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Nova geração de fármacos utilizados na terapêutica antidiabética com base na utilização farmacológica da albumina

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Abbreviations

BSA - Bovine Serum Albumin

DPP-IV - Dipeptidyl peptidase-IV

GLP-1 - Glucagon-Like Peptide-1

HbA1c - Glycated Haemoglobin A1C

HSA - Human Serum Albumin

NPs - Nanoparticles

PK - Pharmacokinetic

$t_{1/2}$ - Half-life time

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Abstract

Ever since insulin was discovered by Banting and Best in 1921, all further researches in this field have been conducted with one goal: to find new insulin molecules which provide better glycemic control with fewer side effects.

Albumin is one of the most extensively studied endogenous proteins which are used in the fabrication of drug delivery and diagnostic technologies during the last ten years. Also, over the past decades, albumin has emerged as a versatile carrier for therapeutic and diagnostic agents, primarily for diagnosing and treating diabetes, cancer, rheumatoid arthritis and infectious diseases. An increasing number of albumin-based or albumin-binding drugs are in clinical trials.

The binding property of albumin can be exploited to develop a method of attaining a longer half-life for small proteins and peptides thus being used as protein carrier to improve the pharmacokinetic profile of the drug or to target the drug to the pathogenic site addressing diseases with unmet medical needs.

Coupling drugs to albumin, conjugation with proteins and encapsulation of drugs into albumin nanoparticles are three strategies in development and with great relevance in anti-diabetic therapeutics.

Key words: albumin; diabetes; conjugation; nanoparticles; half-life.

I. Introduction

For type I diabetes mellitus an ideal antidiabetic therapeutic conveniently uses a method to control blood glucose, without multiple daily insulin injections, that is suitable for all patients, requires no major operative procedure or intervention, is affordable for all patients and requires no or only minimal immunosuppressive therapy (Holz & Chepurny, 2003).

Moreover, among the growing population of individuals with type 2 diabetes mellitus many patients are failing to meet glycemic targets and are therefore at increased risk of complications. Achieving tight glycaemic control remains an unmet need for many of these patients, despite improved treatments (Ahren & Burke, 2012; Freeman, 2009).

To meet glycaemic targets, attempts have been made to improve existing drugs and to develop new classes of drugs.

Scientific literature describing the biological importance of incretin peptides and dipeptidyl peptidase-4 inhibitors in the control of glucose homeostasis has been reviewed (Drucker, 2003). Recent advances include insulin analogues, that more closely mimic physiologic insulin levels, and incretin-based therapies, which capitalize on the glucoregulatory properties of native GLP-1 (Ahren & Burke, 2012). The engineering of this insulin analogues represents a triumph of structure-based protein design (Berenson et al, 2011).

However the therapeutic applicability of a biologically active peptide depends on the possibility of delivering it at its site of action with a suitable time-profile. Peptide and protein drug delivery is associated with several problems. For example, peptides must in general be administered by injection because they are susceptible to enzymic breakdown and because they penetrate poorly through mucosal membranes. