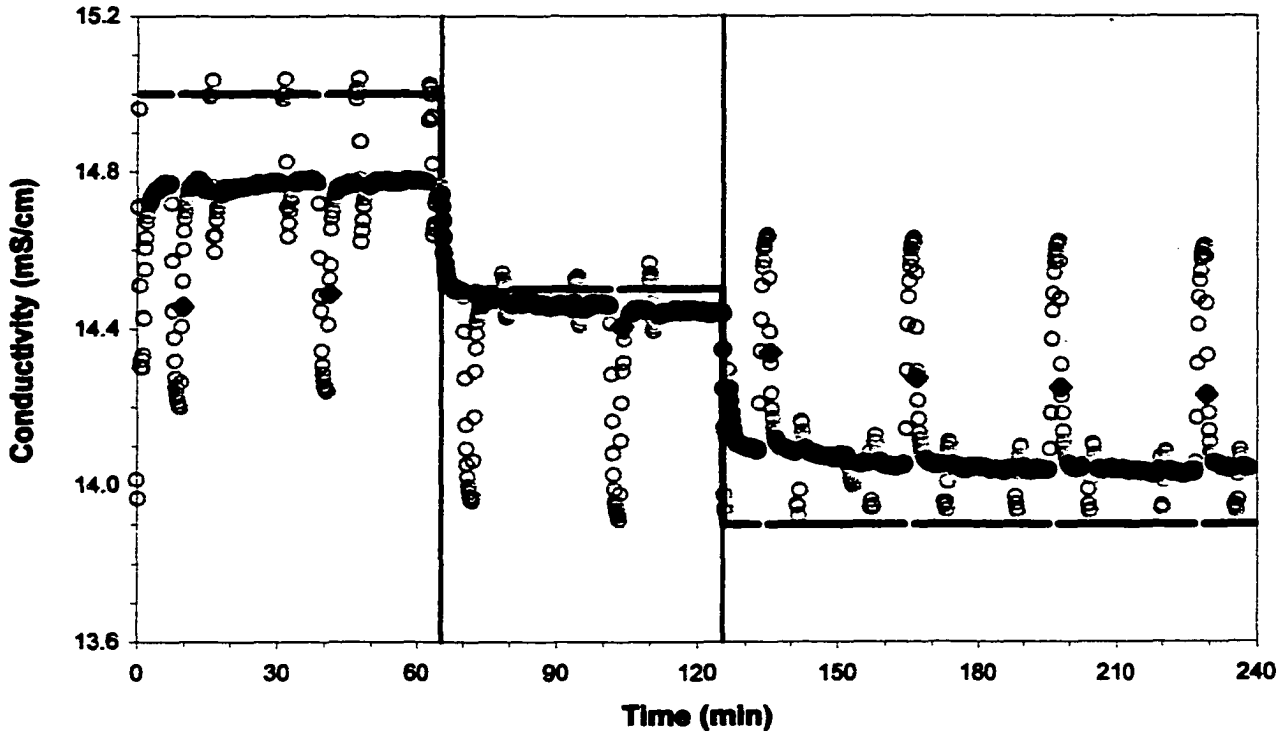

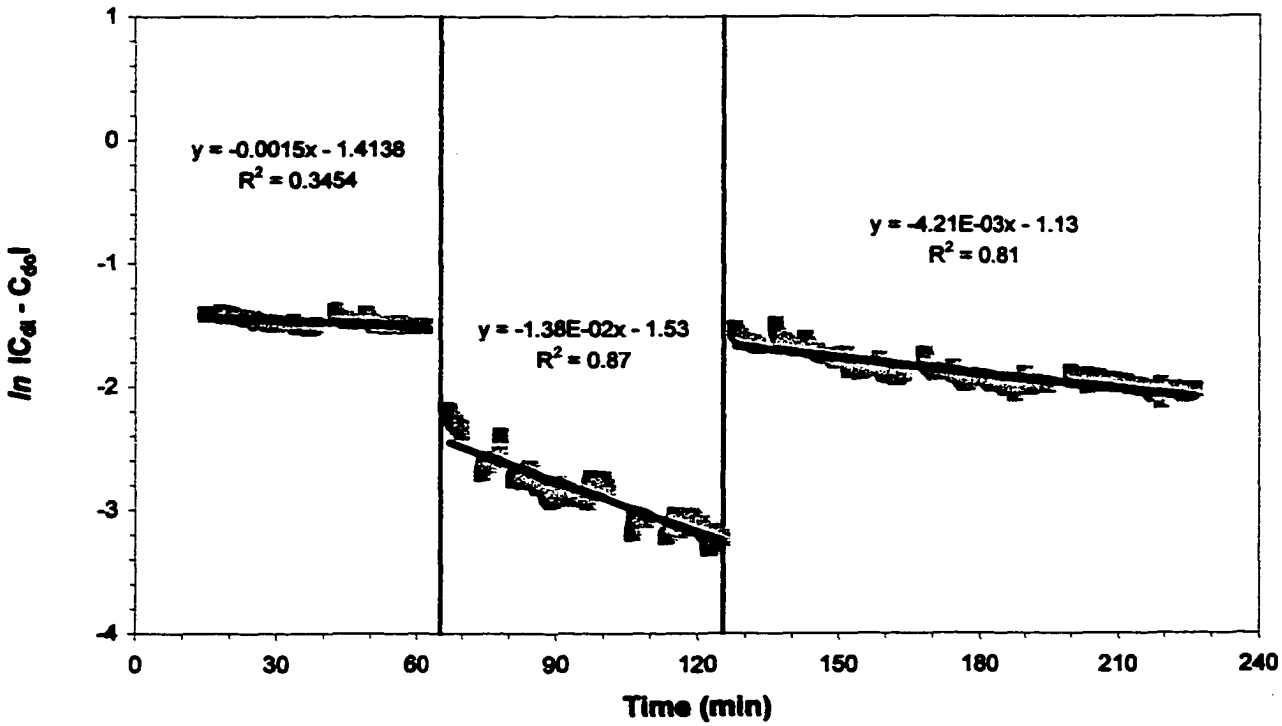

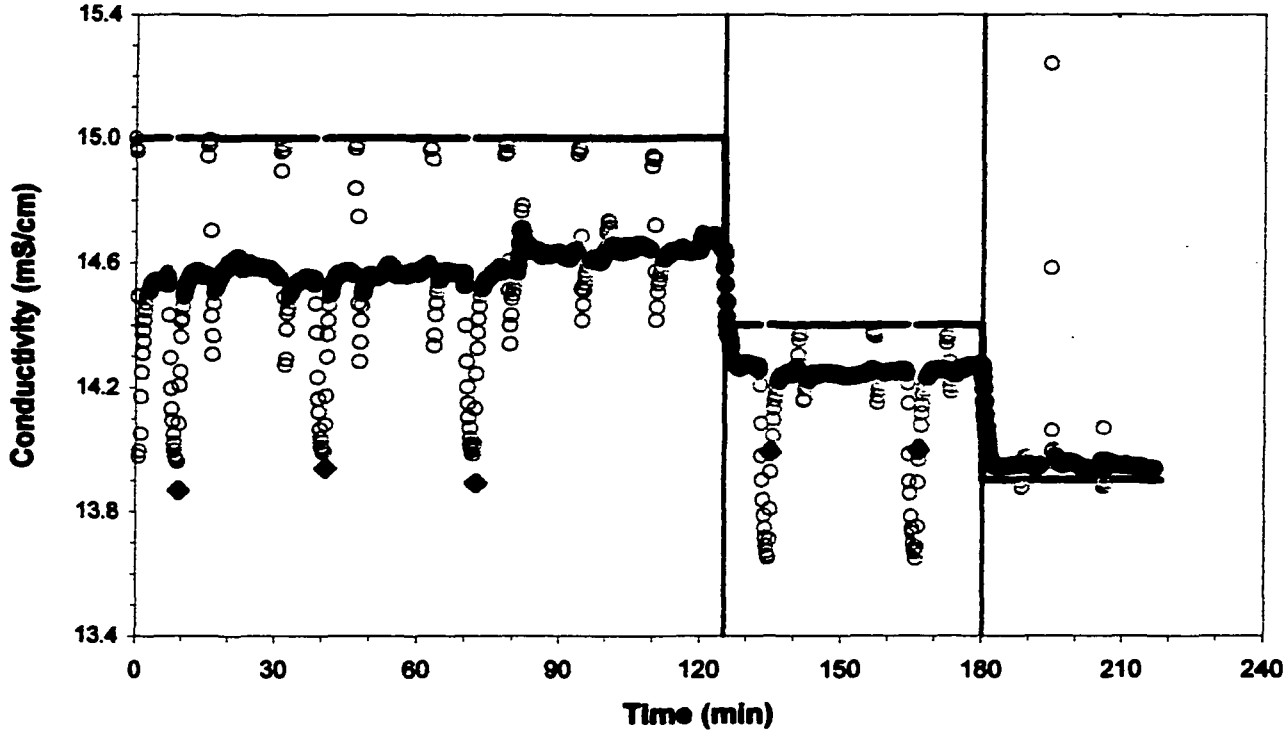

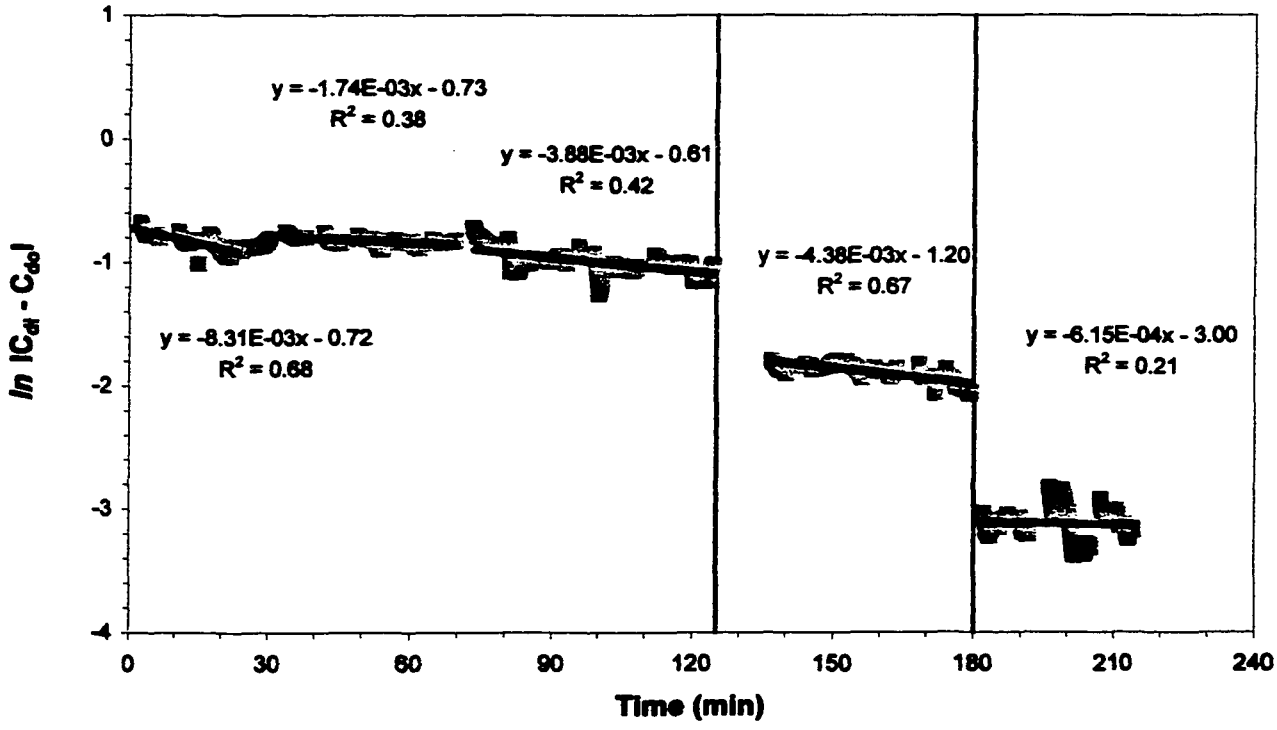

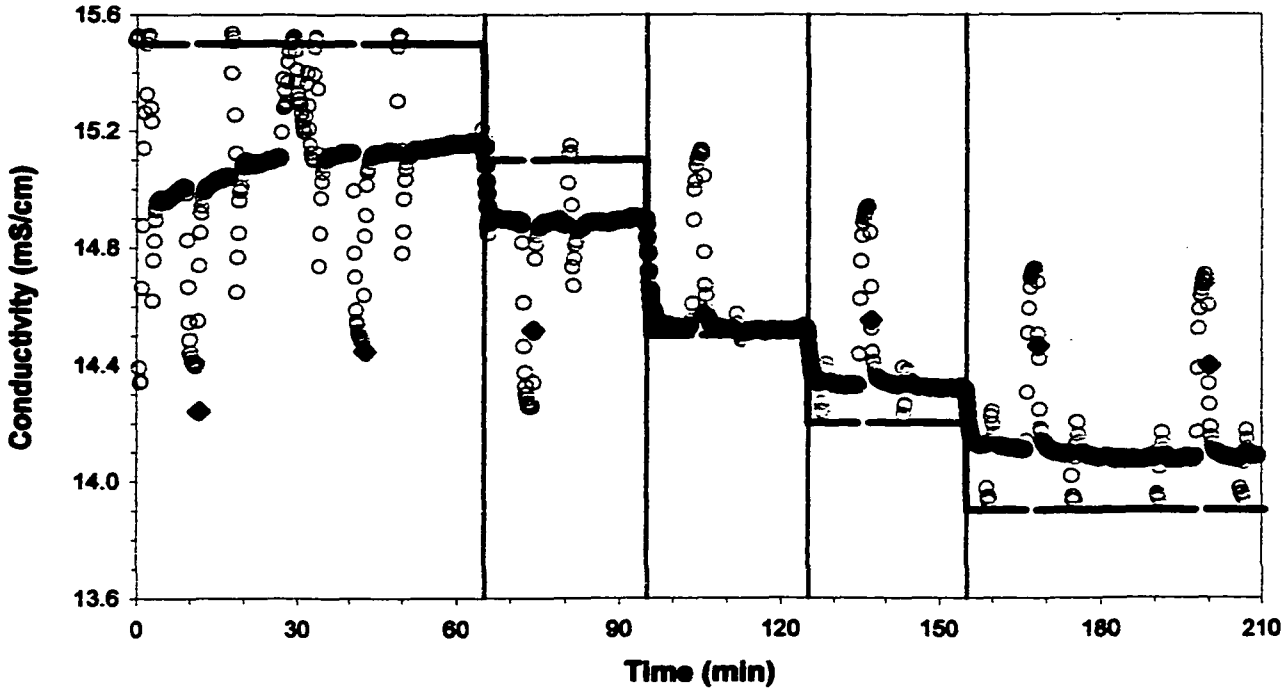

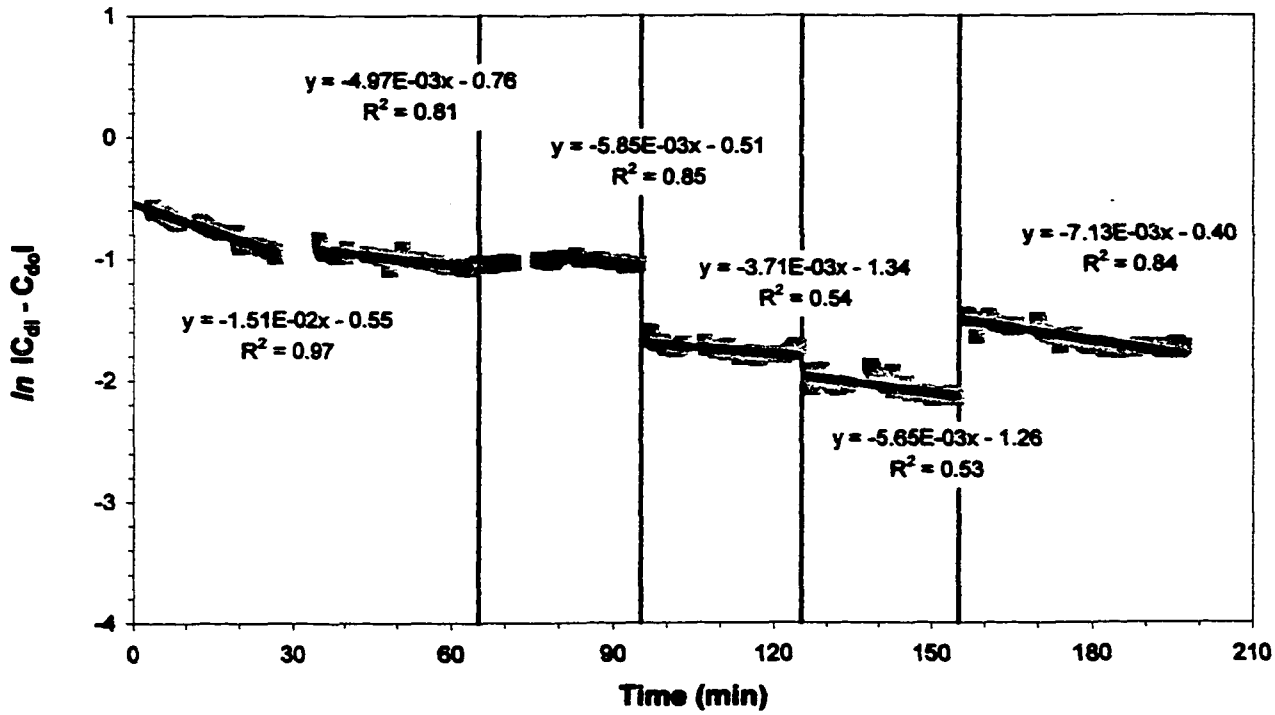

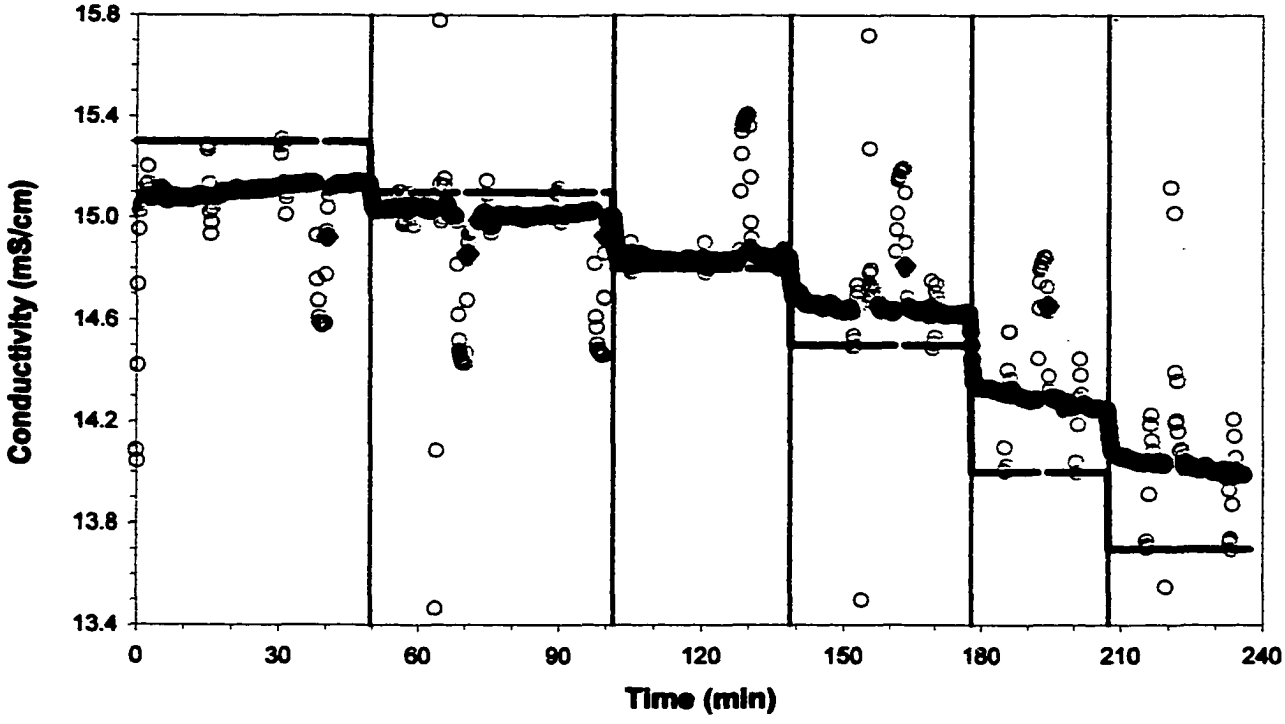

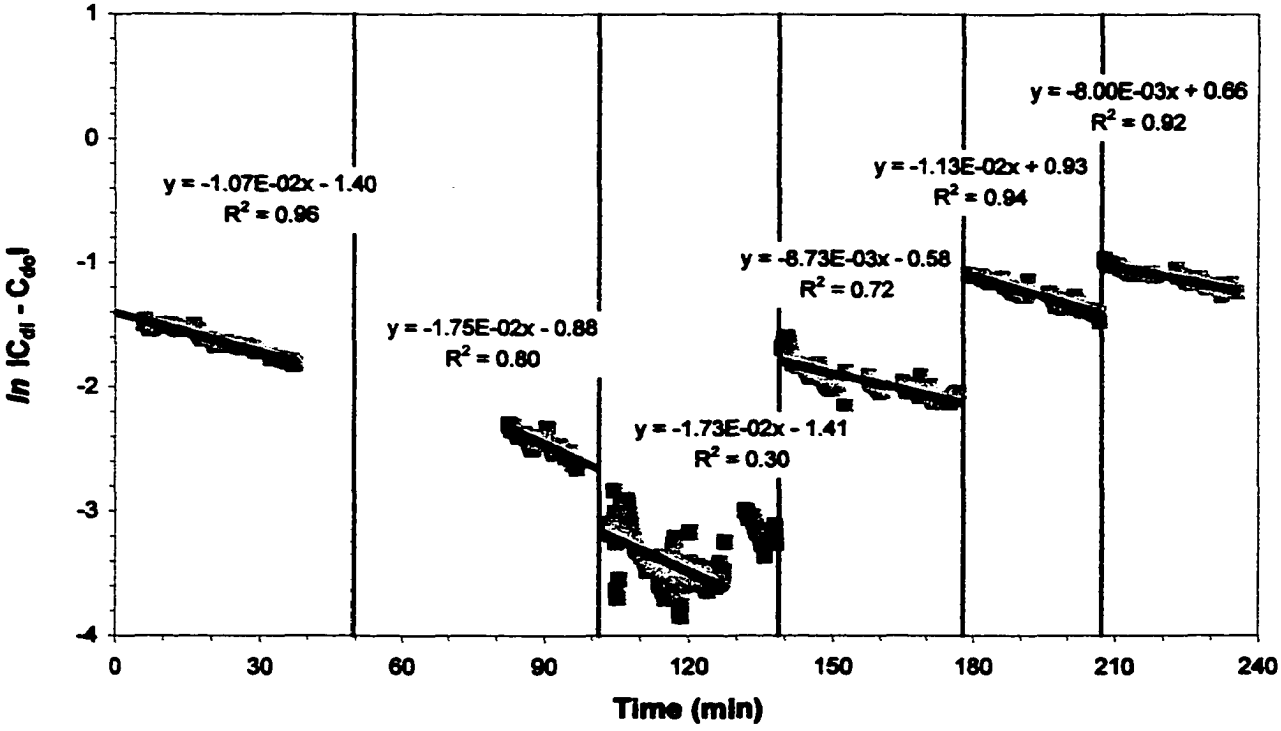

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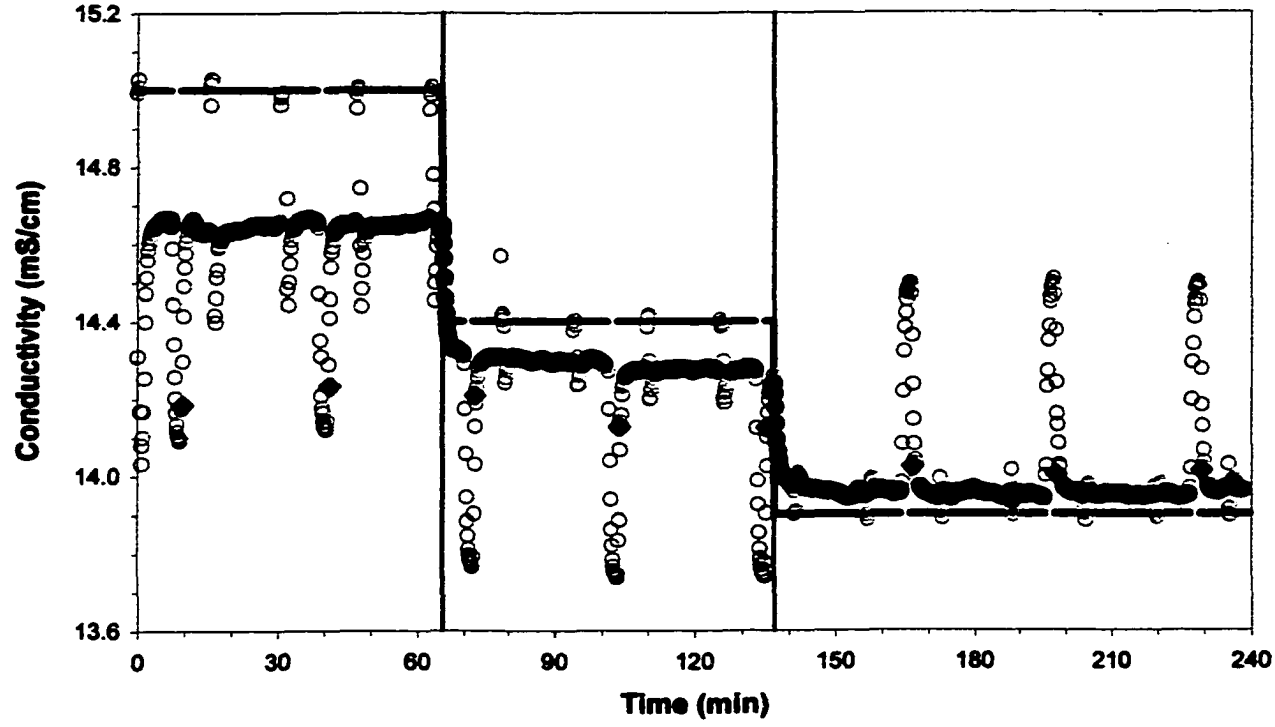

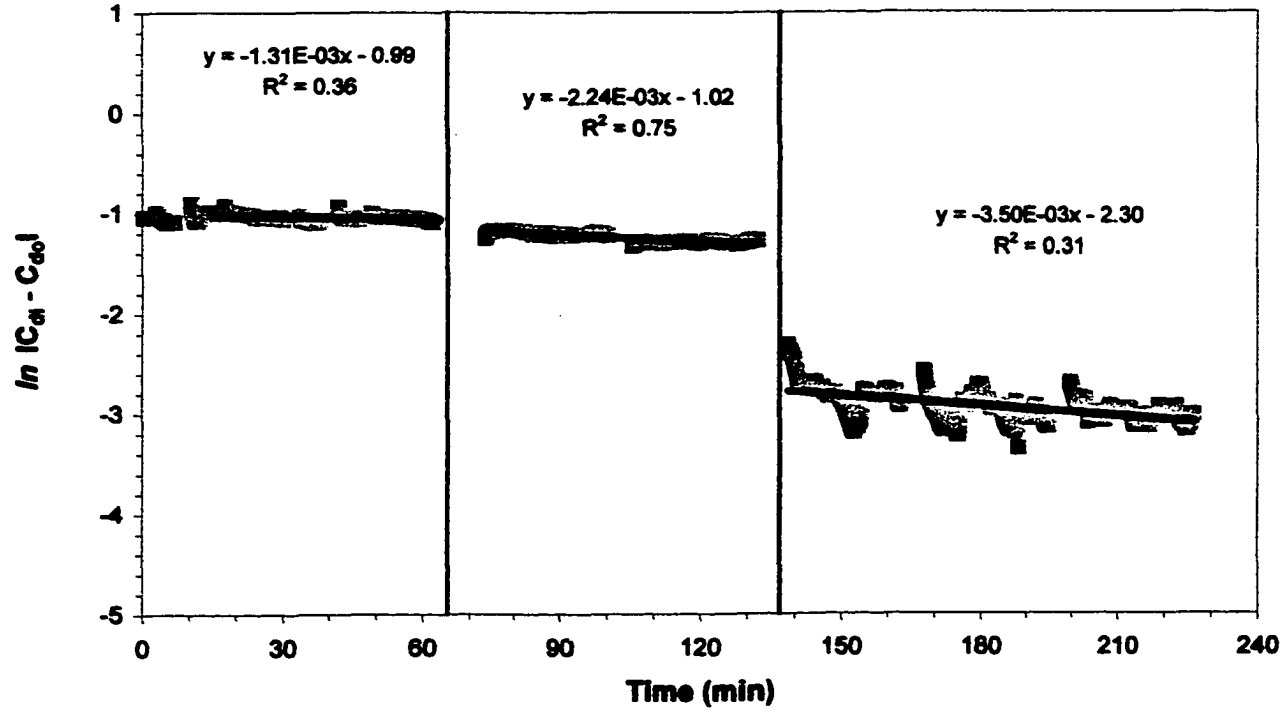

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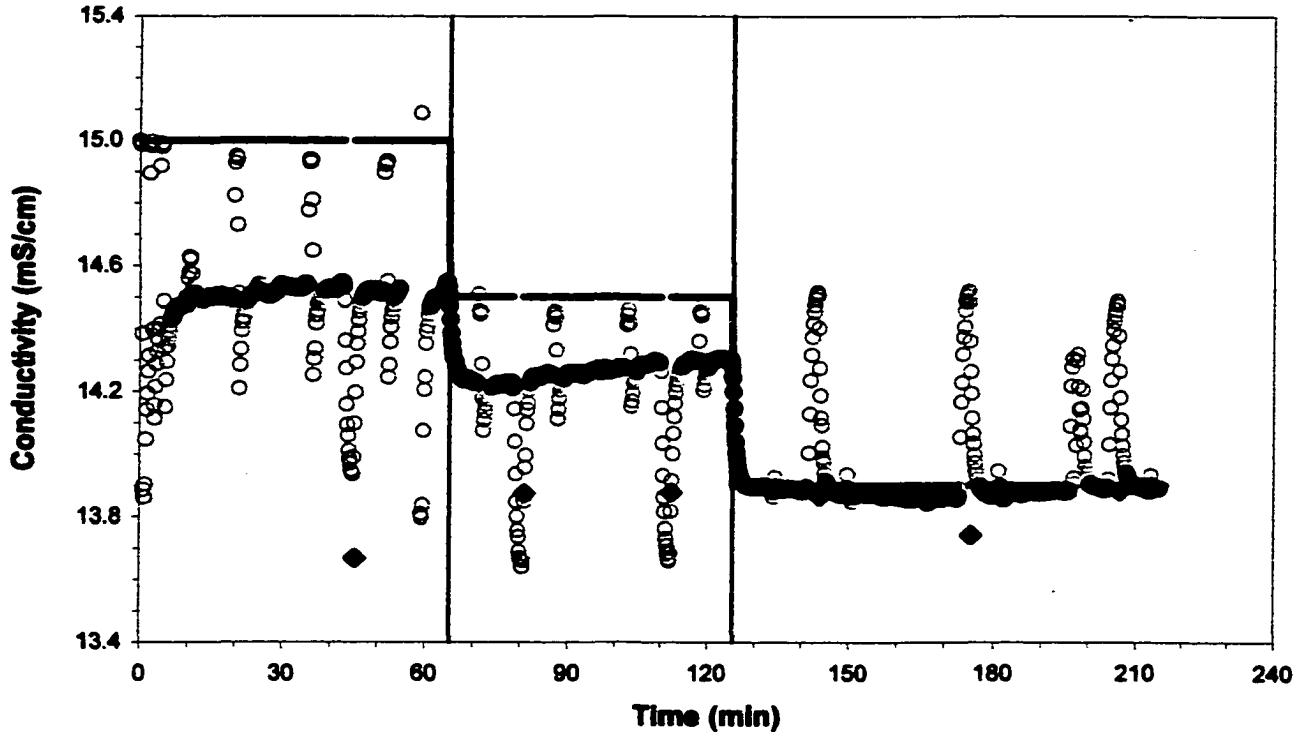

