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Review

Controlled and/or prolonged parental delivery of peptides from the hypothalmic pituitary axis

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Abstract

In recent years, advances in genetic engineering and in several other fields have led to the development of many new pharmaceutically active polypeptides. Because many of these polypeptides have extremely short plasma half-lives and are not active orally, the development of new delivery routes of administration or new delivery systems capable of controlling the release of these materials in their active forms are of considerable interest. Controlled release products for parenteral applications, such as implants or microparticulate systems have gained increasing importance and appropriate delivery systems for peptides have become the subject of intensive research. Therefore, the therapeutic and commercial potential of these peptides will only be fully realized if these advances are accompanied by improvements in the design of dosage forms leading to practical and effective formulations. The intent of this review is to summarize the work done in the field of controlled and/or prolonged release systems for peptides from the hypothalamic pituitary axis and their analogs. The potential in controlled and/or prolonged peptide delivery and the particularity of various kind of controlled delivery systems are discussed. © 1997 Elsevier Science Ireland Ltd.

Keywords: Biodegradable polymers; Biopolymeric systems; Controlled drug delivery systems; Hypothalamic pituitary axis; Peptides; Parenterals; Review

1. Introduction

In 1947, Green and Harris formulated the hypothesis of a humoral control of the anterior pituitary function by the hypothalamus [1]. This formally established neuroendocrinology as a new discipline. In the last 50 years, the remarkable growth of this field has been the result of the parallel developments in medicine and biochemistry, and more recently in biotechnology. The most notable achievement of this multidisciplinary approach was the isolation between 1969 and 1971 of natural products that resulted from extensive extraction and isolation programs culminating in the identification and synthesis of the first hypothalamic releasing factors (thyrotropin-releasing hormone, TRH, and luteinizing hormone-releasing hormone, LHRH) and the validation of the neurohumoral hypothesis. In 1972, Guillemin and co-workers [2] succeeded in isolating from ovine hypothalamus a substance, a tetradecapeptide which they called somatostatin, in the belief that it was a specific hypothalamic factor which modulates the release of growth hormone (somatotropin), similarly to the factor which inhibits the release of prolactin [3]. This has formed the basis for chemical and pharmacological development which extended the field of neuroendocrinology to include clinical application [4–6].

In recent years, the peptide drugs available for clinical use have become a very important class of therapeutic agents as a result of the better understanding of their role in physiology and pathology as well as the rapid advances in the field of biotechnology and genetic engineering. With the advancements in biotechnology,

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several therapeutic peptides have been successfully produced through recombinant DNA technology, such as human growth hormone [7]. In order to take further advantage of their therapeutic properties, synthetic peptide analogs (agonists or antagonists) with modified or enhanced activity have been synthesized [8–12]. These modifications are designed to render the molecule less susceptible to enzymatic degradation by increasing its binding affinity to the receptor and lowering its subsequent rate of dissociation from the receptors, or by increasing the hydrophobicity of the molecule, thereby slowing down plasma clearance. For example, some sparingly soluble salt forms of peptides (e.g. pamoate) [13] have been used. Some peptide analogs are also able to avoid the post infusion rebound hypersecretion [14]. As an example, some somatostatin analogs do not seem to have the immediate 'rebound' effect seen with somatostatin since these analogs have longer plasma half-lives and the therapeutic effects take longer to wear off [15].

Today, the number of polypeptides undergoing evaluation for potential clinical applications is extremely high [16–19]. The past decade has witnessed revolutionary advances mostly in the development of the chemistry and pharmacology of LHRH, somatostatin, TRH and their analogs. Of all the hypothalamic hormones identified so far, LHRH has undergone perhaps the most extensive and successful chemical modification and pharmacological development. Approximately 1600 derivatives have been synthesized to date, such as Buserelin [20], Leuprolide [21] or Nafarelin [22]. Very potent agonistic or antagonistic analogs of LHRH are now available [23,24]. Table 1 shows some pharmaceutical peptides from the hypothalamic pituitary axis and some of their analogs.

2. Potential in controlled and/or prolonged delivery of peptides from the hypothalamic pituitary axis

In 1977, Schally and Guillemin both were awarded the Nobel Prize in Medicine for their identification and synthesis of the so-called 'peptide hormones of the brain'. Their accomplishments paved the way for novel approaches to the regulation of fertility or for treating some hypothalamic disorders. The availability of synthetic forms, identical chemically and biologically to the endogenous hypothalamic hormones has provided the necessary means for investigating their respective regulatory functions and has offered the potential for new clinical approaches to the diagnosis and treatment of hypothalamus related endocrine diseases. Table 2 summarizes the main existing hypothalamic hypophysiotropic factors.

Many peptide hormone receptors are regulated by the homologous hormone, and sometimes by other hormones. The common response to a prolonged exposure to the hormone is an initial phase of receptor activation followed by a period of diminished responsiveness that accompanies the presence of residual hormone on receptor sites, and then a reduction in the number of receptors at the cell surface. Down-regulation may also result from reductions in the concentration of effector molecules which mediate the cellular effects of a peptide interaction with its receptor. This corresponds to the short-term phenomenon described as desensitization [25,26]. The use of the Alzet® osmotic minipump demonstrated that chronic administration of some hormones increased the receptor population, whereas with other hormones, down-regulation was observed. For example, receptors down-regulated by the homologous hormones include those for growth hormone, thyrotropin-releasing hormone or LHRH [27]. The completely reversible nature of the complex formed after the initial phase of hormone binding to the receptor, leads to the possibility of using peptides for long-term treatment. For many hormones, it is desirable to release the drug either intermittently or continuously at a controlled rate over a period of weeks or even months [28]. However, it is difficult to know which type of imput function will be best suited for a particular polypeptide and therapeutic indication. The optimal input function needed in polypeptide delivery is specific to each drug and may also depend on the therapeutic indication itself [25].

As demonstrated in Fig. 1, the optimal input function for a given polypeptide drug should produce effects which satisfy three criteria: (i) maximize the therapeutic effect; (ii) minimize side effects; and (iii) prevent tolerance development to the desired therapeutic effect of the compound.

