
Table of contents

Abstract	13
Zusammenfassung	14
1 Introduction	15
1.1 The concept of morphology and its use as a bioprocess parameter	15
1.2 Objectives	16
2 Theoretical Background	17
2.1 Cultivation of filamentous Mircoorganisms	17
2.1.1 Filamentous fungus Aspergillus niger and the model product fructofuranosidase	17
2.1.2 Growth and morphology of <i>A. niger</i>	19
2.1.3 Impact of environmental parameters on fungal morphology and productivity	26
2.1.4 Digital image analysis methods for characterization of fungal morphology	30
2.1.5 Rheology of filamentous culture broths and its relation to morphology	32
2.2 Production of paclitaxel by submerse cultivation of <i>Taxus chinesis</i>	37
2.2.1 Yew trees and discovery of paclitaxel	37
2.2.2 Cultivation of plant cells in suspension – impact, issues and relevance	39
2.2.3 Particle size measurement of suspended plant cells and aggregates	40
2.2.4 Shear sensitivity of plant cells and determination of viability	42
3 Material and Methods	45
3.1 Microorganism and inoculum preparation for cultivation of <i>A. niger</i>	45
3.2 Media and cultivation conditions	45
3.2.1 Medium for cultivation of <i>A. niger</i>	45
3.2.2 Cultivation conditions for bioreactor and shaking flask cultivations of <i>A. niger</i>	46
3.2.3 Conditions for cultivation of <i>Taxus chinensis</i>	46
3.3 Biomass concentration, osmolality, enzymatic assays and sampling	46
3.4 Microscopy and image analysis methods	47
3.4.1 Microscopic examination of <i>A. niger</i> and automatic image analysis	47
3.4.2 Fractal analysis and lacunarity	48
3.4.3 Microscopy and image analysis of <i>Taxus chinensis</i> samples	49

3.5 Measurement of particle size by laser diffraction.....	51
3.6 Analysis of culture broth viscosity of <i>A. niger</i> cultivation broth.....	53
3.7 Calculation of specific productivity.....	54
3.8 Statistical analysis.....	55
4 Results and Discussion	56
4.1 Morphology – a sensitive process parameter in filamentous cultivations	56
4.1.1 Morphological quantification by image analytic methods.....	56
4.1.2 Osmolality a novel method to improve process performance.....	64
4.1.3 Relation of morphology and productivity for cultivations with increased osmolality.....	71
4.1.4 Influence of osmolality on <i>A. niger</i> conidia aggregation.....	78
4.1.5 Morphology engineering in <i>A. niger</i> by variation of spore inoculum	82
4.1.6 Influence of biomass on culture broth rheology	86
4.1.7 Correlation of fungal morphology with culture broth rheology.....	90
4.1.8 Estimation of productivity from rheological data	99
4.1.9 Linking morphology, productivity and rheology to improve process understanding	101
4.2 Aggregate morphology as a process parameter in submerged cultivation of <i>Taxus chinensis</i>	103
4.2.1 Improved measurement of plant cell aggregate size through laser diffraction	103
4.2.2 Novel methods for assessment of plant cell viability	111
5 Conclusion and future prospects	119
6 References	122
Nomenclature	139