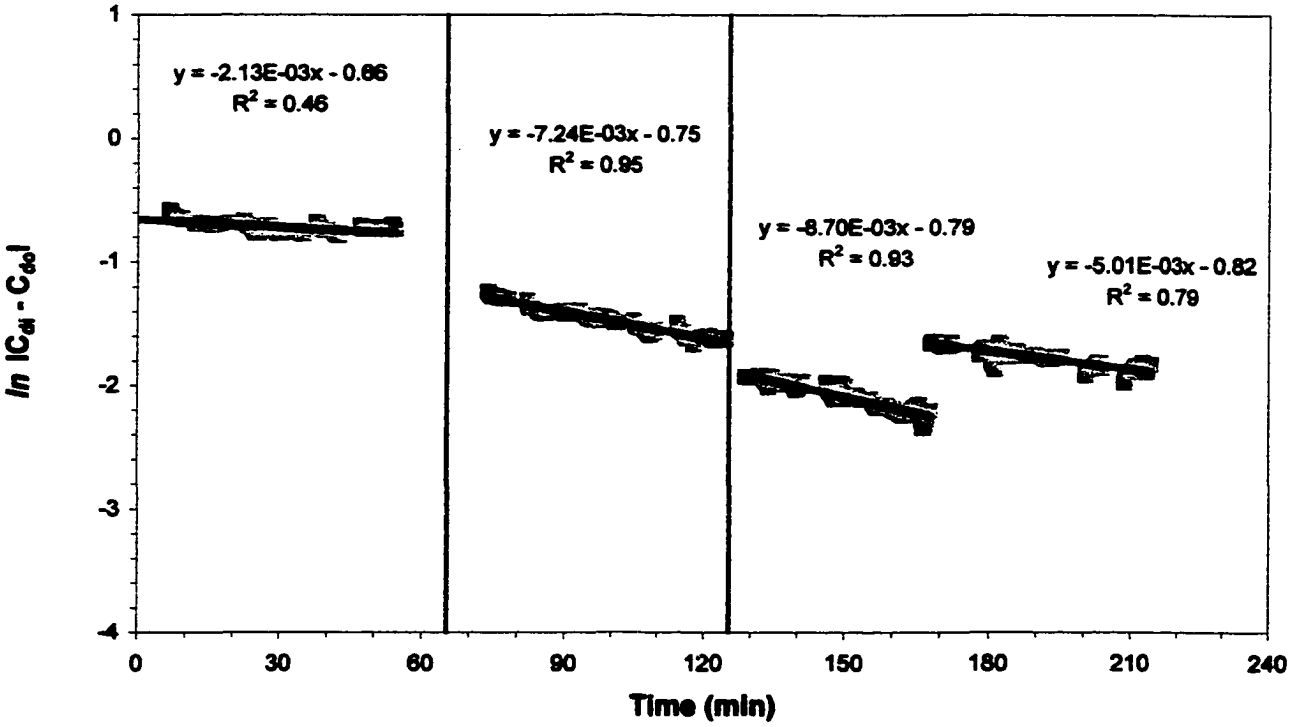

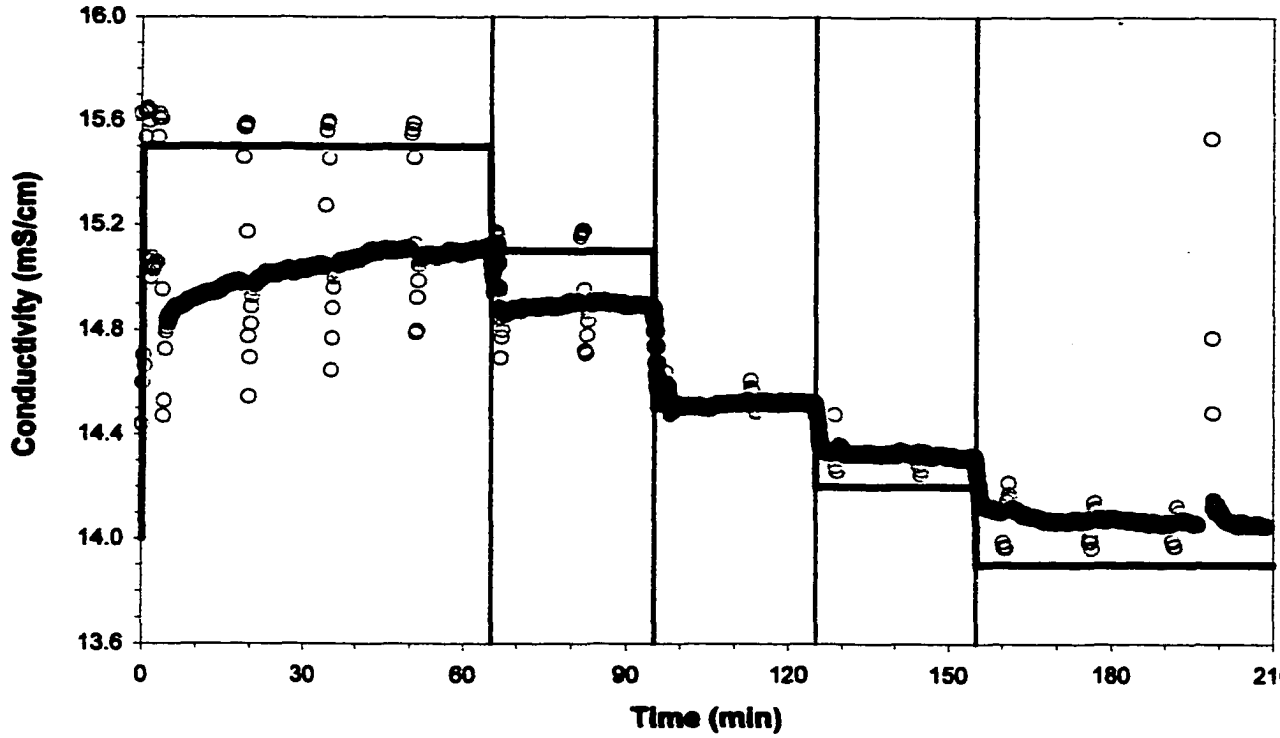

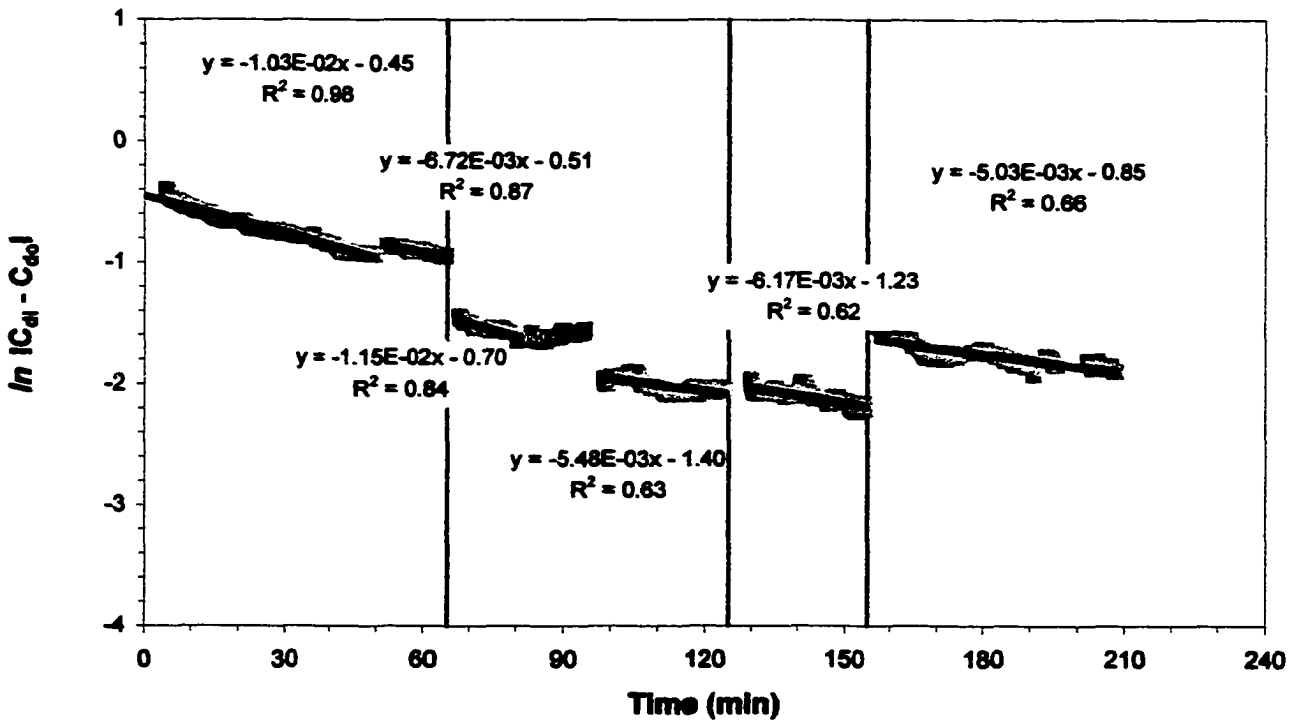

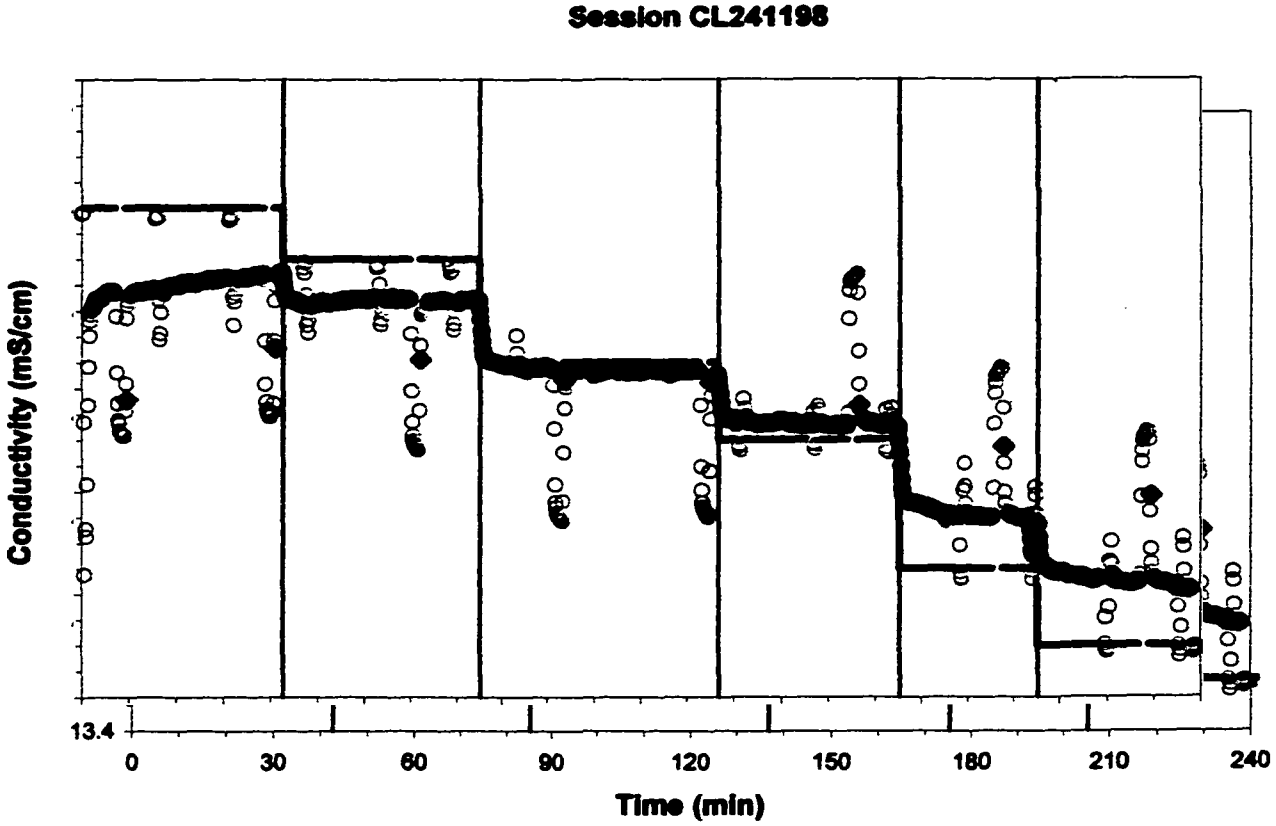

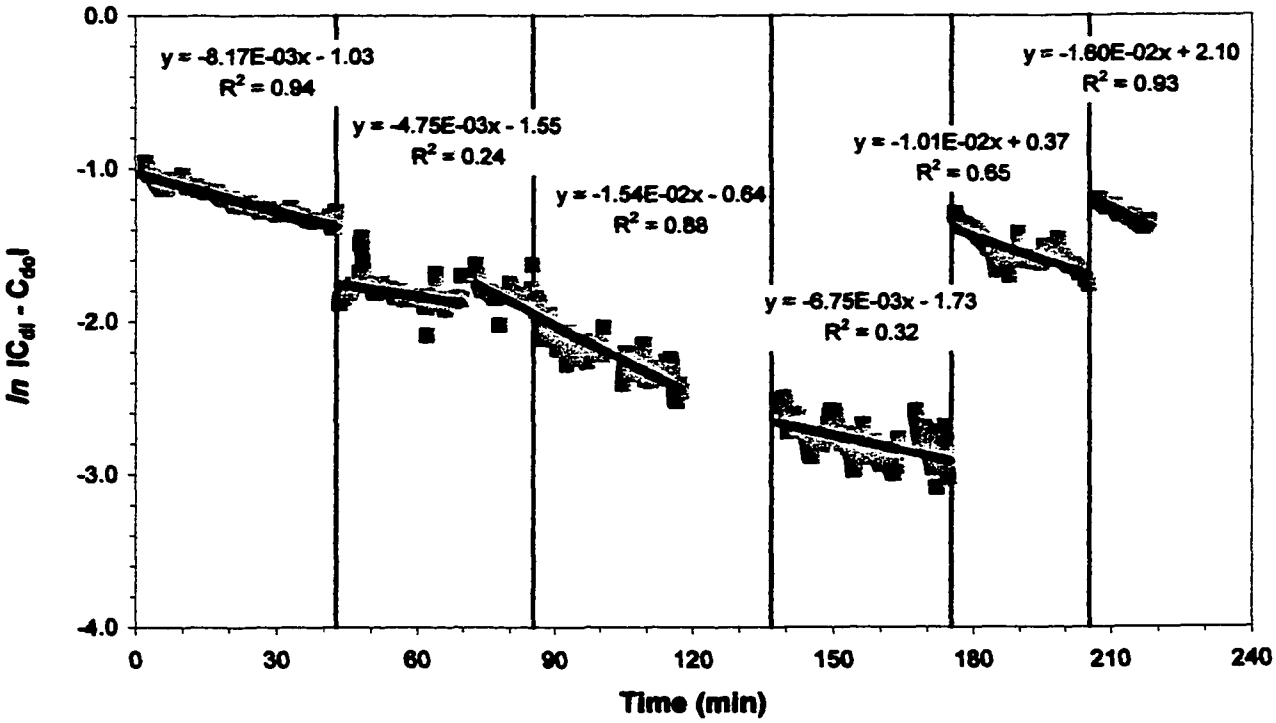

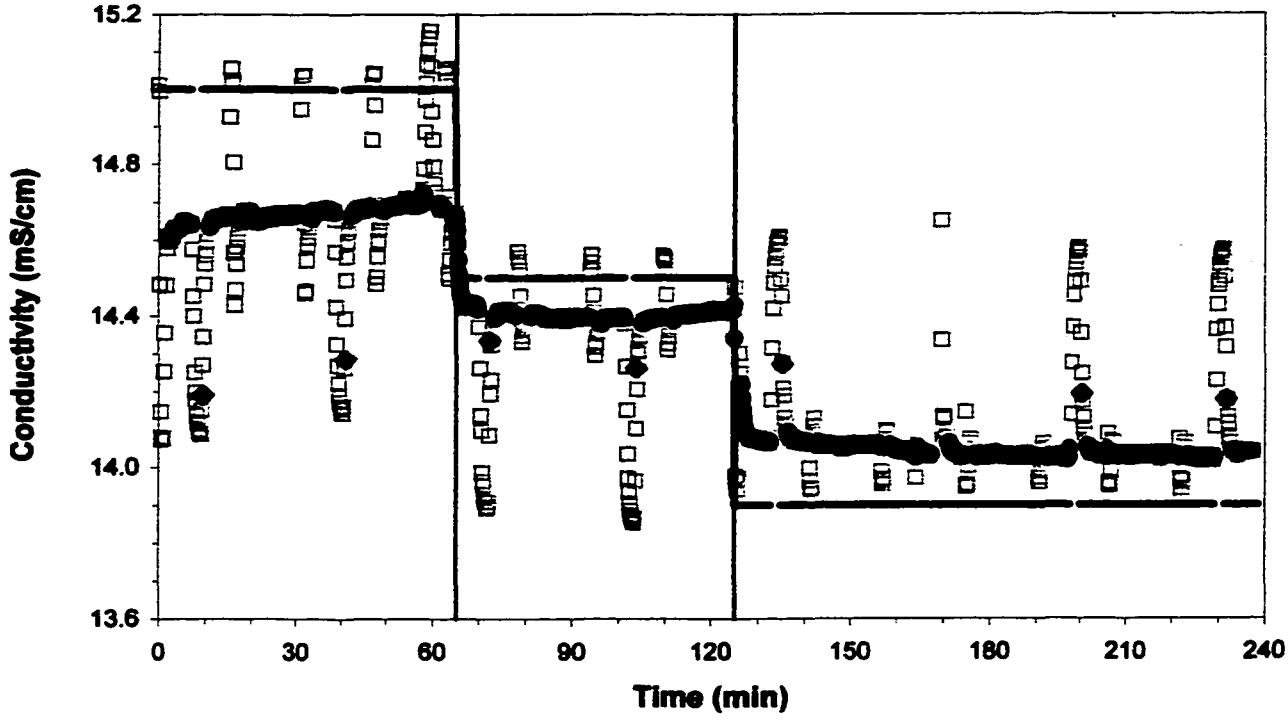

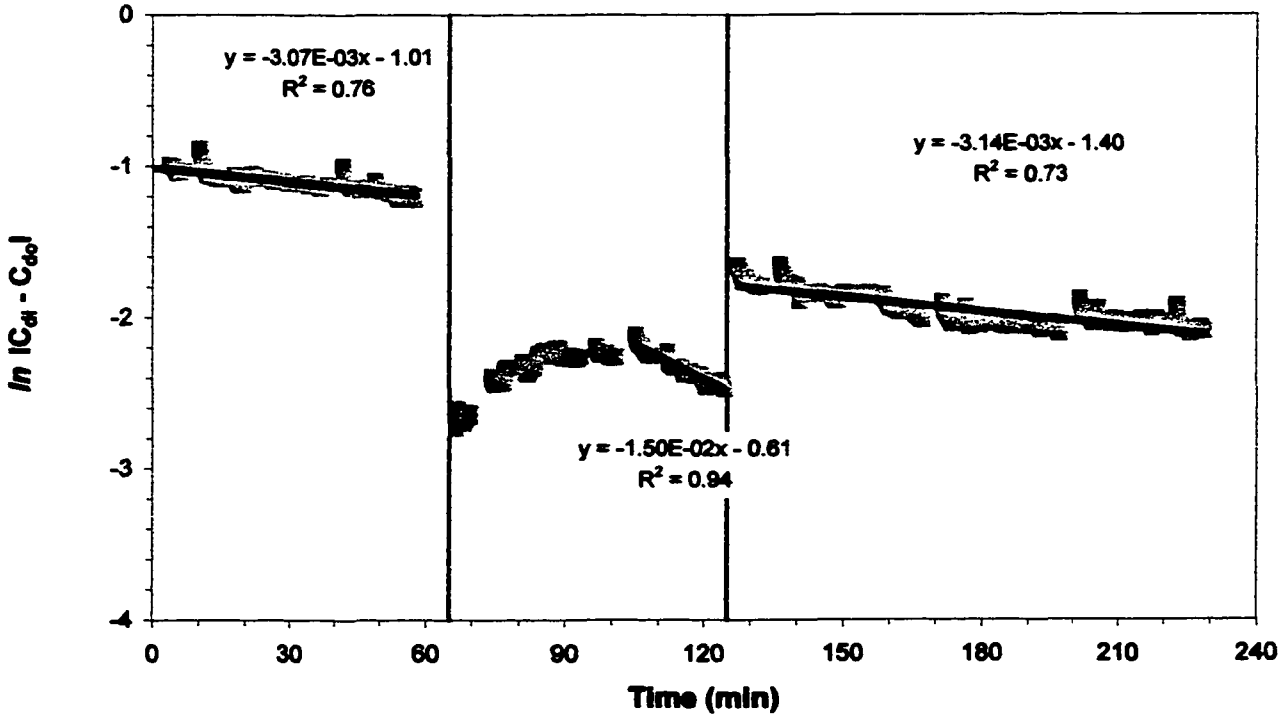

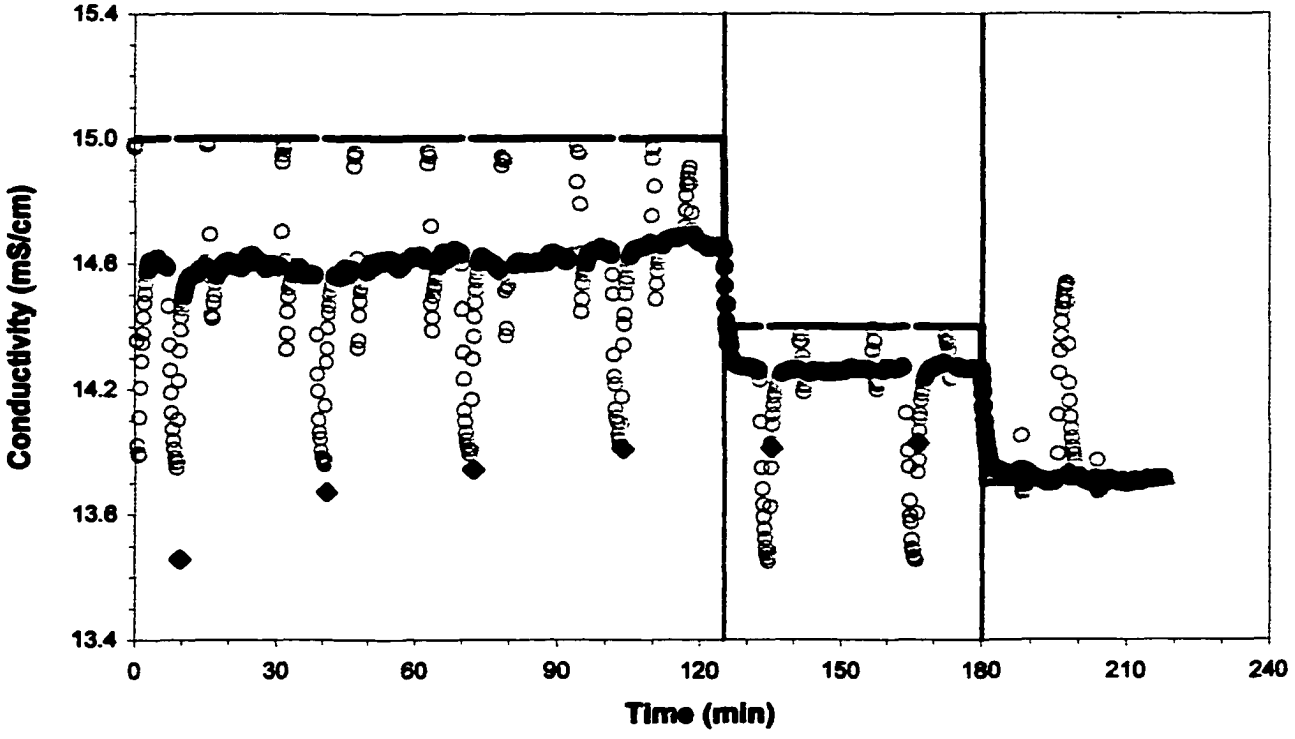

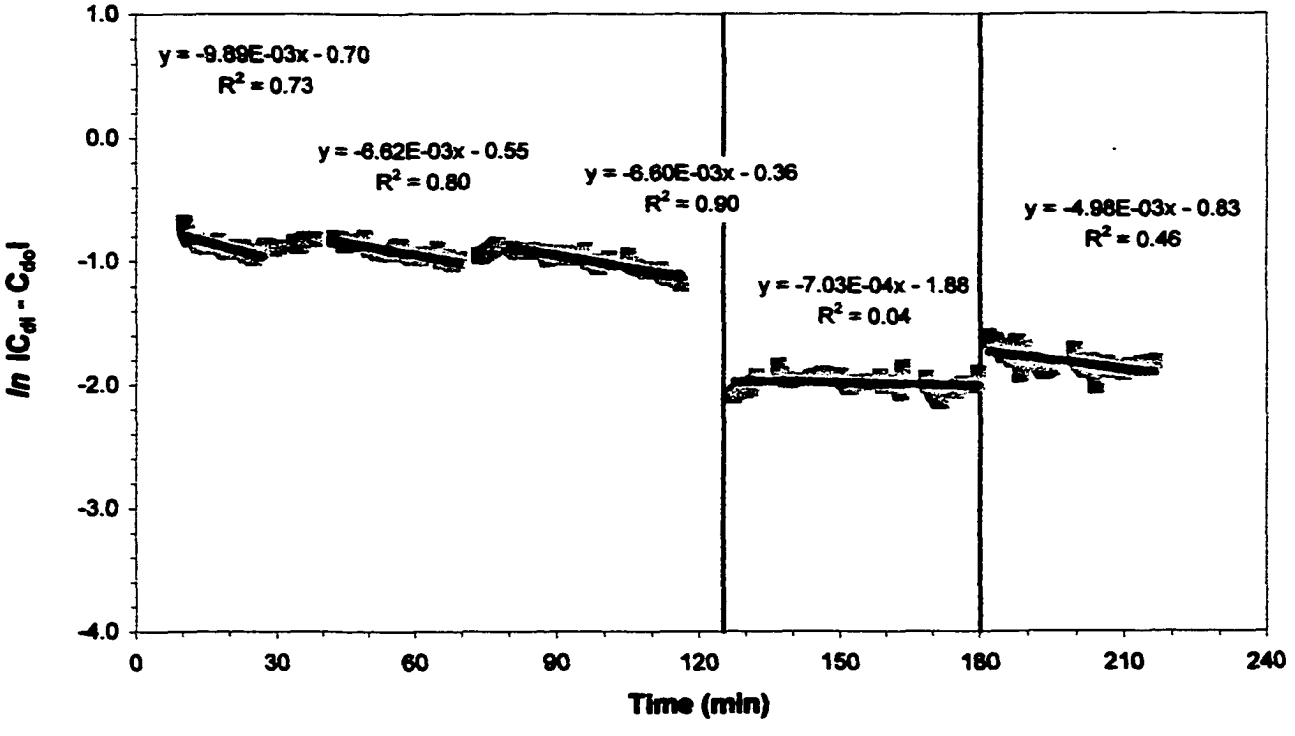

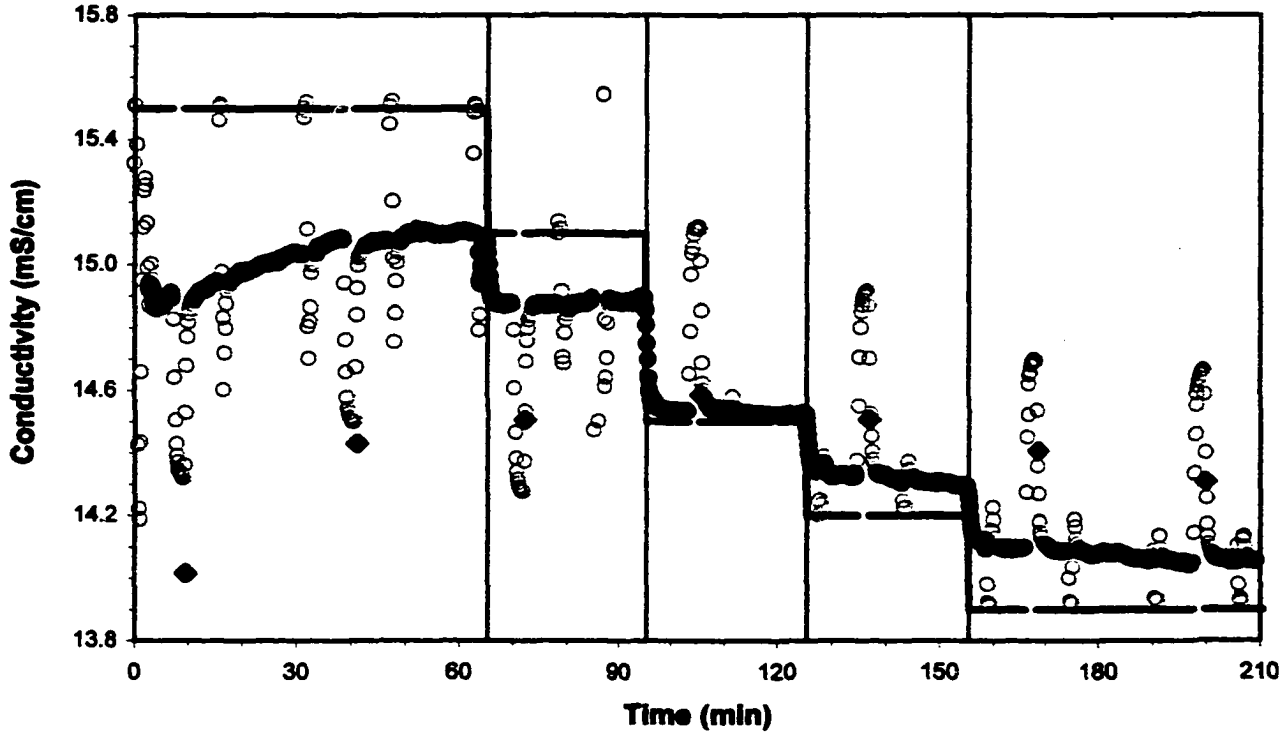

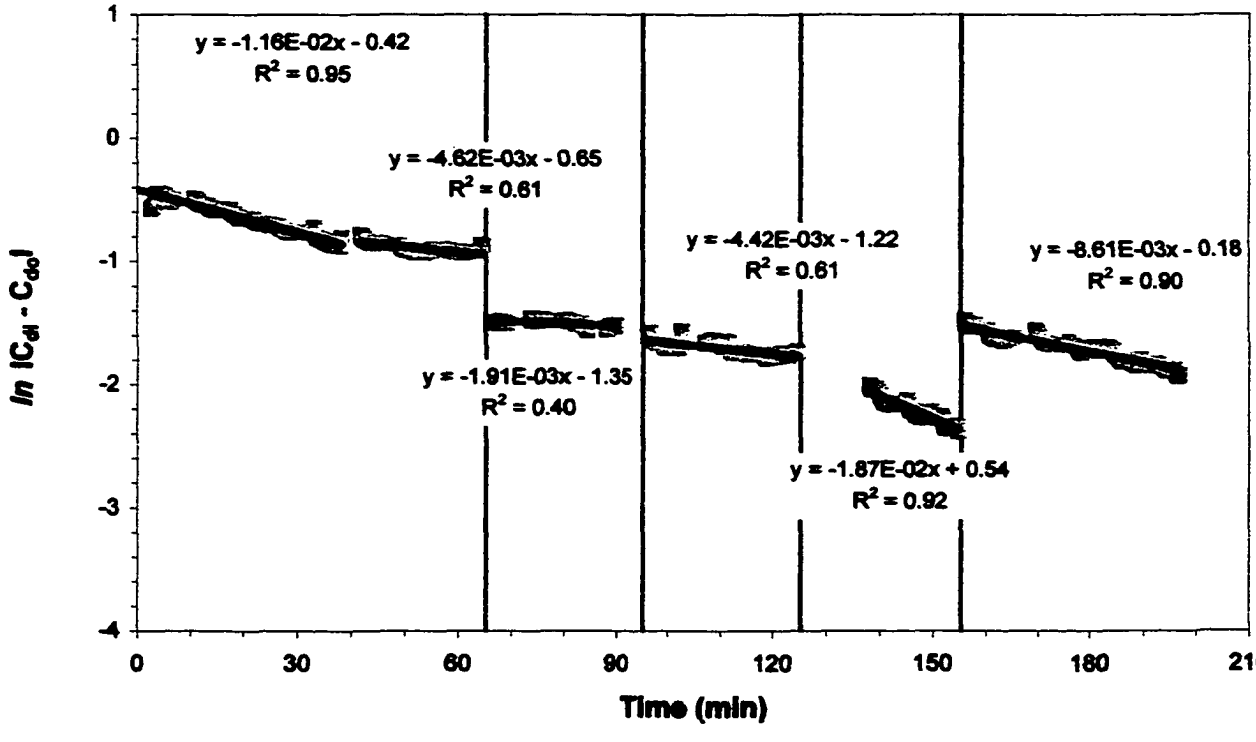

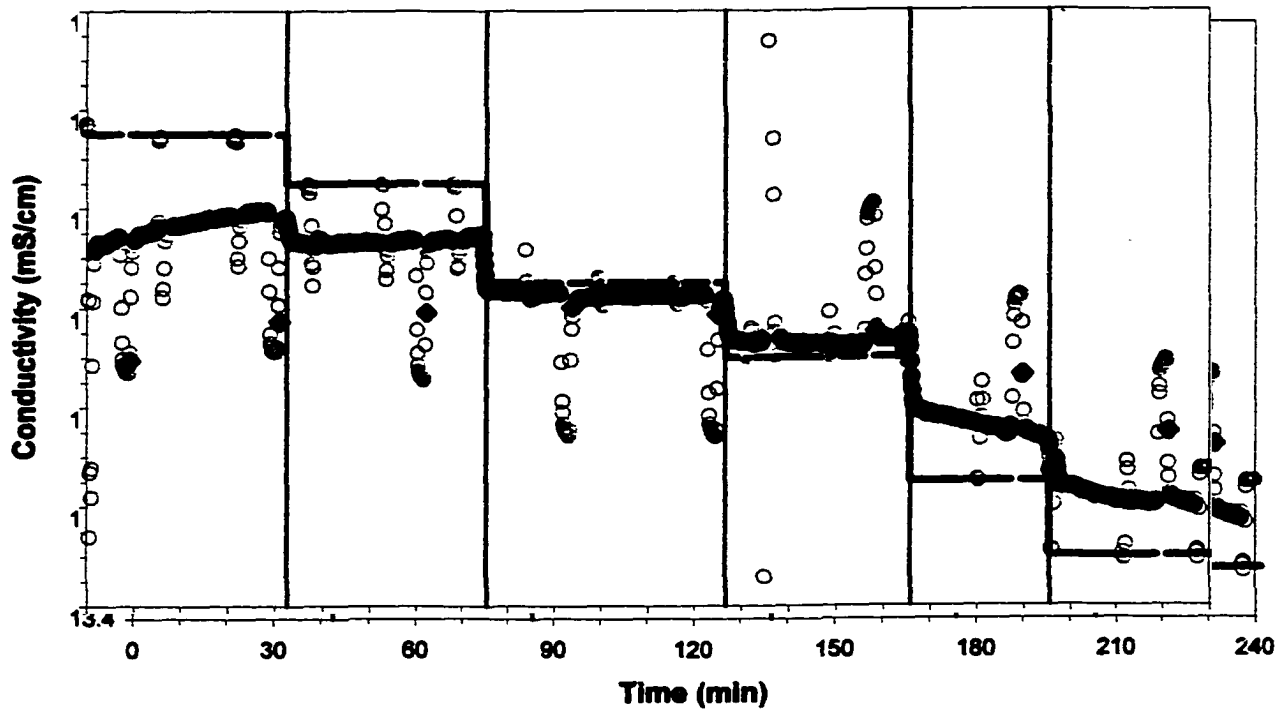

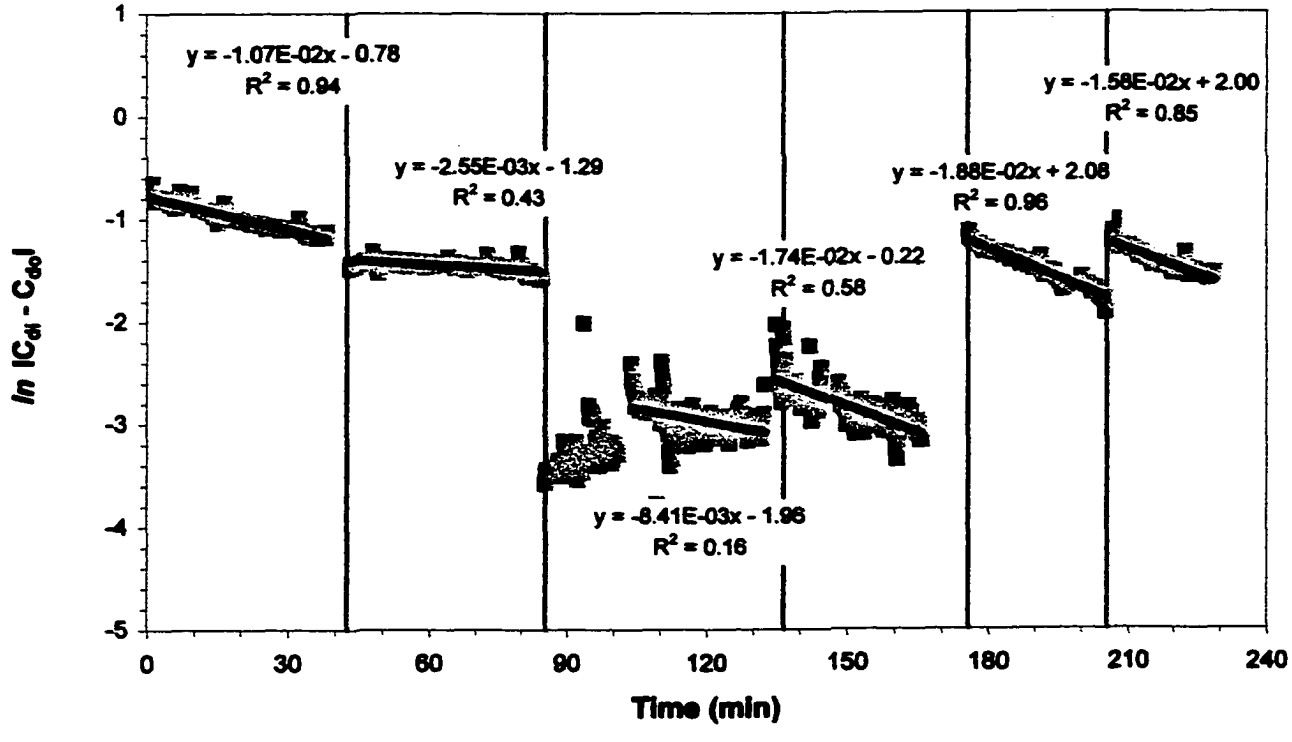

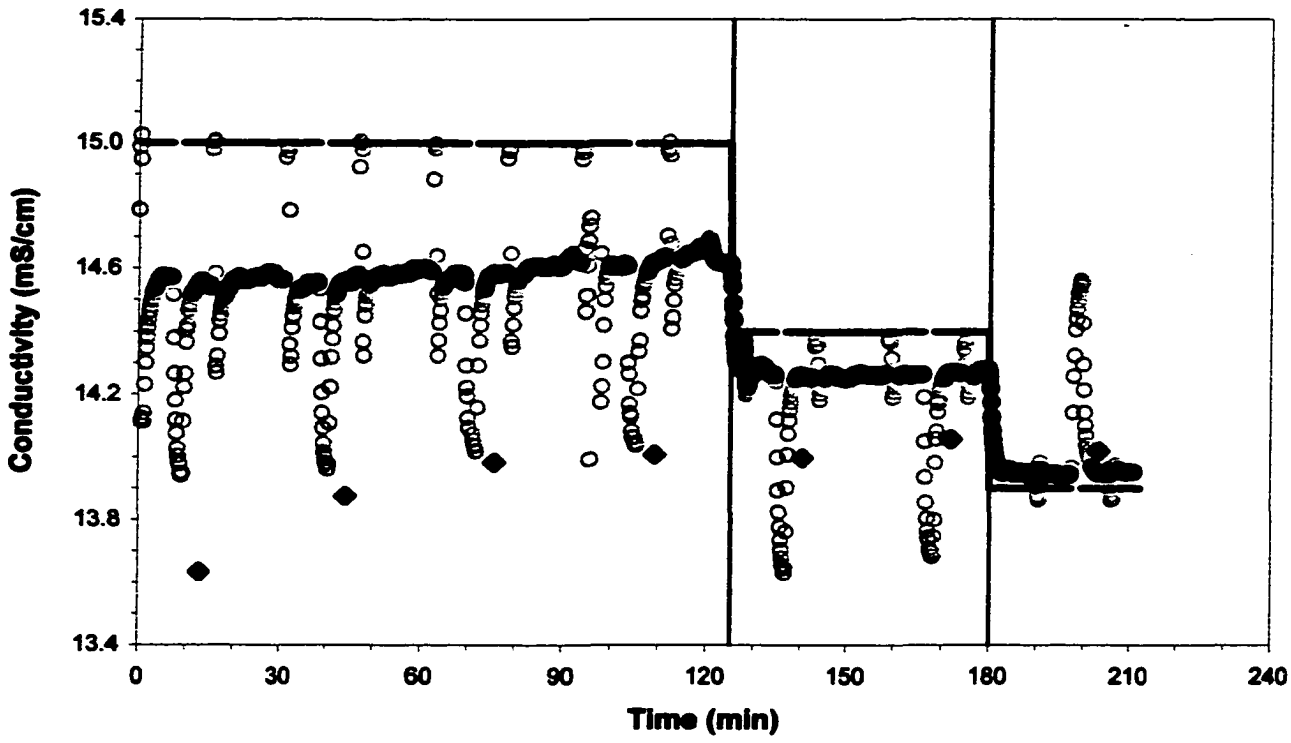