So, continuous infusion and resultant steady state levels of an agent, while not necessarily desirable for agonist action, may be entirely appropriate for antagonist action. For example, the use of superpotent LHRH (Fig. 2) agonist analogs such as Buserelin is a consequence of the observation that LHRH is secreted in a pulsatile manner and that the pituitary gland requires this pulsatility to respond normally. Continuous application of a superpotent analog causes receptor down-regulation and desensitization of the pituitary causing the paradoxical effect of inhibiting gonadal steroid production [29,30]. On the other hand, the pulsed delivery of LHRH may well be the desired mode of delivery for the treatment of primary infertility, for precocious puberty or for contraception, rather than the more conventional steady state which may be desired for treating patients with hormone-dependent disorders, both benign (e.g. endometriosis, uterine leiomyoma, hirsutism and prostatic hypertrophy) and malignant (e.g. breast and prostatic cancer) [13,22]. For example, Crowley et al. [31] and Hoffman et al. [32] stimulated the normal menstrual cycle in a woman with Kallman's syndrome or induce puberty in men by a pulsatile administration of LHRH.

Table 1
Examples of some pharmaceutical peptides from the hypothalamic pituitary axis and some of their analogs

Parent molecule	Analog DCI	Trade name	Company
Vasopressin	Desmopressin	Adiuretin SD®	Spofa
		Concentraid®, Desmospray®, Defirin®, Octostim®, Desurin®,	Ferring
		DAV Ritter®	Ritter
		DDAVP®	Rhône Poulenc
		Minirin®	Mason, Protea, Valeas
		Stimate®	Armour
	Argipressin	Pitressin®	Parke Davis
Lypressin		Dialip®	Sandoz-Wander
		Diapid®, Syntopressin®	Sandoz
		Postacon®	Ferring
Gonadorelin (LHRH)		Cryptorelin®	Hoechst-Roussel
		Cystorelin®	Abbott, Biokema
		Lutamin®	Daiichi
		Lutrelef®	Ferring, Valeas
		Lutrepulse®	Johnson&Johnson, Ortho
		Relisform L®	Serono, Found Trip
		Cryptocur®, Lutal®, Fertiral®	Hoechst
		Luforan®, GnRH Serono®	Serono
		Fertagyl®	Intervet, Veterinaria
		Nialutin®	Novo
		Pulstim®	Cassene
		Stimu-LH®	Roussel
		LRH®	Roche
		HRF®	Ayerst
	Buserelin	Receptal®, Suprecur®	Hoechst
		Suprefact®	Behringwerke, Hoechst
		Suprelin®	Ortho, Roberts
	Histrelin	Carcinil®, Lucrin®, Procrin®	Abbott
	Leuprorelein	Lupron®	Abbott, TAP
		Enantone®, Leuplin®	Takeda
		Prostap®	Lederle
	Triptorelin	Decapeptyl®	Ipesen, Ferring, Ipsen, Pharmachemie, Mason
	Deslorelin	Somagard®	Roberts
	Nararelin	Synarel®	Syntex
	Goserelin	Zoladex®	Zeneca, ICI
Somatostatine		Somatofalk®	Falk, Ferring
		Aminophan®	UCB
		Etaxene®	Wasserman
		Ikestatina®	Iketon
		Modustatina®	Sanofi
		Reducin®	Ferring
		Sumestil®, Somiaton®	Serono
		Stilamin®	Fund Trip, Serono
	Octreotide	Longastatina®	Italfarmaco
		Samilstin®	Samil
		Sandostatin®	Sandoz
	Vapreotide	Octastatin®	n.a.
Somatotropin (GH)		Grescormon®	Kabi Vitrum
		Genotonorm®	Kabi Vitrum, Pharmacia
		genotropin®	Great Eastern, Kabi, Pfrimmer, Pierrel
		Humatrope®	Berna, Eli Lilly, Lilly, Y.C. Wood
		Maxomat®	Choay
		Norditropin®	Mekim, Nordisk, Novo, Yamanouchi
		Protropin II®	Genentech
		Saizen®	Fund Trip, Serono
		Umatrope®	Lilly
Thytropin (TRH)		Actyron®, Thyratrop®	Ferring
		Thyreotropin®	
		Ambinon®, Thyreostimulin®	Organon
		Thytropar®	Armour, Rhône-Poulenc, USV

Table 2
Hypothalamic hypophysiotropic hormones (factors) (adapted from [5])

Hypothalamic principle	Abbreviation	$t^{1/2}$(min) [6]	Anterior pituitary hormone affected	$t^{1/2}$(min) [6]
Corticotropin-releasing hormone	CRH	25–30	ACTH	20–25
Thyrotropin-releasing hormone	TRH	~5	TSH	50
			Prolactin	30
Growth hormone-releasing hormone	GHRH	n.a.	GH	20–25
Growth hormone-inhibitory hormone (Somatostatin)	GHIH(SRIH)	1–3	GH	20–25
			TSH	50
Luteinizing hormone-releasing hormone	FSHRH/LHRH	~4	LH	30
			FSH	60
Prolactin release inhibitory factor	PIF	n.a.	Prolactin	30
Prolactin-releasing factor	PRF	n.a.	Prolactin	30

More recently very potent antagonistic analogs of LHRH have been synthesized. These analogs compete with endogenous LHRH for its receptors and having binding affinities equivalent to those of the most potent agonistic analogs, they require only low doses in vivo to interfere with the gonadotropin release. The antagonistic analogs cause a sharp fall in gonadotropins and steroids in contrast to the effects of even the most potent agonists, where a stimulatory phase precedes shutdown. This difference, together with the suggestion that it may be possible to achieve a greater degree of gonadal inhibition with antagonists than agonists, may well have an influence on their relative utility, particularly in the area of fertility control [18].

In the case of somatostatin, down-regulation of its receptor does not seem to occur, even on prolonged continuous administration, unlike the effect of LHRH agonists on their receptors. The results of most experiments support the view that somatostatin inhibits the release of GH by a direct action on the somatotrophic cell without having any action on GH synthesis [33]. For somatostatin, a long-term controlled releasing system is required to maintain an efficient plasma level of the hormone. But, in contrast with LHRH analogs, it is much more difficult to produce adequate release formulations of somatostatin or of its analogs. Indeed, a too high level of these peptides would causes side effects, whereas a too low level would not be efficient [15]. Analogs of somatostatin are used clinically to inhibit the growth of a variety of tumors [14,17] and may also prove therapeutically useful in some other disorders such as acromegaly, Zollinger-Ellison syndrome, Verner-Morrison syndrome, insulinoma, peptic ulcer, gastrointestinal hemorrhage, dumping syndrome, acute pancreatitis, neuropsychiatric and growth disorders [3]. Very recently, somatostatin was found to have an effect on systemic hemodynamics in patients with cirrhosis [34–36].

