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IMPACT OF HIGH TEMPERATURE, SHAKING AND LIGHT ON QUALITY OF THE THERAPEUTIC PEPTIDE TEDUGLUTIDE (REVESTIVE®) EVALUATED BY LC/MS/MS (ORBITRAP) PEPTIDE MAPPING ANALYSIS AND STRESS

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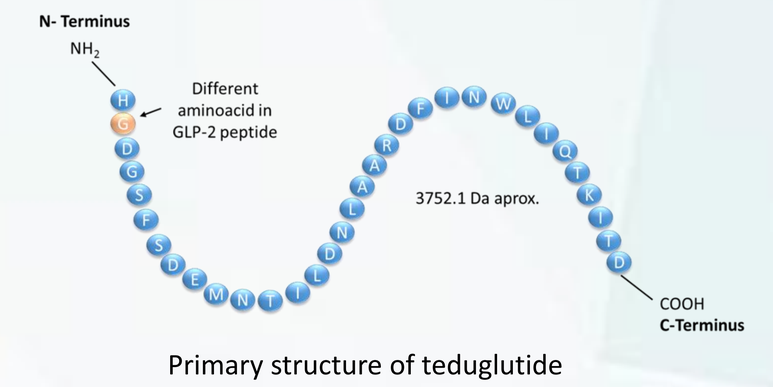
INTRODUCTION

Teduglutide (Revestive®) is a recombinant human GLP-2 analogue indicated in the treatment of the short bowel syndrome, a serious and highly disabling condition which results from either loss of portions of intestine or loss of critical intestinal function. As proteinaceous based-medicine, teduglutide (Revestive®) is indicated to have low stability, thus the study of the effect of possible in-use mishandling and in stress conditions are welcome to get knowledge upon its stability and degradation. However, few of these studies have been carried out on teduglutide to date.

Several post-tralational modifications (PTMs) are related with degradation process and the quality of the medicine i.e. deamidations, isomerizations, and oxidations. The quantification of these specific PTMs could be achieve by the analysis by a multi-attribute method (MAM) based in LC/MS/MS(Orbitrap) peptide mapping.

