Preparation of long-acting release microspheres for octreotide LAR using formulation techniques to control the release kinetics

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PURPOSE

- To prepare microsphere formulations similar to Sandostatin long-acting release (LAR) while achieving similar in vitro release profile

OBJECTIVES

- Long-acting release formulations for controlled drug release provide extended duration of action of peptides and are therapeutically effective pharmaceutical products.
- Sandostatin long-acting release (SLAR) (octreotide acetate) is a somatostatin analogue that has been used in pharmacological treatment of acromegaly and was designed to solve some problems (i.e., dosing frequency) with octreotide delivery.
- The complexity of manufacturing processes of SLAR is one of the reasons that there is a lack of generic products for this formulation of octreotide in the United States. The difficulty in preparation of LAR poly (lactide-co-glycolide) (PLGA) formulations includes the necessity to mimic a very slow release rate of octreotide from the product.
- We designed long-acting octreotide-loaded microspheres by involving annealing and sodium chloride adding to overcome limitations related to high initial burst release.

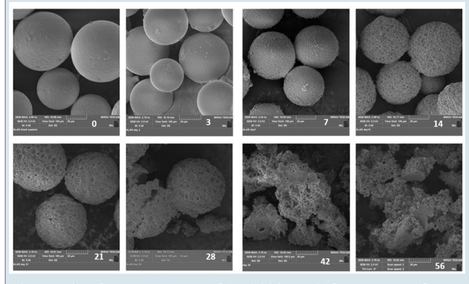
METHODS

- A number of composition comparable formulations were prepared using a solvent evaporation method.
- The kinetics of peptide release from PLGA microspheres was studied by incubating microparticles in PBST buffer (10 mM phosphate-buffered saline (PBS) with 0.02% Tween 80 at pH 7.4) at 37ºC for 56 days and was compared to the release kinetics of SLAR.
- In the release study, the prepared formulations were examined on water uptake, pH of release media, molecular weight of polymer, glass transition temperature (Tg), moisture content changes and mass loss.
- Stability of peptide during release was tested by identifying and measuring acylated products of octreotide using LC-MS and UPLC. Process of degradation of PLGA microspheres and level of erosion were shown using confocal mapping and scanning electron microscopy (SEM).

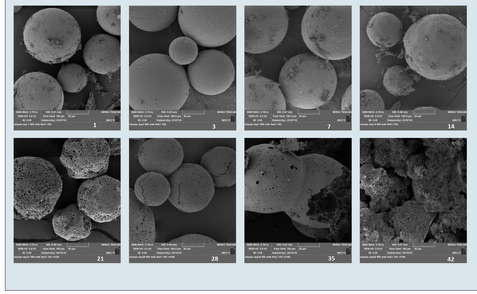
RESULTS

- Adding NaCl in concentration of 5% or 10% to inner water phase and annealing of prepared microspheres at 50ºC for 3 days resulted in slower release rate of octreotide, which was similar to the release rate of SLAR.
- Mass loss of microspheres with NaCl was slower compared to the mass loss of SLAR microspheres. Molecular weight (MW) of PLGA in the prepared formulations also decreased less rapidly than the SLAR during the release study.
- SEM images showed that erosion process was slightly more intensive on the surface of SLAR microspheres. However, degradation behavior inside the SLAR particles (confocal imaging) was similar to degradation process of microspheres with NaCl.
- Dry Tg curves of the formulations with NaCl and SLAR had a peak in the beginning of release unlike blank microspheres. This peak may indicate occurrence of peptide-polymer interactions.

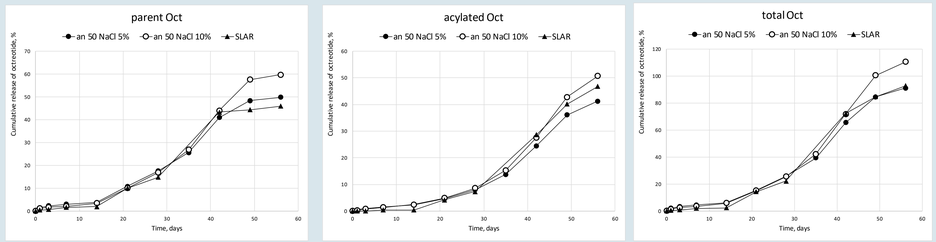
SEM of SLAR microspheres incubated in PBST pH 7.4 for 56 days



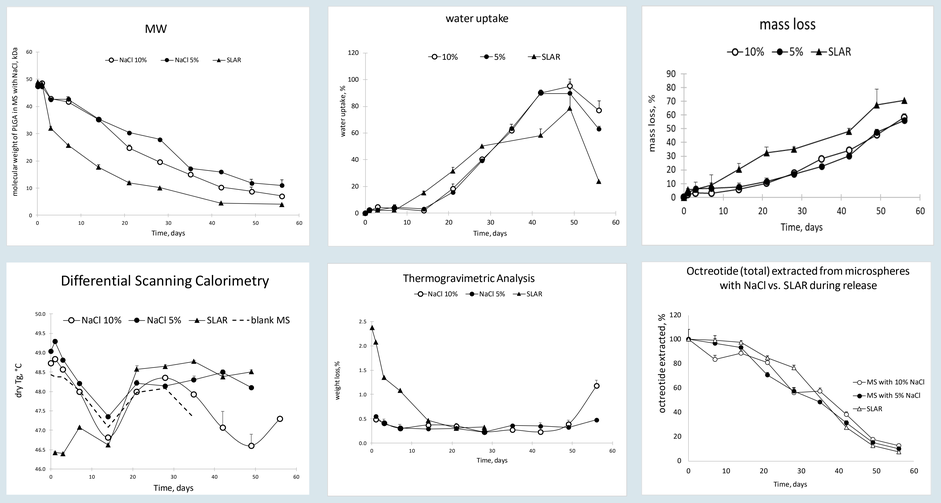
SEM of microspheres with 10% NaCl incubated in PBST pH 7.4 for 56 days



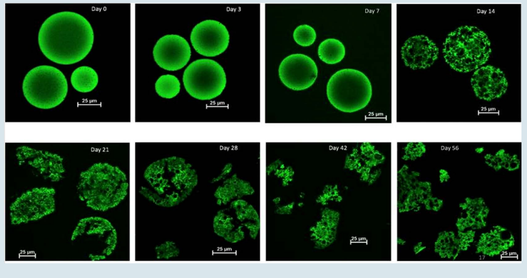
Release kinetics and stability of octreotide (Oct) (n=3, mean ± SD)



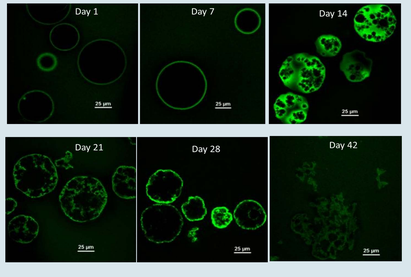
Characterization of degradation process during release (n=3, mean ± SD)



Confocal images of SLAR microspheres incubated in PBST pH 7.4 for 56 days



Confocal images of microspheres with 10% NaCl incubated in PBST pH 7.4 for 56 days



CONCLUSIONS

- Preparing PLGA microspheres often is associated with a problem of rapid release rate because of formation of large pores.
- Effective techniques (annealing at 50ºC for 3 days and adding sodium chloride to inner water phase) were applied to reduce the pore size of PLGA formulations with octreotide and to decrease release rate of the drug, allowing preparation of formulations with similar drug release rates to the SLAR release kinetics.
- It was shown that octreotide-loaded microspheres had significant peptide acylation during in vitro release testing. This can potentially complicate the development of generic products.
- Assessing peptide-polymer interactions and peptide impurities of PLGA formulations and comparing them to those of SLAR will improve safety and efficacy of the drug. These considerations are also valuable when developing generic products.

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DISCLAIMER

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