3. Peptide administration

Although peptides are highly potent and specific in their physiological functions, most peptides are difficult to administer clinically. They are subject to degradation which begins at the site of administration, by numerous enzymes or enzyme systems, and continues throughout the body. Peptides are particularly susceptible to hydrolysis of amide bonds and oxidation of disulphide bonds [37]. Usually, because of their susceptibility to the unfavorable environment and the proteolytic enzymes in the gastrointestinal tract, the oral bioavailability of most potential peptide drugs is very low. Even if the drugs are stable to enzymatic digestion, their molecular weights are usually too high for absorption through the intestinal wall [38]. A major challenge in peptide drug delivery is to overcome the enzymatic barrier that limits the amount of peptide drugs reaching their targets [39]. The current mode of delivery is by the transmucosal and parenteral routes. Both have their limitations: transmucosal delivery, while offering the convenience of self-administration, raises some questions on patient compliance. A simple injectable solution, while being very useful in experimental studies, is obviously less than ideal for chronic therapy. Therefore, to have a therapeutic action, polypeptides generally require long-term parenteral delivery [28]. Various types of controlled delivery systems have been studied, such as mechanical, osmotic or peristaltic infusion pumps, diffusion-controlled systems including reservoirs or matrix systems, chemically controlled systems composed of biodegradable or nonbiodegradable polymers, swelling-controlled systems and magnetically controlled systems [40,41].

We will distinguish between long-term systemic pulsatile drug delivery and long-term systemic sustained drug delivery.

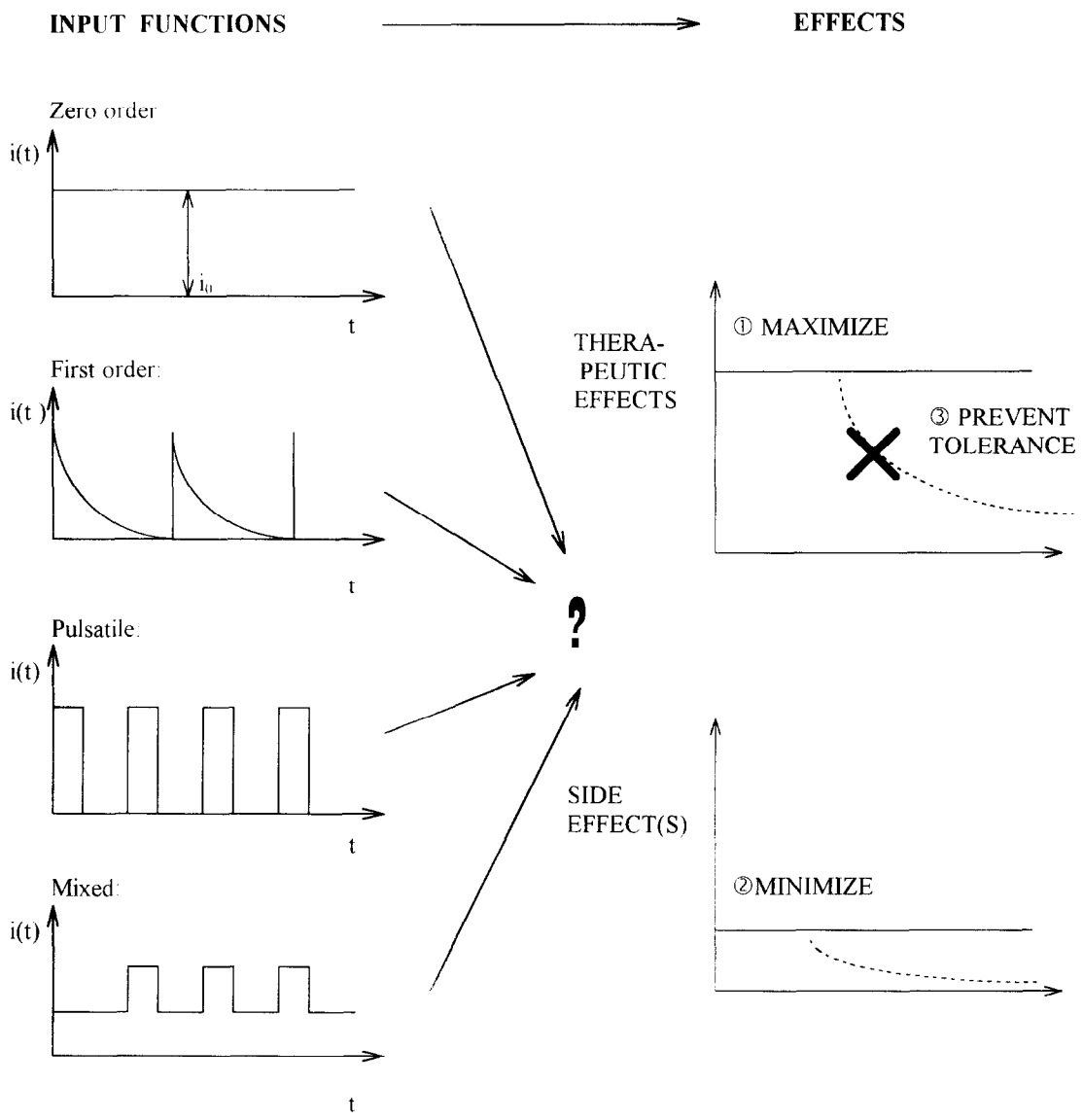

Fig. 1. The optimal input function for a given polypeptide drug (left side of figure) may be zero-order, first-order, pulsatile, mixed or some other wave form. It should produce effects which satisfy three pharmacodynamic criteria (right side of figure): (1) maximize therapeutic efficacy; (2) minimize side effects; and (3) prevent down-regulation (adapted from [25]).

