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Dry heat stress stability of model peptide: buserelin

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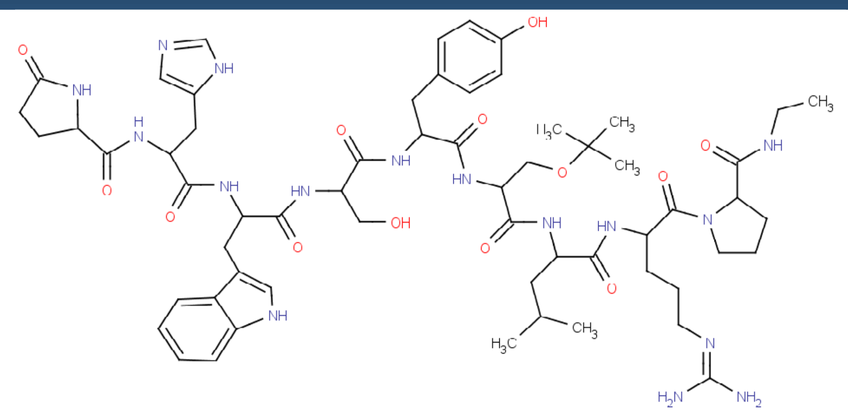
INTRODUCTION

Recently, the pharmaceutical industry showed a renewed interest in therapeutic peptides. Depending on the therapeutic application, processing of therapeutic peptides into controlled release implants would result in a patient friendly, long-term treatment. Hot melt extrusion (HME) is a fast and cost-efficient processing technique with 3 critical aspects: high temperature exposure during short time periods, mechanical shear stress influence and polymer/matrix influence.

Buserelin, an gonadotropin hormone releasing agonist peptide implemented in the treatment of prostate cancer, was subjected in its dry powder state to short-term heat exposure to evaluate the first critical HME aspect [1].



pGlu-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-NHEt
(mono acetate form)

EXPERIMENTAL

Stability indicating UPLC method:

Acquity BEH300 C18 1.7µm (2.1 100 mm)
MF A: 95/5 H_2O/ACN + formic acid
MF B: 5/95 H_2O/ACN + formic acid
Linear gradient from 0 to 21% Bin 9.5 min.; 1.5 min, 7 min isocratic hold in begin and end of gradient, resp.

Dry heat conditions

Temp (°C)	150	157.5	165	172.5	180
Time (min)	40	25	15	10	10
	80	50	30	20	20
	120	75	45	30	30
	160	100	60	40	40

