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Sustained drug delivery system in fish and the potential for use of PLGA microparticles: a review

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Abstract: Many fish species display some form of reproductive disorder in captivity. Captive fish reared in conditions outside the natural spawning environment show a failure of the pituitary to release the maturational gonadotropin luteinizing hormone thus necessitating administration of the hormone to induce spawning. A controlled sustained-release delivery system can conquer the issue of short half-life of gonadotropin releasing hormone (GnRH) in blood and avoid the necessity of using re-injections. Sustained release of GnRHa can induce long-term enhancement in semen production and multiple spawning in species with asynchronous or multiple batch group synchronous ovarian physiology. The most recent development is the incorporation of GnRHa into microparticles of biodegradable polymers that release the drug during a certain period of time ranging from days to weeks. The most attractive polymeric candidate used as a carrier for administering a pharmaceutical products is poly(lactic-co-glycolic acid); (PLGA). PLGA has excellent biodegradability and biocompatibility and is generally recognised as safe by international regulatory agencies including the European Medicines Agency and the United States Food and Drug Administration. This review describes methods of hormonal treatment in fish, highlights the advantage of sustained drug delivery system and discusses the potential of PLGA microparticles as a tool for achieving successful reproduction.

Keywords: GnRHa; reproductive dysfunction; induced spawning; aquaculture

Contents

1. Introduction

The potential to manipulate ovulation and spermiation of reared fish species, without which aquaculture would depend on broodstock, larvae, and fry from nature stock, is of great interest (Bromage 1995). Many economically relevant fish species do not breed naturally in fish farms, possibly as

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a result of stress or environmental conditions differing from their natural habitat, leading to inadequate supplies of quality juveniles for culture (Donaldson and Hunter 1983). A constant supply of high-quality sexual products and fry is essential for profitable intensive aquaculture.

It is necessary to develop techniques for controlled reproduction in fish kept in fish farms to address complications associated with spawning synchronization, egg collection, seasonal reproduction, and reproductive dysfunction. Sustained drug release systems have enormous potential to overwhelm obstacles to successful reproduction of many fish species (Rather et al. 2013).

2. Hormonal treatment

In aquaculture, reproduction can be stimulated using manipulation of the environment or hormones (Bromage et al. 2001). The first hormones used to induce spawning in captive fish were pituitary homogenates (hypophysation) (Fontenele 1955). The efficiency of the treatment is on account of high luteinizing hormone (LH) amount. However, the major disadvantage is that pituitary homogenate used in hatcheries is generally not standardised with respect to the precise LH dose, due to the changeable LH amount in fish pituitary (Yaron 1995).

Gonadotrophin releasing hormone (GnRH) is used for stimulation of gametogenesis (Lam 1982). It has the advantage of acting at the upper level of the reproductive axis, specifically on the pituitary, supporting a more complete physiological provocation of the entire reproduction process (Duncan et al. 2003), whereas pituitary homogenates act directly on the gonads. These treatments are believed to induce an enhancement of LH production. Nevertheless, adequate spawning often does not result, due to the short life of GnRH in the blood stream. This is caused by very quick degradation of GnRH by specific endopeptidases and non-specific exopeptidases (Goren et al. 1990).

Successful approaches in the control of reproduction in a variety of many species have been reached by the administration of synthetic gonadotrophin releasing hormone analogue (GnRHa) (Crim and Bettles 1997). Chemical synthesis of GnRHa eliminates the danger of transferof infectious diseases and allows for administration of precise dosages. The process is simplified by the high grade of interspecies similarity in the GnRH peptide (Chen and Fernald 2008). The biggest advantages of GnRHa over LH preparations are higher affinity to GnRH receptors and higher resistance to enzymatic cleavage (Well et al. 1992), allowing GnRHa to remain in the blood stream for a longer time than do native forms of GnRH. As a result, longer and stronger stimulation of LH occurs (De Leeuw et al. 1988).