3.1. Long-term pulsatile drug delivery

Intercellular communication often proceeds in a pulsatile, rythmic manner. An increasing number of hormones have been found to be secreted in a pulsatile manner into the circulation. The physiological efficiency of all these pulsatile signals appears to be closely related to their frequency [29]. For many therapies, especially those involving hormone replacement or supplementation, long-term pulsatile i.v. infusions, given at the physiologically appropriate pulse frequency, are required to mimic the endogenous secretory pattern, and treatments that do not imitate the endogenous program are unsuccessful [42]. For example, in the treatment of GH insufficiency, the hormone must be administered from infancy to late childhood, to enable them to reach normal height [30,43,44]. Some clinical trials report that more frequent GH injections result in higher growth rates than giving the same amount, but less frequently. In most cases it has been reported that

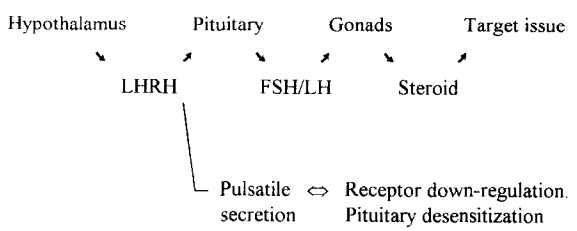

Fig. 2. Physiological and pharmacological state of LHRH analogues (adapted from [30]).

treatment with higher frequencies of application results in better biological utilization for a given dose. For some treatments, several daily injections have been used, but this therapeutic regimen is very risky to the patient without close medical supervision and also often difficult for most patient to accept. Thus, the commercial success of peptide drugs for some clinical applications will depend on the development of systems which could allow pulsatile administration and deliver precise doses of a drug at rates varying from low to high values over desirable time intervals [45].

The above considerations have led to the development of many new drug delivery systems [37,46,47] such as for example, multiple-pulse systems. These systems can be classified as follows: (i) systems releasing in response to physical changes (pH, temperature, ionic strength); (ii) systems releasing in response to chemical or enzymatic reactions [48]; and (iii) systems exhibiting periodic changes due to magnetism, ultrasounds or electricity. In the first cases, the principle of operation is a significant alteration of the phase diagram of polymer/water/drug with shifting towards the critical point. The result of this shift is a syneresis (collapse) of the polymer structure from an initial expanded structure, allowing the previously incorporated drug to be released during the phase separation changes. In the second cases, due to a chemical or enzymatic reaction, the polymer structure is altered significantly (usually by an increase of the pore size) and the incorporated drug is released. Alternatively, the chemical reaction may occur on a third substance, unrelated to the controlled release device, which may be affecting the swelling or structural characteristics of the polymer. In the last cases, release rates can be controlled ultrasonically, electrically (iontophoresis) or by using a magnetic oscillating field [49,50]. Magnetically triggered systems may be prepared from any polymer, in which there have been dispersed microbeads of a magnetic material and particles of the drug to be released. When the system is placed in a magnetic field, the magnetic beads begin to pulsate and micropores are formed. Due to the pulsation of the beads, release of the incorporated drug can be achieved through the pores. The process is reproductible, in the sense that the same field can produce the same rate of release [51]. The release rates from polymeric systems can also be affected by ultrasounds. Experimental evidence indicates that cavitation induced by the ultrasonic waves may be partially responsible for augmented polymer degradation and drug release. One of the goals of future research in magnetically and ultrasonically controlled release systems is to achieve a better understanding of the factors controlling release kinetics. Those already studied provide the ability to control release rates externally. However, actual clinical implementation will require still further in vitro and in vivo studies [52]. Iontophoresis can be described as a process which facilitates the transport of ionic species across the skin, by the application of electric current. The drug flux induced by iontophoresis may be controlled by manipulating the current density and the applied concentration of drug in the delivery system. An advantage of the iontophoretic drug delivery system is that a larger fraction of the drug contained within the reservoir can be delivered since the driving force is supplied by the applied electric field and not solely by the concentration gradient, as in passive delivery systems. The driving force is maintained as long as there is sufficient battery capacity. Transdermal delivery of drugs is usually painless, hence patient compliance should be excellent [42,53–57]. Among the iontophoretic delivery devices, a transdermal periodic iontotherapeutic system (TPIS) has been developed to provide a constant pulse current for either periodic or continuous programmed drug delivery [58].

A variety of pumps have also been developed for pulsatile drug delivery. For example, a device developed in Sweden (Zyklomat®, Ferring) has been used to deliver gonadorelin acetate in order to induce ovulation. The pump contains a 10 day supply and is active every 90 min for a 1 min duration, delivering on each occasion 50 μg of drug [37].

Research on absorption enhancers for transmucosal routes [59], especially the nasal [60], is also active.

3.2. Long-term sustained drug delivery

Most peptide drugs cannot produce their full therapeutic effects when administered by the parenteral route, owing to their extremely short-lived biological activity. Also, several repeated injections or continuous infusions are often required daily to produce an effective therapy, as for example, when the goals are down-regulation of physiological response to natural peptides or long term therapy with a hormone [61–63]. However, besides inconveniences, the primary drawback of multiple daily injections is the delay inherent in changing the basal drug concentrations. Therefore, in order to obtain a long-term, constant therapeutic effect, a controlled delivery system is desired to avoid repeated drug injections. A long-term controlled delivery system must serve two purposes: first, to release the drug continuously such as to avoid side effects arising from the multiple and high-dosage injections required to achieve desirable drug levels over a period of weeks or even months, and second to protect the drug from the body [7,64–66]. Some advantages of a controlled release formulation include increased patient compliance by reducing the number of injections, feasibility of treatment on pediatric or geriatric patients to whom other means of delivery would not be practicable, increased therapeutic benefit by eliminating the fluctuations in blood levels, and potentially lowering the total

amount of drug administered by reducing these fluctuations. Okada et al. [67] reported that the chemical castration caused by an injection of microspheres containing an LHRH analog can be equal or superior to that obtained by pulsatile daily injections of the analog solution. Another example of the usefulness of sustained delivery is that of somatostatin, where a subsequent immediate rebound of the therapeutic effect has been noted following withdrawal of the hormone and has been associated with a rapid rise in the target hormone. This rebound effect is, therefore, highly undesirable, particularly in situations where prolonged continuous activity is absolutely essential, and the phenomenon should be avoided as much as possible in cancer patients, since tumor growth should not be allowed [15]. Different approaches of controlled-release delivery systems have been explored, such as hydrogels, self-diffusion systems, porous membranes, pumps, liposomes and biodegradable polymer systems.

