On-Line Optical Glucose Monitoring System for Microgravity Cell Culture System

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In cell cultivation, physiological environmental parameters such as temperature, pHHHH, aeration, agitation, dissolved oxygen, and liquid volume could potentially be monitored and controlled in reliable and stable manner.1-3 However, fixed control of nutrients such as carbohydrates (i.e. glucose), amino acids (i.e. glutamine), and byproducts (ammonia and lactate) in cell culture media is presently expensive and unreliable. Usually, the measurement of these analytes during cell culturing is carried out using off-line methods.4-6These measurement methods require sample extraction from the bioreactor. The off-line measurements can be time consuming, laborious, may cause cell contamination, and may not reflect the real time status of the cells.

In a typical cell culture media, glucose is a major carbohydrate energy source. Cell proliferation causes rapid consumption of glucose, which in turn causes growth limitation of the cells. Thus, the relative concentration change of glucose is a determining factor for the rate of cell culture growth. Therefore, accurate and reliable sensors to measure glucose concentration in the cell culture media need to be developed for optimal cell cultivation.

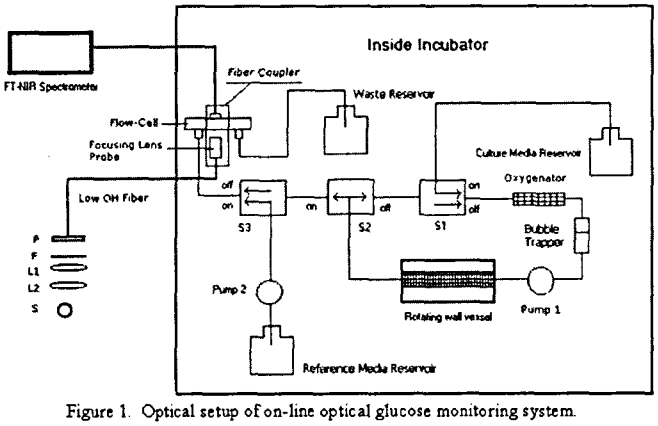

Figure 1. Optical setup of on-line optical glucose monitoring system.

The goal of this work is to develop an on-line optical glucose monitoring system for microgravity cell culture system (MCCS) based on NIR absorption spectroscopy. The system was connected to MCCS in which cells were cultivated and absorbance spectra were then recorded on-line from the cell-free culture media using the modified system during the bioreactor cell culture run. A calibration model for glucose measurement was generated with PLS regression analysis. One key component of this system is that the data collection was carried out using a noninvasive, on-line, measurement system.

For the remote, noninvasive, and on-line measurement of glucose concentration of cell

culture media, the optical, noninvasive, on-line monitoring system depicted in Figure 1 was developed. This system consists of a FTIR spectrometer coupled to optical throughput fibers. The fibers were used in transmission mode, in which the light from one fiber was directed through the flow cell and a

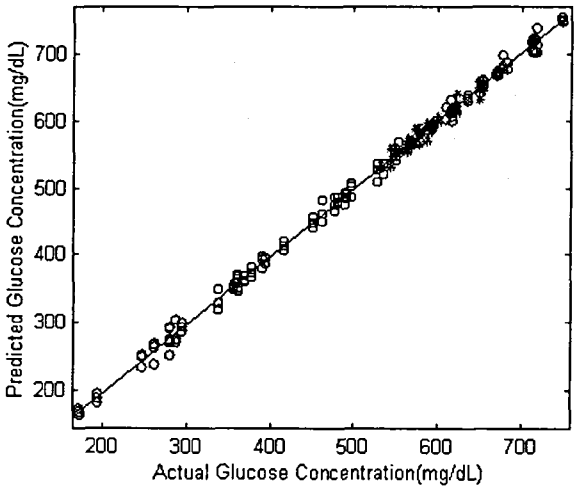

Figure 2. PLS calibration model of glucose in the cell culture media.

second fiber was used to collect the light from the cell. The collected light was then directed through the FTIR machine. An automatic sampling system was developed and controlled by a LabView program to direct the fluid from the bioreactor or reference through the test cell. The entire bioreactor and fluid system were housed in an incubator and the optical fibers were used to direct light to and from the system within the incubator. Using the system, calibration and validation data set were acquired and statistically processed for quantifiable measurement of glucose concentration in cell culture media.

Thesystem was designed to allow for absorbance spectral measurements rather than single-beam spectra which provided for real-time spectral background referencing. The results of the calibration model (Figure 2) were comparable with the previous work done using off-line measurements in both cell culture and aqueous solutions. Although only glucose was measured in this study, it is expected that with an appropriate calibration model and depending on the cell type and culture conditions, that other analytes, such as lactate, ammonia, glutamine, and glutamate can also be noninvasively measured with this system since the absorbance spectra of each these analytes have been quantified by this group and others using this wavelength range. Overall, these results provide encouragement for the development of a, noninvasive, on-line monitoring system that will provide quantifiable analyte concentration information and potentially closed-loop control for optimizing cell culture growth.

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