Administered GnRHa induces the production and release of the endogenous LH (Breton et al. 1990), which in turn stimulates final oocyte maturation and ovulation (Nagahama and Yamashita 2008) via steroidogenesis and synthesis of the maturation inducing steroid (Goetz and Garczynski 1997). GnRHa may be administered as saline injection or a sustained-release delivery system (Weil and Crim 1983). Dependent upon the GnRHa type (e.g., leuprorelin, triptorelin, buserelin), fish species, and water temperature, one GnRHa injection evokes a LH wave that remains efficient for 12–72 hours (Carrillo et al. 2000). In some fish species, a single injection of GnRHa is sufficient to promote spawning for 2–3 days post-treatment (Zakes and Demska–Zakes 2005), but re-injections are frequently essential to provoke long lasting LH release and promote complete maturation and reproduction (Pankhurst et al. 1986; Dabrowski et al. 1994; Slater et al. 1995). Multiple injections are stressful and often increase mortality of valuable broodstock. Stress may, in itself, inhibit the reproductive process and induce pathologies and even death (Schreck et al. 2001).

3. Delivery systems used for regulation of fish reproduction

Long acting preparations constitute a frontier area of science. These technologies have considerable benefits compared to conventional administration, containing controlled release, low toxicity, and better efficacy and convenience (Lin et al. 2014). It has been demonstrated that GnRHa has a half-life of less than 30 min in the blood stream (Gothilf and Zohar 1991). In contrast, the sustained release of GnRHa increases plasma GnRHa concentrations that may last for several weeks (Mylonas et al. 1995). Sustained administration of GnRHa efficiently induces a sustained LH release. The induced endogenous LH release stimulates the go-

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nads more effectively than externally administered LH (Mylonas and Zohar 2000). Sustained delivery of GnRHa is advantageous compared to conventional dosage forms (Mylonas et al. 2007). Particularly in fishes with asynchronous ovarian development, sustained administration of GnRHa stimulates a long lasting elevation of plasma LH that causes multiple spawnings (Crim et al. 1988; Carrillo et al. 2000).

The first long acting preparation for the manipulation of spawning in fish used was cholesterol (Weil and Crim 1983; Carolsfeld et al. 1988). The agent was imbedded in cholesterol pellets with included cellulose to slow the release. Cholesterol pellets with imbedded mammalian GnRHa (mGnRHa) released an initial burst. After this initial burst, a sustained release follows that may last for over 28 days (Sherwood et al. 1988). The disadvantage of this system is a significant variation in GnRHa release from individual pellets (Carolsfeld et al. 1988). Moreover, there were concerns that cholesterol as an active biomolecule and a precursor to steroid hormone synthesis may influence gonad function (Mylonas and Zohar 2000). On the other hand, administration of cholesterol pellets is simple, and they can be stored without loss of bioactivity at room temperature for at least 4 weeks (Garcia 1996). Its positive effect on induction of maturation was confirmed in many species of fish including rainbow trout *Oncorhynchus mykiss* (Crim et al. 1983), herring *Clupea harengus pallasi* (Carolsfeld et al. 1988), sea bass *Dicentrarchus labrax* (Almendras et al. 1988), milkfish *Chanos chanos* (Marte et al. 1988), Pacific white snook *Centropomus viridis* (Ibarra-Castro et al. 2017), and beluga *Huso huso* (Aramli et al. 2017).

Following the success of cholesterol pellets containing mGnRHa, commercially available cholesterol pellets containing salmon GnRHa (sGnRHa) were developed (Ovaplant, Syndel International). With this preparation, 40–60% of the sGnRHa is released during the first day, and the rest of the drug is released over the ensuing 7–21 days (U.S. Fish & Wildlife Service 2016). The preparation was successfully used in empurau *Tor tambroides* (De Silva et al. 2004), hybrid catfish *Clarias microcephalus* × *C. gariepinus* (Abol-Munafi et al. 2006), Atlantic salmon *Salmo salar* (Anderson et al. 2017) and inpacu *Piaractus mesopotamicus* (Kuradomi et al. 2017).