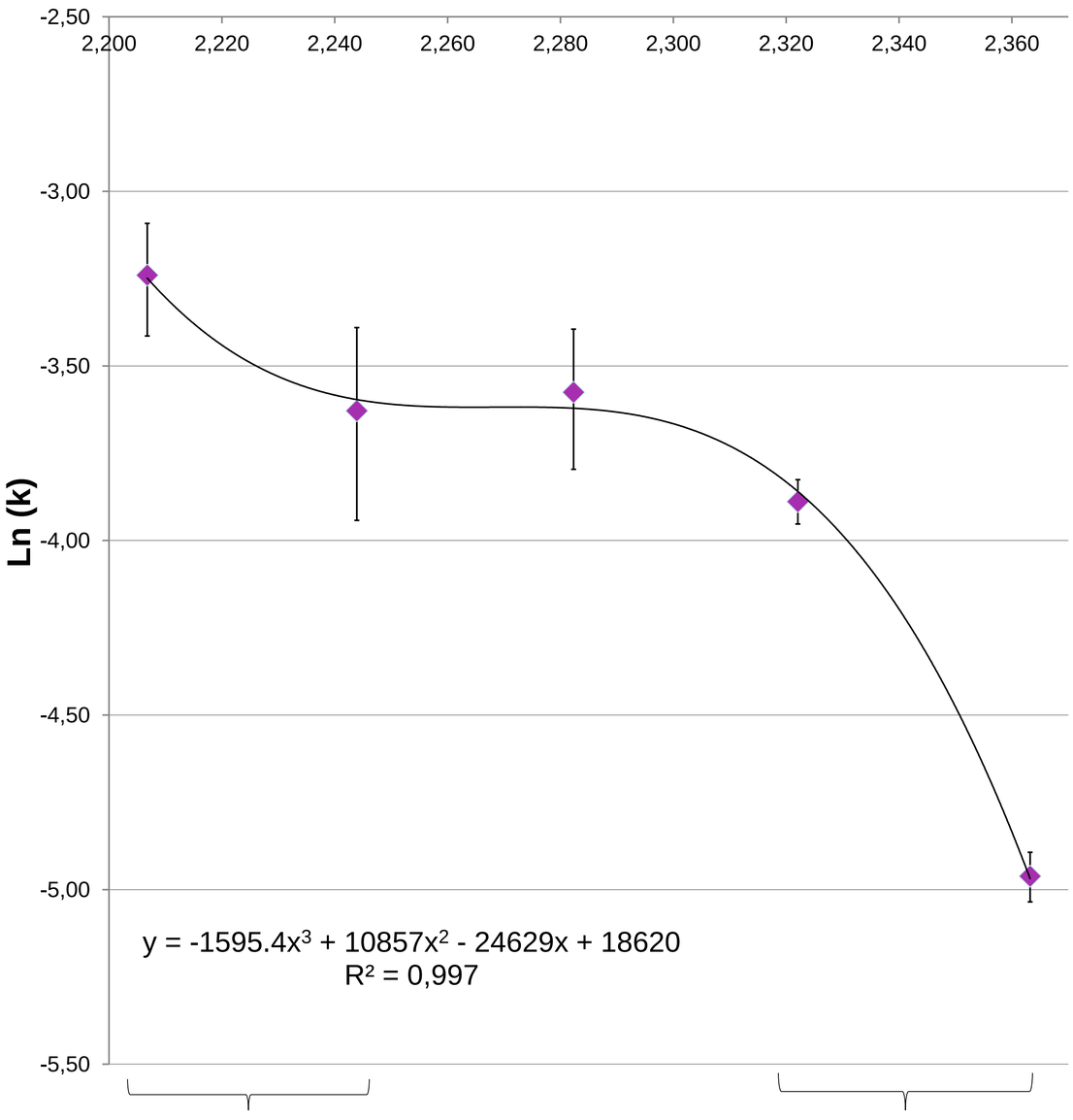
In duplicate

Data evaluation

- Calculate degradation constant k at each temperature, assuming first order kinetics
- Derive E_a from Arrhenius equation
- Identify degradants using LCQ IonTrap MS

RESULTS and DISCUSSION

Arrhenius

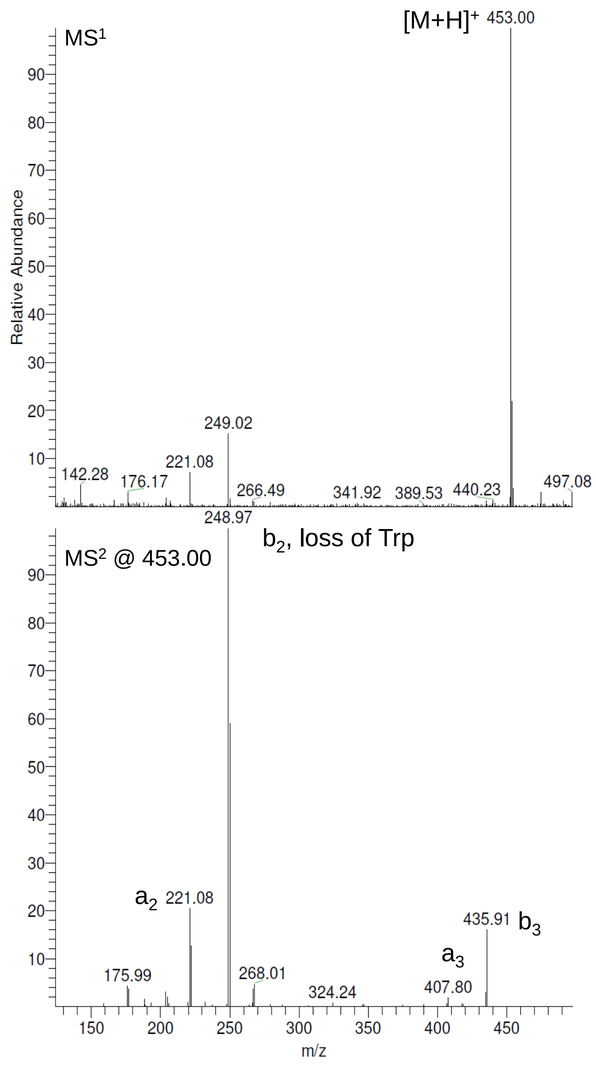


Molten state:
E_a: 87.0 kJ/mol

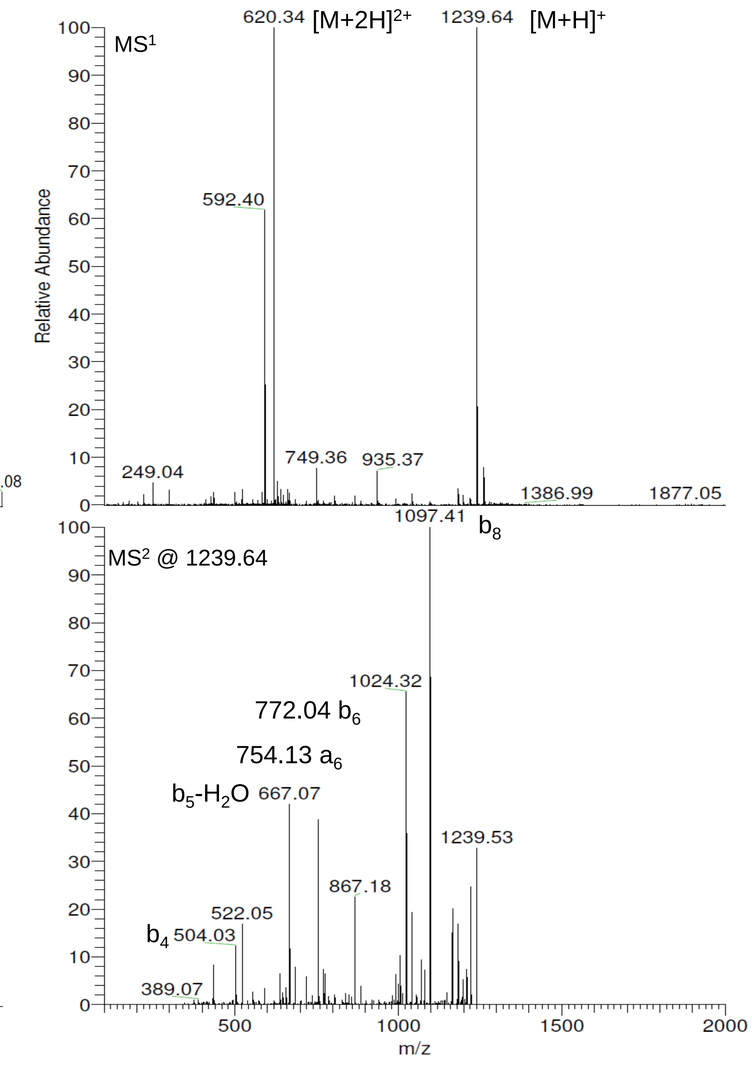
Solid state:
E_a: 216.8 kJ/mol

Degradant identification:

•pGlu-His-Trp



•Buserelin isomers



•Other, *e.g.* Tyr-D-Ser(tBu)-Leu-Arg-ProNHEt

CONCLUSIONS

The activation energy of buserelin was estimated to be 216.8 and 87.0 kJ/mol in dry and molten state, resp. Therefore, buserelin is a valid candidate for hot melt extrusion processing . Moreover, new low melting polymers, *i.e.* <100 C, and short HME exposure time, *i.e.* 5 minutes, should limit the thermal stress on the peptide API.

The structures of a number of buserelin degradants were identified using mass spectrometry.

REFERENCES

[1] M. D'Hondt, B. De Spiegeleer. *manuscript in preparation.*