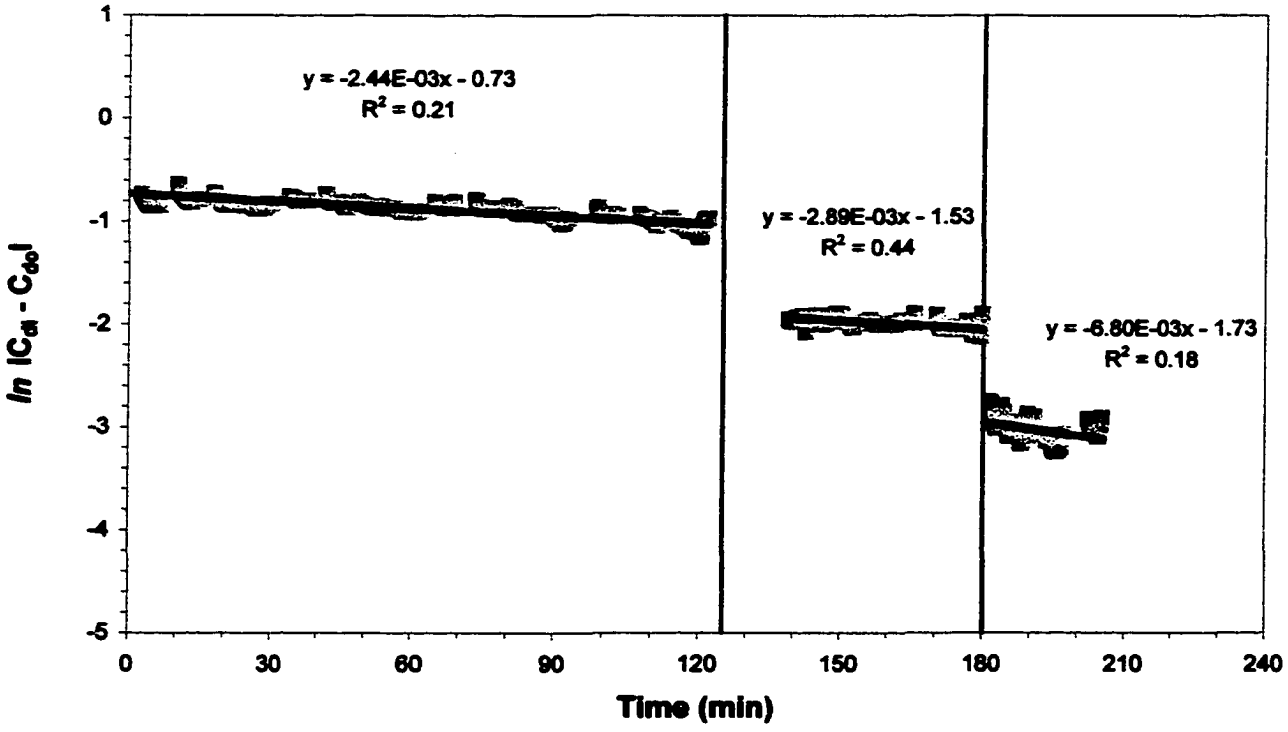

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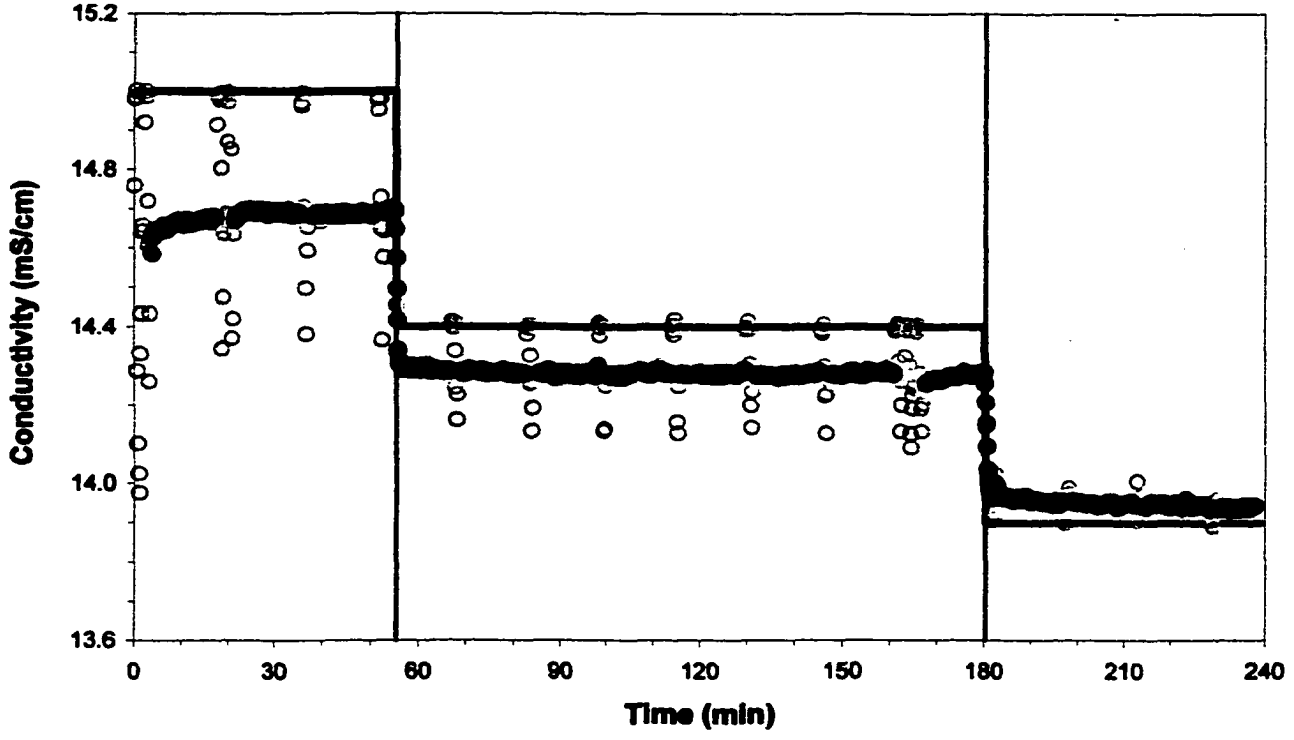

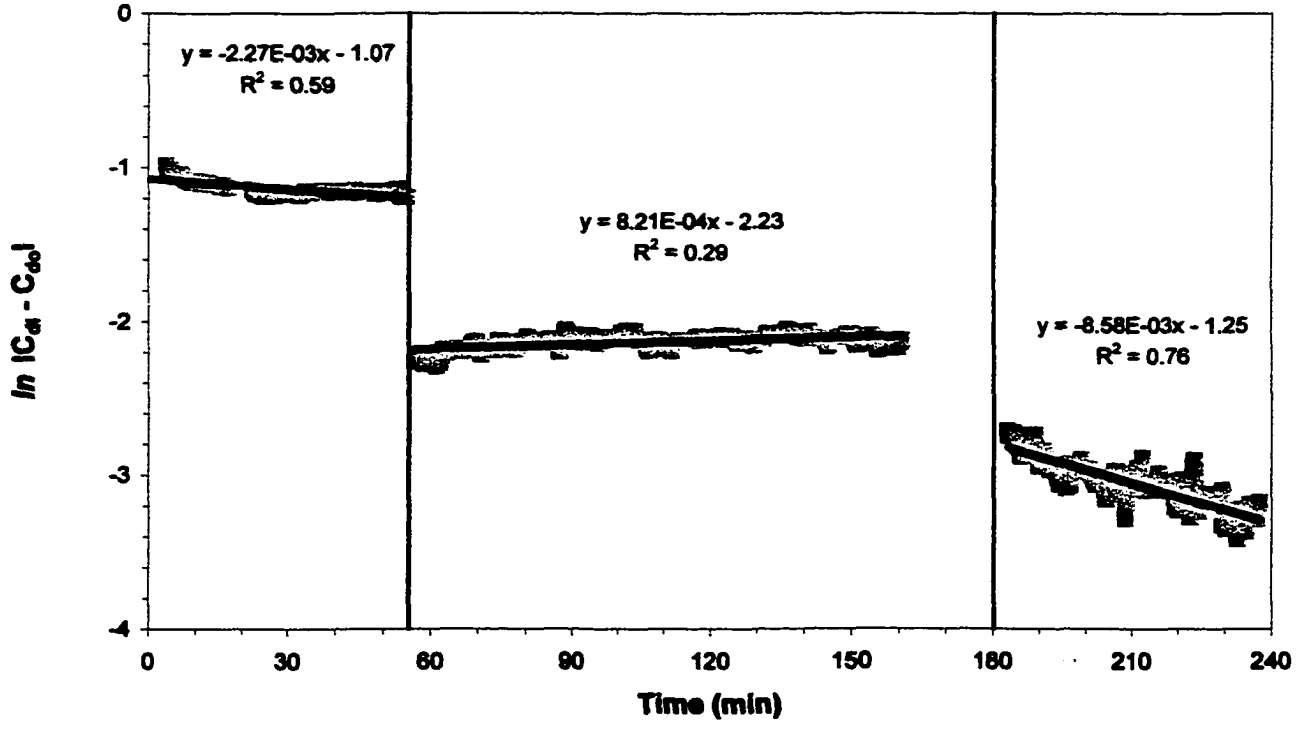

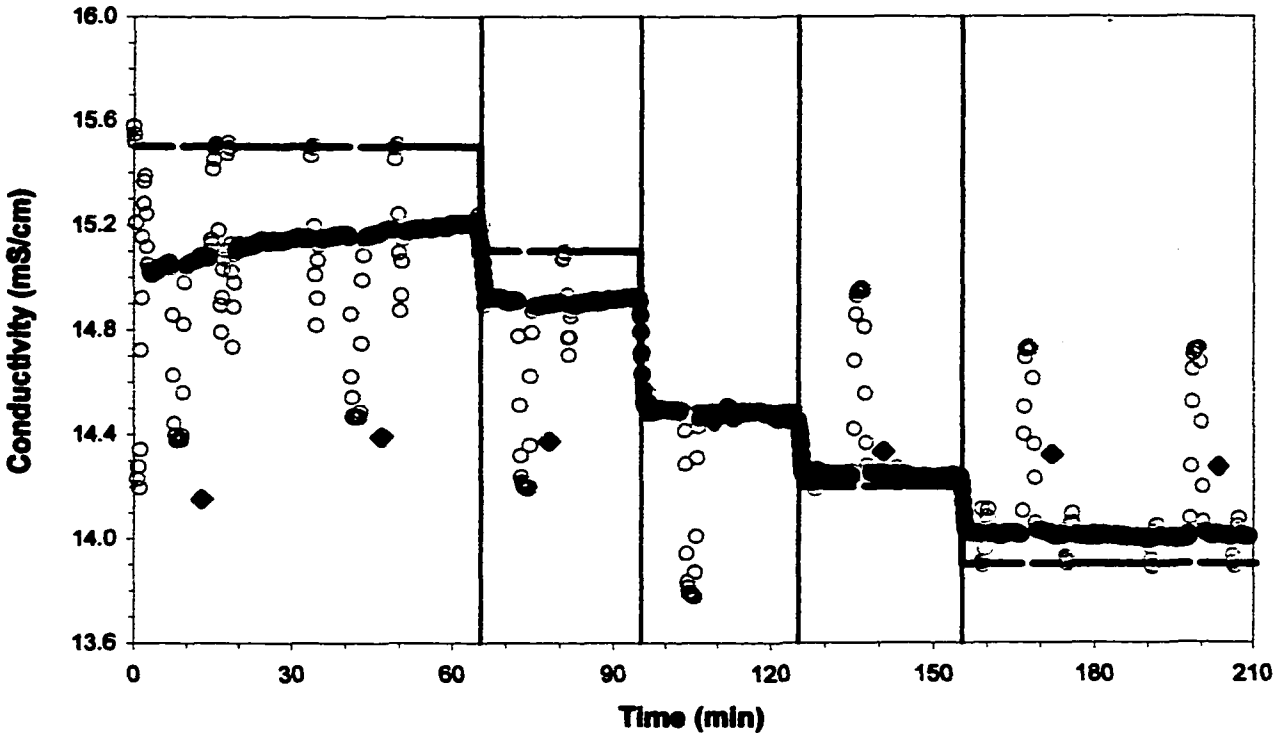

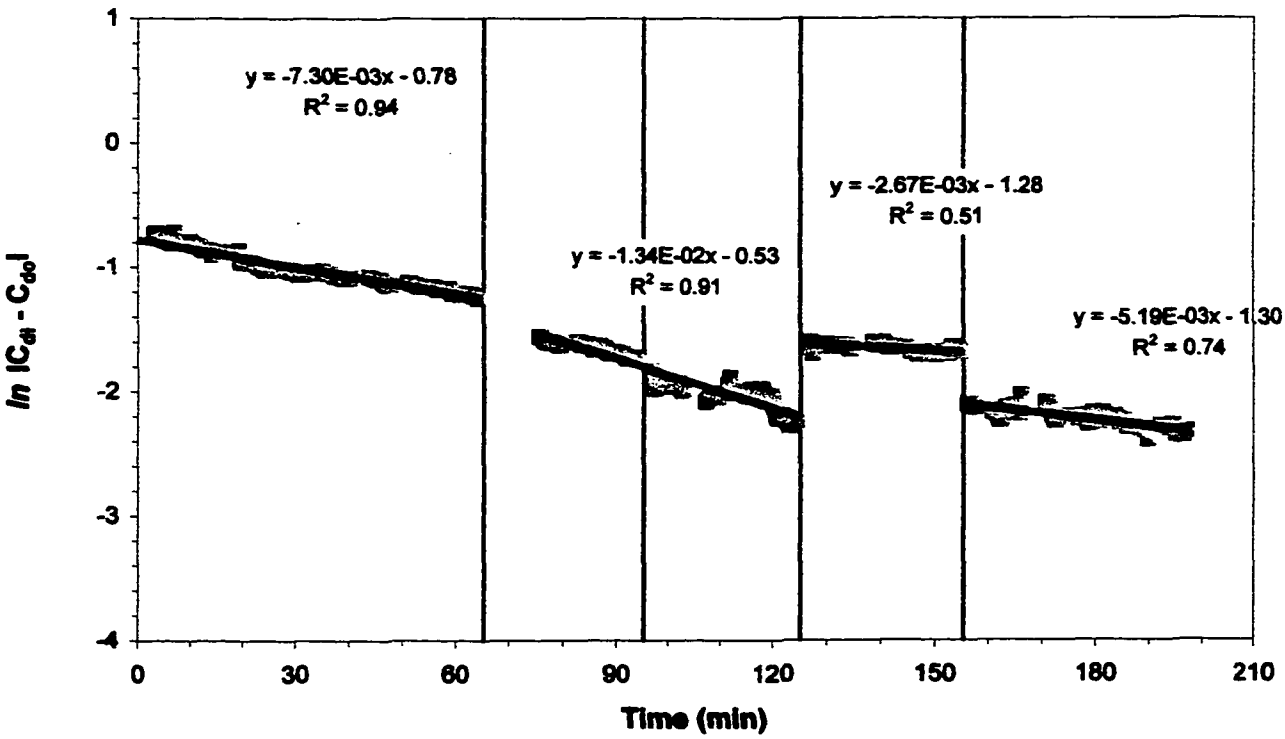

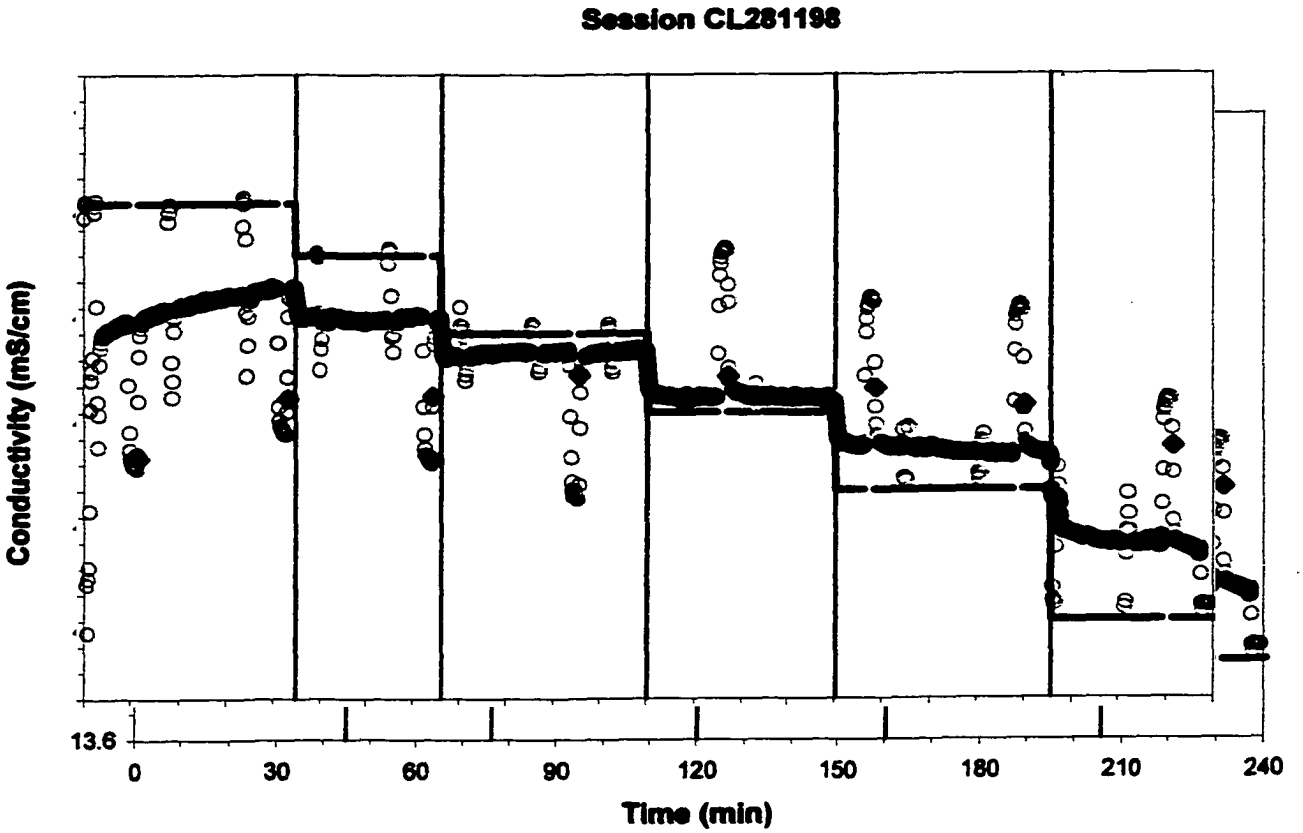

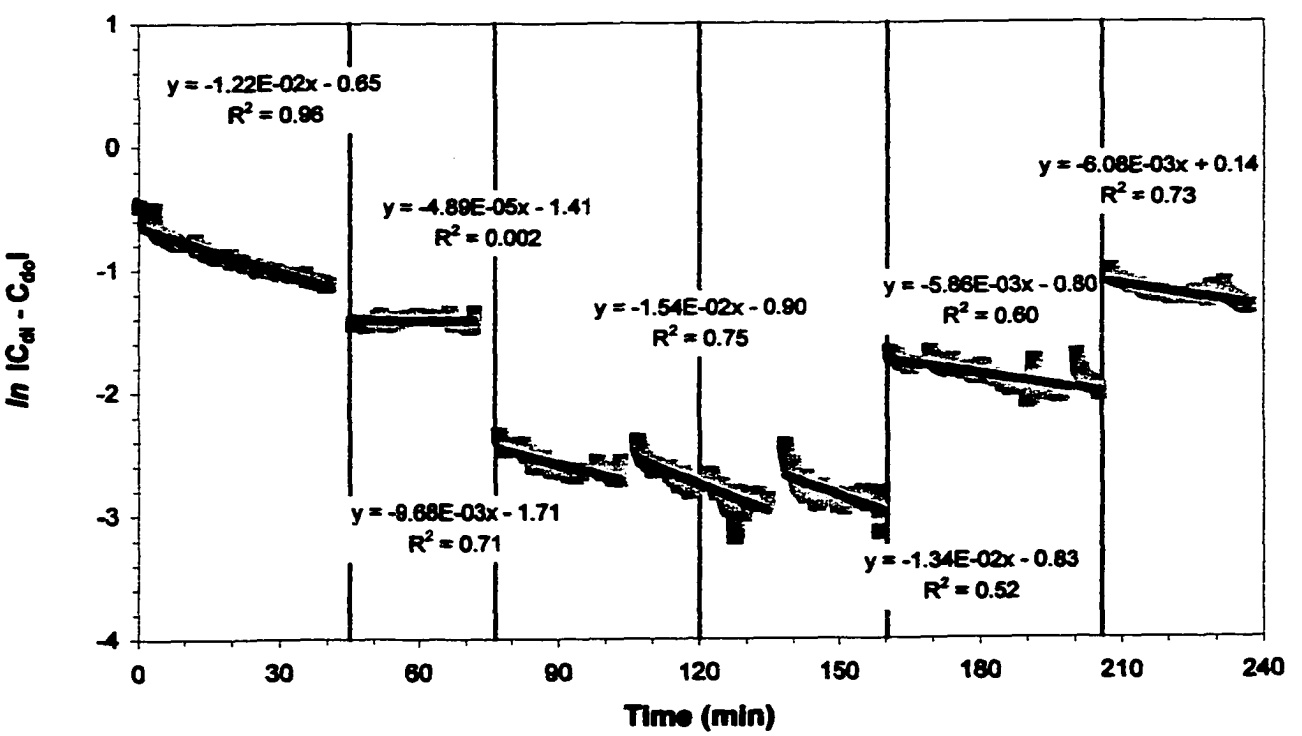

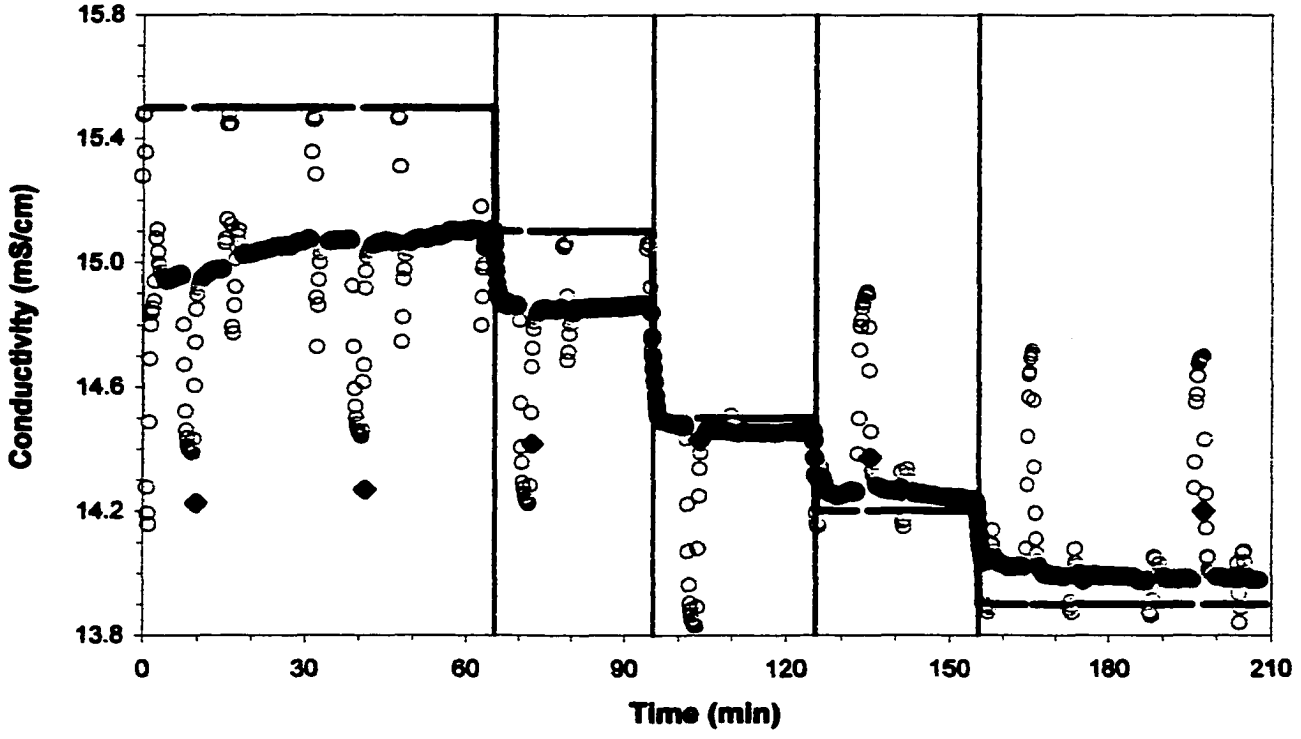

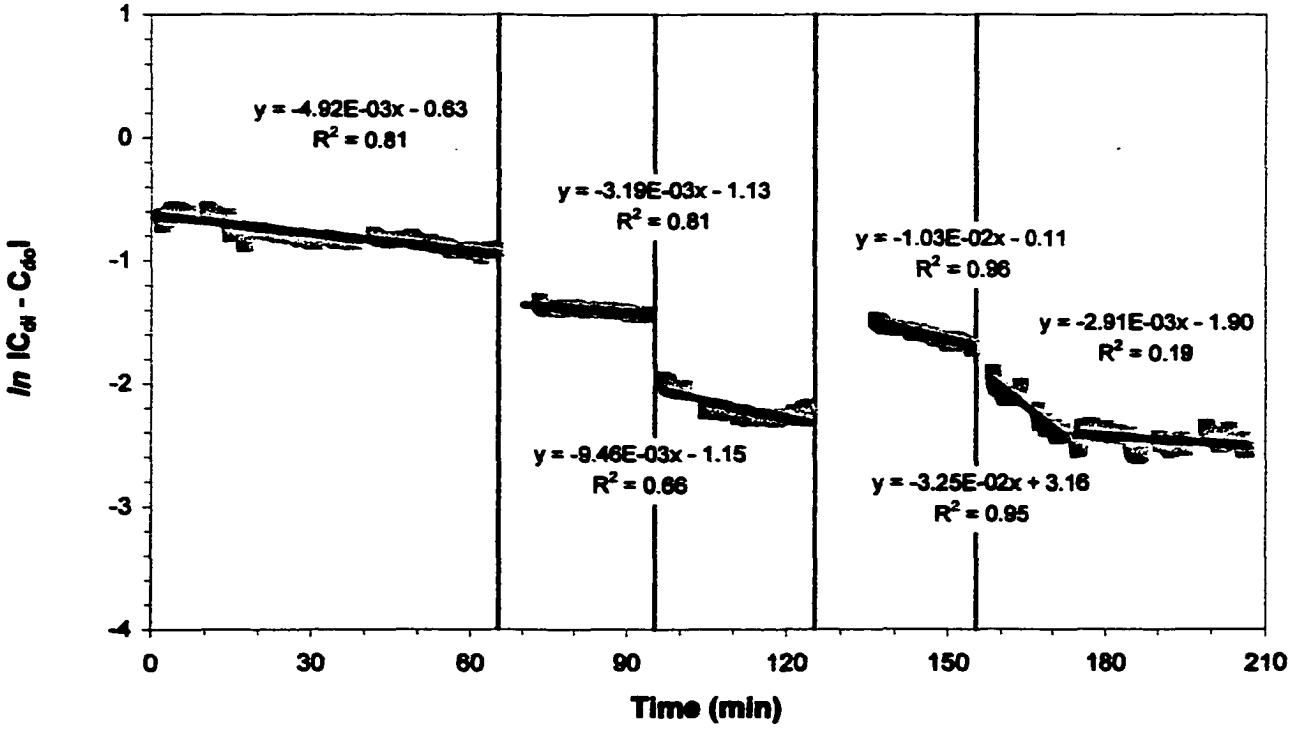

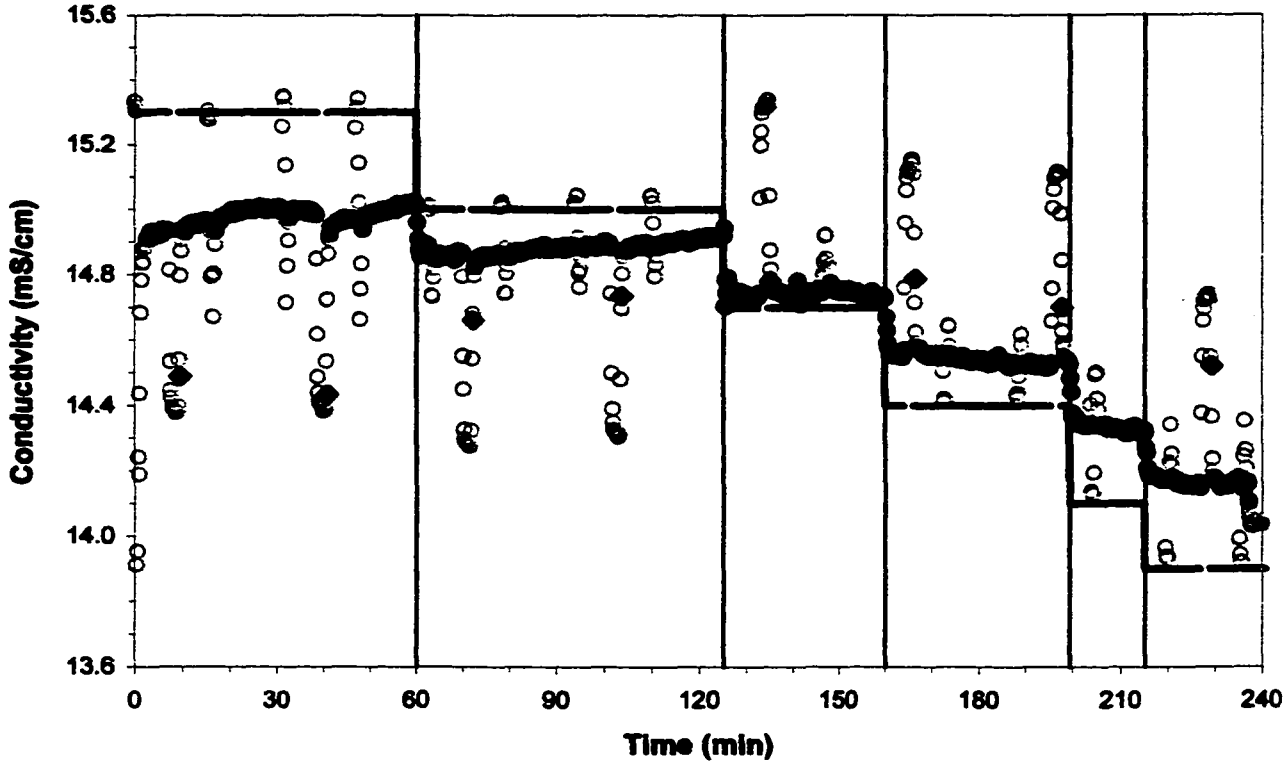

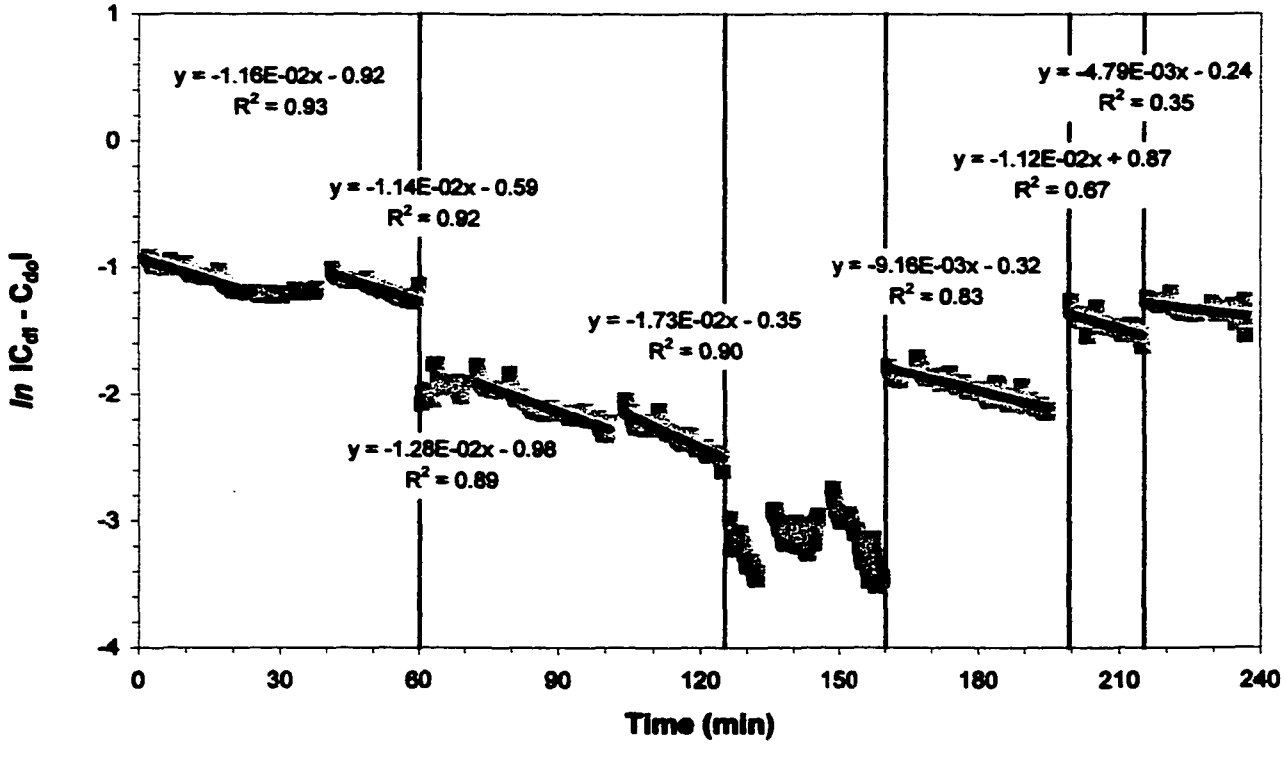

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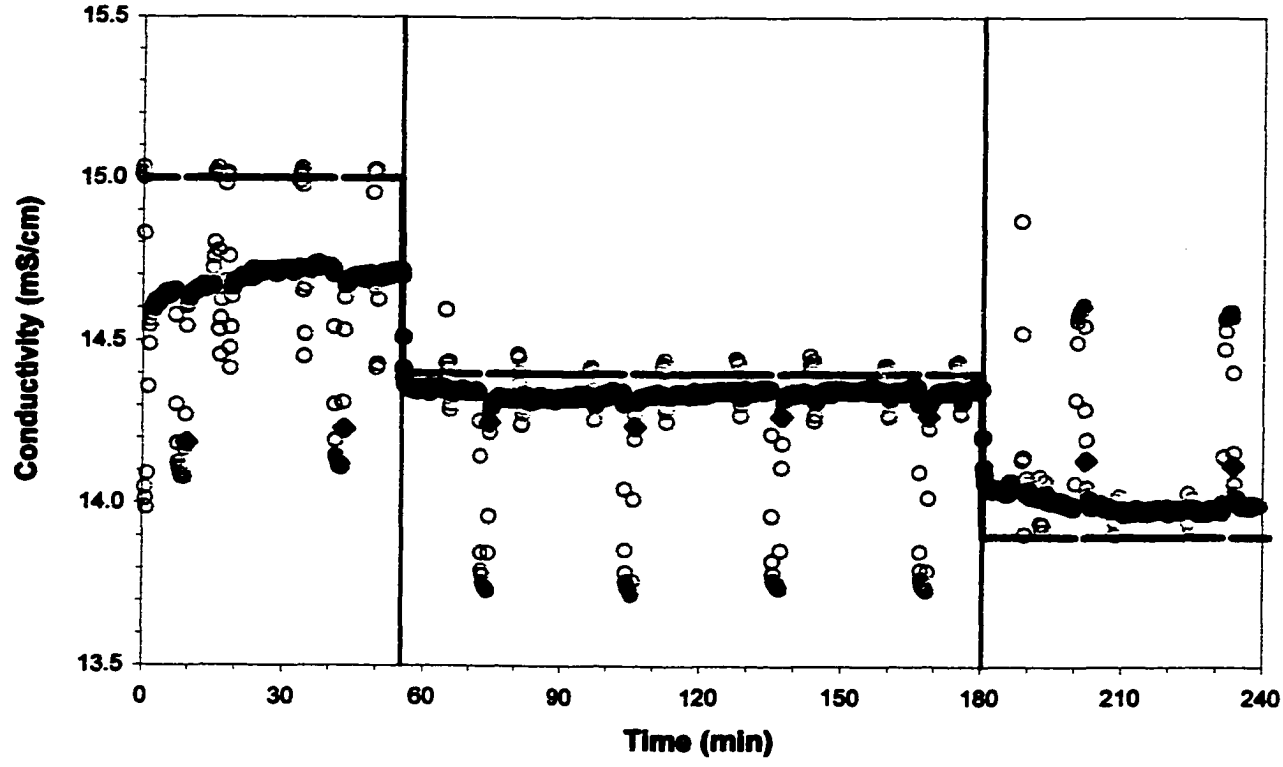

