International Journal of Pharmaceutics 496 (2015) 676–688

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Extended release microparticle-in-gel formulation of octreotide: Effect of polymer type on acylation of peptide during in vitro release

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ARTICLE INFO

Article history:
Received 21 June 2015
Received in revised form 25 October 2015
Accepted 2 November 2015
Available online 10 November 2015

Keywords:
Polycaprolactone
Polyglycolic acid
Polylactic acid
Hydrogel
Peptide
Microparticles
Drug delivery
Sustained delivery
Peptide chemical stability

ABSTRACT

Polymeric microparticles (MPs)-in-gel formulations for extended delivery of octreotide were developed. We investigated influence of polymer composition on acylation of octreotide and kinetics of release during *in vitro* release from biodegradable polymeric formulations. Polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA) and polyethylene glycol (PEG) based triblock (TB ≈ PCL_{10k}-PEG_{2k}-PCL_{10k}) and pentablock (PBA ≈ PLA_{3k}-PCL_{7k}-PEG_{2k}-PCL_{7k}-PLA_{3k} and PBB ≈ PGA_{3k}-PCL_{7k}-PEG_{2k}-PCL_{7k}-PGA_{3k}) polymers were investigated. Octreotide was encapsulated in MPs using methanol–oil/water emulsion solvent evaporation method. The particles were characterized for size, morphology, encapsulation efficiency, drug loading and *in vitro* release. Release samples were subjected to HPLC analysis for quantitation and HPLC-MS analysis for identification of native and chemically modified octreotide adducts. Entrapment efficiency of methanol-oil/water method with TB, PBA and PBB polymers were 45%, 60%, and 82%, respectively. A significant fraction of released octreotide was acylated from lactide and glycolide based PBA (53%) and PBB (92%) polymers. Substantial amount of peptide was not released from PBB polymers after 330 days of incubation. Complete release of octreotide was achieved from TB polymer over a period of 3 months with minimal acylation of peptide (13%). PCL based polymers resulted in minimal acylation of peptide and hence may be suitable for extended peptide and protein delivery. Conversely, polymers having PLA and PGA blocks may not be appropriate for peptide delivery due to acylation and incomplete release.

1. Introduction

Proteins and peptides based biotherapeutics are currently being introduced rapidly into the clinical trials for treatment of a number of diseases. Proteins/peptides suffer from a myriad of delivery related constrains such as poor bioavailability, permeability across biological membranes and *in vivo* stability. Short *in vivo* half-life leads to frequent multiple parenteral administrations, which lowers patient compliance. Sustained delivery of biologics may address these issues and improve their potential as therapeutics. Among the approaches investigated for sustained delivery of biologics, nano- and microparticles are in the forefront and clinically available for various ailments, such as Sandostatin LAR® depot containing octreotide (Fogueri and Singh, 2009; Vaishya et al., 2015a; Wang et al., 2013).

Octreotide is a semisynthetic cyclic octapeptide, a somatostatin analogue, indicated for acromegaly (Fig. 1a) (Feelders et al., 2009). It is also recommended for symptomatic relief by suppressing severe diarrhea and flushing episodes associated with metastatic carcinoid tumors (De Martino et al., 2010; Feelders et al., 2009; Modlin et al., 2006). Half-life of this peptide following S.C. and I.M. administrations is short, about 100 min (Chanson et al., 1993). It is marketed as solution for subcutaneous injection (lactate buffer, pH 4.2) and as a depot form for intramuscular administration. PLGA-glucose star polymer microparticles (MPs) (size ~40 μm) provide delivery over a period of 4 weeks. PLGA has been widely investigated for the delivery of bioactive peptide and proteins (Kapoor et al., 2015; Ma, 2014; Sadat Tabatabaei Mirakabad et al., 2014; Vaishya et al., 2015a). However, it may not be the best polymer for delivering peptide and protein biologics due to acylation of biologics during release (Ghassemi et al., 2012; Ibrahim et al., 2005; Murty et al., 2003). It has been well documented that chemical stability of octreotide is compromised due to acylation during the release (Ghassemi et al., 2012). Less than 20% of native octreotide was released from Sandostatin LAR® depot during *in vitro* release (Ghassemi et al., 2012). Nearly 60%

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http://dx.doi.org/10.1016/j.ijpharm.2015.11.002
0378-5173/