For the design of a system in which controlled release is provided by diffusion of the compound through the intact polymer, it is necessary to select a sufficiently hydrophilic carrier that offers appropriate diffusivity to the compound. Hydrogels are one class of polymers that meet this description [4]. The crosslink density of hydrogels provides a restricted aqueous environment for diffusional migration of the peptide, by controlling both the degree of hydratation and the permeability of hydrogels to peptides [65,68]. The greater the size of the peptide, the greater is the sensitivity of the diffusion coefficient to changes in crosslink density. Since the rate of diffusion of the drug in the unhydrated polymer is generally insignificant, the rate of diffusional drug release is determined by the rate of advancement of the water front. The rate of water access may be controlled by partially or completely coating the hydrophilic polymer core with a semi-permeable polymer [69]. Biodegradable hydrogels have also been tested, but their usefulness was limited by the fact that the crosslink density controlled the rates of both the hydrogel dissolution and the diffusional release of the incorporated drug. Only gels with a very low crosslink density dissolved within a reasonable time period, but such gels, by virtue of their highly porous structure, were unable to retain the entangled drug and rapid diffusional release occurred. An unusual example of a hydrogel delivery system is the use of the protein itself as a hydrated matrix for controlled release. This has been done for the controlled delivery of bovine somatotropin from a compressed pellet of the protein which has been partially coated to control the initial dissolution rate [65].

With self-diffusion systems, the release mechanism does not involve dissolution of the drug in the matrix or swelling of the polymer bulk as in the case of a hydrogel. Rather, it involves diffusion through aqueous channels created by the drug itself. Water soaks into the matrix, dissolving the peptide powder, which, once dissolved, leaves behind pores in the polymer matrix. Peptides are presumably diffused through water filled pores and thus, one would expect the relevant diffusion coefficient to be that of the peptide in water. However, the diffusion through porous media is retarded. Classically, this retardation is attributed to the 'tortuosity' of the medium, due to the randomness of the position of the pores. Potential limitations of the use of a self-diffusion system arise from the fact that the kinetics of drug release are typically not zero order and from the instability of many peptides in the concentrated aqueous solution which constitutes the pores of this type of device.

On the contrary, diffusion through a rate-controlling membrane allows construction of drug delivery devices that release the drug by zero order kinetics and where rate of delivery can be readily adjusted by changing the rate-limiting membrane and/or membrane thickness and area. The membrane serves as permeable barrier through which the drug must cross before reaching the blood stream [70]. A distinction can be made between porous membranes and other polymeric membranes. Porous membranes are defined as having stable pores, the size and distribution of which do not depend on the hydratation of hydrophilic polymer sequences (hydrogels) or the presence of hydrophilic drugs (self-diffusion systems).

Pumps can be distinguished from other diffusion-based systems in that the primary driving force for delivery by a pump is pressure difference rather than concentration difference of the drug between the formulation and the surroundings. The pressure difference can be generated by pressurizing a drug reservoir, by osmotic action, or by mechanical action. Pumps can be externally portable or implantable. The design requirements for implantable pumps are: (i) the system should be capable of maintaining a constant flow rate, and the fluid reservoir should be of sufficient size to obviate the need for constant refilling; (ii) post-implantation adjustment and refilling should be possible; and (iii) the reservoir must be small enough to be readily implanted and the pump must provide long-term tissue compatibility. For example, syringe pumps, which use a synchronous motor to drive the plunger, are among the earlier pump devices for continuous hormone delivery which do not depend on gravity for the energy of delivery. These pumps are still commonly used for oxytocin delivery [71], Table 3.

Liposomes, spherical vesicles formed when phospholipids are allowed to swell in aqueous media, have also been proposed to improve the delivery of peptides, by functioning as a 'microreservoir' for sustained release and/or as target-specific carriers. They consist of one or a number of concentric bilayers surrounding aqueous

Table 3
Examples of implant delivery systems for peptides from the hypothalamic pituitary axis

Publication year	Author	Peptide	In vivo duration	Delivery system	Carrier	Reference
1984	Kruisbank J	Vasopressin	8 weeks	Implants	Polypropylene	[41]
1984	Williams G	Goserelin	4 weeks	Implants	PLGA	[116]
1985,1989	Asano M	LHRH analog	16 weeks	Implants ø2/10 mm length	PLA, PLGA	[117,118]
1985,1992	Furr BJA	Goserelin	4 weeks	implants ø1/3–6 mm length	PLGA	[119,120]
1985	Asano M	LHRH analog	12 weeks	Implants ø2/10 mm length	PLGA	[87]
1985	Sanders LM	Nafarelin	23 weeks	Implants ø3 mm	PLGA	[121]
1986	Sanders LM	Nafarelin	36 weeks	Implants ø3/5 mm length	PLGA	[122]
1986	Yoshida M	LHRH analog	10 weeks	Implants ø11/0.6 mm thick	Diethyleneglycoldimethacrylate-polyethyleneglycoldimethacrylate	[123]
1986	Heller J	LHRH analog	20 weeks	Implants	poly(ortho ester)	[77]
1987	Hutchinson FG	Goserelin	4 weeks	Implants	PLGA	[79]
1987	Lemay A	LHRH	4 weeks	Implants	PLGA	[88]
1987	West CP	Goserelin	4 weeks	Implants ø1/3–6 mm length	PLGA	[124]
1987	Kaetsu I	LHRH	6–9 weeks	Implants	D,L PLA, Diethyleneglycoldimethacrylate-polyethyleneglycoldimethacrylate	[125]
1988	Davidson BWR	Nafarelin	1 year	Implants	HEMA, MMA	[68]
1989	Asano M	LHRH analog	20 weeks	Implants ø2/10 mm length	PLGA	[126]
1989	Waxman JH	Buserelin	8 weeks	Implants	PLGA	[127]
1990	Hutchinson FG	Goserelin	4–6 weeks	Implants	PLGA	[38]
1990	Fraser HM	Buserelin	6 weeks	Implants ø1.3/10 mm length	PLGA	[86]
1990	Burns R	LHRH analog	1 year	Implants ø3/10 mm length	silicone elastomer	[76,128]
1990	Iversen P	Goserelin	4 weeks	Implants ø1/3–6 mm length	PLGA	[129,130]
1991	Goldspiel BR	Goserelin	4 weeks	Implants	PLGA	[23]
1991	Asano M	LHRH analog	11 weeks	Implants ø2/10 mm length	PLA	[131]

phases. Hydrophilic or lipophilic drugs can be encapsulated in their aqueous or lipid phases, respectively. Liposomes can provide protection and reduce immunogenicity and other adverse side effects by acting as a 'depot' for the peptide drug at the injection site, the drug being released slowly as the liposomes are degraded by local hydrolytic enzymes. They can also offer the advantages of being biodegradable and nontoxic, and they can be prepared from naturally occurring phospholipids [45,72,73].