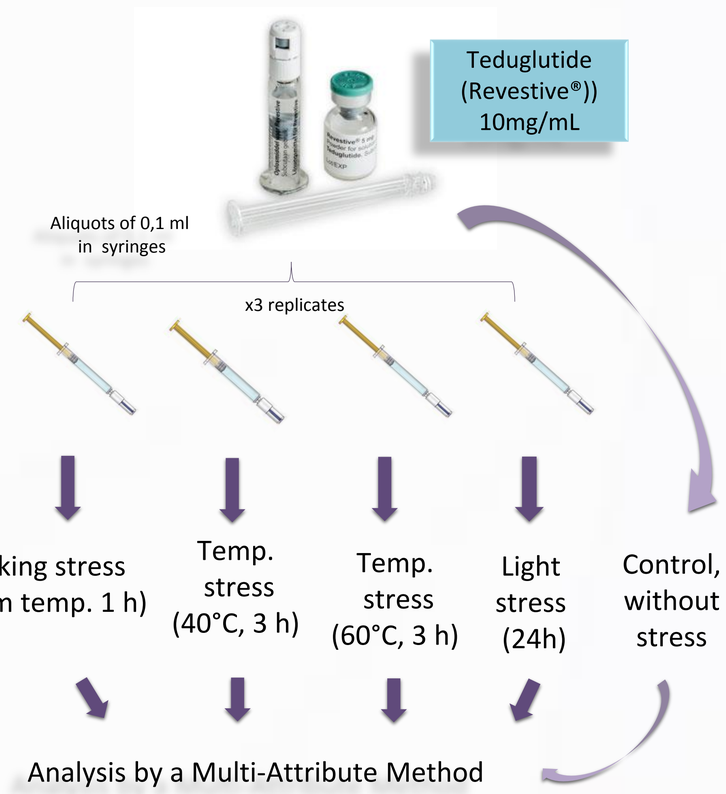


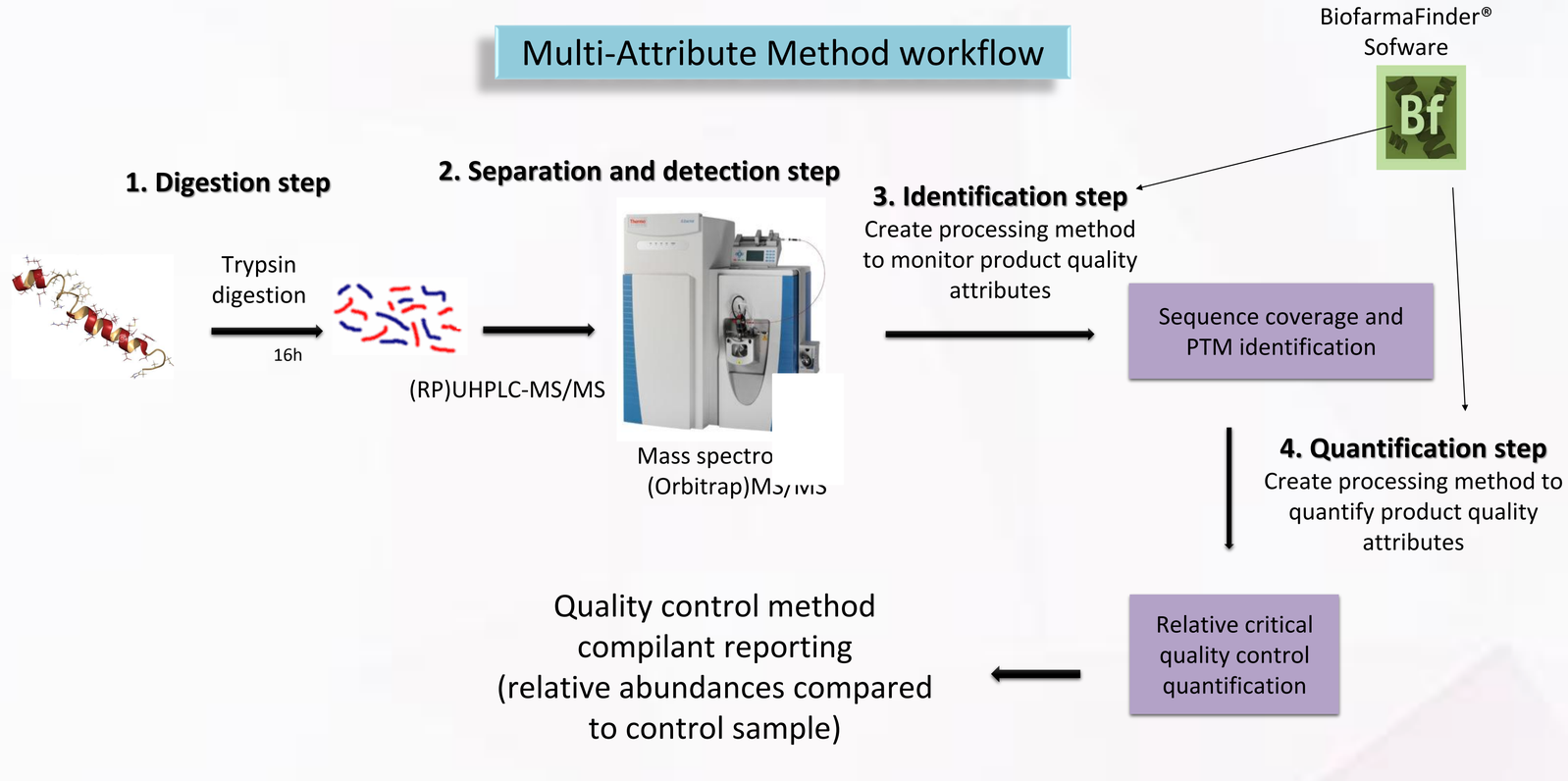
Primary structure of teduglutide

AIM AND OBJETIVES

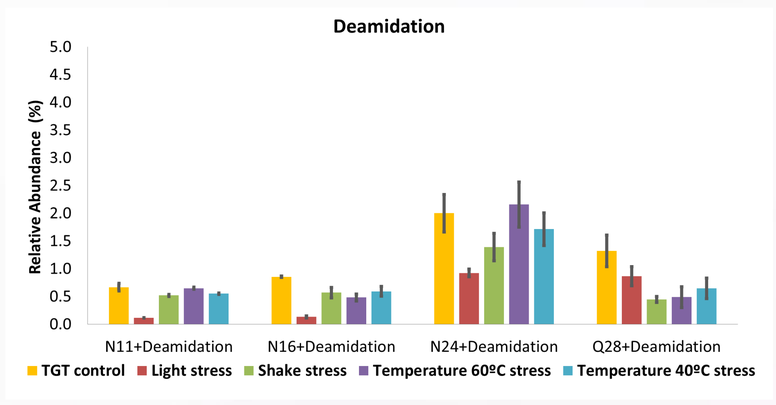
To evaluate the impact on teduglutide chemical structure when in-use mishandling and when degraded by the characterization of its PMTs obtained by LC/MS/MS(Orbitrap) peptide mapping analysis after submitted teduglutide samples to 40ºC and 60ºC, to smooth shaking and to accelerated light exposition.

METHODOLOGY

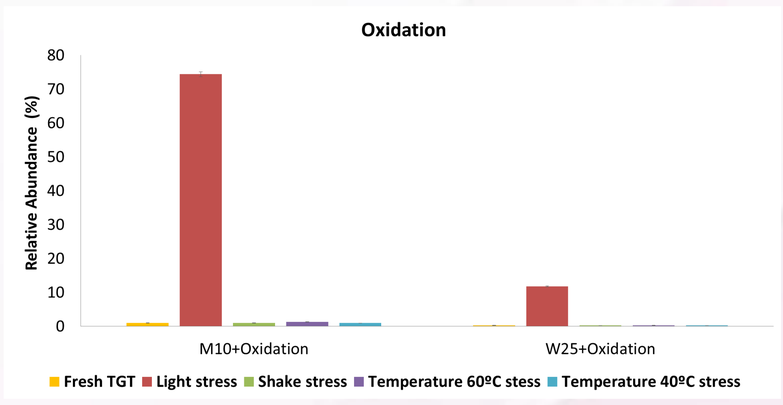




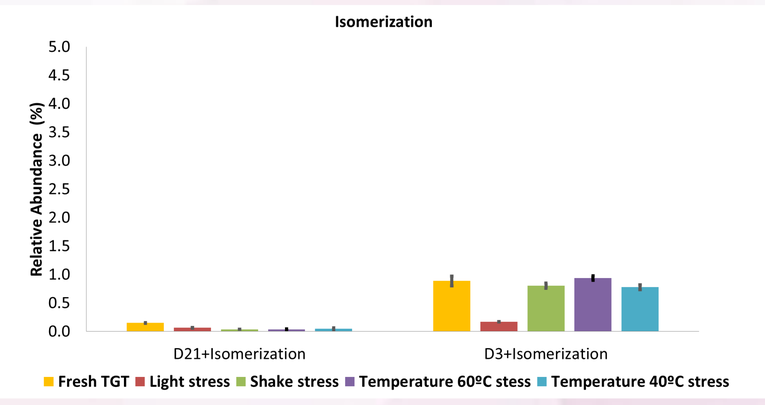
RESULTS



The deamidation relative abundances were very low (lower than 2.5% in all cases) and were unaffected by the stress conditions applied. The low abundances found in TGT and stressed samples could be attributed to the digestion process effect.



A clear increase in oxidation levels in response to light stress was observed, especially for M10 residue reaching 80% of abundance . The W25 also displayed an increase from roughly 0.3% (fresh TGT) to 12%. Shake and temperature 40ºC stress did not affect TGT oxidation in a relevant way.



The isomerization % of abundance in D21 and D3 were almost unappreciable (<1%), and the % of abundances do not vary significatively across stress stimuli, indicating that this PTMS were caused by the digestion protocol.

CONCLUSIONS

- The exposition to light stress modified the PTMs profile of teduglutide inducing oxidations in the primary structure (methionine and tryptophan residues). M10 and W25 are involved in the TGT binding with its target (GLP-2R) thus these PTMs might affect the teduglutide security, efficacy and quality. Therefore, it is highly recommended to protect the drug from light during in-use manipulation.
- For temperature exposition (40°C and 60°C) and agitation, PTMs profile was not modified, thus no special recommendation might be taken in this regard.

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