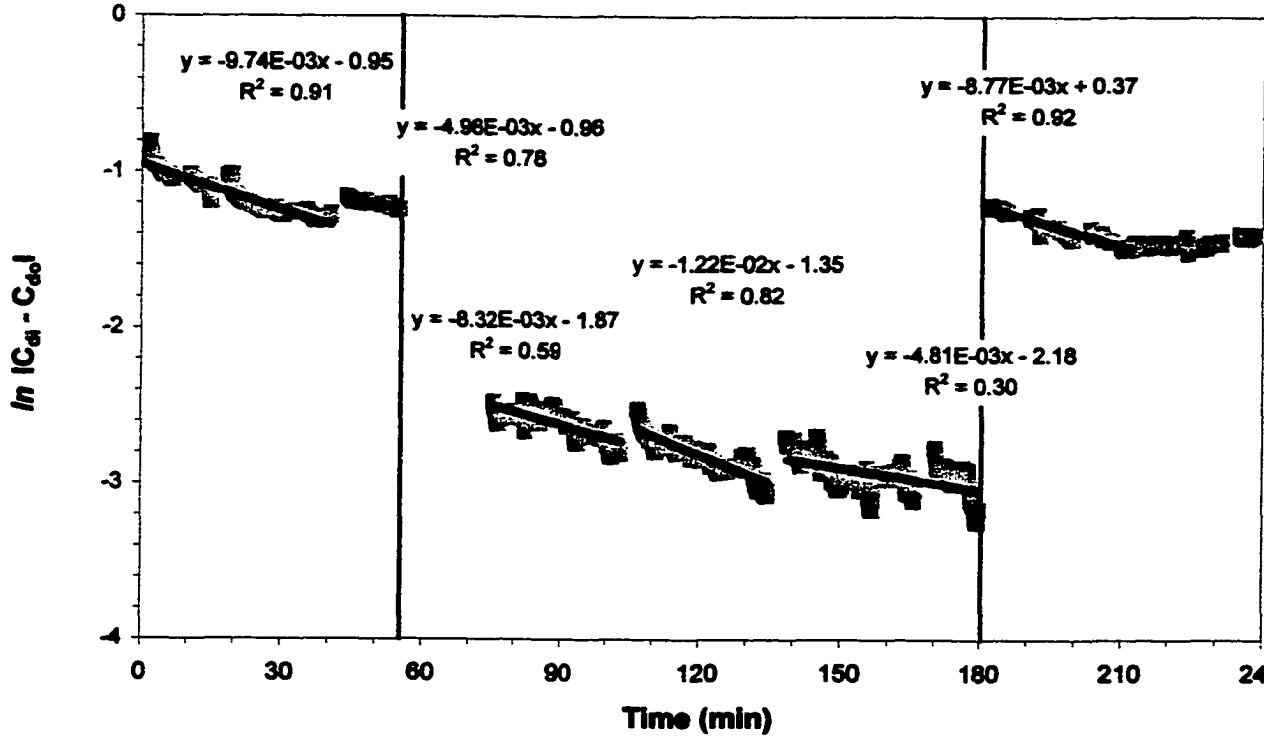

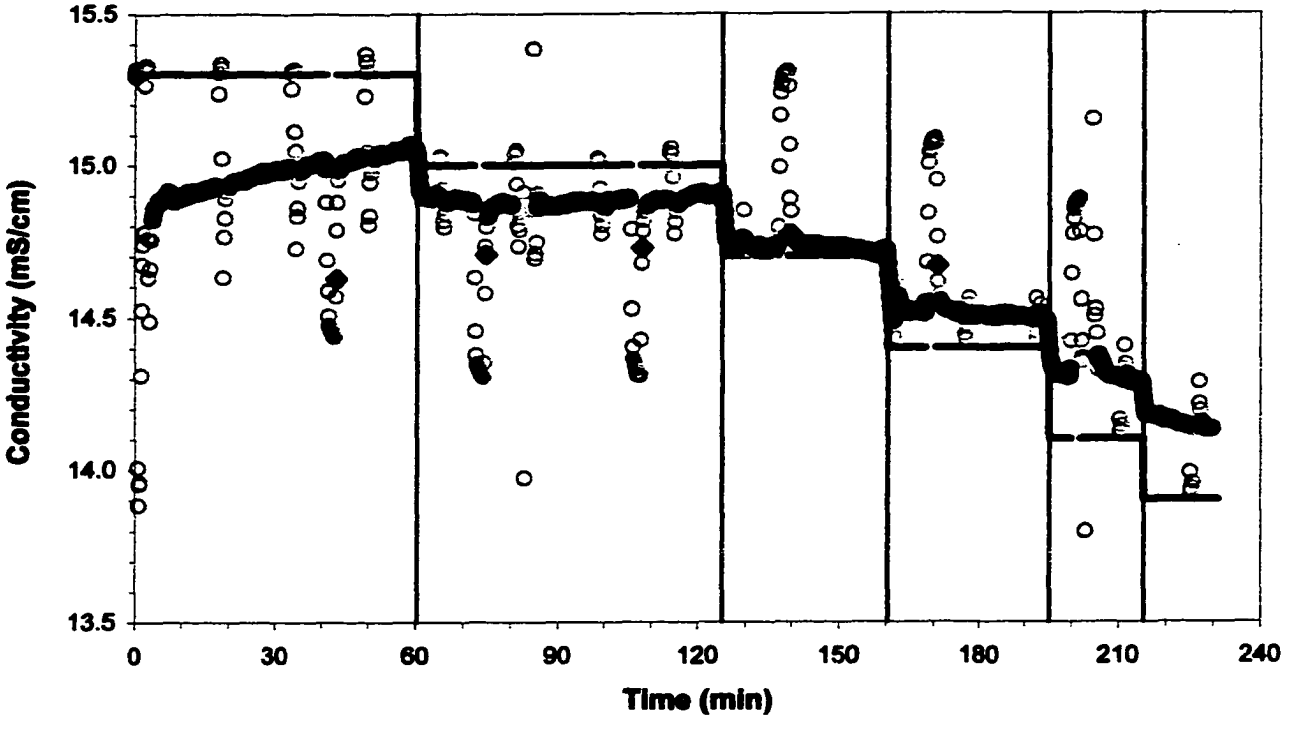

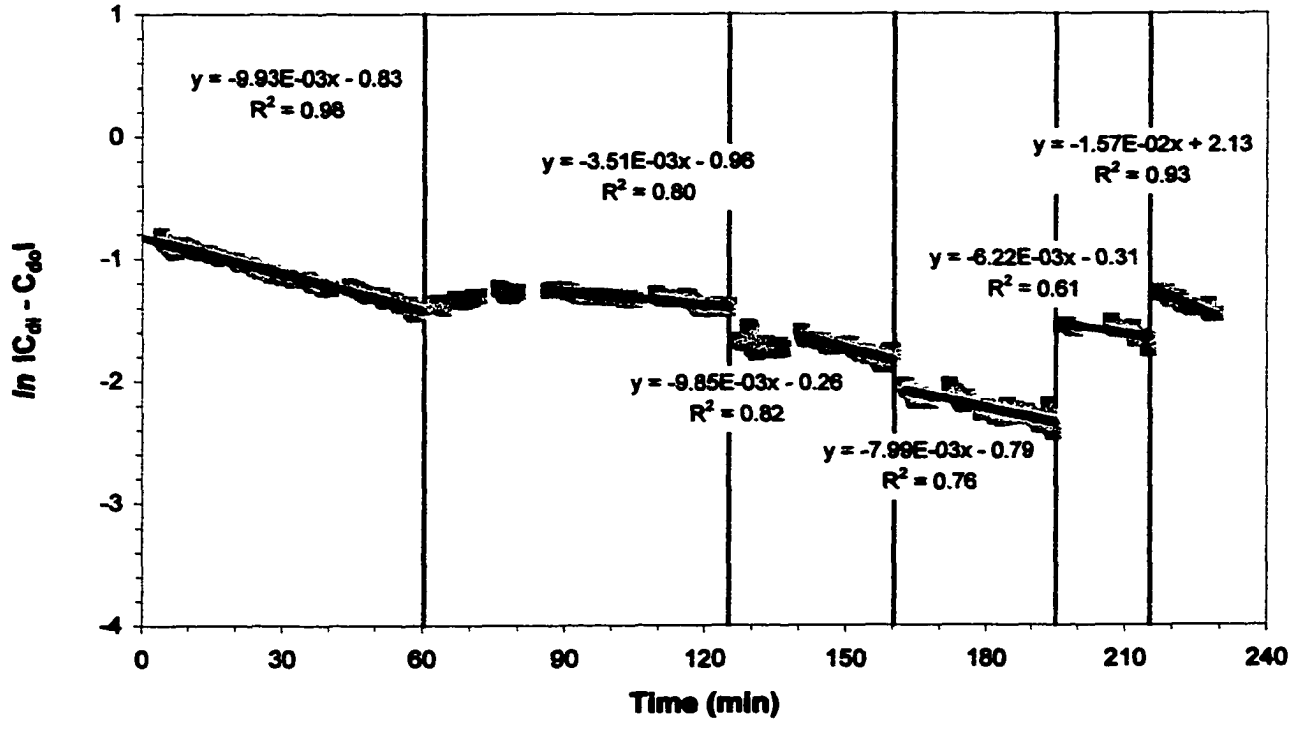

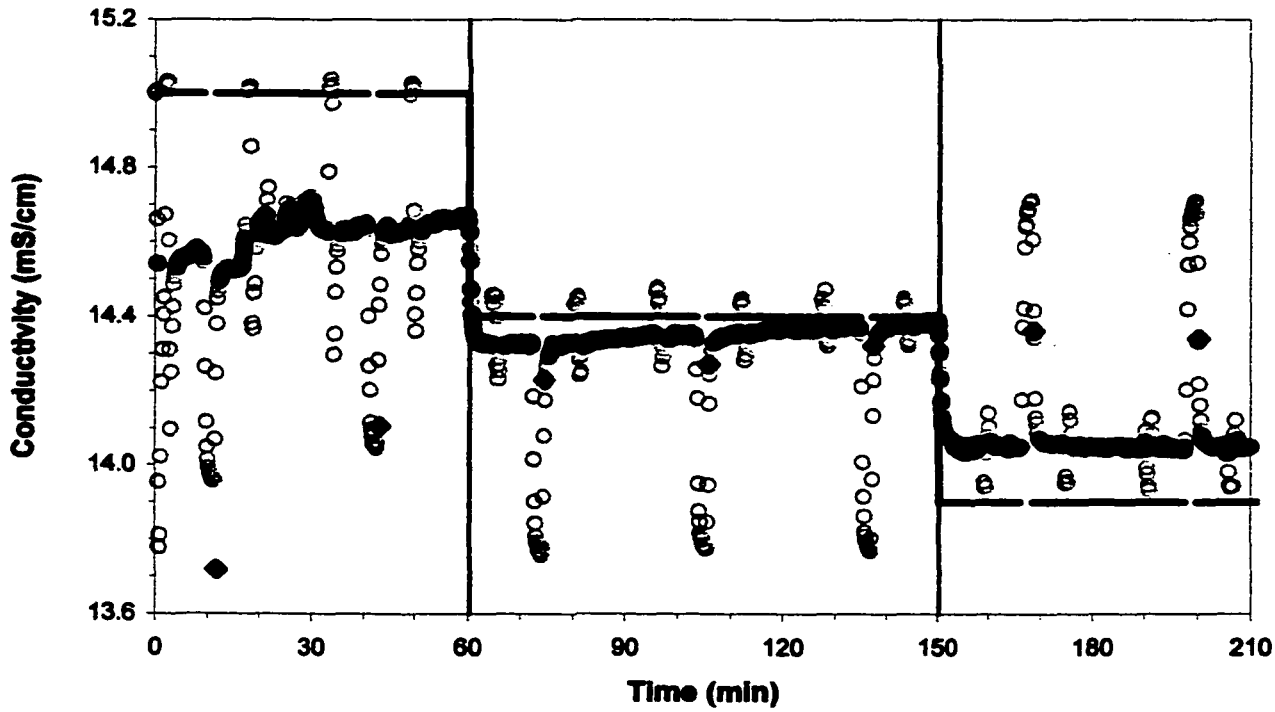

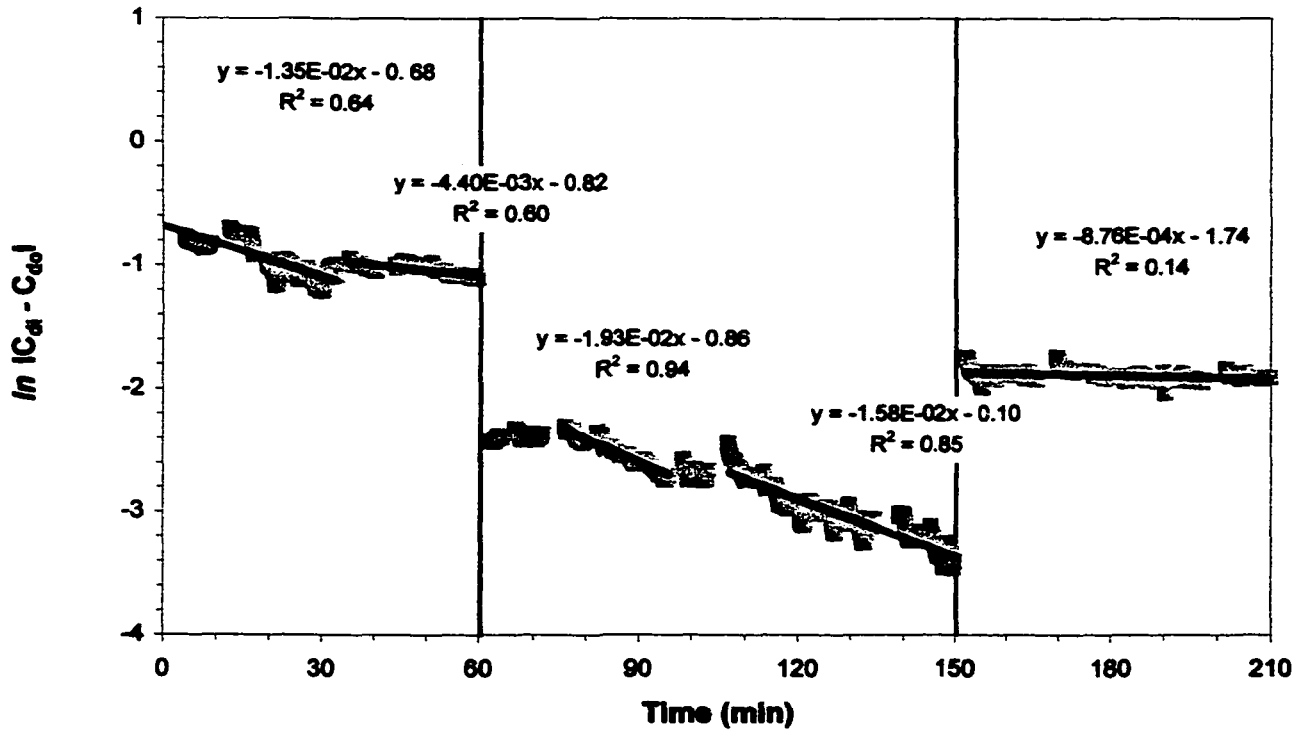

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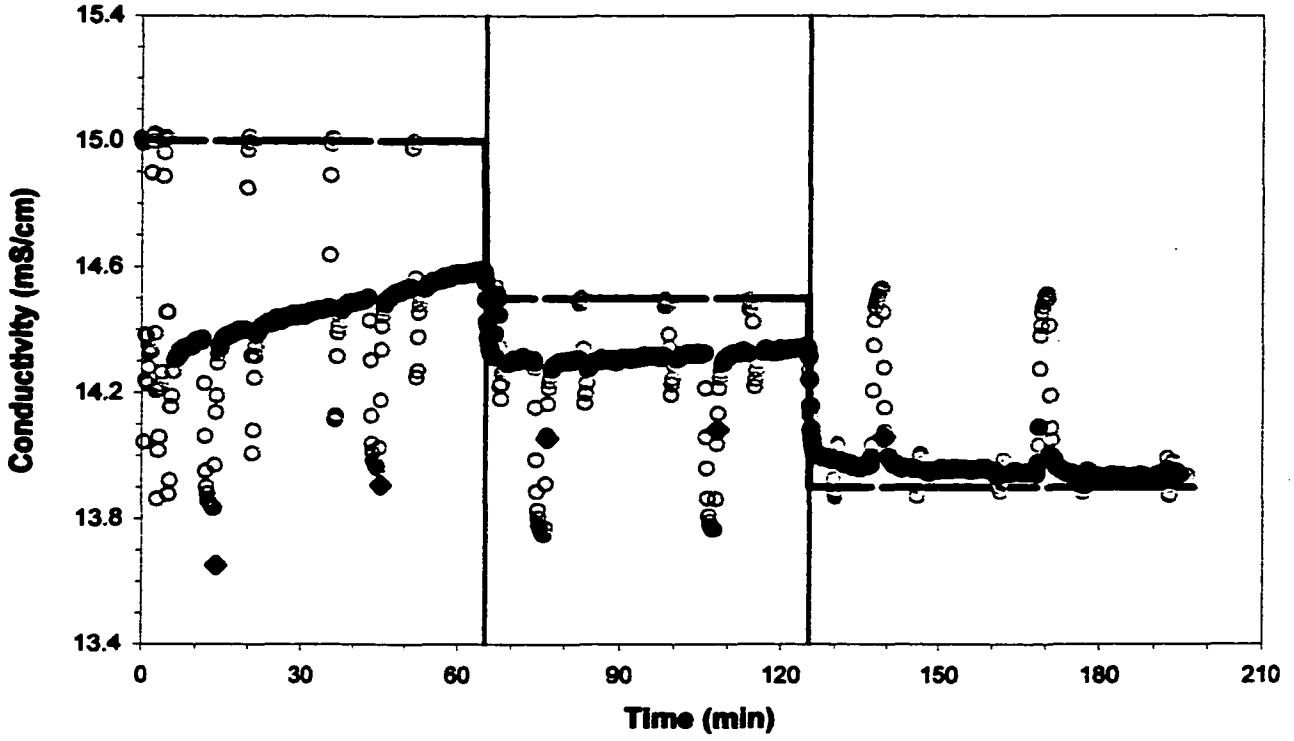

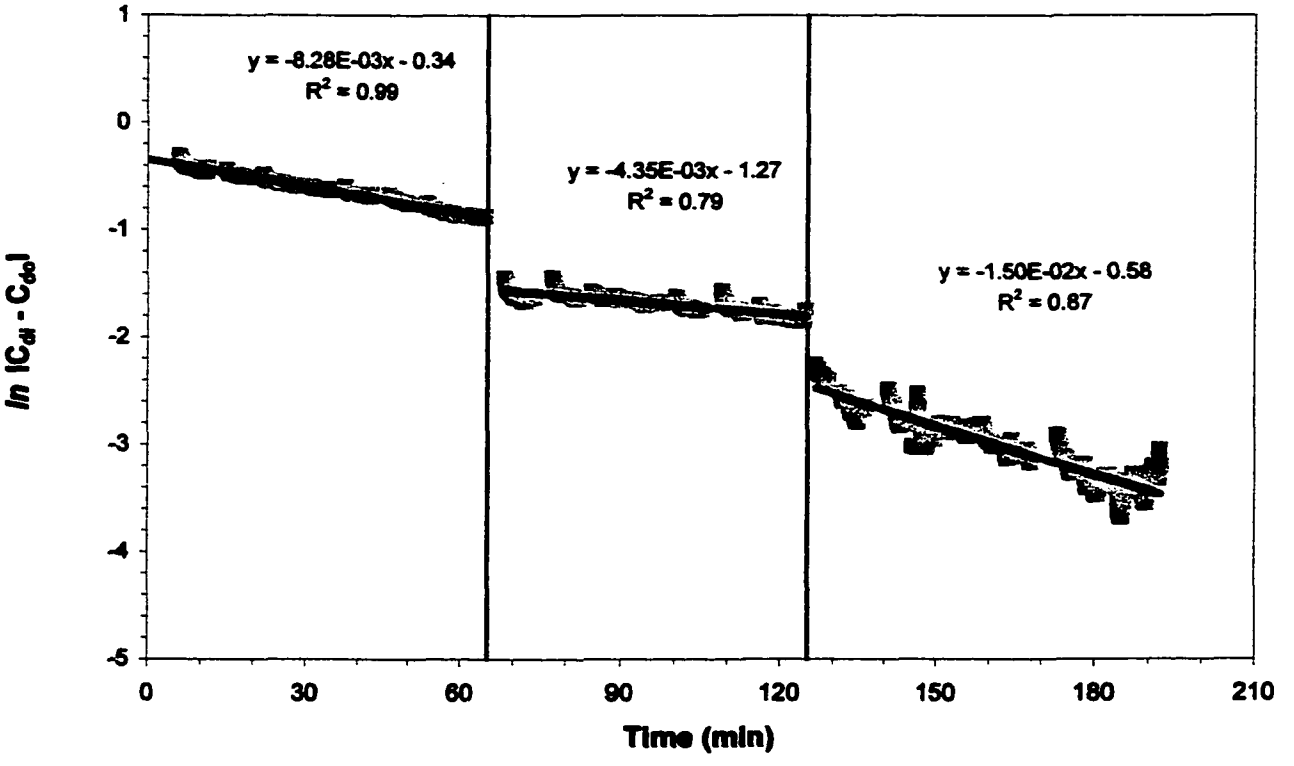

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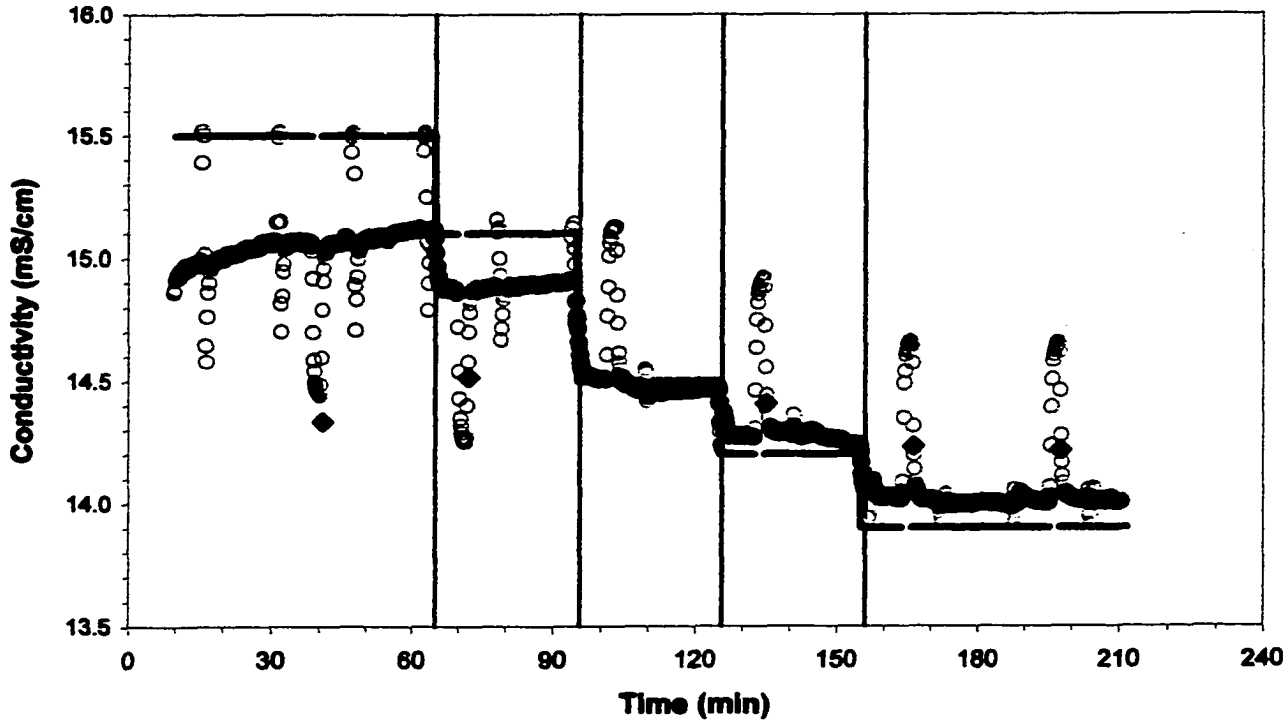

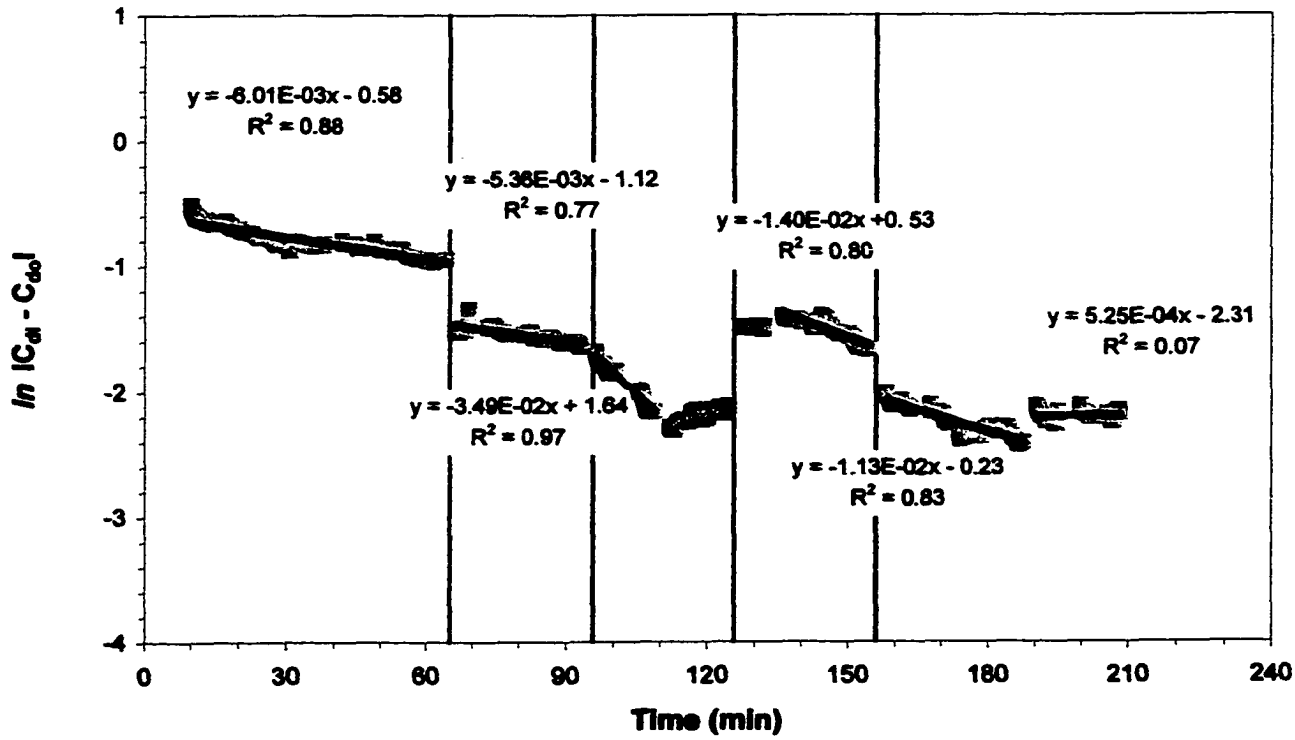

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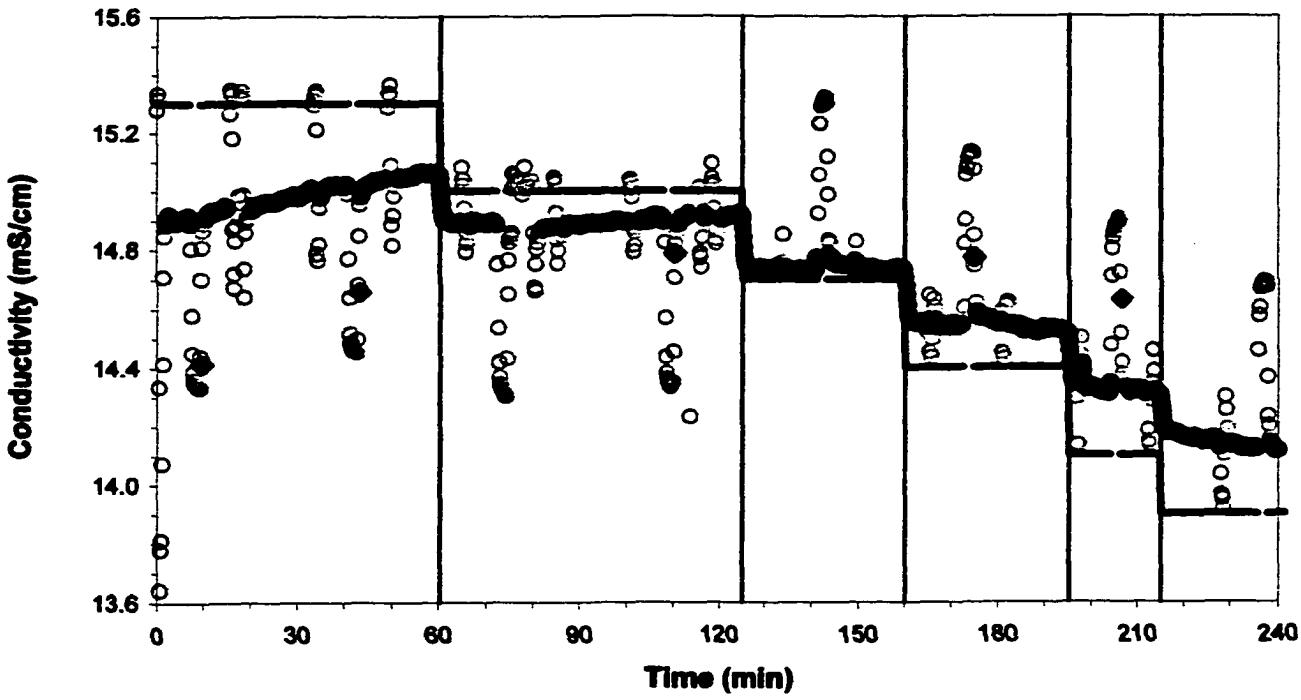