Polymeric delivery systems for long-term maintenance of therapeutic drug levels can be divided into two groups: those in which no residual material remains at the implant site at the end of the delivery period and those in which some non-degradable or non-absorbable material remains. Not surprisingly, biodegradable polymers are preferred because follow-up procedures pose various risk levels, and significant invasive procedures are both costly and worrying to the patient [74]. Non-degradable systems will also be more invasive to administer and may be more obtrusive once in place. In bioerodible and/or biodegradable systems, the drug may be distributed uniformly throughout a polymer in the same way as in the diffusion controlled systems, or incorporated in a polymeric structure. The difference, however, relates to the fact that while the polymer phase in diffusion controlled systems remains unchanged with time, the polymer phase in bioerodible and/or biodegradable erodes and/or degrades with time. As the polymer surrounding the drug is eroded,

the drug escapes [28]. The concept of a biodegradable controlled release system for a peptide is very attractive. It ensures the patient compliance and convenience needed, and also a closer control of administration by the physician. The device must however be totally reliable and no adjustment be needed during the delivery once the device is installed, [4].

4. Biodegradable controlled delivery systems

Controlled-release delivery systems are designed to maintain the drug concentration within the therapeutic range over the desired treatment interval, thus minimizing the undesirable situation of drug excesses occurring and ensuring that efficacy has not been compromised by drug deficiency before the next dose [71]. However, optimum dosage forms are difficult to develop. One means for controlling blood levels of a compound is to administer it in the form of a polymeric matrix that releases compounds as a function of polymer degradation and/or drug diffusion. A variety of polymers have been used for such applications, including polyacrylamide, hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA) and their copolymers [68,75], polydimethylsiloxane, ethylene/vinyl acetate copolymers, silicone elastomer [76] as non biodegradable polymers and polylactide, polyglycolide, poly(lactic acid-co-glycolic acid), poly(e-caprolactone), poly orthoesters [77,78], polycyanoacrylates as biodegradable polymers [79]. We will only deal with biodegradable systems which have an obvious advantage over mechanical or non biodegradable polymeric systems, such as long-lasting depot silicone elastomer implants, in that they only need to be originally implanted or injected, and not removed later [80]. Degradable polymers avoid this problem, but are more difficult to use. Release rates depend on many factors [81]:

- the physicochemical properties of the drug
- the core loading (percentage) of the drug in the device
- the homogeneity of the drug dispersion in the matrix
- the particle size of the drug in the system
- the rate of biodegradation and the stability of the polymeric matrix
- the affinity of the drug for the polymer
- the stability of the drug in the polymeric matrix before and after injection

Ideally, erosion should be confined to a narrow, advancing layer by ensuring that the rate of erosion is not less than the rate of aqueous penetration. Most of the peptide will then be protected from degradation and the rate of release will be determined solely by the peptide core loading, the geometry of the device and the rate of erosion. Poly(ortho esters) stem from investigations directed towards obtaining polymers exhibiting a release of the active principle following zero order kinetics. Many polymers can be expected to degrade in such a manner, although the matrices based on polylactides (PLA) and poly (D,L-lactide-co-glycolide) (PLGA) are those which have received most attention. Their long clinical use as surgical sutures demonstrates that they are biocompatible in physiological environments and degrade to toxicologically acceptable products that are eliminated from the body. Several peptides and proteins have been successfully incorporated into PLA and PLGA microspheres [82–85] and implants [86–88]. Actually, peptide release from these matrices occurs by a complex process in which channels capable of transporting large molecules which have low diffusitivity through intact polymer, are created by bulk degradation. A lowering of polymer molecular weight occurs immediately from the beginning. This degradation can decrease the rigidity of the polymer chain, which in turn can influence the pore structure and swelling of the matrix [89]. Degradation of PLGA proceeds by hydrolytic scission of ester groups, generating polymers containing one terminal carboxyl group per chain [90]. Depolymerization is affected by molecular weight, glycolide-lactide ratio, polydispersity and crystallinity, factors which can be used to control the release rate. For example, Sanders et al. [83] studied the influence of some of these factors on the release from microspheres of the copolymer containing the decapeptide nafarelin acetate [91].

The kinetic studies suggest that there are in vivo three phases of release: (1) a 'burst' or initial period of rapid release that occurs by diffusion of peptide close to the surface of the polymer; (2) a period of relatively minimal peptide release, during which the polymer is gradually hydrolyzed in bulk but has not yet decreased sufficiently in molecular weight to allow for increased diffusional release of the peptide; and (3) release of the remaining peptide after the molecular weight of the polymer is sufficiently low to allow its solubilization in the aqueous environment and the release of the peptide as the polymer is eroded away [45,92]. The three phases of release are illustrated in Fig. 3.Typically, the initial phase of release is controlled, for example, by drug

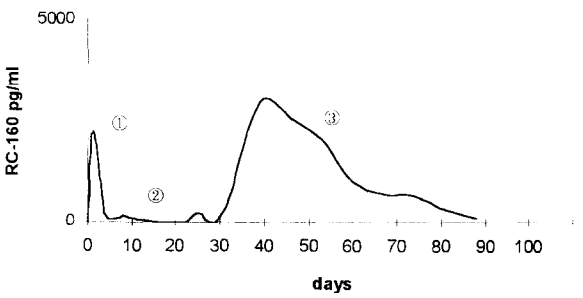

Fig. 3. In vivo release pattern in rats of a somatostatin analog, Vapreotide (50:50 PLGA implants: core loading: 7.5% [115]).