A non-degradable co-polymer of ethylene and vinyl acetate (EVAc) is also used as a sustained delivery system (Rhine et al. 1980). The EVAc is produced in the shape of solid implants that are administered intramuscularly (Brown et al. 1986). The release rate of EVAc implants can extend from 15 days (Gothilf 1990) to 5 weeks, depending on the structure (Zohar 1996). EVAcs are simple to manufacture, and batches of 200–500 implants can be produced in a single preparation, minimizing GnRHa content variation among implants (Mylonas and Zohar 2000). The implants remains useable for up to three years when stored dried at –20 °C (Zohar and Mylonas 2001). The EVAc systems ability to induce multiple ovulation was confirmed in European sea bass at 60 µg/kg (Fornies et al. 2001), turbot *Scophthalmus maximus* at 25 µg/kg (Mugnier et al. 2000), in Atlantic bluefin tuna *Thunnus thunnus* at 40–80 µg/kg (Rosenfeld et al. 2012), and in great amberjack *Seriola dumerili* at 50 µg/kg (Jerez et al. 2018). These results may be attributed to long term elevation of plasma LH caused by long acting release of GnRHa (Fornies et al. 2001).

4. Poly(lactic-co-glycolic acid) microparticles

Microparticle is a dosage form that can be used for delivering of drugs by many ways and efficaciously manage the release of agent (Donbrow 1991; Birnbaum and Brannon-Peppas 2004). The name microparticle refers to a particle of diameter 1–1000 µm (Birnbaum and Brannon-Peppas 2004). Microparticles can be extremely helpful to protect the encapsulated agent against enzymatic degradation. Other advantages of microparticles are the possibility of controlled release of the agent, local delivery of the incorporated agent over intervals ranging from a few hours to several weeks, and simple administration compared to normally used forms of long-acting preparations, such as implants that are often used in aquaculture (Siepmann and Siepmann 2006).

A large range of natural as well as synthetic biodegradable polymers have been examined for use as matrix for microparticles (Hoffman 2008). Among them, the thermoplastic aliphatic poly(esters) as for example poly(lactic-co-glycolic acid); (PLGA) have caused concern owing to their extremely good tissue biocompatibility, biodegradability in the body (Lewis 1990) and show high flexibility in the en-

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capsulation of different agents. Bacterial (Altun et al. 2010), viral (Adomako et al. 2012) and parasitic antigens (Harikrishnan et al. 2012) encapsulated in PLGA were successfully used in fish and offered effective protection against pathogens.

Majority of biodegradable polymers decompose via hydrolysis to biologically tolerable and progressively minor compounds. In PLGA, the polymer eventually breaks down into lactic and glycolic acid, which enter the Krebs cycle. Afterwards it is further decomposed to carbon dioxide and water (Houchin and Topp 2009).

Microspheres of PLGA and other polymers are usually formed by solvent evaporation (Wakiyama et al. 1981; Bai et al. 2001; Ruan and Feng 2003). Frequently a double emulsion is used in which medicament that will be encapsulated is primarily dissolved in water. The aqueous phase is dissipated in an organic solvent (Dichloromethane) that includes the degradable polymer, and a water/oil emulsion is formed. Dispersion of the first emulsion in a steady aqueous medium, normally with poly(vinyl alcohol) as stabilizer, forming the final water/oil/water double emulsion. Microspheres are produced when the dichloromethane vaporizes and the polymer solidifies, incorporating the encapsulated pharmaceutical agent (O'Donnell and McGinity 1997).

5. Factors affecting drug release

Drug release kinetic is affected by the form of the matrix in which the active substance is incorporated and the chemical characteristics of the polymer and the medicament (Freiberg and Zhu 2004). A consistent release rate over time is desirable but release profiles may consist of an initial burst of medication released from the microparticle uppermost layer followed by a constant sustained release that depends on diffusion as well as on decomposition (Mogi et al. 2000).