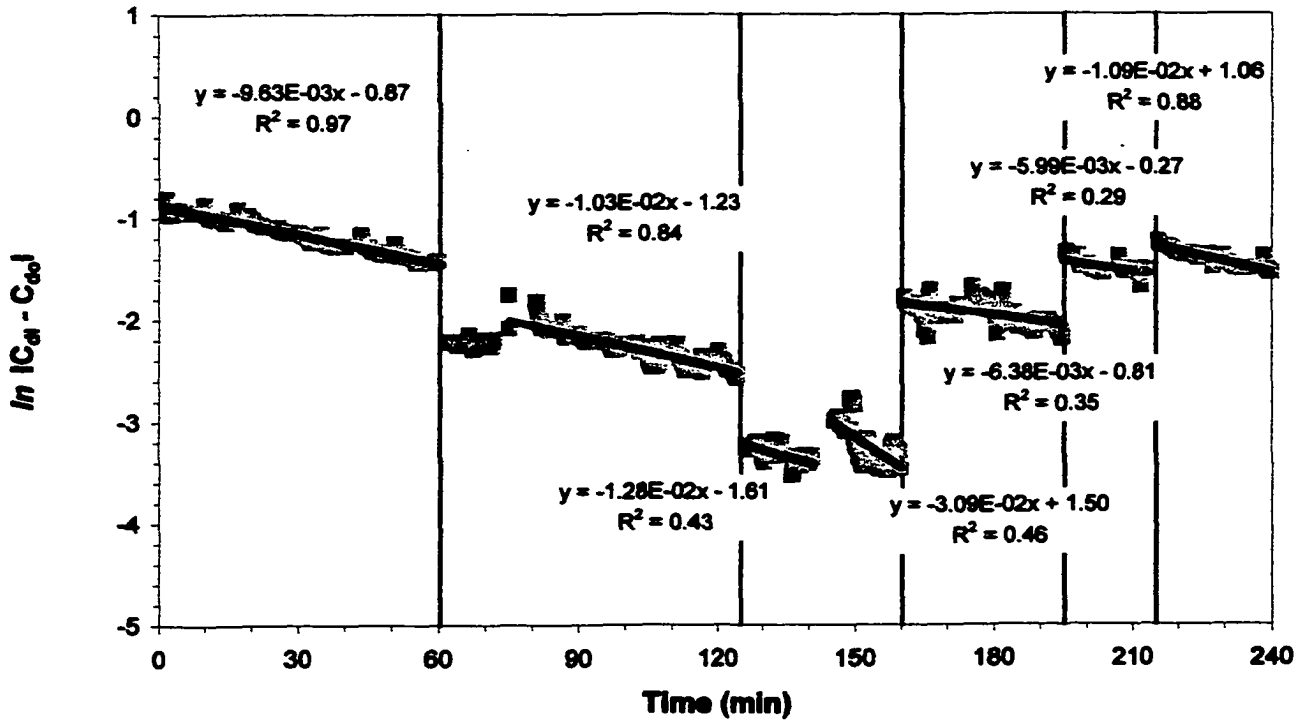

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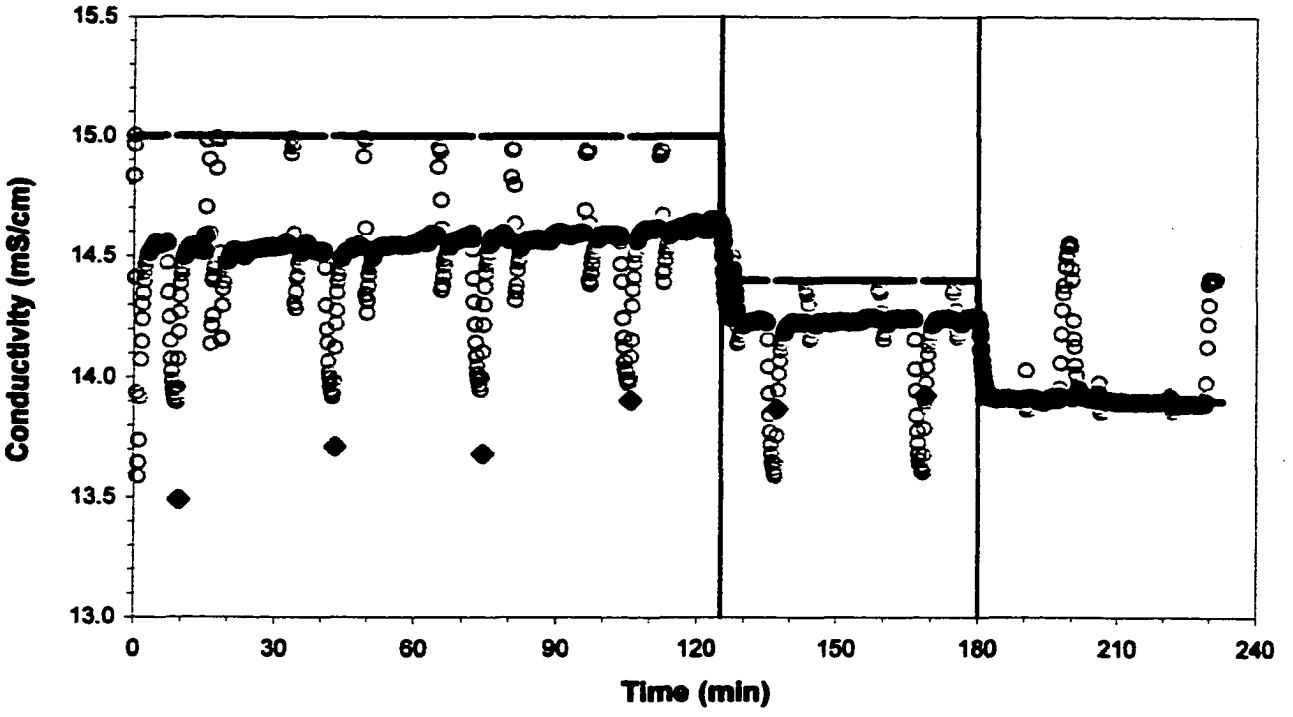

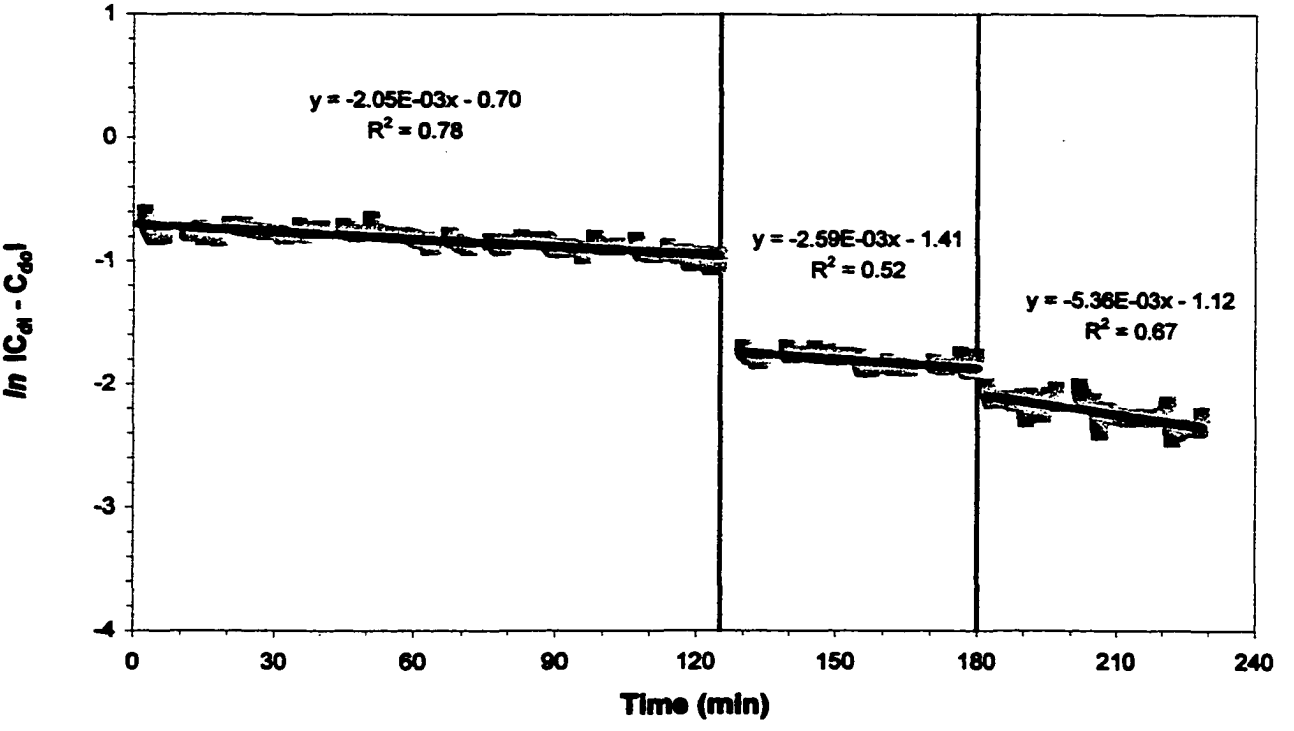

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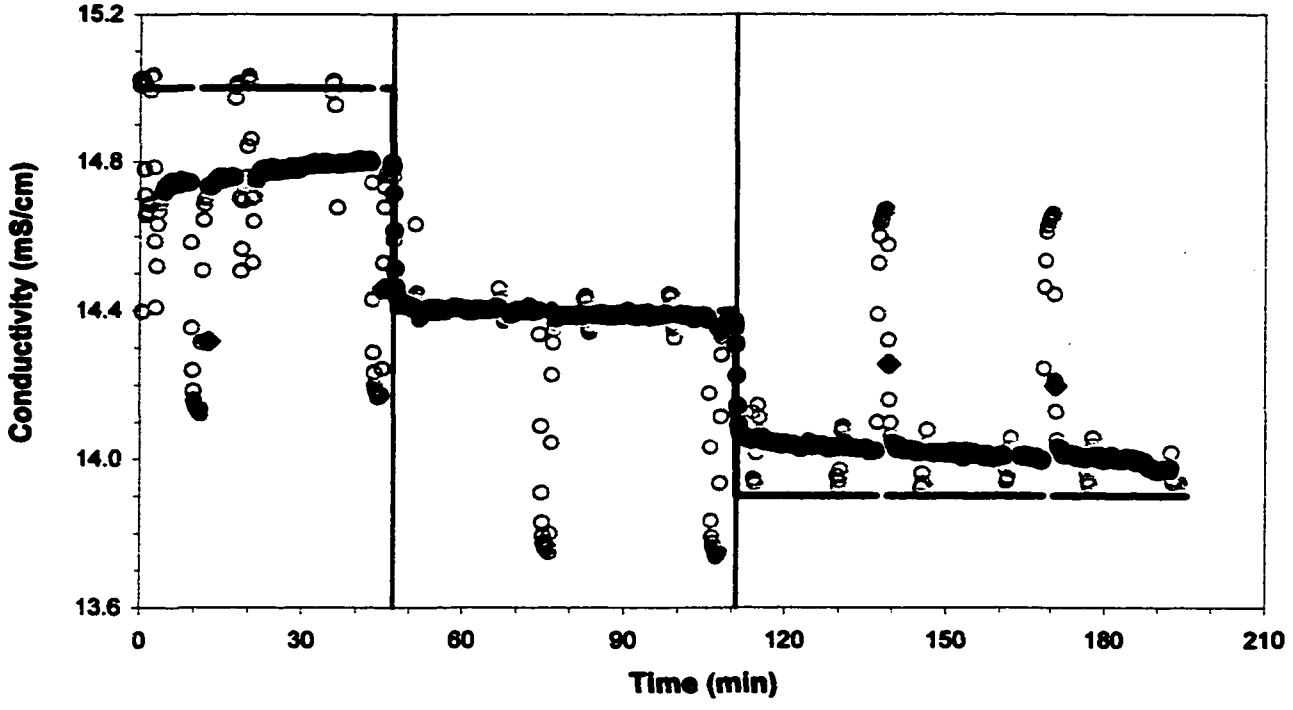

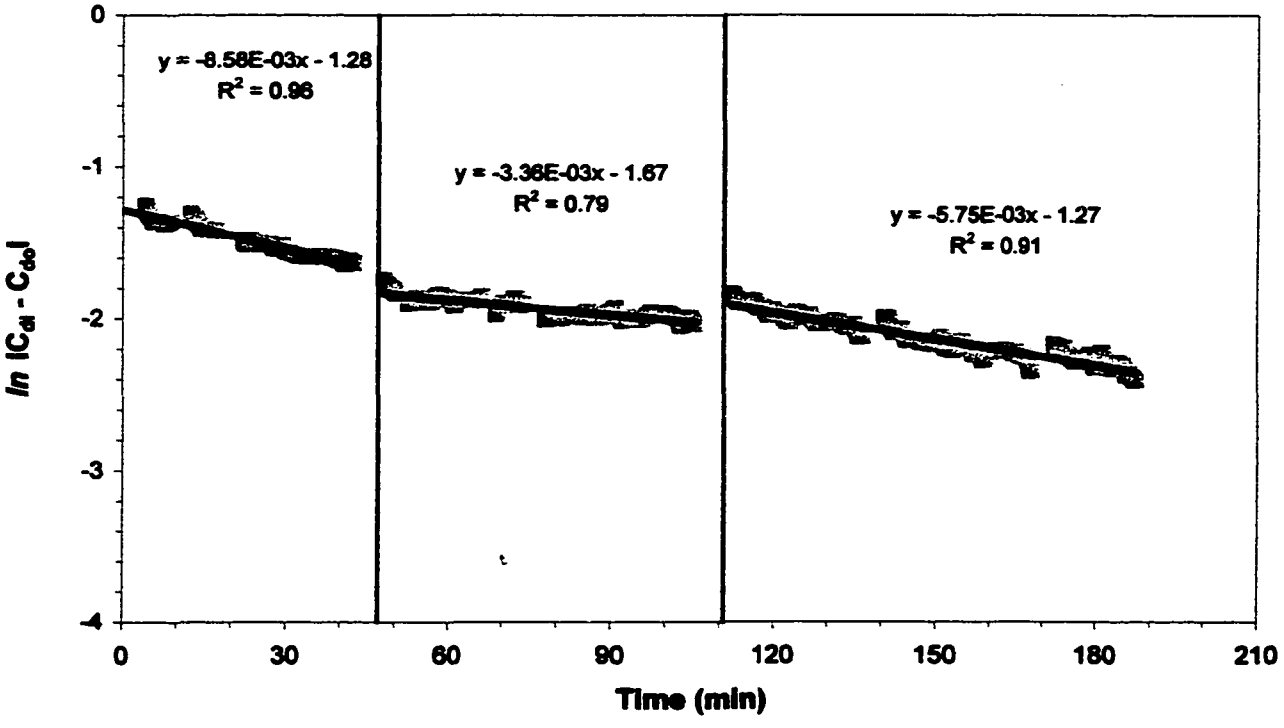

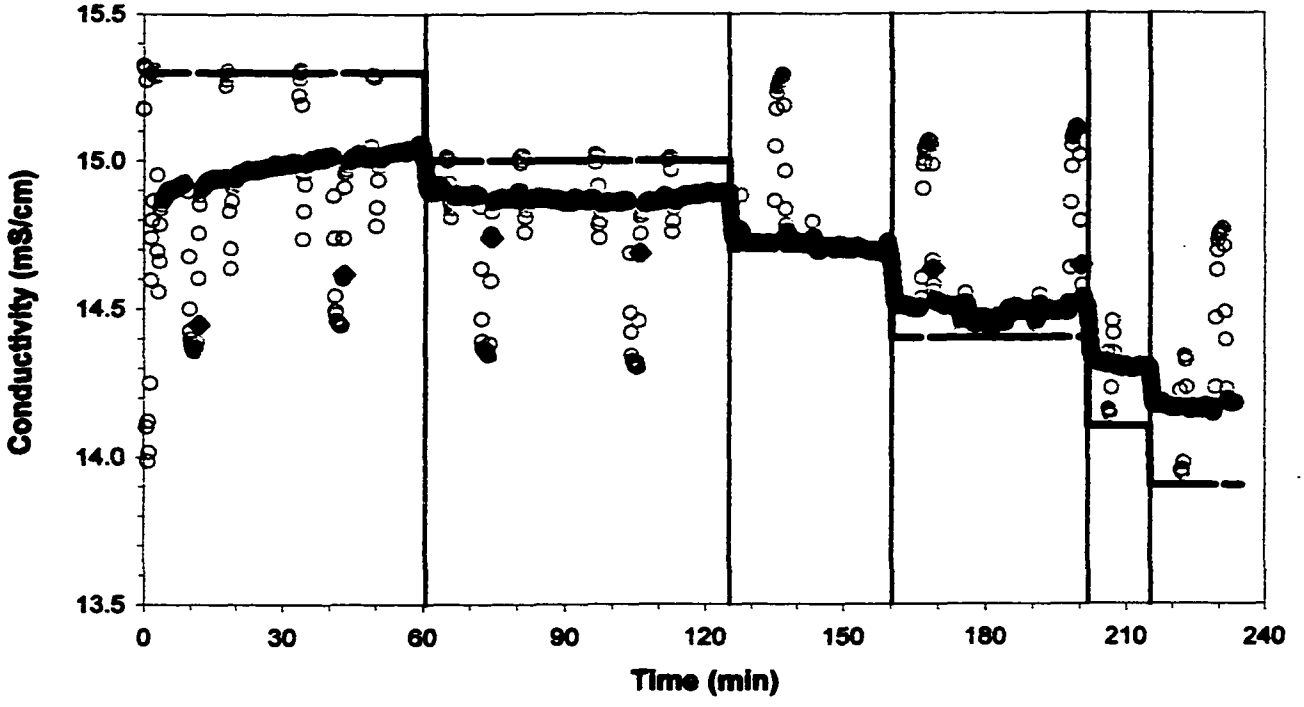

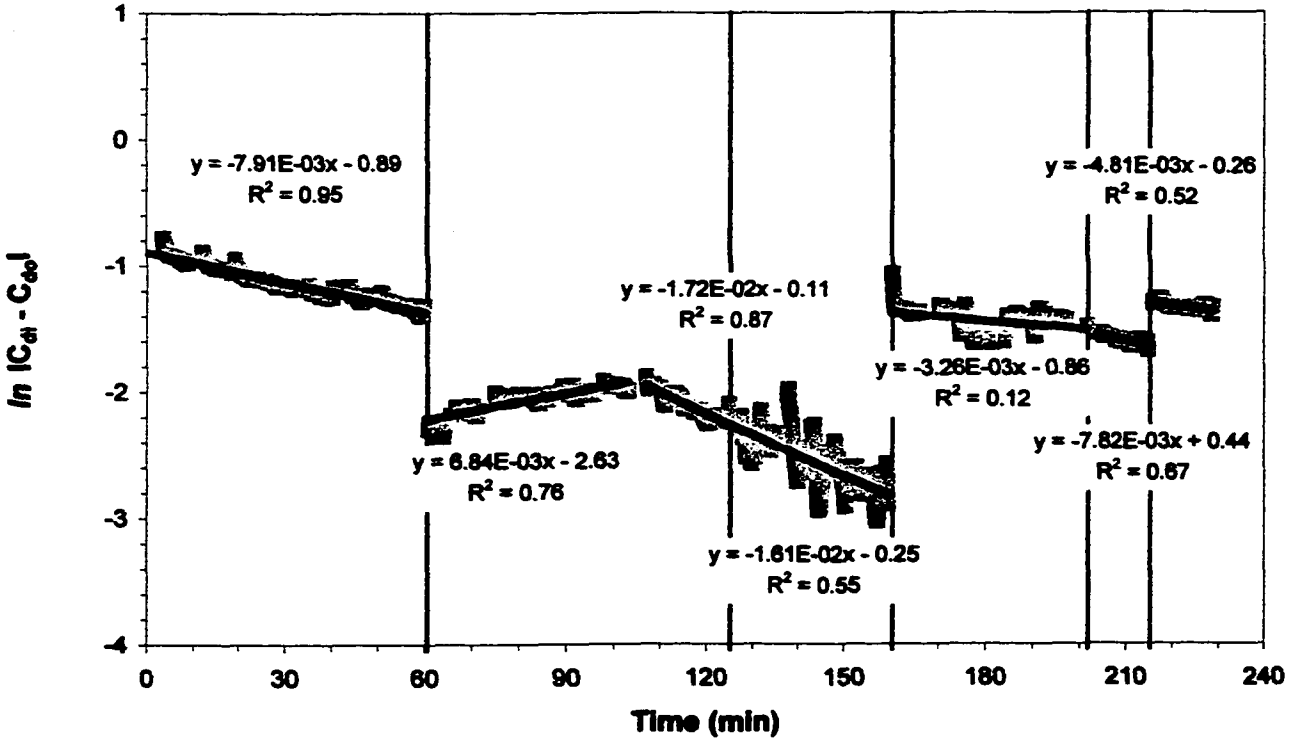

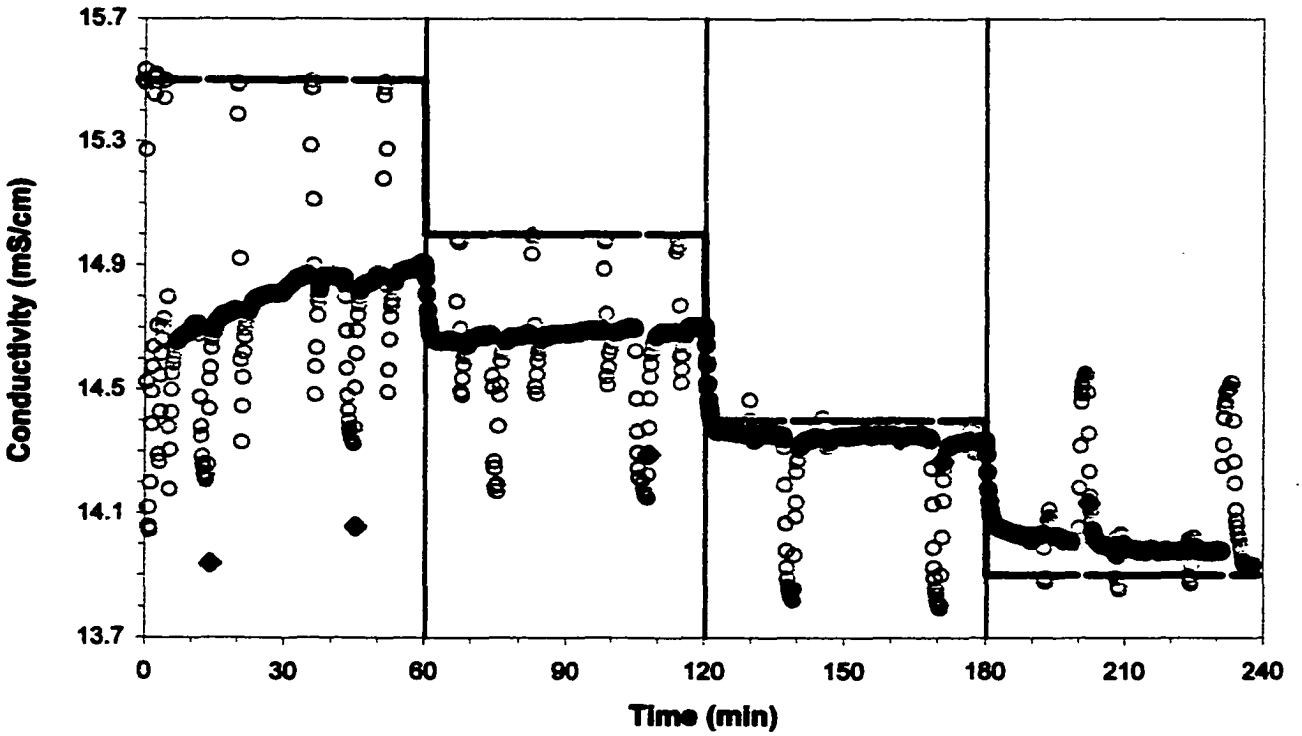

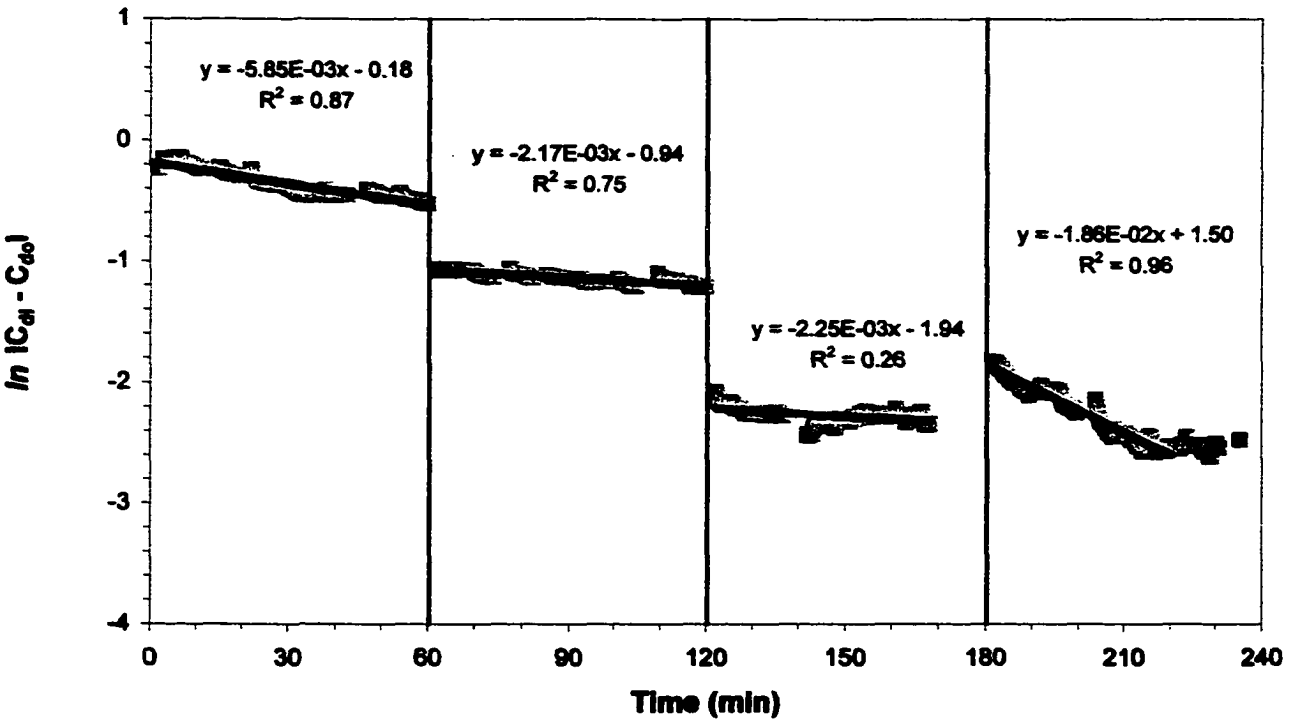

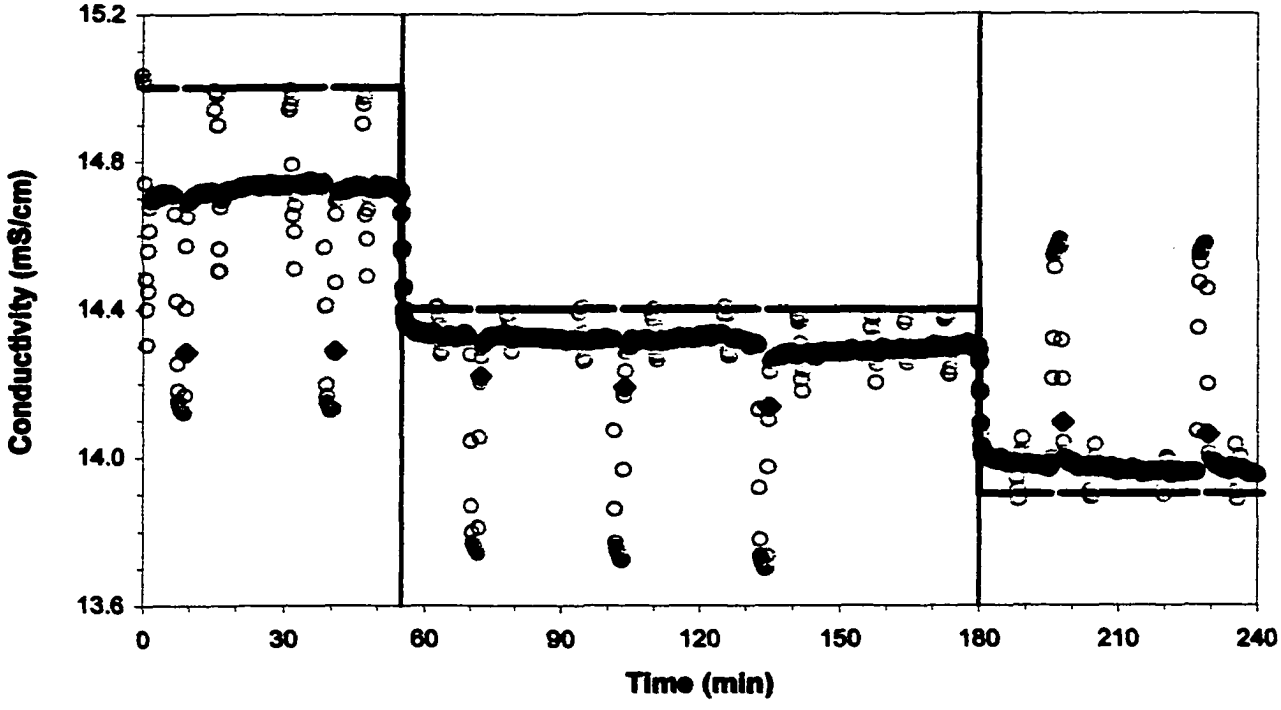

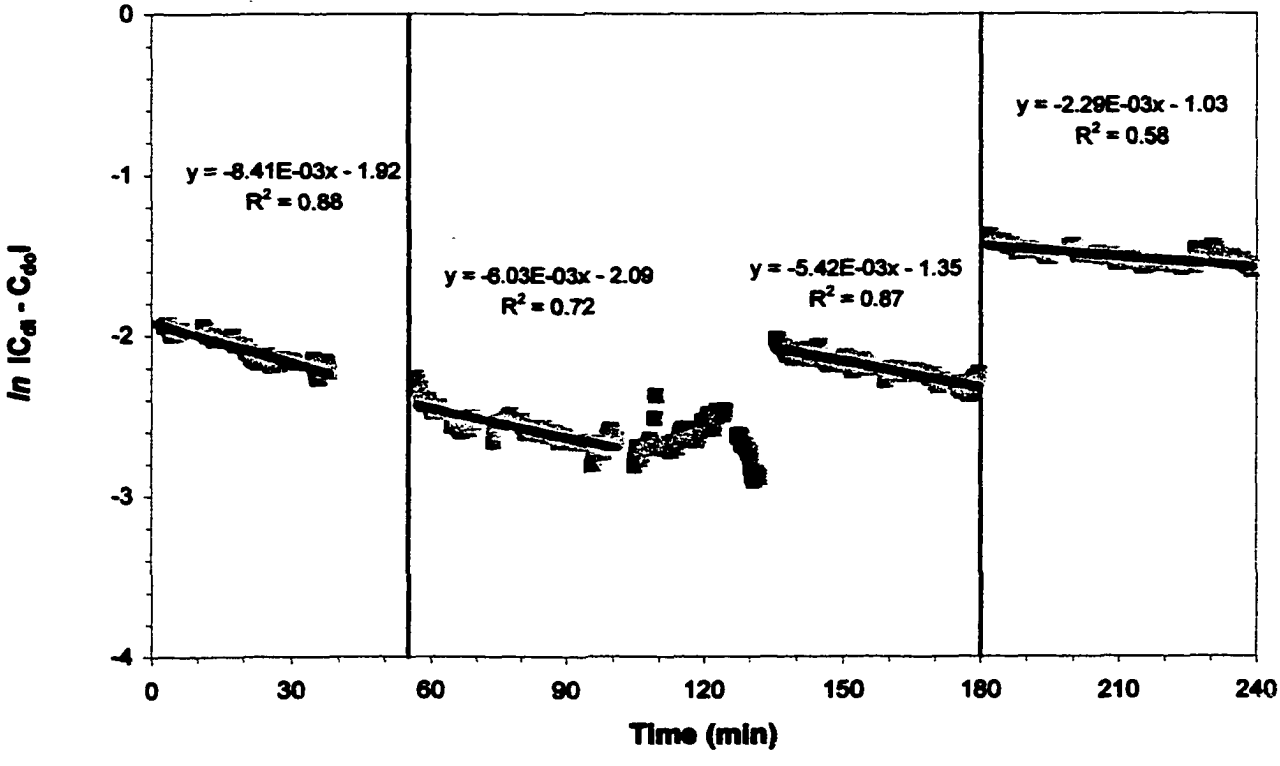

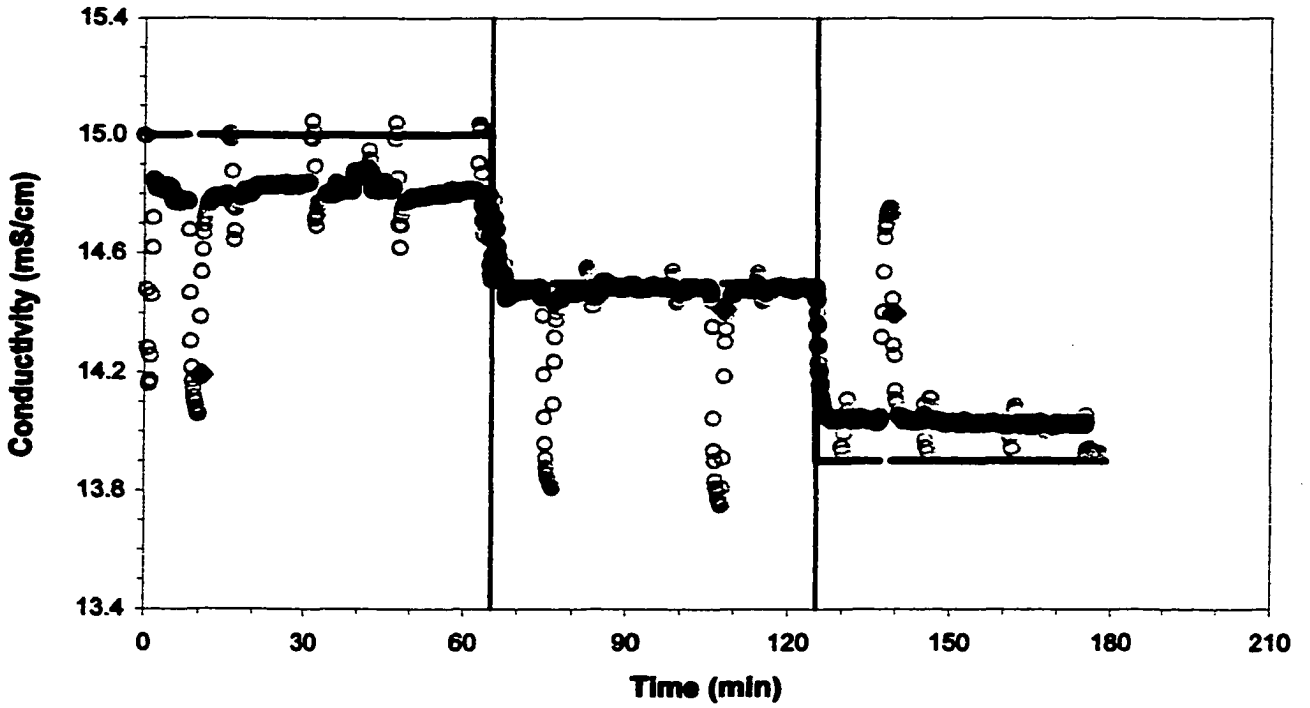

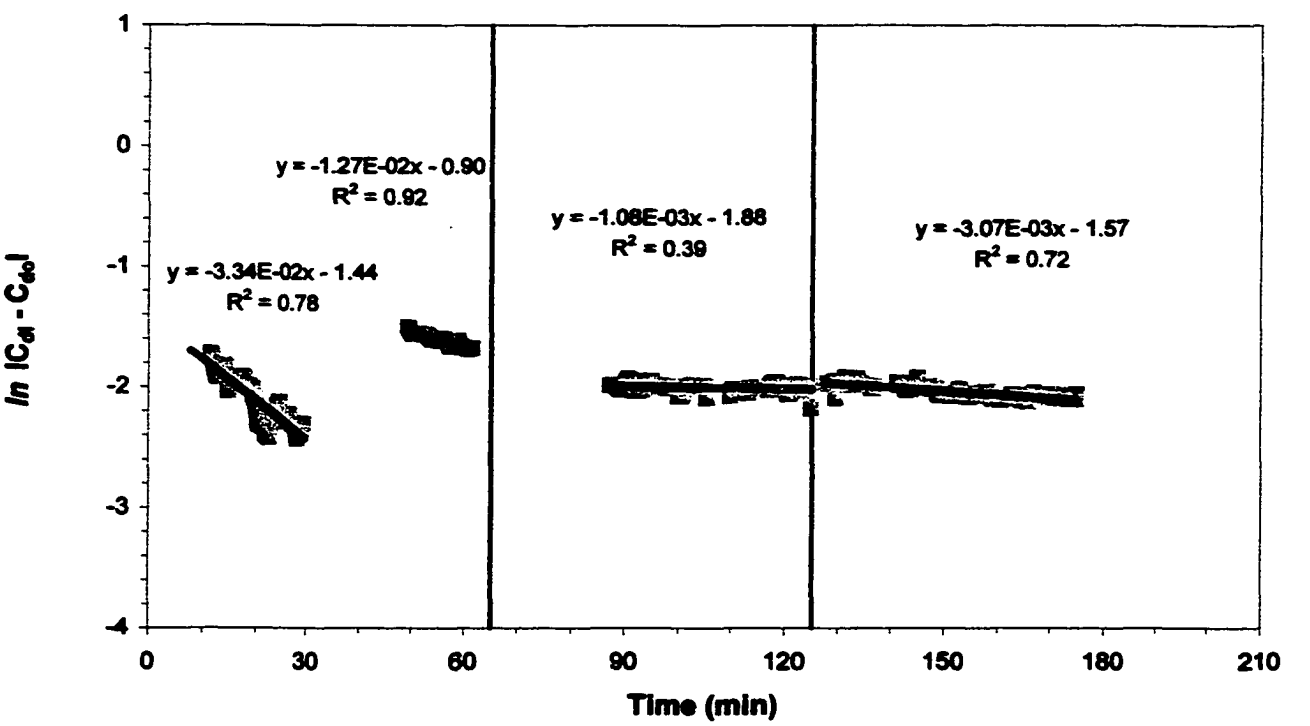

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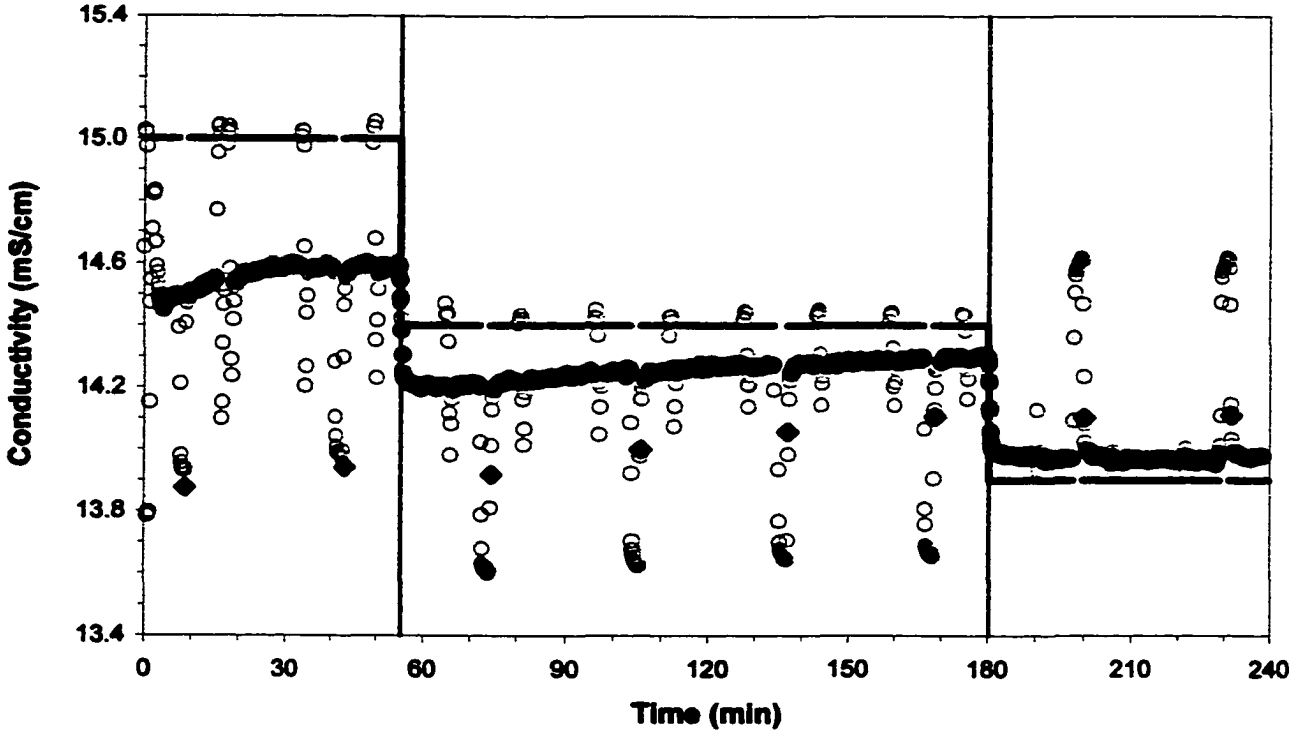