Table 4
Examples of microparticulate sustained delivery systems

Publication year	Author	Peptide	In vivo duration	Delivery system	Carrier	Reference
1984	Redding TV	D-Trp LHRH	4 weeks	Microcapsules	PLGA	[132]
1985	Asch RH	D-Trp LHRH	4 weeks	Microcapsules	PLGA, polyalkylcyano-acrylate	[133]
1985	Mason-Garcia M	D-Trp LHRH	4 weeks	Microcapsules	PLGA	[134]
1985	Ogawa Y	Leuprolide	5 weeks	Microcapsules	PLGA	[21]
1985	Parmar H	D-Trp LHRH	4 weeks	Microcapsules	PLGA	[135]
1985	Schally AV	LHRH analog	14 weeks	Microcapsules	PLGA	[136]
1986	Ezan E	LHRH analog	4 weeks	Microcapsules	PLGA	[137]
1987	Maulding HV	lys-8vasopressin	7 weeks	Microcapsules	PLGA	[81]
1987	Okada H	Leuprolide	4 weeks	Microcapsules	PLGA	[138]
1987	Tice TR	LHRH analog	13 weeks	Microcapsules	PLGA	[139]
1988	Ogawa Y	Leuprolide	4 weeks	Microcapsules	PLA, PLGA	[140]
1988	Sanders L	Nafarelin	8 weeks	Microcapsules	PLGA	[141]
1988	Bokser L	RC-160	1–2 weeks	Microcapsules	PLGA	[142]
1988	Mason-Garcia M	RC-160	4 weeks	Microcapsules	PLGA	[143]
1988	Mason-Garcia M	RC-160	4 weeks	Microcapsules	PLGA	[144]
1989	Bokser L	D-Trp LHRH	4 weeks	Microcapsules	PLGA	[145]
1989	Zalatnai A	D-Trp LHRH	4 weeks	Microcapsules	PLGA	[146]
1991	Korkut E	D-Trp LHRH	8 weeks	Microcapsules	PLGA	[147]
1992	Redding TW	LHRH analog	6 weeks	Microcapsules	PLGA	[148]
1994	Pinski J	RC-160	n.a.	Microcapsules	PLGA	[149]
1994	Betoin F	RC-160	1 week	Microcapsules	PLGA	[150]
1995	Cleland JL	GH	6 weeks	Microcapsules	PLGA	[151]
n.a.	Tice TR	D-Trp LHRH	4 weeks	Microcapsules	PLGA	[152]
n.a.	Kent JS	Nafarelin	12 weeks	Microcapsules	PLGA	[153]
1984	Sanders LM	Nafarelin	4 weeks	Microspheres	PLGA	[83]
1984	Williams G	Goserelin	4 weeks	Microspheres	PLGA	[116]
1985	Sanders LM	Nafarelin	4–12 weeks	Microspheres	PLGA	[102,154]
1987	Hutchinson FG	Goserelin	7 weeks	Microspheres	PLGA	[79]
1987	Tice TR	LHRH	4 weeks	Microspheres	PLGA	[106]
1988	Burns R	Nafarelin	8 weeks	Microspheres	n.a.	[155]
1988	Dunn RL	Nafarelin	12 weeks	Microspheres	PLGA	[156]
1988	Kissel T	LHRH analog	n.a.	Microspheres	PLGA	[157]
1988	Sanders LM	Nafarelin	7 weeks	Microspheres	PLGA	[141]
1989	Waxman JH	Buserelin	8 weeks	n.a.	PLGA	[127]
1989	Okada H	Leuprolide	4 weeks	Microspheres	PLGA	[67,158]
1990	Burns RA	Nafarelin	8 weeks	Microspheres	PLGA	[159]
1990	Sharifi R	Leuprolide	4 weeks	Microspheres	PLGA	[160]
1990	Wolterink G	ACTH analog	3 weeks	Microspheres	PLGA	[161]
1991	Bodmer D	Octreotide	6–7 weeks	Microspheres	PLGA	[162]
1991	Heya T	TRH	4 weeks	Microspheres	PLGA	[163]
1991	Okada H	Leuprolide	4–6 weeks	Microspheres	PLGA	[164,165]
1991	Ruiz JM	Triptorelin	4 weeks	Microspheres	PLGA	[85]
1992	Hashimoto T	TRH	3–4 weeks	Microspheres	PLGA	[166]
1993	Heron I	Somatostatin analog	4 weeks	Microspheres	PLGA	[167]
1993	Miyamoto M	TRH	3 weeks	Microspheres	PLGA	[168]
1994	Okada H	Leuprorelin	12 weeks	Microspheres	PLGA	[82,169]
n.a.	Vickery BH	Nafarelin	7 weeks	Microspheres	PLGA	[13]

loading, drug polymer morphology and matrix geometry whereas the second and third phases depend on the degradation properties of the polyester [79].

Especially interesting for sustained delivery of peptides are rod-like structures of diverse sizes and forms obtained by various manufacturing techniques, and microparticulate or even nanoparticulate systems, Table 4.

A novel implant system has also been developed that may be injected as a liquid and subsequently solidify in situ. This injectable implant system is comprised of a water insoluble biodegradable polymer dissolved in a water miscible biocompatible solvent. Upon intramuscular or subcutaneous injection into an aqueous environment, the biocompatible solvent diffuses out of the

Table 5
Advantages and disadvantages of implants and microparticulate-systems

	Advantages	Disadvantages
Implants	Can eventually be removed.	Require a trochar or surgical incision for administration.
	Prepared by extrusion or melt-pressing technique, so mixing and shaping treatment between polymer and drug are performed without use of organic solvent.	Need high temperatures for preparation by extrusion or melt pressing techniques.
Microparticulate systems	Flexible route of administration (parenteral, oral, nasal, buccal,...).	Can not be removed, potential for catastrophic release [81].
	Great surface allows higher release rates if desired.	Need mostly the use of organic solvent for the preparation. Should be administered immediately following suspension to avoid degradation of the matrix material.

polymer while water diffuses into the polymer matrix. Due to the polymer's water insolubility, the polymer coagulates or precipitates upon contact with water thus, resulting in a solid polymeric implant. The release characteristics of compounds from these injectable implant systems are analogous to those reported for implant systems prepared ex vivo [40].

Microparticles consist of a multiplicity of small spherical particles less than 200 μm in diameter. Particle sizes of 50–100 μm are preferred. The nomenclature of microparticulate systems is not universally accepted and to avoid confusion three micro-morphologies should be distinguished: microcapsules are reservoir-systems consisting of a drug containing core coated by a rate-controlling biodegradable membrane. Microspheres or microparticles are monolithic systems consisting of a polymeric matrix in which the drug substance is either dispersed or dissolved, depending on its solubility [93].

Nanoparticles are submicronic (< 1 μm) polymeric systems. According to the process used for the preparation of nanoparticles, nanospheres or nanocapsules can be obtained. There are only a few examples of incorporation of peptides into nanoparticles [94–99]. This is probably because these technologies are more complex and are difficult to implement under physicochemical conditions needed for peptide stability [49].

Implants and microparticles have both advantages and disadvantages which are summarized in Table 5.

5. Difficulties with peptide formulations

The process to produce a slow-release formulation for a peptide is difficult and depends on many factors. Some important parameters must be considered, such as the peptide, the polymeric carrier, time for optimal release and the process used (i.e. for microspheres: spray-drying, solvent evaporation or phase separation, residual solvents; for implants: extrusion or compression moulding).

5.1. Influence of the peptide

The physicochemical properties of many peptides make it difficult to obtain satisfactory formulations, in particular since inactivation is possible during their incorporation into the release system. Several environmental factors are known to affect peptide stability: pH, organic acids, ionic strength, metal ions, detergents, heat, light, pressure, agitation, moisture, adsorption and/or interaction with excipients [43]. The stability of peptides in solution varies widely. Certain peptides tend to undergo self-association resulting in the formation of dimers or multimers, aggregation or changes in conformation. Peptides may also cause special difficulties in their handling, especially because most of them have a significant hydrophobic component and thus, have a tendency to adsorb onto surfaces such as glass and plastic. Such adsorption can lead to significant losses in the amount of material available for delivery [37]. In addition, the amount of drug to be incorporated into the delivery system is dependent on the peptide. For example, a drug delivery system for somatostatin or its analogs, must support a high core loading to deliver relatively high doses of drug required to maintain the drug levels sufficiently high to suppress GH [15], whereas for LHRH or its analogs, the doses needed for therapeutic effect do not need to be as high. An estimate of the clinical dose is thus, essential, since this will define some boundaries of possibility in the design of a controlled release system. Chronic administration of some hormone agonists did result in an initial period of stimulation of the target. This can be overcome by giving during this period a drug which can inhibit this first effect. For LHRH, the initial flare-up in the first few days of treatment of potent analogs may cause transient androgen stimulation, and possibly result in the exacerbation of the disease-related symptoms. It has been suggested that combined therapy with antiandrogens, such as cyproterone acetate and flutamide, may reduce the problems by suppressing the initial phase of stimulation of LHRH agonists [63,67].

5.2. Influence of the polymer carrier on drug release profiles over a prolonged period

Controlled diffusion through a matrix or membrane may not be appropriate for a high molecular weight polypeptide. In order for the drug to diffuse through the polymer, it must have some solubility in the high molecular weight polymeric carrier. This is often the case for low molecular weight drugs but not for polypeptides. There is an approximate log–log correlation between molecular weight (MW) and diffusion coefficient (D) where $\log D = a - b \log MW$ such that D decreases when MW increases. Consequently, the choice of the polymeric matrix is very important. With PLA or PLGA, the rate of degradation will be a critical factor in determining transport of the high molecular weight polypeptide from the dosage form [90]. For these polymers, the rate of release depends on the rate of degradation which in turn depends on molecular weight, lactide-glycolide ratio, crystallinity and core loading [89]. For some indications, the problem with sustained release formulations is to avoid or minimize the burst effect. The initial drug-burst can be beneficial in some therapeutic applications since the high initial release ensures a prompt effect, which can be subsequently maintained for prolonged periods by a relatively slower, but continuous release of the peptide [100]. But, this is certainly not true for all peptides, and a high initial burst can lead to severe side effects [93].

5.3. Influence of the process employed

The characteristics of the polymer may influence the manufacturing process directly or indirectly by influencing one or more process variables. These variables appear to have the greatest potential for modulating the peptide release profile. For example, the kind of polymer selected as carrier will influence the choice of a solvent for the preparation of microspheres or the temperature for an extrusion process. Susceptibility of peptides to thermal inactivation can seriously limit the range of methods that can be used for the manufacturing of the delivery system [43]. Furthermore, a sterilization process after manufacturing, or an aseptic manufacturing process are also required for an injectable product. This is a major problem because sterilization often influences the performance of the release system. In some cases, the sterilization process may lead to denaturation of the peptide. If a molecule is large enough to exhibit a tertiary structure, this structure will probably be altered and the compound denatured by autoclaving. Therefore, γ irradiation for terminal sterilization is frequently used [4]. However, this process is known to reduce the MW of the polymeric carrier, for example in the instance of the polylactide-co-glycolide polymer, and therefore the kinetics of release of the drug [101,102]. It was found that with γ irradiation, minimal changes occurred when the dose was limited to 2.5 Mrad or less [43].

The tissue damage caused by the injection process could contribute to the initial burst effect, by increasing the local blood flow. However, no evidence of this increased blood flow is at this time available.

Pharmaceutical aspects such as good manufacturing practice regulations, validation of excipients, processes and equipment and an appropriate infra-structure for parenterally applied dosage forms have also to be taken into account to ensure reproducible manufacture [93].

Another problem common to the development of all controlled release systems is that of the timeframe of development being directly related to the duration of release required. For example, if a 3 months system is under study, every screening of a candidate formulation will take up to 3 months to determine its performance. The variability in release kinetic also increases with target duration of release. These factors all contribute to the strategic decision on optimal duration of the system, longer not always being preferred [4].

6. Conclusion

In the near future, numerous new polypeptide drugs will surely emerge and it is easy to predict that the current interest in the development and application of polypeptide drugs will continue. This can be illustrated by the growing number of patents dealing with sustained delivery systems for peptides or proteins [20,103–114].

As shown in this review, for chronic therapy and in the absence of non-parenteral alternatives, various sustained-release depot formulations for hypothalamic pituitary hormone analogs are at different stages of development. An universal delivery system for peptides is neither possible nor perhaps desirable. The appropriate delivery system for a particular peptide will indeed depend upon the physical and chemical nature of the agent being delivered, its clinical application, and the site and mode of action within the body. The types of carriers being considered for controlled delivery application vary largely and comprise also a wide range of biological response modifiers.

Although some biodegradable polymers have very interesting degradation properties, PLA and PLGA will probably still be the polymers of choice in the near future, as they have already been approved by the regulatory authorities. Other polymers, such as poly(ortho esters) or poly(ε-caprolactone), still require investigations concerning toxicological and immunological aspects. A goal will be to develop polymeric systems that erode homogeneously even at high drug loadings, that are non toxic and that will not interfere with the

incorporated peptides. The development of such delivery systems will allow greater flexibility in treatment regimens, but remains a challenging problem.

Domains for further research include pulsatile delivery, which may be essential for proper efficacy of some compounds and self regulated, or physiologically responsive systems. Methods for self-regulating delivery, responsive to biological needs, are still in an exploratory stage.

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