The method of particle fabrication governs the incorporation and release of the therapeutic agent. A complex range of elements containing the kind of polymer, its molecular weight, the co-polymer structure, the nature of pharmaceutical ingredients incorporated to the microparticle mixture (therapeutic agent stabilization), and microparticle size can affect the release rate (Raman et al. 2005).

The kind of polymer employed in microparticle production and the process in which it breaks down surely affects therapeutic agent release kinetics (von Burkersroda et al. 2002). Bulk-eroding polymer microspheres such as PLGA are frequently distinguished in release of up to 50% of the complete therapeutic agent load over the first few hours after application. This initial burst is succeeded by slow release and occasionally a third stage during which the remainder is released rapidly due to the polymer decomposition (O'Donnell and McGinity 1997).

Both acidic and strongly alkaline media accelerate degradation of PLGA (Holy et al. 1999). Nevertheless, the contrast between neutral and slightly acidic environment is less significant because of autocatalysis by the carboxylic end groups (Zolnik and Burgess 2007). Enzymatic degradation also influences drug release. Poly(lactic-co-glycolic acid) is decomposed firstly via hydrolysis, but it has also been proposed that enzymatic decomposition can affect the drug release from the microparticles. Lack of uniformity *in vivo* makes it complicated to compare the contribution of obtainable enzymes to the degradation process (Cai et al. 2003).

6. Conclusions

Sustained delivery systems for GnRHa have shown to be effective methods for hormonal regulation of fish spawning. Apart from the type of hormonal treatment, the form of its administration is a major factor influencing the efficacy of the preparation. In the case of conventional drug release treatment, the hormonal preparation is dissolved in physiological saline, but a significant obstacle is the rapid enzymatic degradation of the administered peptide reducing its efficacy (Goren et al. 1990). Therefore, multiple administration is required to maintain the effective level of the preparation, otherwise the plasma concentration of the peptide falls below the therapeutic level (Schreck et al. 2001). The development of advanced drug delivery system opens new possibilities for effective administration of biologically active substances in the structure of microparticles enabling the release of bounded hormonal substances at the desired dose and for a set time.

Drug delivery using PLGA is an interesting field with extensive potential for biomedical investigation. They are easily produced and can preserve the agent from degradation and increase its stability. Microparticles of PLGA can increase the effica-

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cy of treatment through long acting of the drug. It is approved by the US Food and Drug Administration and European Medicine Agency in diverse long acting systems. PLGA microparticles show potential as a long acting preparation in fish reproduction.

7. References

Abol-Munafi A, Liem P, Ambak M, Siraj S (2006): Effects of maturational hormone treatment on spermatogenesis of hybrid catfish (Clarias macrocephalus X C. gariepinus). Journal of Sustainability Science and Management 1, 24–31.

Adomako M, St-Hilaire S, Zheng Y, Eley J, Marcum R, Sealey W, Donahower B, LaPatra S, Sheridan P (2012): Oral DNA vaccination of rainbow trout, Oncorhynchus mykiss (Walbaum), against infectious haematopoietic necrosis virus using PLGA [Poly(D,L-Lactic-Co-Glycolic Acid)] nanoparticles. Journal of Fish Diseases 35, 203–214.

Almendras JM, Duenas C, Nacario J, Sherwood NM, Crim LW (1988): Sustained hormone release. III. Use of gonadotropin releasing hormone analogues to induce multiple spawnings in sea bass, Lates calcarifer. Aquaculture 74, 97–111.

Altun S, Kubilay A, Ekici S, Didinen BI, Diler O (2010): Oral vaccination against lactococcosis in rainbow trout (Oncorhynchus mykiss) using sodium alginate and poly (lactide-co-glycolide) carrier. Kafkas Universitesi Veteriner Fakultesi Dergisi 16, 211–217.