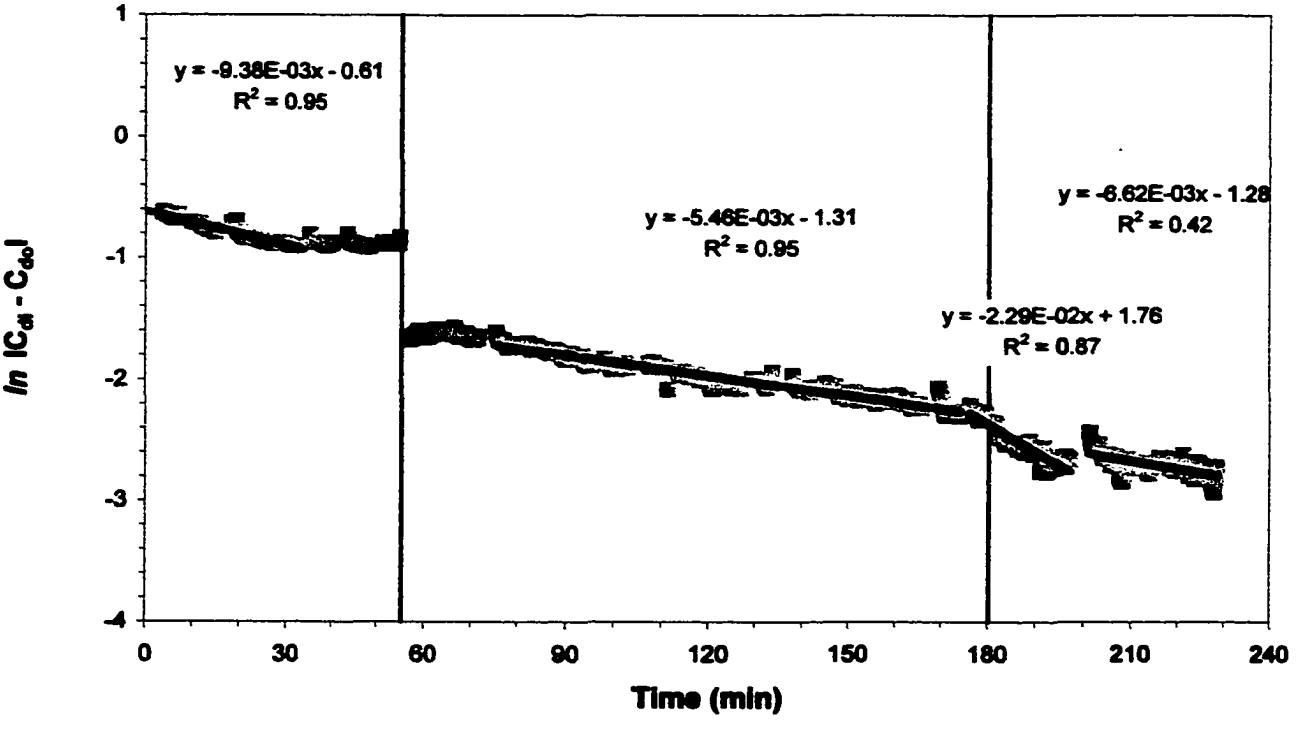

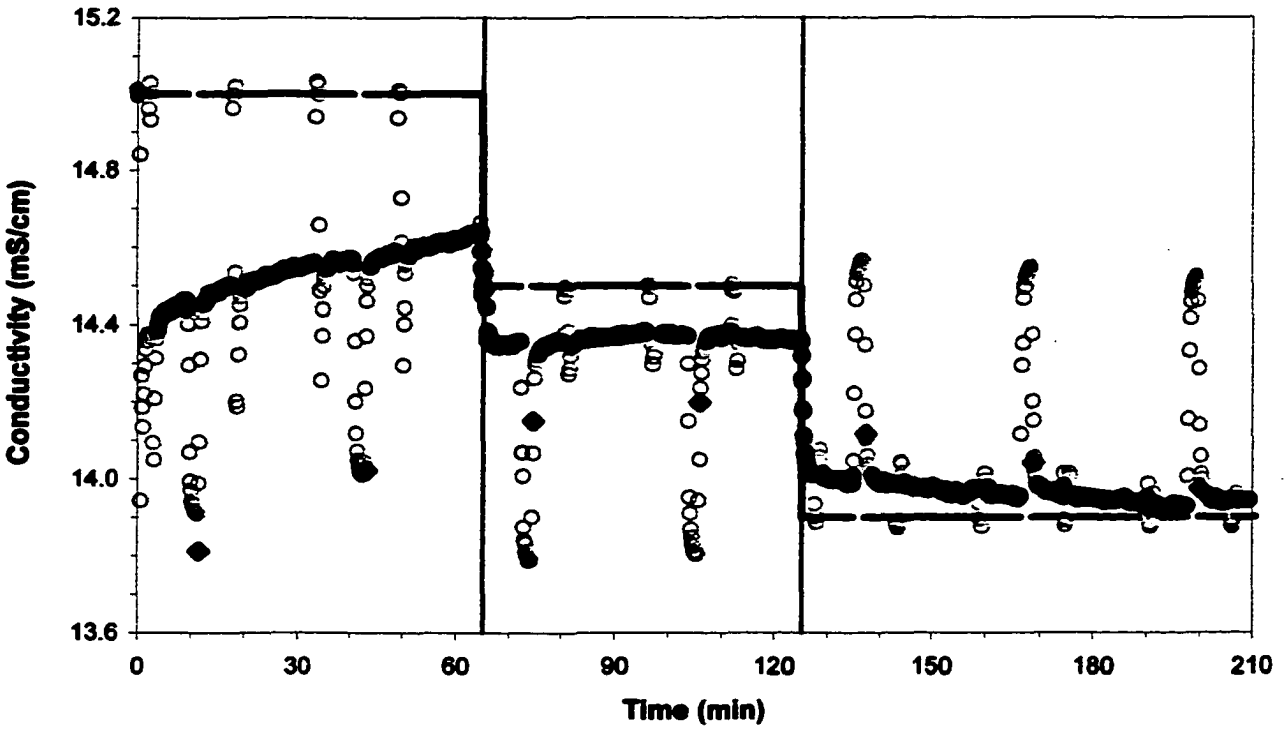

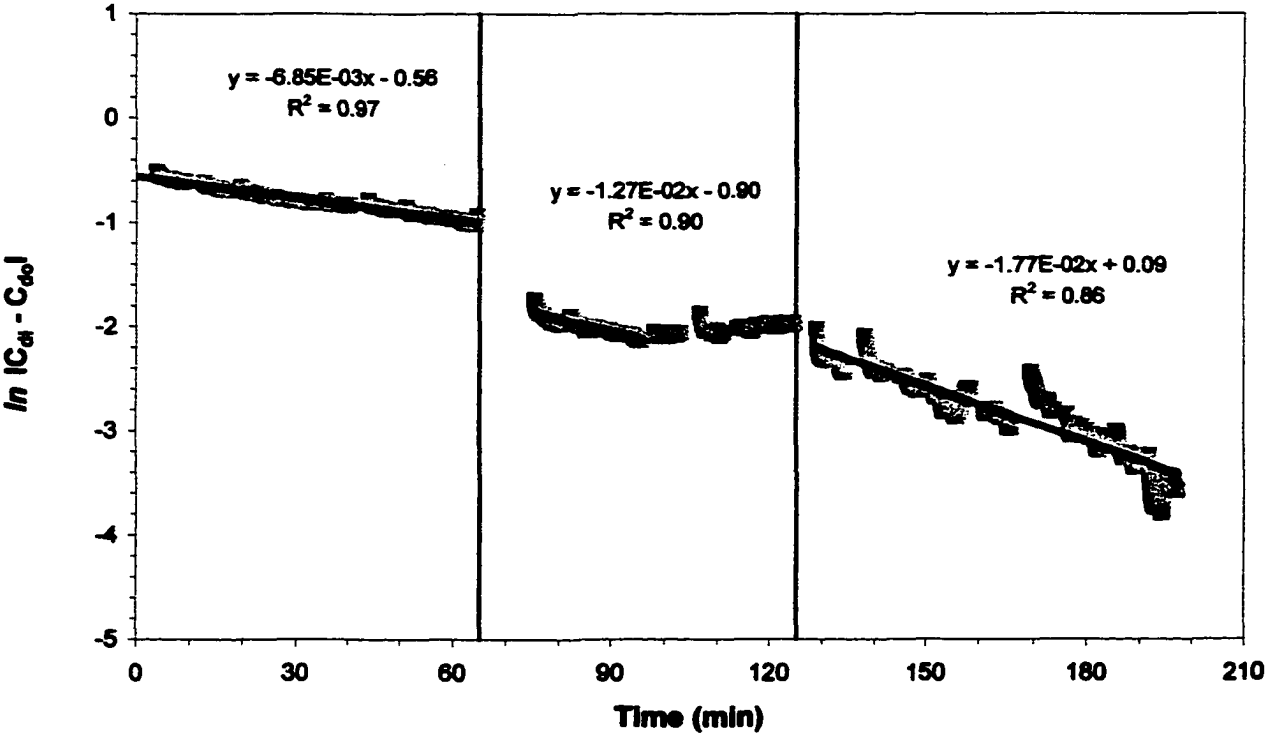

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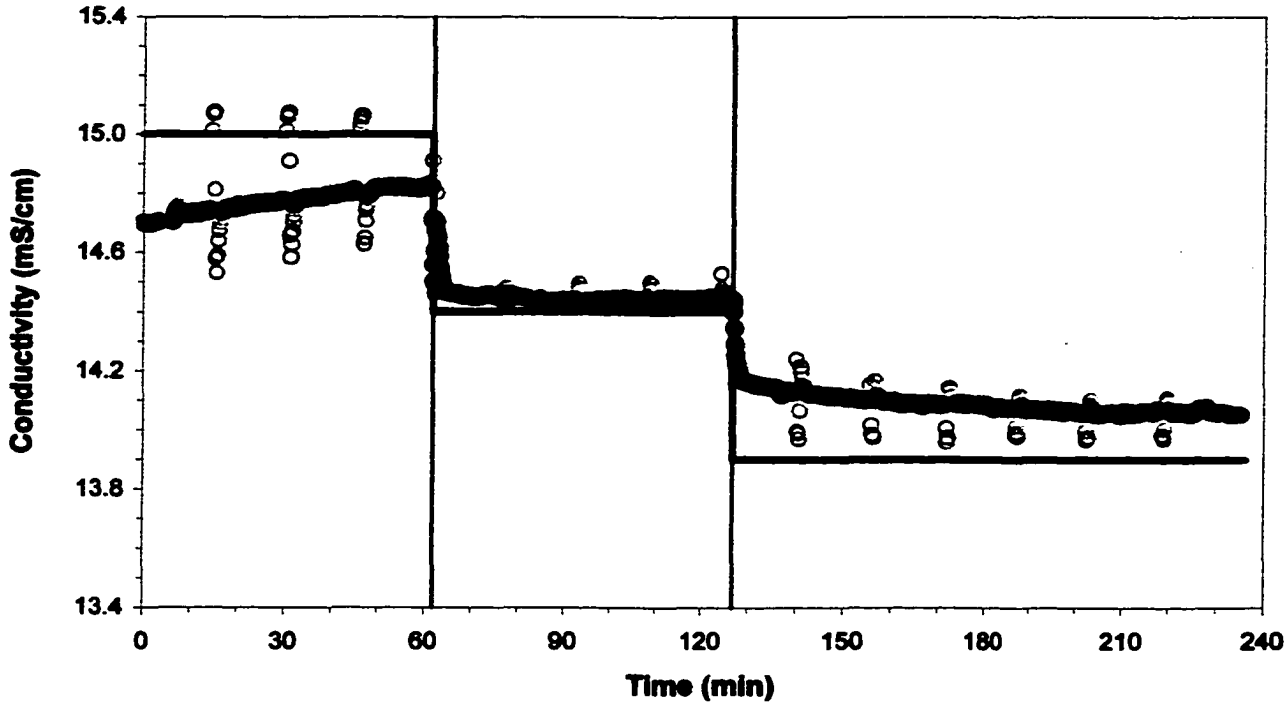

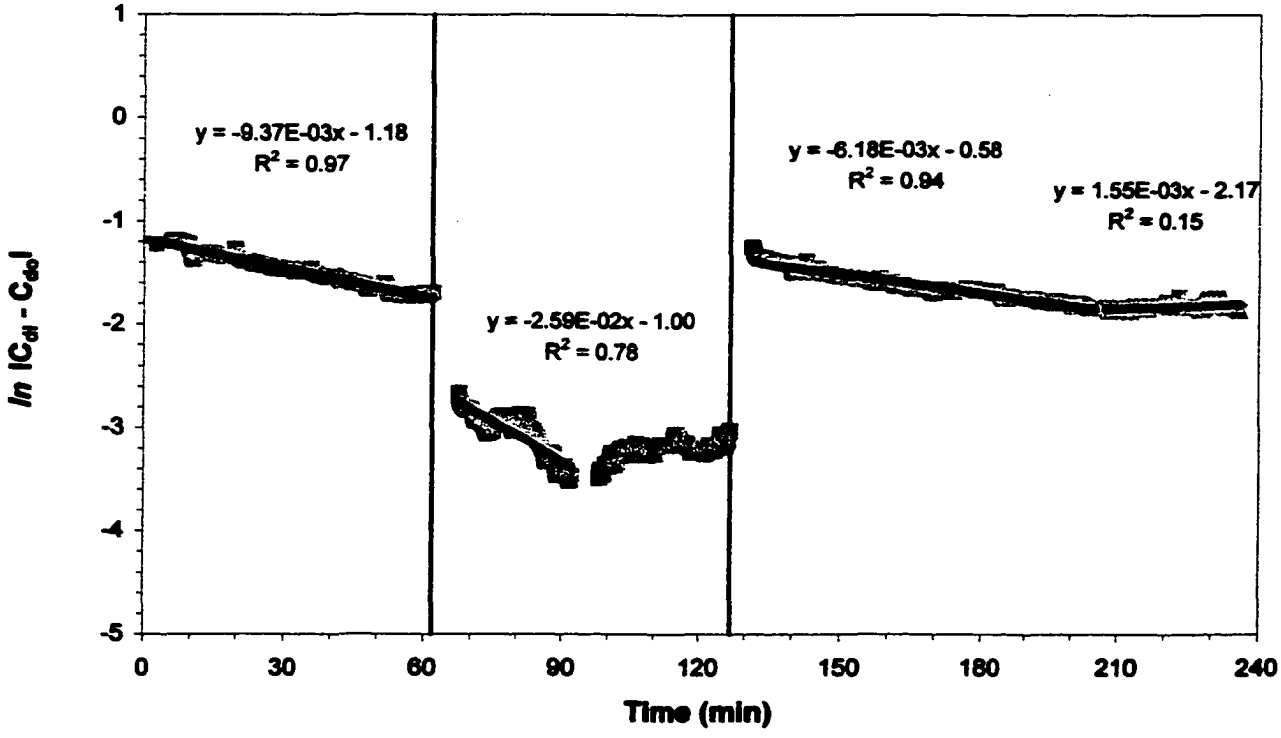

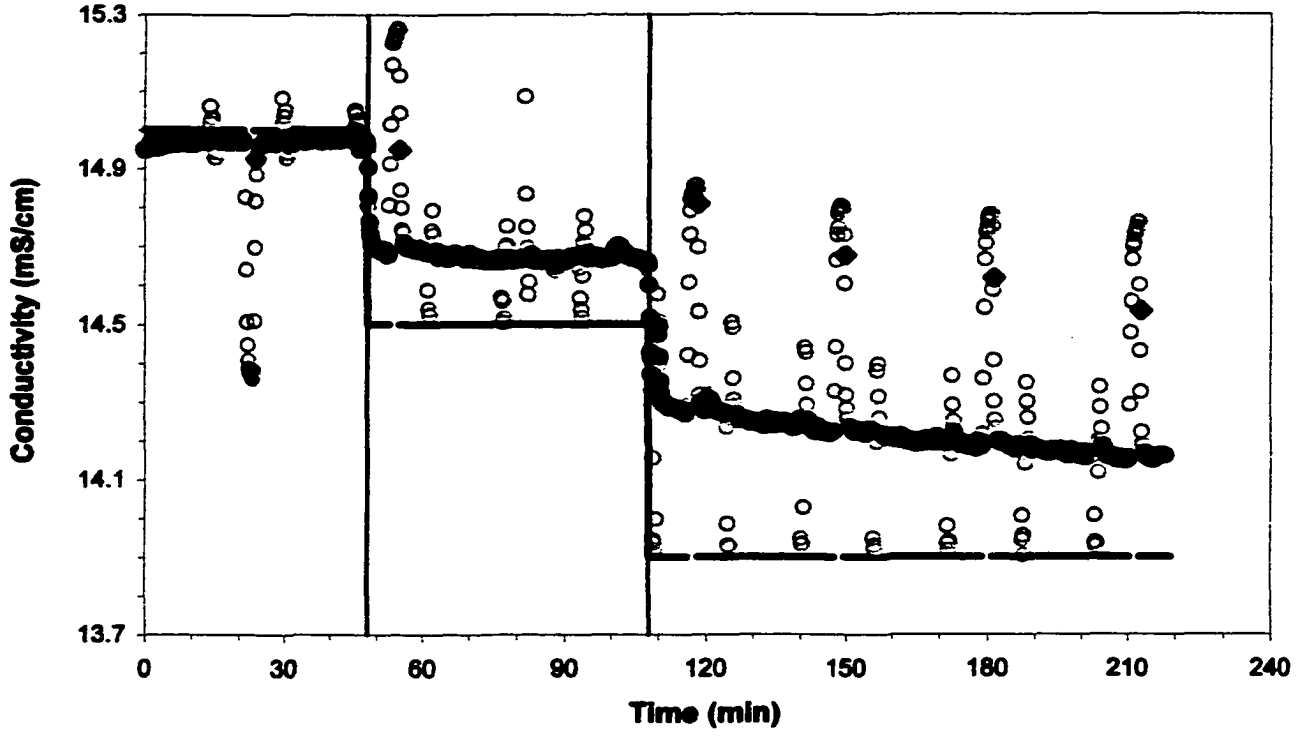

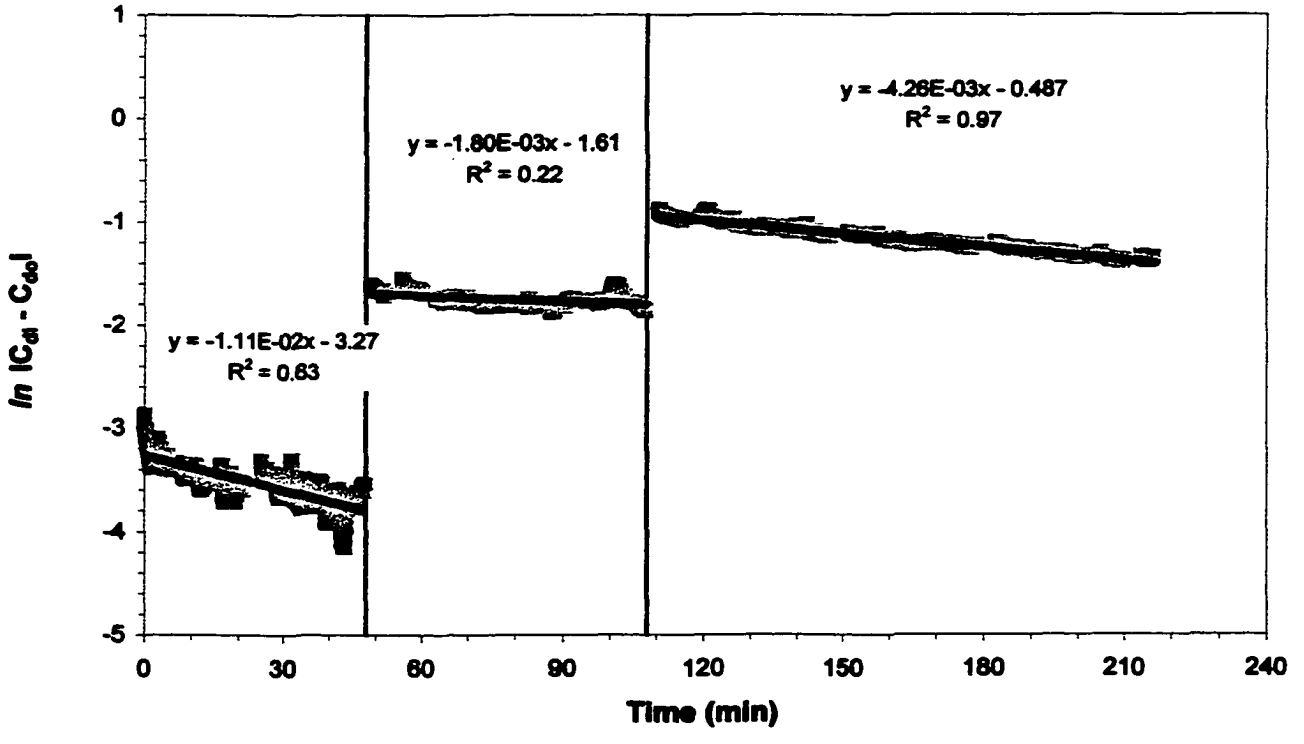

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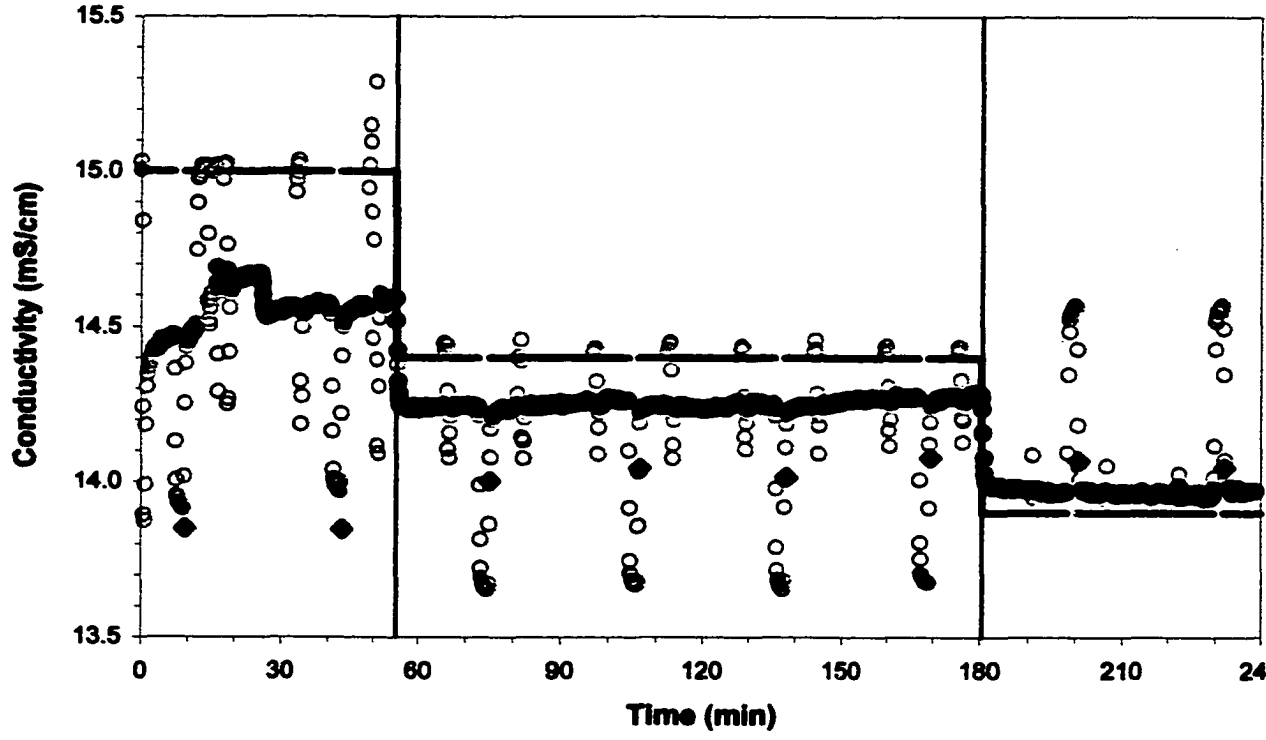

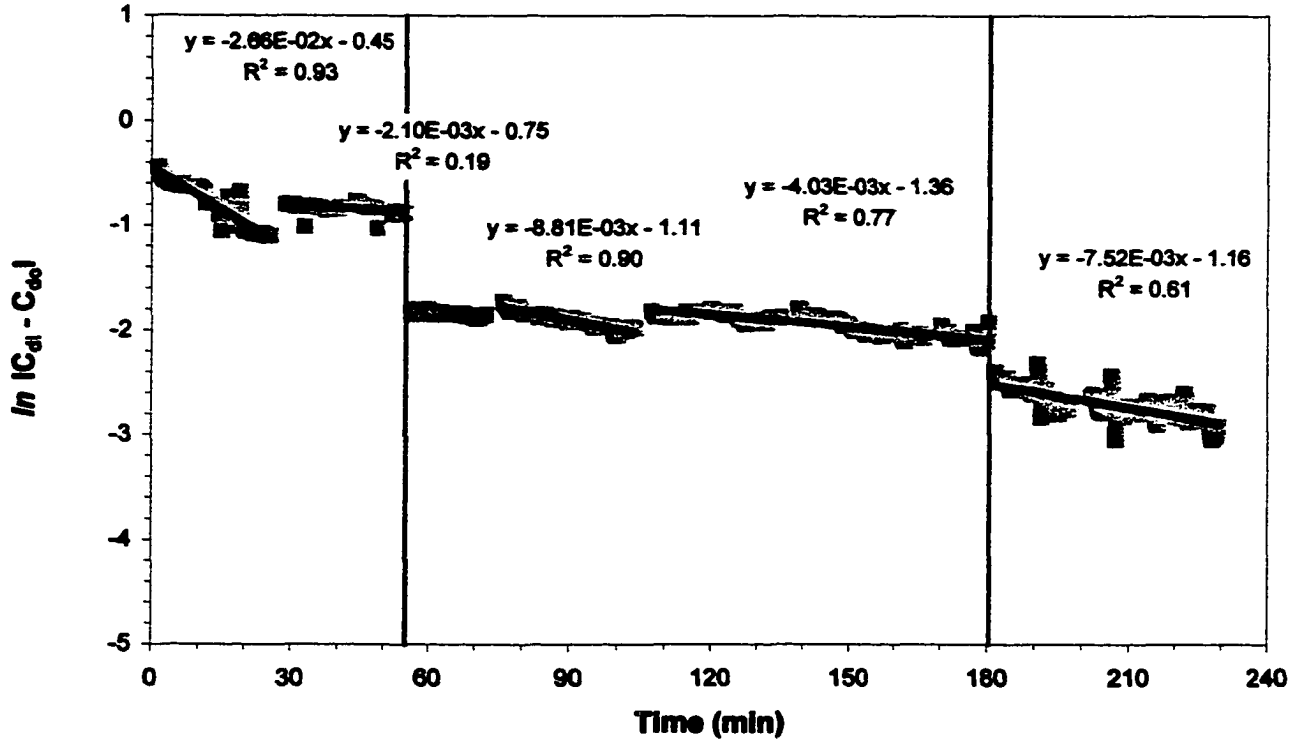

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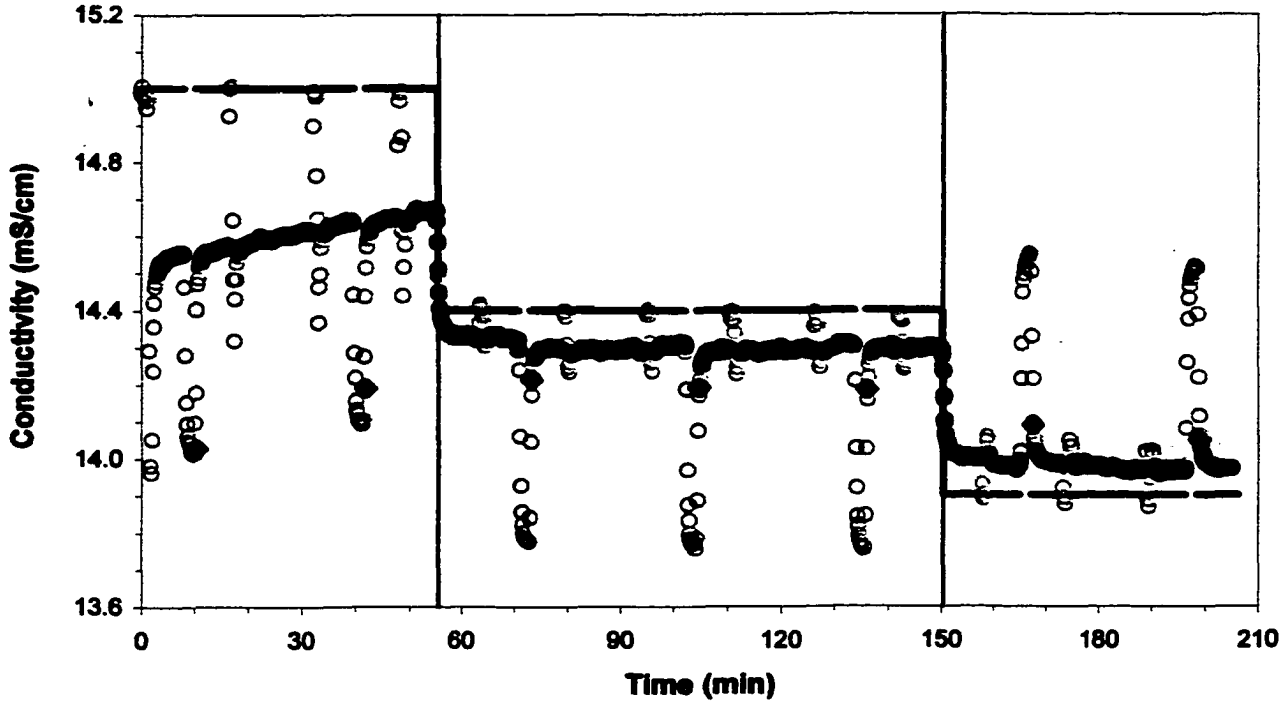

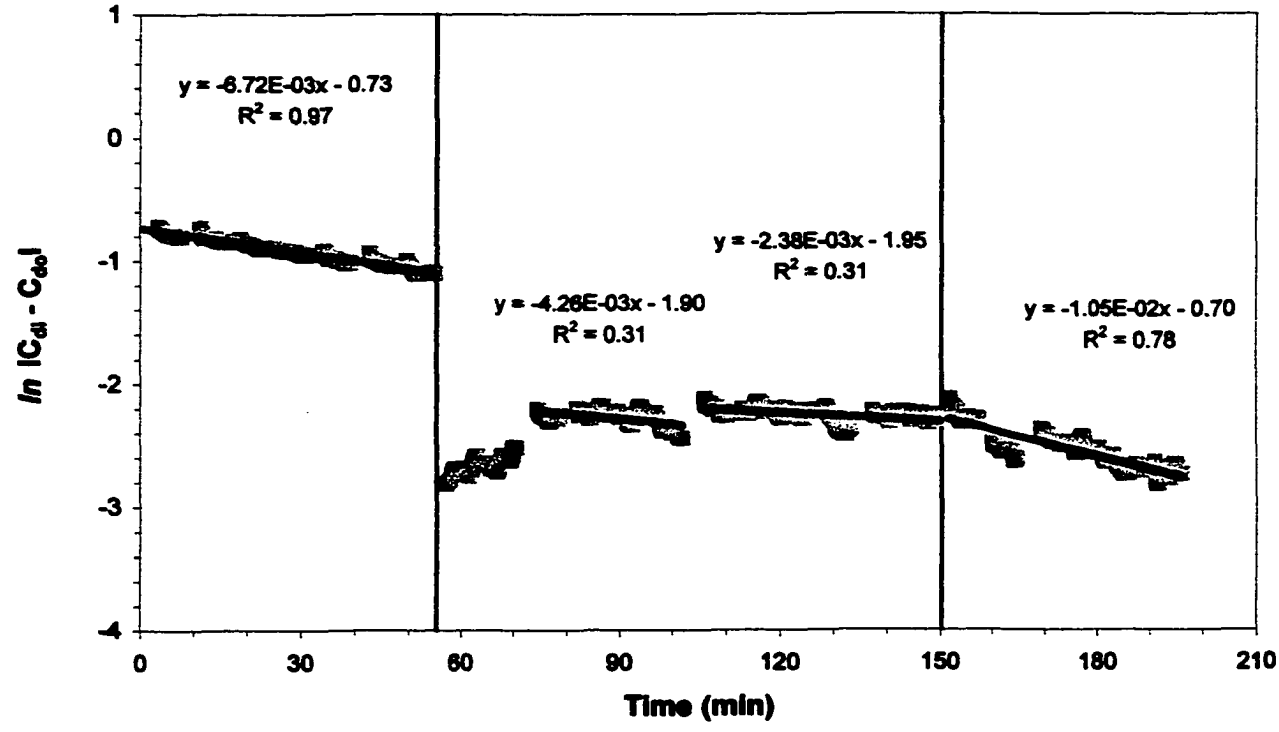

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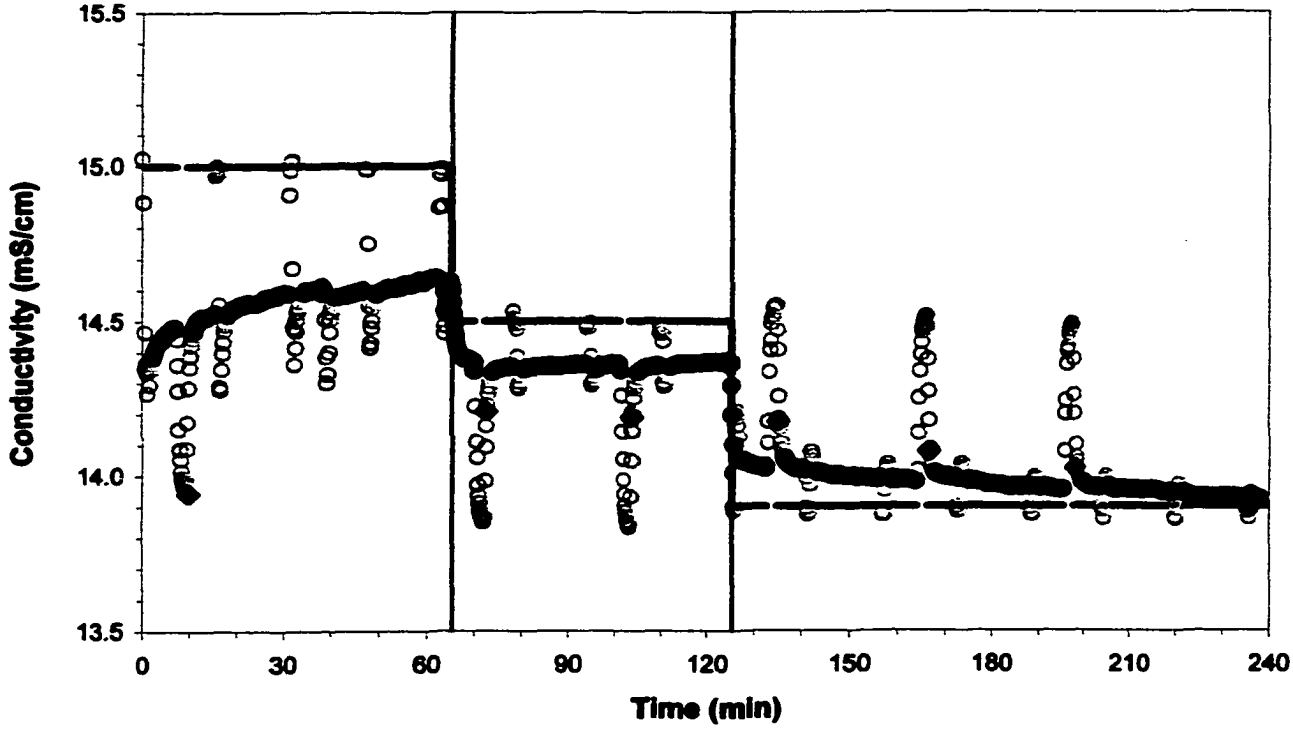

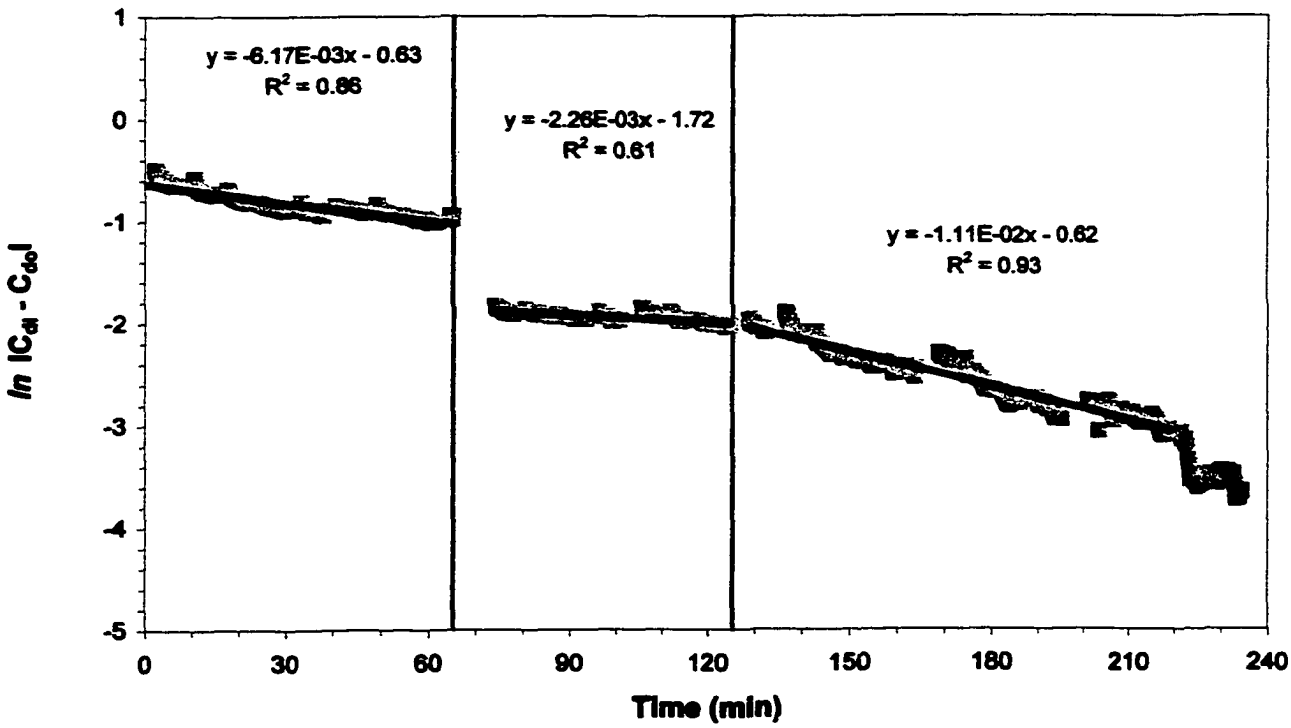

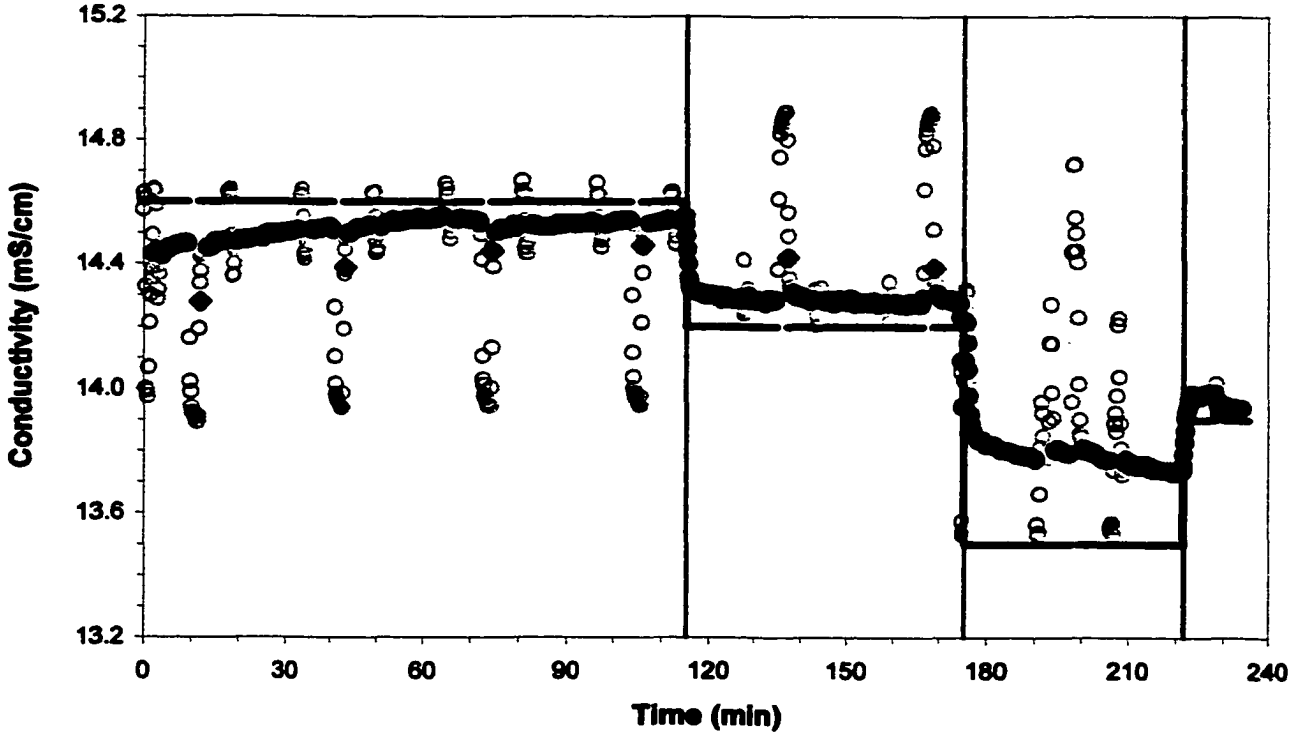

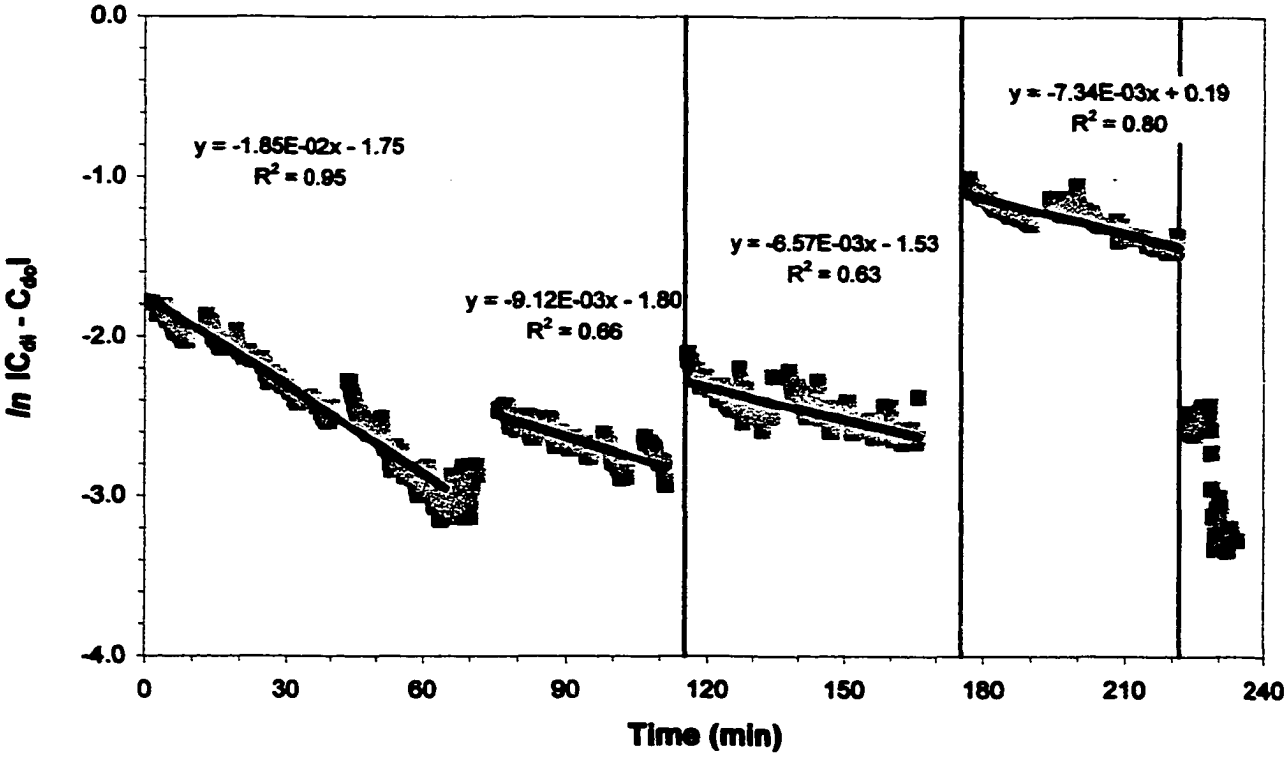

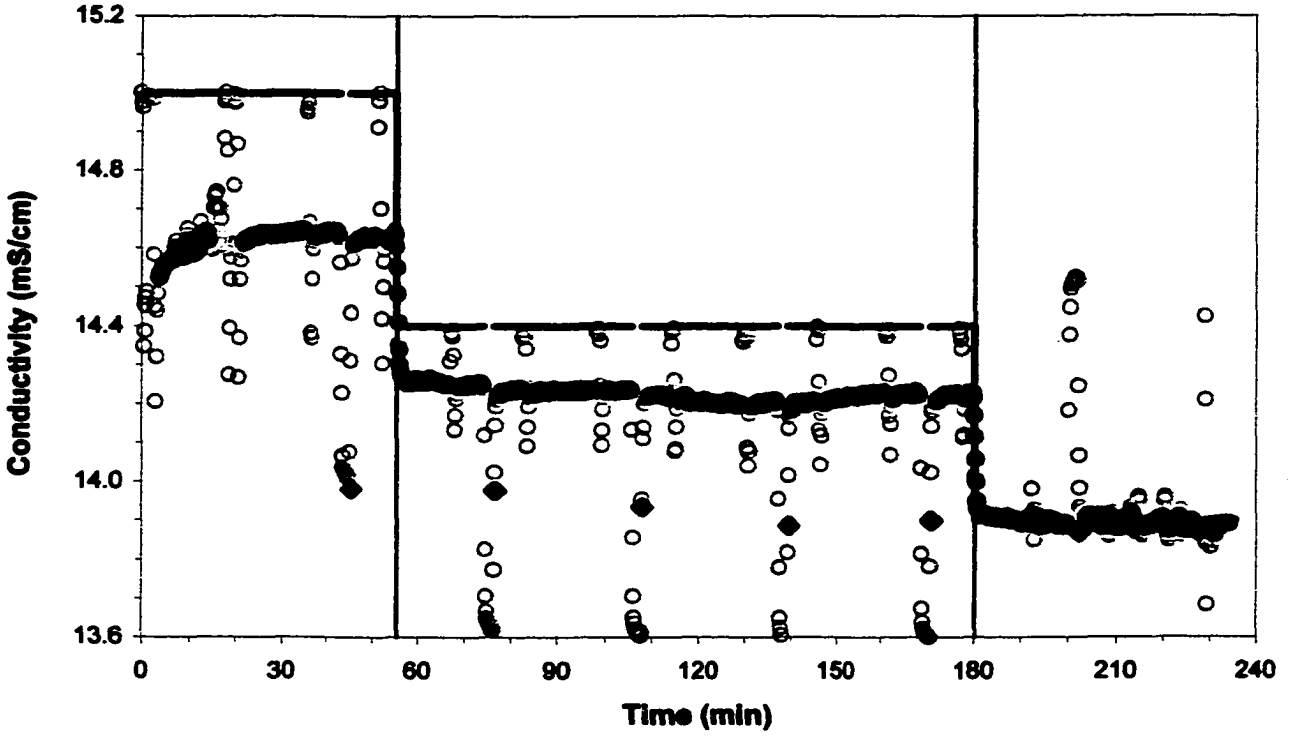

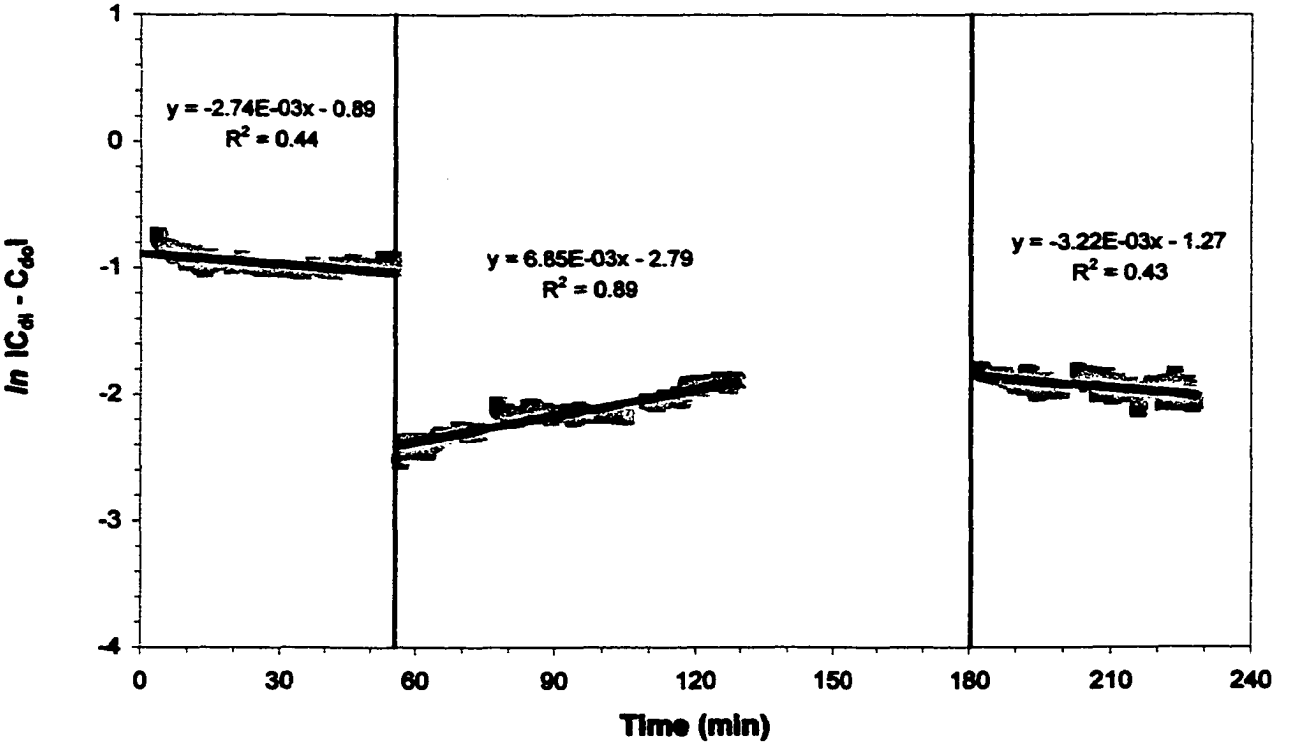

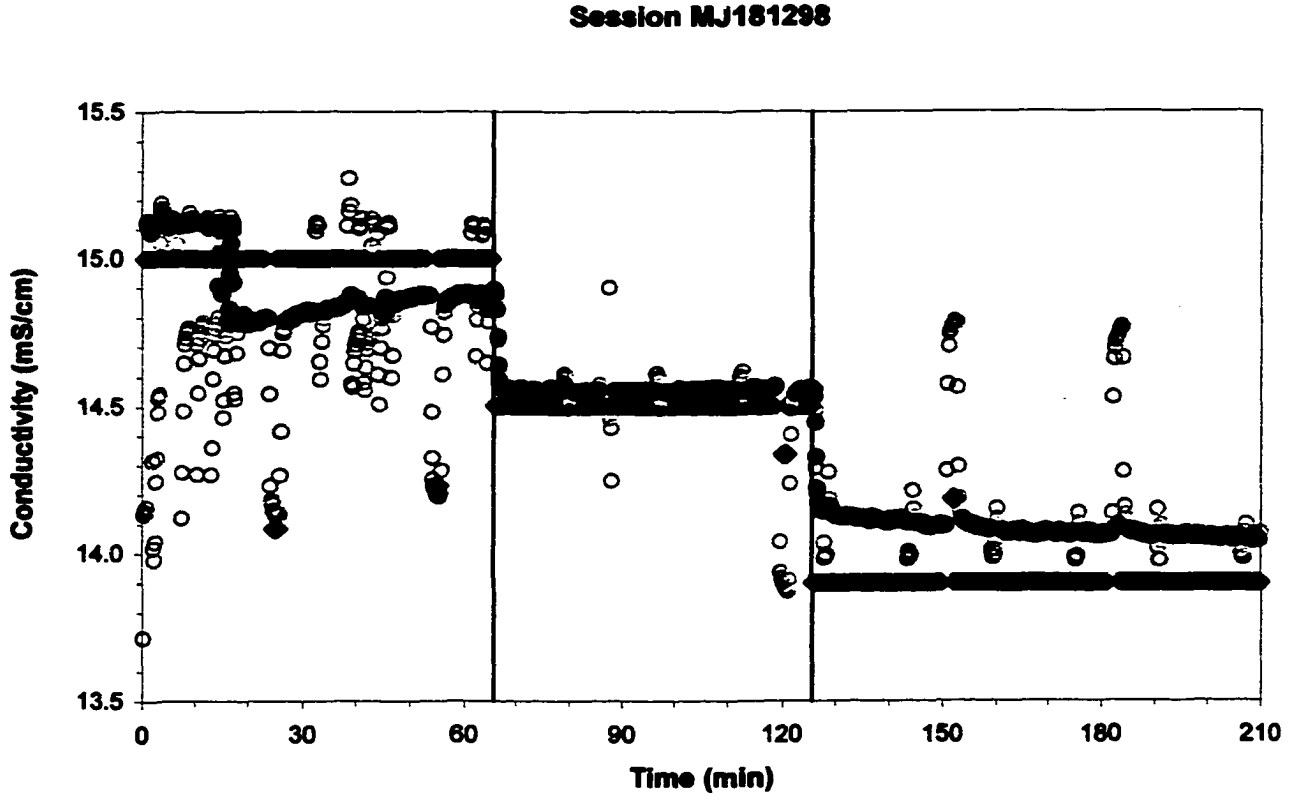

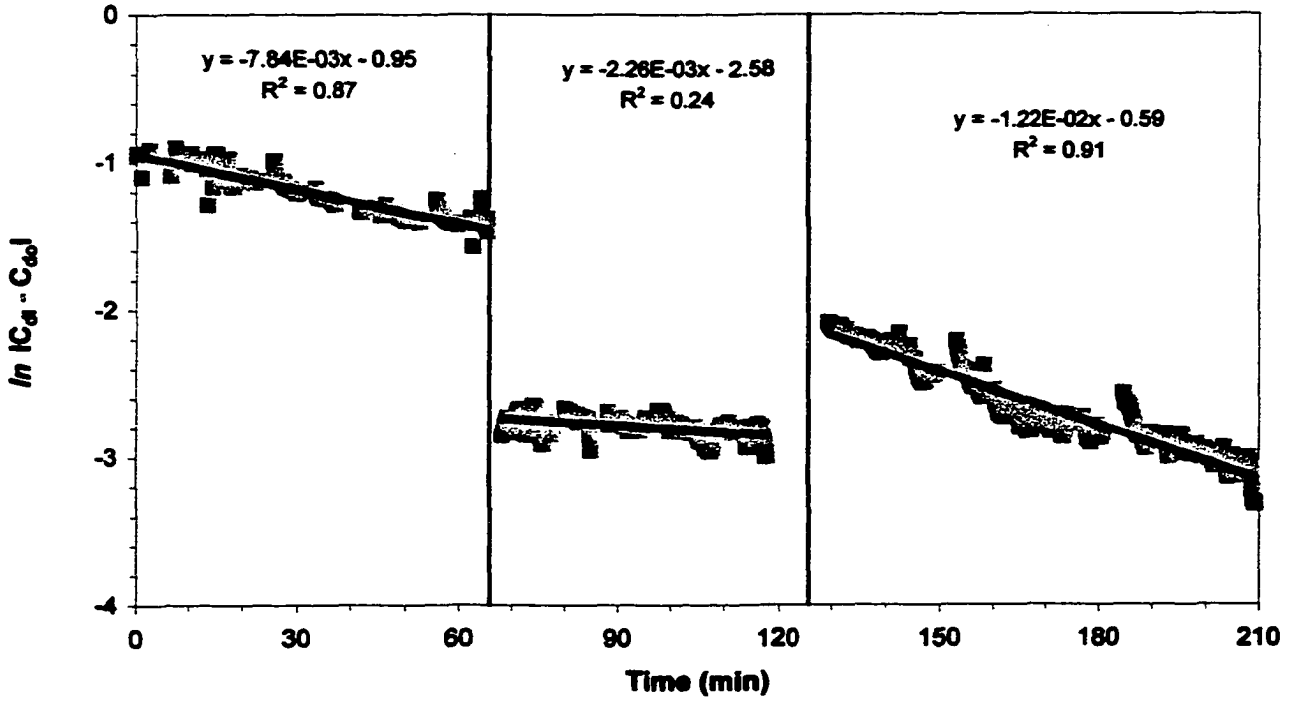

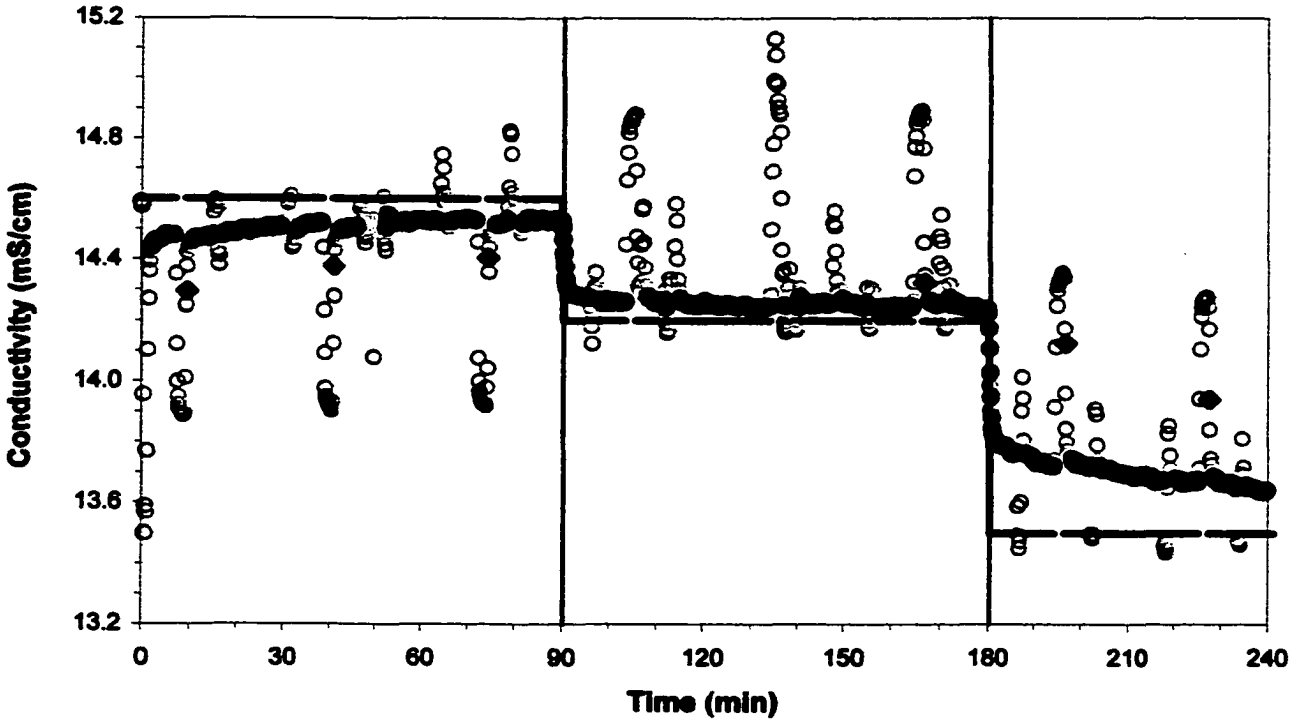

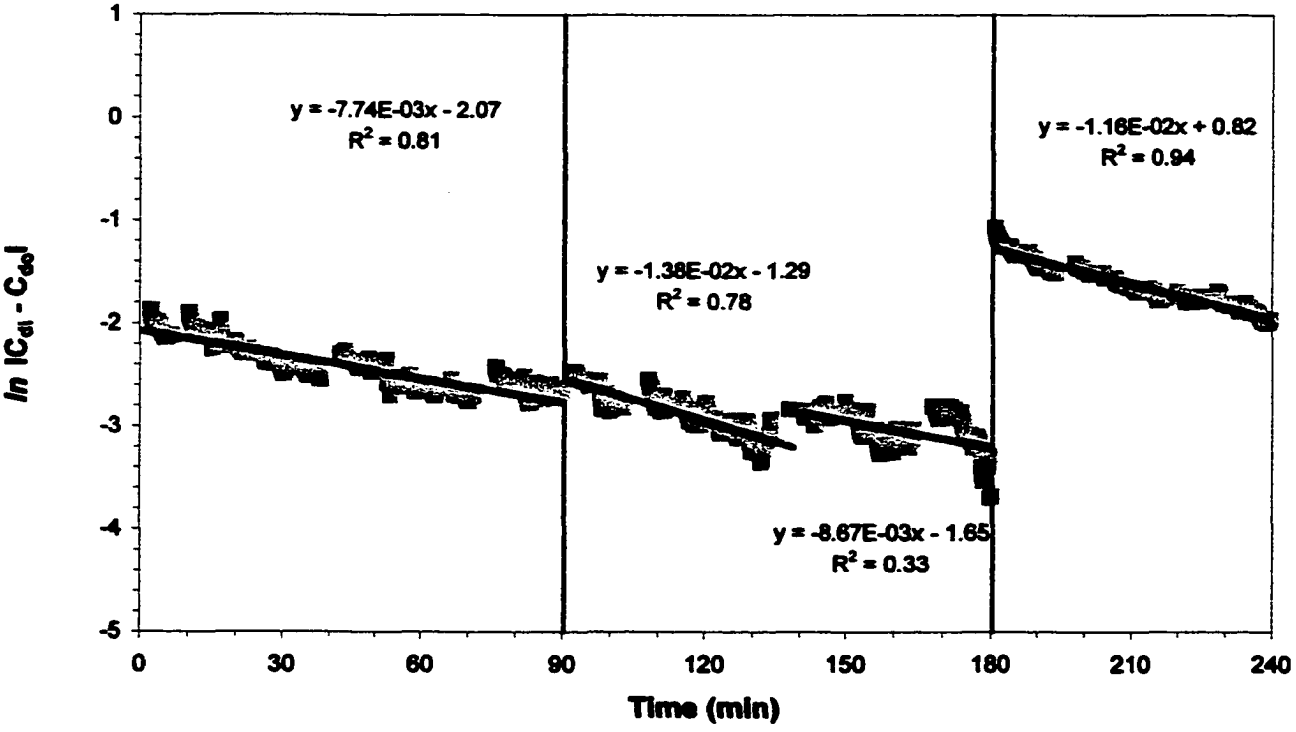

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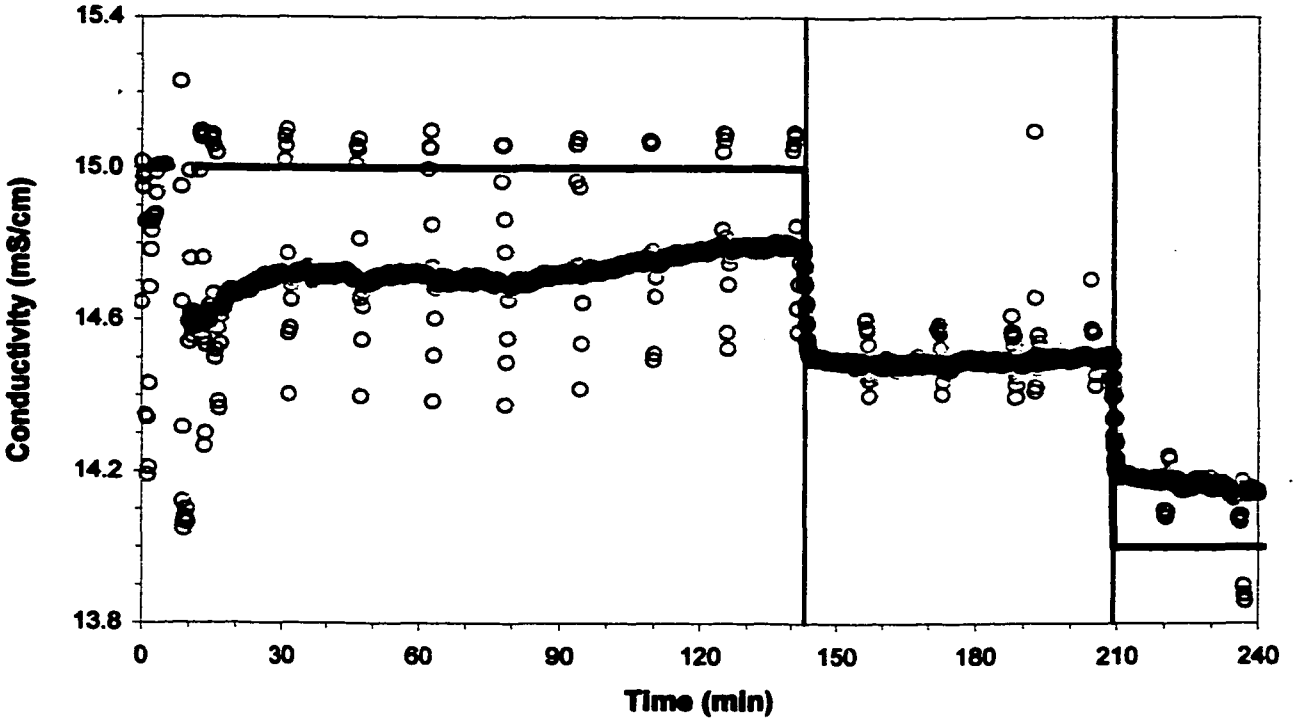

