Abstract: Setmelanotide (ImcivreeTM) was developed as a daily injectable therapeutic peptide for the treatment of rare forms of syndromic obesity, such as POMC deficiency and leptin receptor deficiency. The important option of poly(lactide-co-glycolic acid) (PLGA) controlled release microspheres has become more attractive for this class of drugs upon the discovery that net positively charged peptides can be remote-loaded rapidly from aqueous peptide solution into blank microspheres at high loading and encapsulation efficiency. Here we sought to remote-load setmelanotide in PLGA microspheres and examine its potential for long-term controlled release and body weight control. The influence of PLGA microsphere porosity was investigated with respect to morphology, drug loading and in vitro release profiles. Increased density of the microspheres inhibited the progress of encapsulation of the dicationic peptide. A diet-induced obese murine model was then used to determine the pharmacokinetic profile and to evaluate long-term efficacy of an optimal formulation. Remote loaded PLGA formulation encapsulated setmelanotide at as high as ~63% efficiency (~6.3% w/w loading) and exhibited slow and continuous peptide release over ~6 weeks in vitro largely independent of microsphere porosity. The obtained in vivo release pattern from deconvolution of the pharmacokinetics after subcutaneous microsphere injection was consistent with the in vitro release profile but with a lower initial burst release and overall slightly faster release rate. After a single injection of remote-loaded setmelanotide, continuous long-term inhibition of food intake and body weight control was observed over 17 and 30 days, respectively. The improvement in body weight control over drug-free microsphere vehicle-treated control groups matched well with the PK profile. This study provides the first report of long-acting release formulation for 1-month controlled release of setmelanotide and body weight control in a diet induced obese murine model, and supports the further development of long-acting treatment options for obese patients.