Establishment of a Wave bioreactor scale-down model for process development and characterization studies

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Establishment of a Wave™ bioreactor scale-down model for process development and characterization studies

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Introduction

The Wave™ Bioreactor system is typically applied to the inoculum train process. We evaluated the 10-L system as a scale-down model for production of a fusion protein by Chinese Hamster Ovary (CHO) cells. The Wavebag was operated in fed-batch mode and the results were compared to a 5-L stirred-tank bioreactor (STR).

The disposable technology allows faster turnaround and is simple to implement. Training, cleaning and validation are minimal for the system. This study investigated the feasibility of upstream characterization and development in a Wave™ bioreactor system[1].

Figure 1. Representation of a 5-L bioreactor system and Wave™ Bioreactor

Lab-scale (5-L) Production Bioreactor

Wave™ (10-L bag) Production Bioreactor[2]

Methodology

Wave™-specific :
- Rocking speed (rpm)
- Rocking angle

Bioreactor-specific:
- Mixing speed
- Sparge rate

Culture conditions for the Wave bioreactor

- Rocking speed	30 rpm
- Rocking angle	7°
- DO profile	not controlled
- pH setpoint	7.0 +/- 0.1
- Back pressure	Ambient
- Air flow rate	0.1 LPM
- pH control	% CO_2 and caustic

Culture conditions for 5-L bioreactor

- DO profile	50%
- pH setpoint	7.0 +/- 0.05
- Back pressure	Ambient
- Bottom air flow rate	0.005 LPM
- Top air flow rate	0.050 LPM
- Mixing speed	180-200 rpm
- pH control	% CO_2 and caustic

Two medias were evaluated:
1. Version 1 basal and feed media
2. Version 2 basal and feed media

Results- Version 1 Basal/Feed

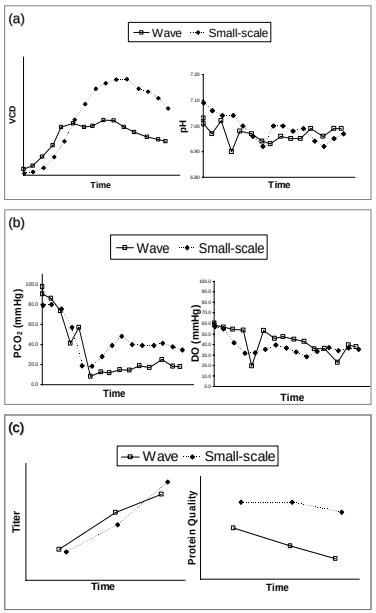

Figure 2. Operating conditions critical for protein yield and quality. A) Viable cell density and pH profile B) pCO_2 and DO profile C) Protein Yield and Quality

Results- Version 2 Basal/Feed

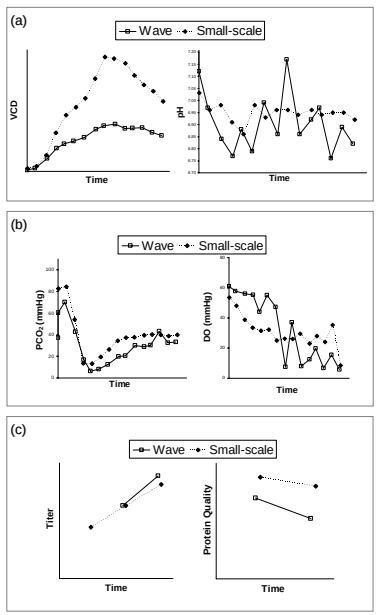

Figure 3. Operating conditions critical for protein yield and quality. A) Viable cell density and pH profile B) pCO_2 and DO profile C) Protein Yield and Quality

Discussion

Although a lower peak VCD is achieved, the protein production is comparable to small-scale bioreactor production. Media changes were discernible in the Wave™ bioreactor suggesting that this technology is applicable for upstream characterization and development studies. Results were within the acceptable range defined for protein yield and quality.

The differences in VCD can be attributed to the pH deadband. Cell culture growth is significantly affected by pH control. Current technology for the Wave unit does not provide for fine pH control.

Significant differences were also seen in the DO profile (Figure 3b) which cannot be improved upon unless oxygen is delivered to the Wavebag™ (currently only air/CO_2).

Conclusions

Wave™ bioreactors operated in fed-batch mode can indicate changes in cell culture performance and produce similar results as seen in stirred-tank bioreactors. The technology can be applied in upstream development to quickly and easily evaluate media and process variable conditions. The results achieved in a Wave™ bioreactor system can be utilized for development and process characterization studies.

Future Work

- Optimization of pH control is critical for protein quality and cell growth. The current Wave™ bioreactor pH control has a deadband of 0.1 while in the bioreactors, a deadband of 0.05 is possible.
- Differences in pCO_2 and DO are critical parameters that cannot be adjusted in the current system.
- Higher peak VCD and IVCD can be achieved in the Wave bioreactor system with optimization of feeding strategy and improved pH control.

References

1. Singh, V. 1999. Disposable bioreactor for cell culture using wave-induced agitation. *Cytotechnology* 30:149-158.

2. http://wavebiotech.com/products/wave_bioreactor/system20/index.html#

Acknowledgments

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