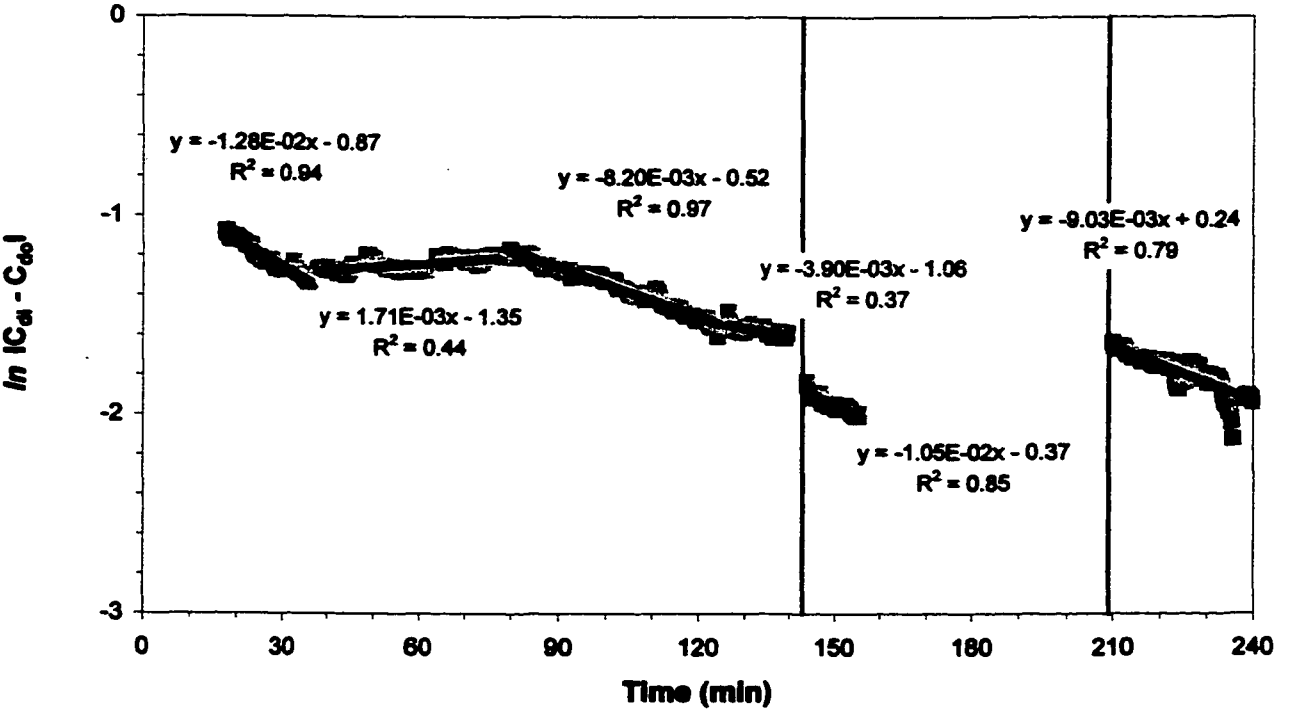

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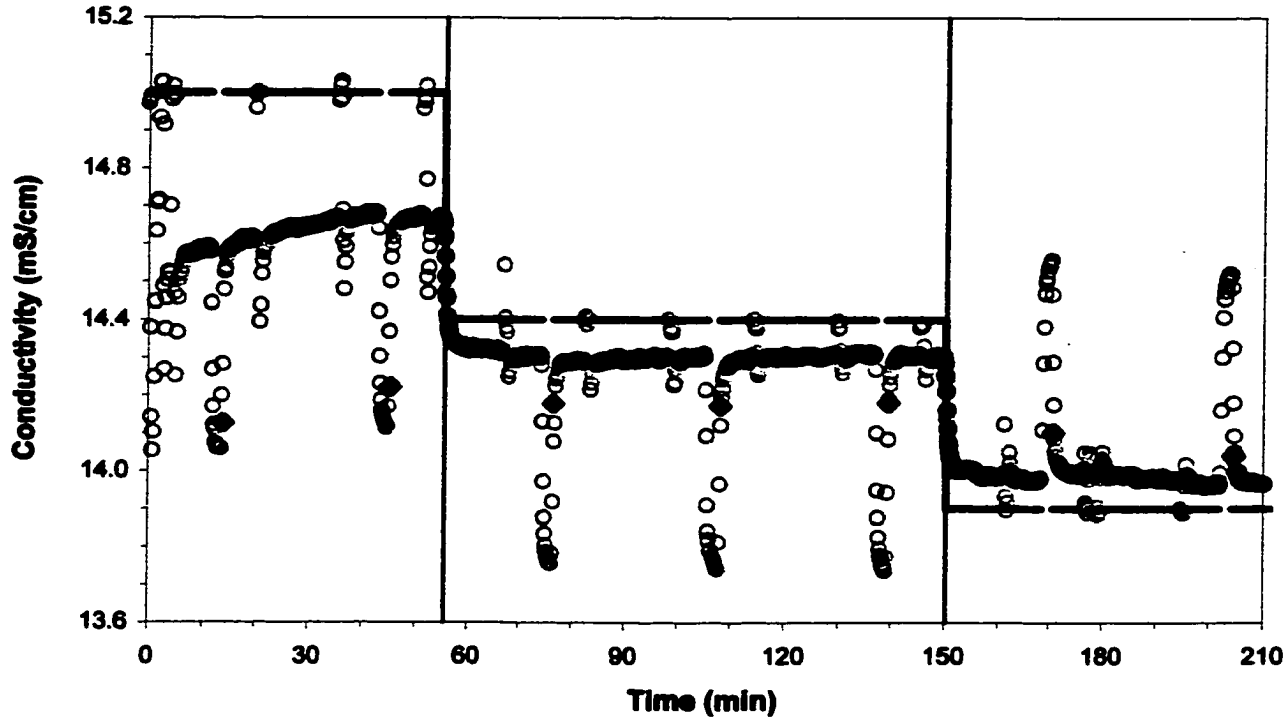

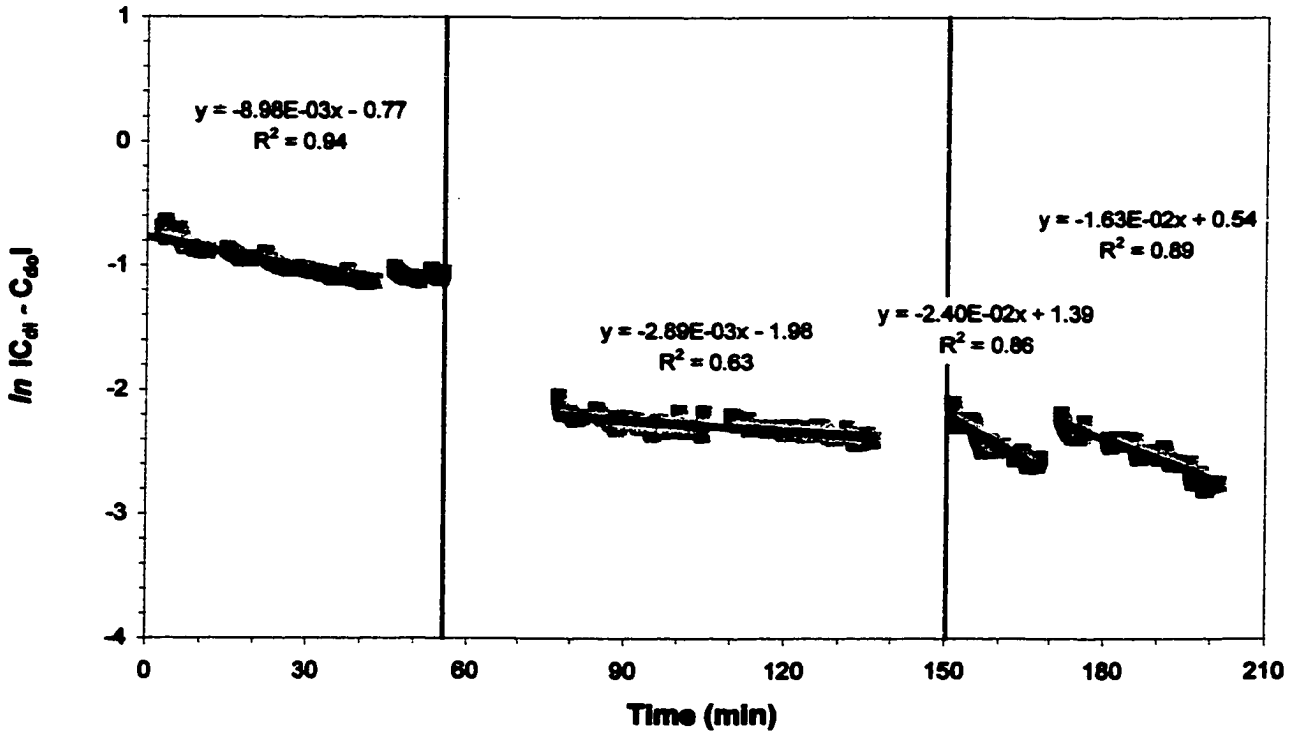

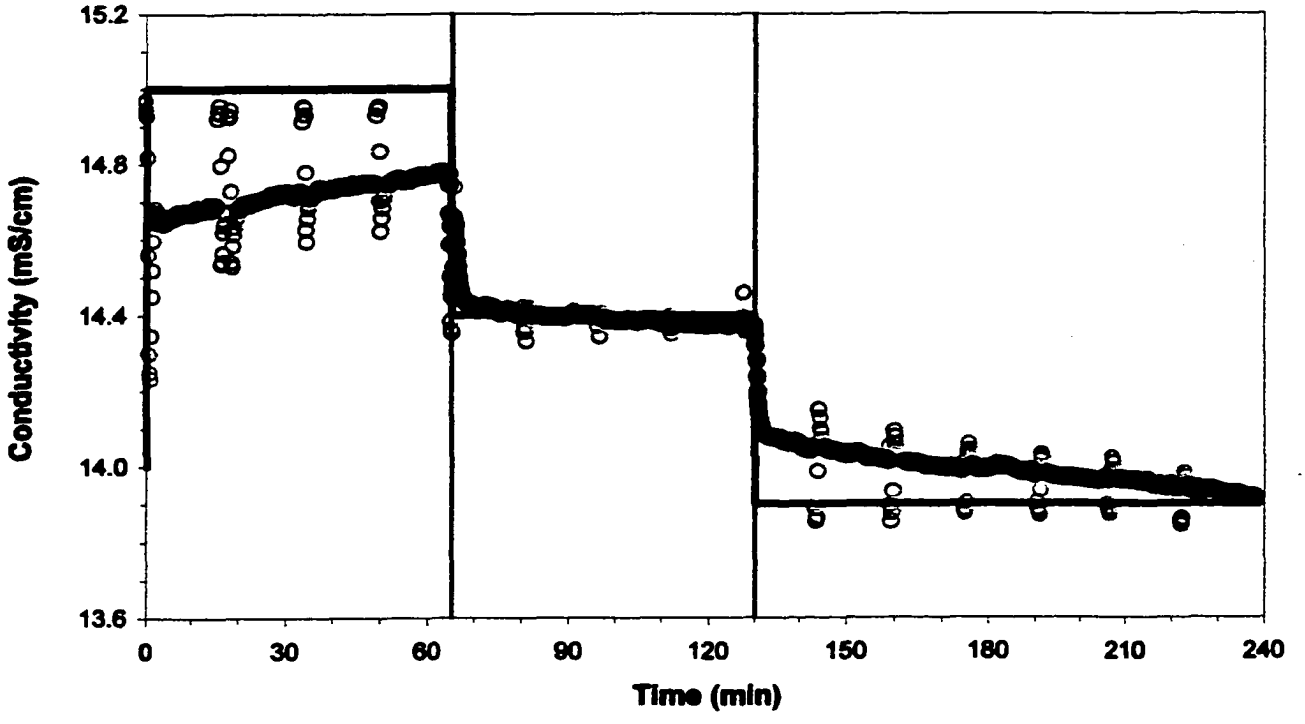

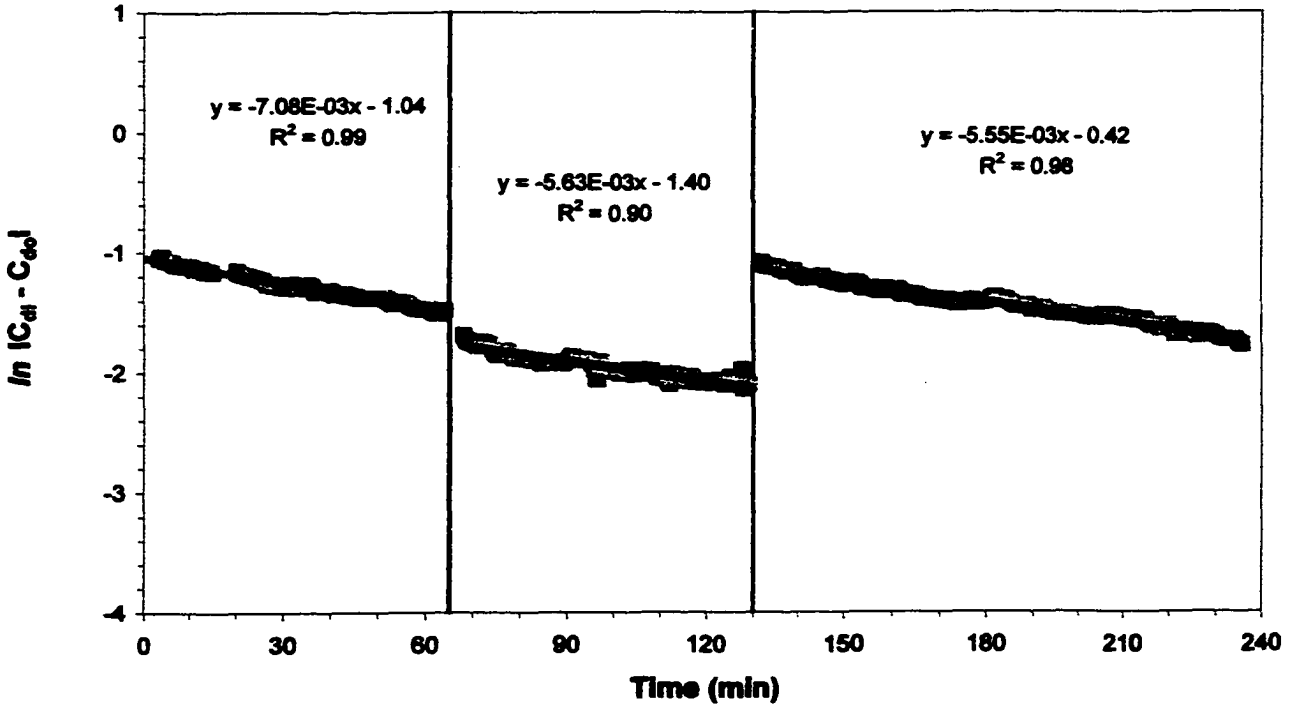

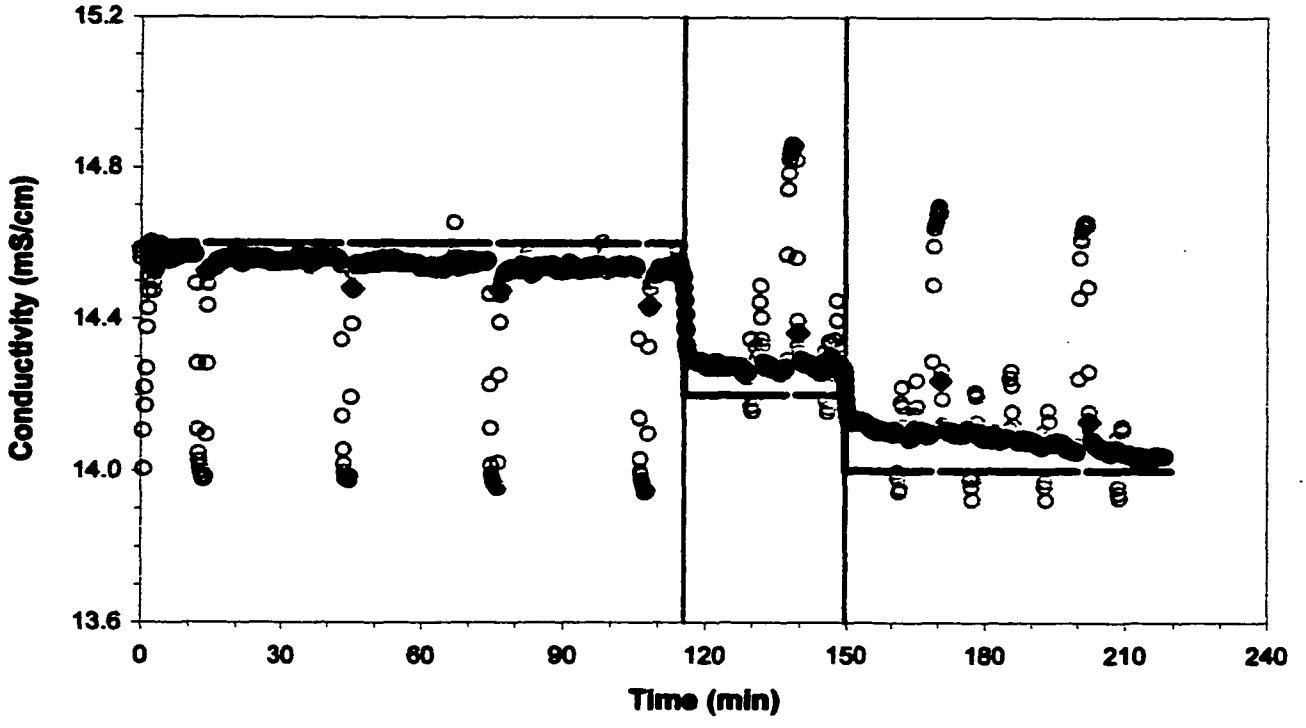

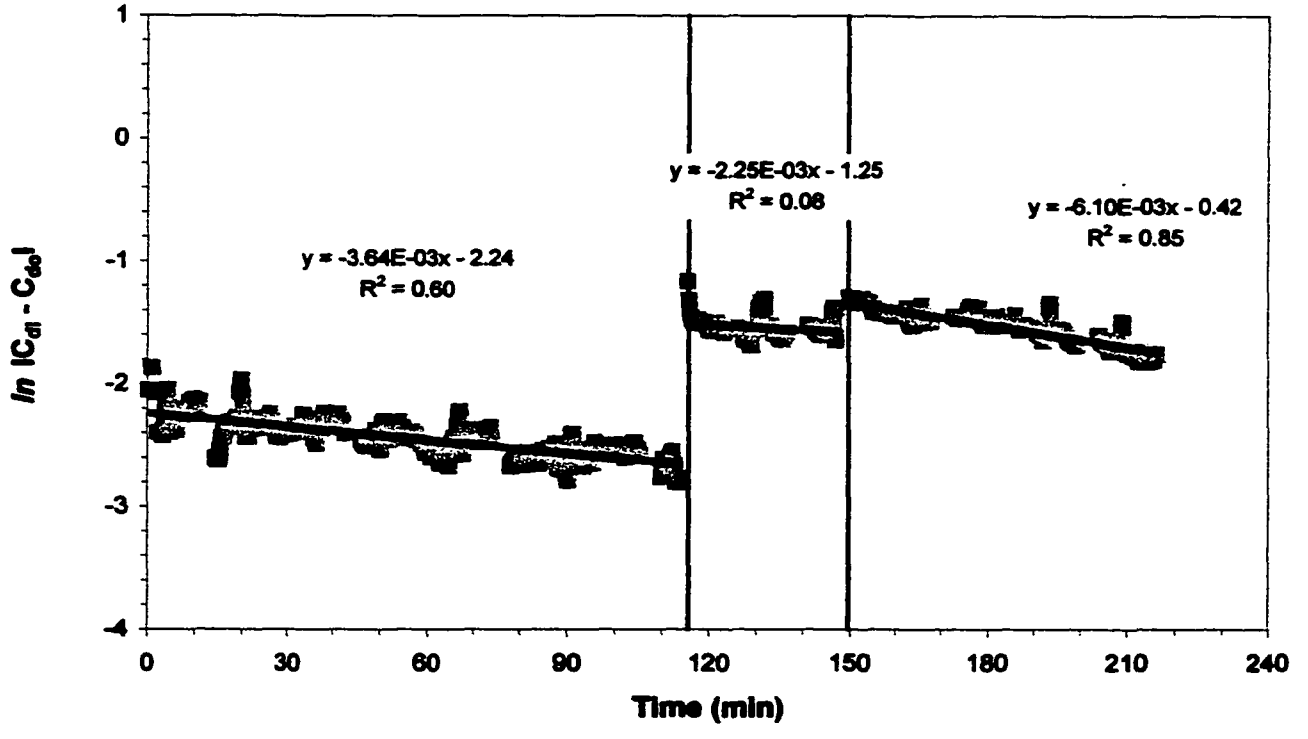

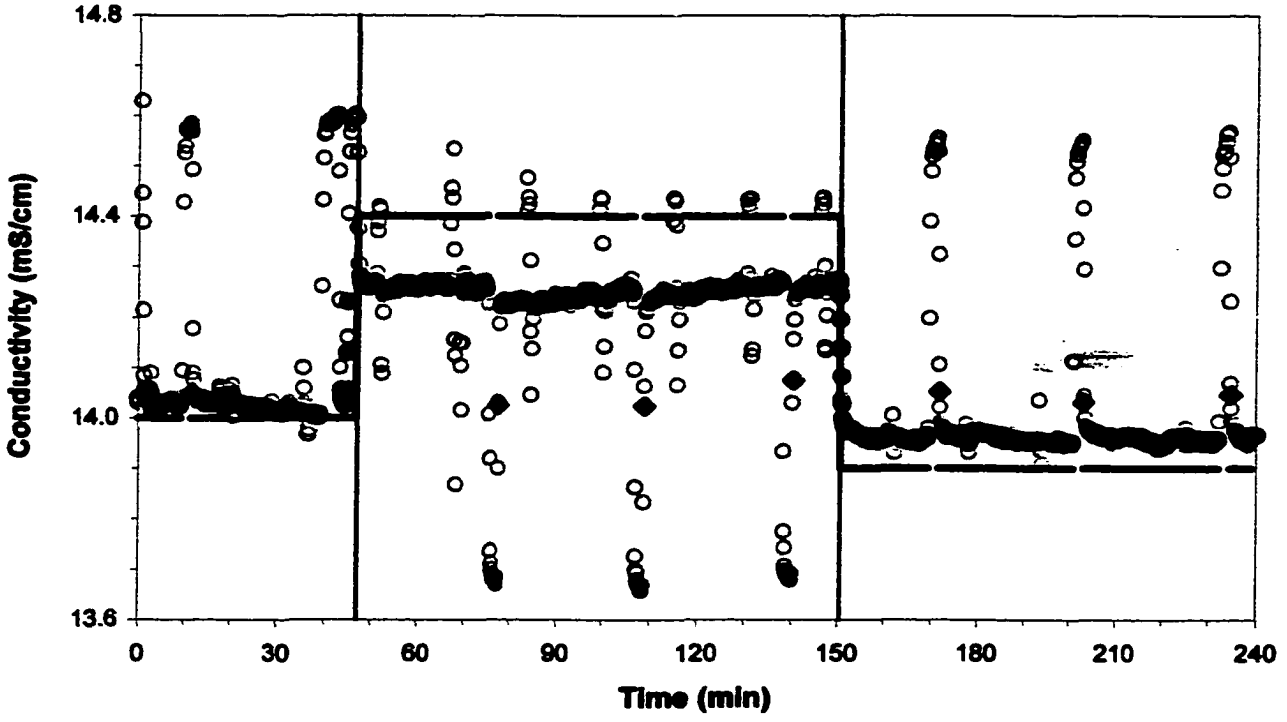

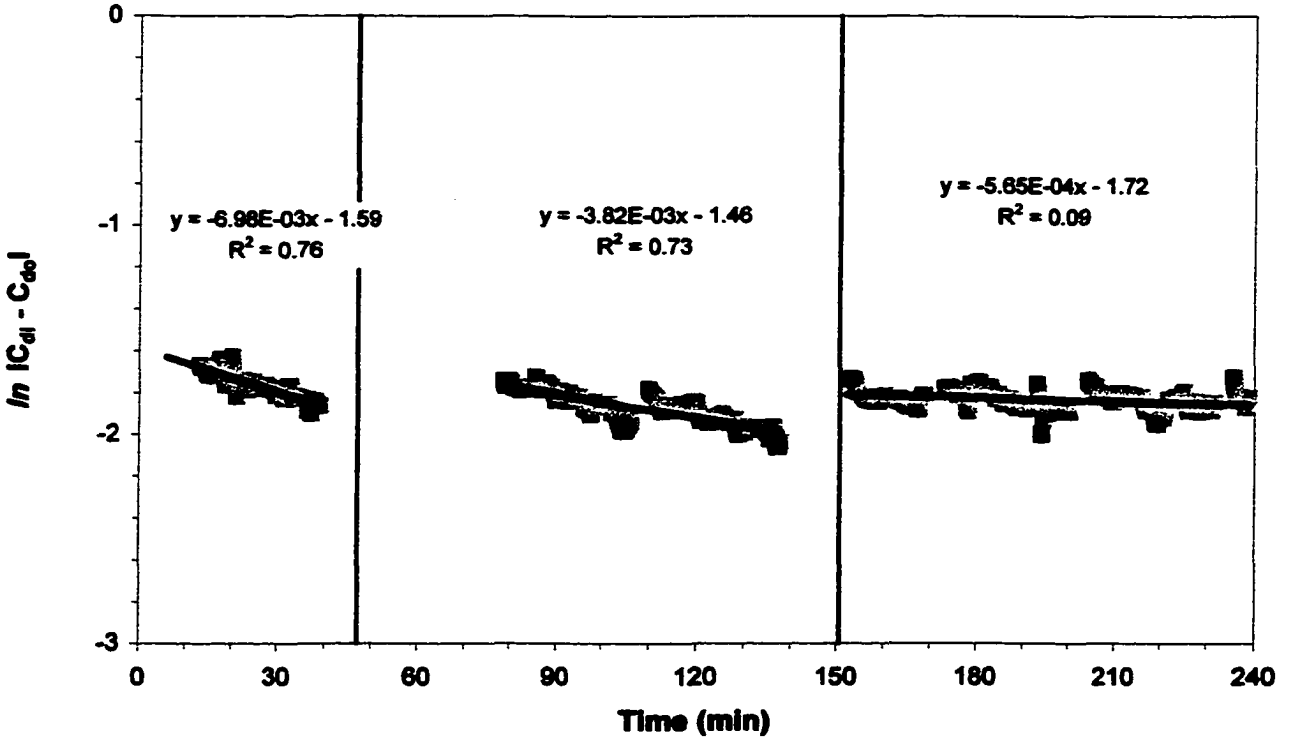

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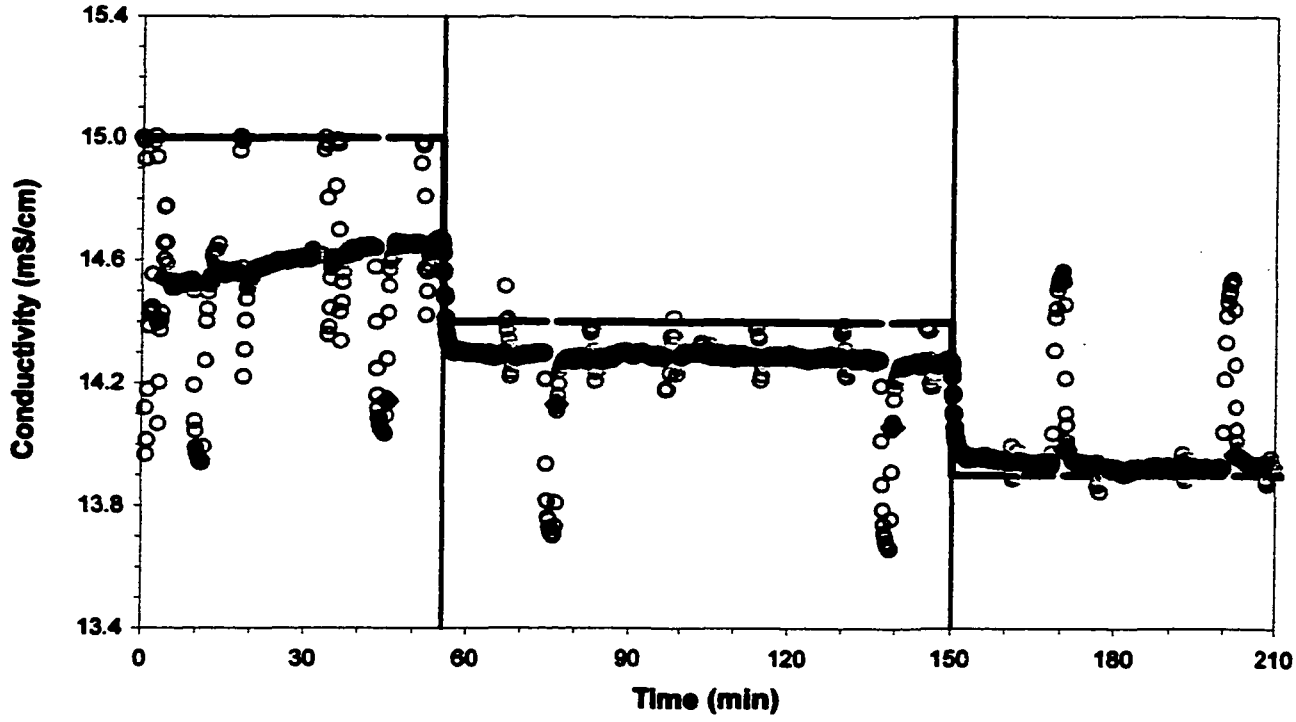

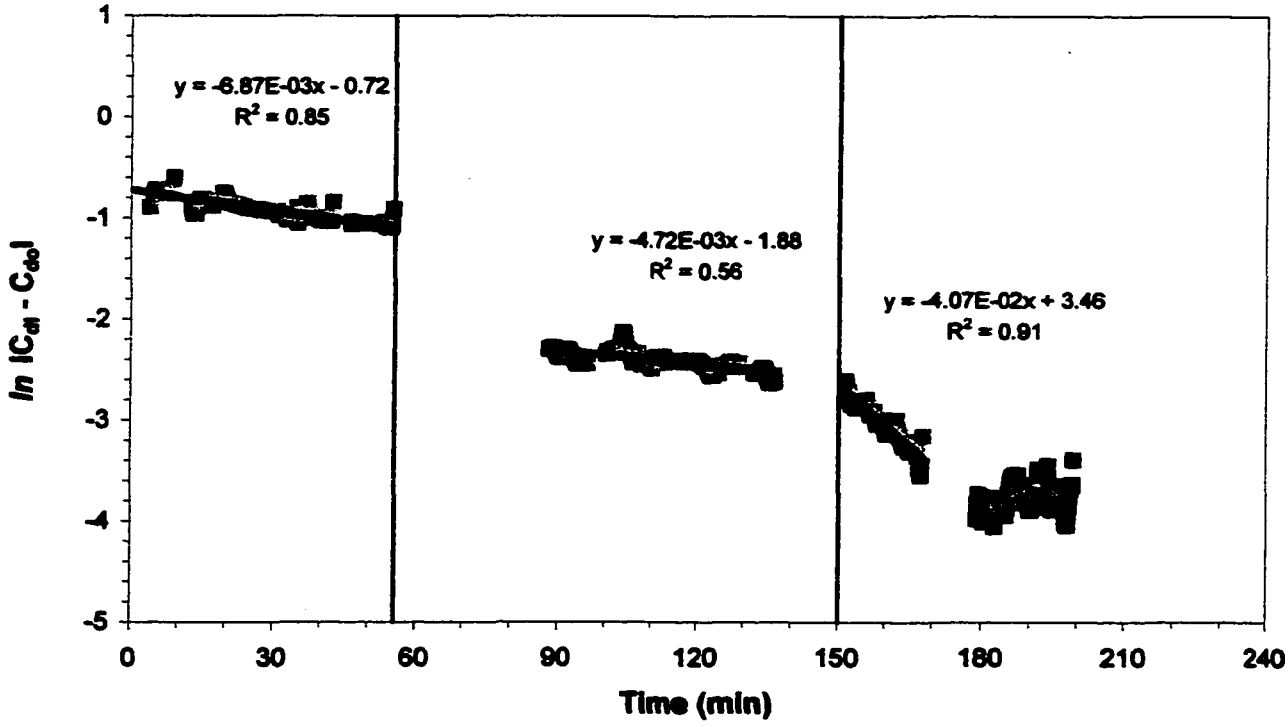

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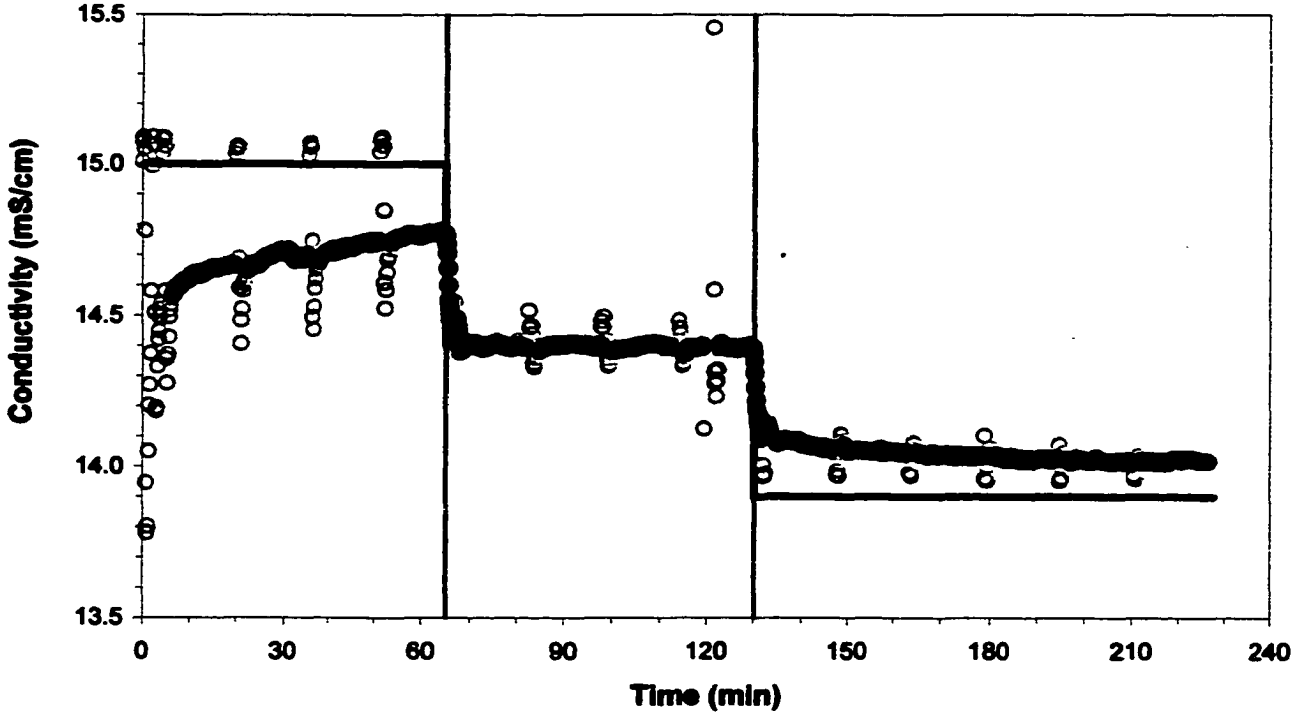

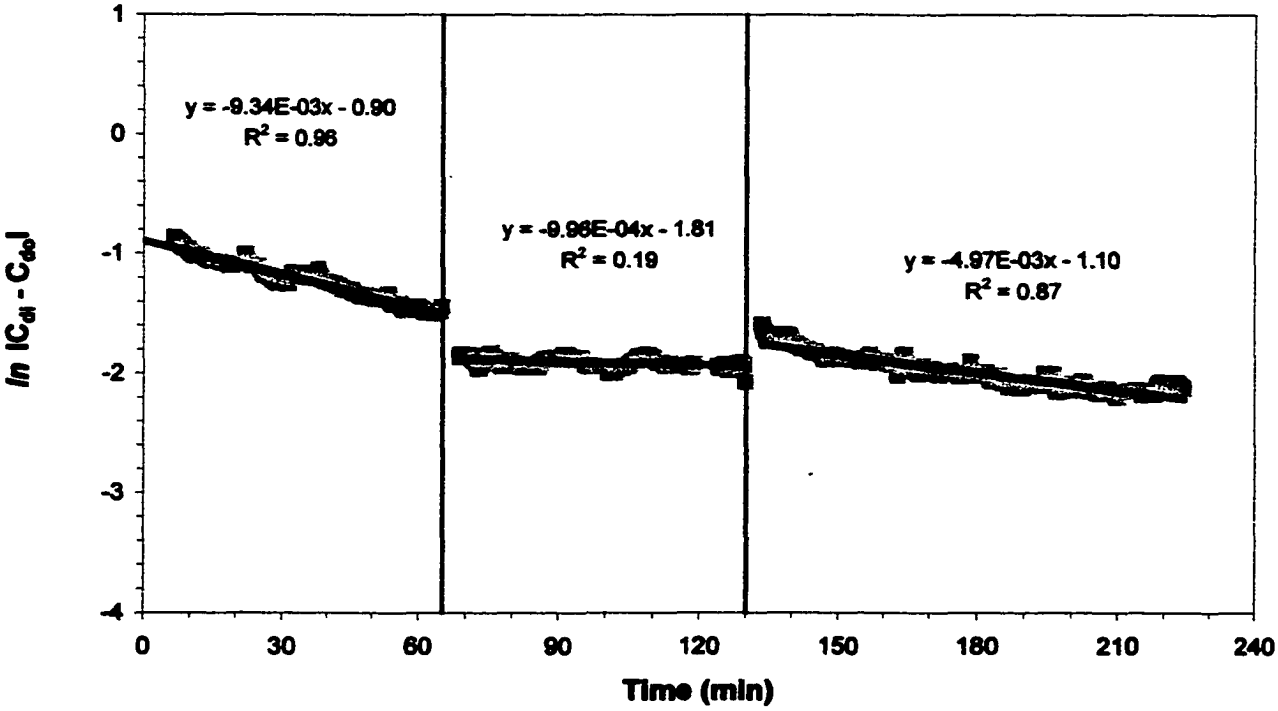

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