Anderson K, Pankhurst N, King H, Elizur A (2017): Effects of GnRHa treatment during vitellogenesis on the reproductive physiology of thermally challenged female Atlantic salmon (Salmo salar). PeerJ 5, e3898. doi: 10.7717/peerj.3898.

Aramli MS, Nazari RM, Farsi P, Mehdinejad N, Aramli S, Sotoudeh E (2017): Retracted: Effectiveness of carp pituitary extract and luteinizing hormone releasing hormone analogue administration (by either injection or cholesterol pellet implantation) on spawning performance in female sturgeon, Huso huso. Aquaculture Research 48, 1915–1922.

Bai XL, Yang YY, Chung TS, Ng S, Heller J (2001): Effect of polymer compositions on the fabrication of poly(orthoester) microspheres for controlled release of protein. Journal of Applied Polymer Science 80, 1630–1642.

Birnbaum DT, Brannon-Peppas L (2004): Microparticle drug delivery systems. In: Brown DM (ed.): Drug Delivery Systems in Cancer Therapy. Humana Press, New Jersey. 117–136.

Breton B, Weil C, Sambroni E, Zohar Y (1990): Effects of acute versus sustained administration of GnRHa on GtH release and ovulation in the rainbow trout, Oncorhynchus mykiss. Aquaculture 91, 373–383.

Bromage NR (1995): Broodstock management and seed quality – General consideration. In: Bromage NR, Roberts R (eds): Broodstock Management and Egg and Larval Quality. Blackwell Science, London. 1–24.

Bromage N, Porter M, Randall C (2001): The environmental regulation of maturation in farmed finfish with special reference to the role of photoperiod and melatonin. Aquaculture 197, 63–98.

Brown L, Munoz C, Siemer L, Edelman E, Langer R (1986): Controlled release of insulin from polymer matrices: control of diabetes in rats. Diabetes 35, 692–697.

Cai Q, Shi G, Bei J, Wang S (2003): Enzymatic degradation behavior and mechanism of poly(lactide-co-glycolide) foams by trypsin. Biomaterials 24, 629–638.

Carolsfeld J, Sherwood NM, Kreiberg H, Sower SA (1988): Induced sexual maturation of herring using GnRH 'quick-release' cholesterol pellets. Aquaculture 70, 169–181.

Carrillo M, Mananos E, Sorbera L, Milonas C, Cuisset B, Zohar Y, Zanuy S (2000): Effects of sustained administration of GnRHa on gonadotropin–II (GtH–II) and gonadal steroid levels in adult male sea bass (Dicentrarchus labrax). Proceedings of the 6th International Symposium on the Reproductive Physiology of Fish, 393–395.

Crim L, Sutterlin A, Evans D, Weil C (1983): Accelerated ovulation by pelleted LHRH analogue treatment of spring-spawning rainbow trout (Salmo gairdneri) held at low temperature. Aquaculture 35, 299–307.

Crim LW, Bettles S (1997): Use of GnRH analogues in fish culture. Recent Advances in Marine Biotechnology 1, 369–382.

Crim LW, Sherwood NM, Wilson CE (1988): Sustained hormone release. II. Effectiveness of LHRH analog (LHRHa) administration by either single time injection or cholesterol pellet implantation on plasma gonadotropin levels in a bioassay model fish, the juvenile rainbow trout. Aquaculture 74, 87–95.

Dabrowski K, Ciereszko A, Ramseyer L, Culver D, Kestemont P (1994): Effects of hormonal treatment on induced spermiation and ovulation in the yellow perch (Perca flavescens). Aquaculture 120, 171–180.

De Leeuw R, Van 't Veer C, Smit-Van Dijk W, Goos HT, Van Oordt P (1988): Binding affinity and biological activity of gonadotropin-releasing hormone analogs in the African catfish, Clarias gariepinus. Aquaculture 71, 119–131.

De Silva SS, Ingram B, Sungan S, Tinggi D, Gooley G, Sim SY (2004): Artificial propagation of the indigenous Tor species, empurau (T. tambroides) and semah (T. douronensis), Sarawak, East Malaysia. Aquaculture Asia 9, 15–20.

Donaldson EM, Hunter GA (1983): Induced final maturation, ovulation, and spermiation in cultured fish. In: Hoar

https://doi.org/10.17221/161/2018-VETMED

WS, Randall DJ, Donaldson EM (eds): Fish Physiology. Academic Press, New York. 351–403.

Donbrow M (1991): Microcapsules and Nanoparticles in Medicine and Pharmacy. CRC press, London. 347 pp.

Duncan NJ, Alok D, Zohar Y (2003): Effects of controlled delivery and acute injections of LHRHa on bullseye puffer fish (Sphoeroides annulatus) spawning. Aquaculture 218, 625–635.

Fontenele O (1955): Injecting pituitary (hypophyseal) hormones into fish to induce spawning. The Progressive Fish-Culturist 17, 71–75.

Fornies M, Mananos E, Carrillo M, Rocha A, Laureau S, Mylonas C, Zohar Y, Zanuy S (2001): Spawning induction of individual European sea bass females (Dicentrarchus labrax) using different GnRHa-delivery systems. Aquaculture 202, 221–234.

Freiberg S, Zhu XX (2004): Polymer microspheres for controlled drug release. International Journal of Pharmaceutics 282, 1–18.

Garcia LMB (1996): Bioactivity of stored luteinizing hormone-releasing hormone analogue (LHRHa) in sea bass, Lates calcarifer Bloch. Journal of Applied Ichthyology 12, 91–93.

Goetz F, Garczynski M (1997): The ovarian regulation of ovulation in teleost fish. Fish Physiology and Biochemistry 17, 33–38.

Goren A, Zohar Y, Fridkin M, Elhanati E, Koch Y (1990): Degradation of gonadotropin-releasing hormones in the gilthead seabream, Sparus aurata: I. Cleavage of native salmon GnRH and mammalian LHRH in the pituitary. General and Comparative Endocrinology 79, 291–305.

Gothilf Y (1990): Pharmacokinetics, metabolism and bioactivity of gonadotropin releasing hormone (GnRH) and its analogs in the gilthead seabream (Sparus aurata). [M.Sc. Thesis] The Hebrew University, Jerusalem. 78 pp.

Gothilf Y, Zohar Y (1991): Clearance of different forms of GnRH from the circulation of the gilthead seabream, Sparus aurata, in relation to their degradation and bioactivities. Reproductive physiology of fish. Fish Symposium 91, 35–37.

Harikrishnan R, Balasundaram C, Heo MS (2012): Poly d,l-lactide-co-glycolic acid-liposome encapsulated ODN on innate immunity in Epinephelus bruneus against Vibrio alginolyticus. Veterinary Immunology and Immunopathology 147, 77–85.

Hoffman AS (2008): The origins and evolution of "controlled" drug delivery systems. Journal of Controlled Release 132, 153–163.

Holy CE, Dang SM, Davies JE, Shoichet MS (1999): In vitro degradation of a novel poly (lactide-co-glycolide) 75/25 foam. Biomaterials 20, 1177–1185.

Houchin M, Topp E (2009): Physical properties of PLGA films during polymer degradation. Journal of Applied Polymer Science 114, 2848–2854.

Chen C, Fernald R (2008): GnRH and GnRH receptors: distribution, function and evolution. Journal of Fish Biology 73, 1099–1120.

Ibarra-Castro L, Navarro-Flores J, Sanchez-Tellez JL, Martinez-Brown JM, Ochoa-Bojorquez LA, Rojo-Cebreros AH (2017): Hatchery production of Pacific white snook at CIAD-Unity Mazatlan, Mexico. World Aquaculture 48, 25–29.

Jerez S, Fakriadis I, Papadaki M, Martin M, Cejas J, Mylonas C (2018): Spawning induction of first-generation (F1) greater amberjack Seriola dumerili in the Canary Islands, Spain using GnRHa delivery systems. Fishes 3, 35. doi: 010.3390/fishes3030035.

Kuradomi RY, Foresti F, Batlouni SR (2017): The effects of sGnRHa implants on Piaractus mesopotamicus female breeders. An approach addressed to aquaculture. Aquaculture International 25, 2259–2273.

Lam T (1982): Applications of endocrinology to fish culture. Canadian Journal of Fisheries and Aquatic Sciences 39, 111–137.

Lewis DH (1990): Controlled release of bioactive agents from lactide/glycolide polymers. Drugs and the Pharmaceutical Sciences 45, 1–41.

Lin Z, Gao W, Hu H, Ma K, He B, Dai W, Wang X, Wang J, Zhang X, Zhang Q (2014): Novel thermo-sensitive hydrogel system with paclitaxel nanocrystals: High drug-loading, sustained drug release and extended local retention guaranteeing better efficacy and lower toxicity. Journal of Controlled Release 174, 161–170.

Marte CL, Sherwood N, Crim L, Tan J (1988): Induced spawning of maturing milkfish (Chanos chanos) using human chorionic gonadotropin and mammalian and salmon gonadotropin releasing hormone analogues. Aquaculture 73, 333–340.

Mogi T, Ohtake N, Yoshida M, Chimura R, Kamaga Y, Ando S, Tsukamoto T, Nakajima T, Uenodan H, Otsuka M (2000): Sustained release of 17β–estradiol from poly (lactide–co–glycolide) microspheres in vitro and in vivo. Colloids and Surfaces B: Biointerfaces 17, 153–165.

Mugnier C, Guennoc M, Lebegue E, Fostier A, Breton B (2000): Induction and synchronisation of spawning in cultivated turbot (Scophthalmus maximus L.) broodstock by implantation of a sustained–release GnRH–a pellet. Aquaculture 181, 241–255.

Mylonas C, Tabata Y, Langer R, Zohar Y (1995): Preparation and evaluation of polyanhydride microspheres containing gonadotropin–releasing hormone (GnRH), for inducing ovulation and spermiation in fish. Journal of Controlled Release 35, 23–34.

https://doi.org/10.17221/161/2018-VETMED

Mylonas CC, Bridges C, Gordin H, Rios AB, Garcia A, De La Gandara F, Fauvel C, Suquet M, Medina A, Papadaki M (2007): Preparation and administration of gonadotropin-releasing hormone agonist (GnRHa) implants for the artificial control of reproductive maturation in captive–reared Atlantic bluefin tuna (Thunnus thynnus thynnus). Reviews in Fisheries Science 15, 183–210.

Mylonas CC, Zohar Y (2000): Use of GnRHa–delivery systems for the control of reproduction in fish. Reviews in Fish Biology and Fisheries 10, 463–491.

Nagahama Y, Yamashita M (2008): Regulation of oocyte maturation in fish. Development, Growth & Differentiation 50, S195–S219.

O'Donnell PB, McGinity JW (1997): Preparation of microspheres by the solvent evaporation technique. Advanced Drug Delivery Reviews 28, 25–42.

Pankhurst N, Van Der Kraak G, Peter R (1986): Effects of human chorionic gonadotropin, DES–GLY^{o} (D–ALA") LHRH-ethylamide and pimozide on oocyte final maturation, ovulation and levels of plasma sex steroids in the walleye (Stizostedion vitreum). Fish Physiology and Biochemistry 1, 45–54.

Raman C, Berkland C, Kim KK, Pack DW (2005): Modeling small-molecule release from PLG microspheres: effects of polymer degradation and nonuniform drug distribution. Journal of Controlled Release 103, 149–158.

Rather MA, Sharma R, Gupta S, Ferosekhan S, Ramya V, Jadhao SB (2013): Chitosan-nanoconjugated hormone nanoparticles for sustained surge of gonadotropins and enhanced reproductive output in female fish. PloS One 8, e57094. doi: 10.1371/journal.pone.0057094.

Rhine WD, Hsieh DS, Langer R (1980): Polymers for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics. Journal of Pharmaceutical Sciences 69, 265–270.

Rosenfeld H, Mylonas CC, Bridges CR, Heinisch G, Corriero A, Vassallo-Aguis R, Medina A, Belmonte A, Garcia A, De la Gandara F, Fauvel C, De Metrio G, Meiri-Ashkenazi I, Gordin H, Zohar Y (2012): GnRHa–mediated stimulation of the reproductive endocrine axis in captive Atlantic bluefin tuna, Thunnus thynnus. General and Comparative Endocrinology 175, 55–64.

Ruan G, Feng SS (2003): Preparation and characterization of poly (lactic acid)–poly (ethylene glycol)–poly (lactic acid)(PLA–PEG–PLA) microspheres for controlled release of paclitaxel. Biomaterials 24, 5037–5044.

Sherwood NM, Crim L, Carolsfeld J, Walters SM (1988): Sustained hormone release. I. Characteristics of in vitro release of gonadotropin-releasing hormone analogue (GnRH–A) from pellets. Aquaculture 74, 75–86.

Schreck CB, Contreras-Sanchez W, Fitzpatrick MS (2001): Effects of stress on fish reproduction, gamete quality, and progeny. Aquaculture 197, 3–24.

Siepmann J, Siepmann F (2006): Microparticles used as drug delivery systems. Smart Colloidal Materials: Progress in Colloid and Polymer Science 133, 15–21.

Slater CH, Schreck CB, Amend DF (1995): GnRHa injection accelerates final maturation and ovulation/spermiation of sockeye salmon (Oncorhynchus nerka) in both fresh and salt water. Aquaculture 130, 279–285.

U.S. Fish & Wildlife Service (2016): Ovaplant®; Salmon Gonadotropin–Releasing Hormone Analogue (sGnRHa) INAD #11–375.

von Burkersroda F, Schedl L, Gopferich A (2002): Why degradable polymers undergo surface erosion or bulk erosion. Biomaterials 23, 4221–4231.

Wakiyama N, Juni K, Nakano M (1981): Preparation and evaluation in vitro of polylactic acid microspheres containing local anesthetics. Chemical and Pharmaceutical Bulletin 29, 3363–3368.

Weil C, Crim L (1983): Administration of LHRH analogues in various ways: effect on the advancement of spermiation in prespawning landlocked salmon, Salmo salar. Aquaculture 35, 103–115.

Well C, Breton B, Sambroni S, Zmora N, Zohar Y (1992): In vitro bioactivities of various forms of GnRH in relation to their susceptibility to degradation at the pituitary level in the rainbow trout, Oncorhynchus mykiss. General and Comparative Endocrinology 87, 33–43.

Yaron Z (1995): Endocrine control of gametogenesis and spawning induction in the carp. Aquaculture 129, 49–73.

Zakes Z, Demska-Zakes K (2005): Artificial spawning of pikeperch (Sander lucioperca (L.)) stimulated with human chorionic gonadotropin (hCG) and mammalian GnRH analogue with a dopamine inhibitor. Archiwum Rybactwa Polskiego 13, 63–76.

Zohar Y (1996): New approaches for the manipulation of ovulation and spawning in farmed fish. Bulletin of National Research Institute of Aquaculture 2, 43–48.

Zohar Y, Mylonas CC (2001): Endocrine manipulations of spawning in cultured fish: from hormones to genes. In: Donaldson EM, Lee CS (eds): Reproductive Biotechnology in Finfish Aquaculture. Elsevier, Amsterdam. 99–136.

Zolnik BS, Burgess DJ (2007): Effect of acidic pH on PLGA microsphere degradation and release. Journal of Controlled Release 122, 338–344.

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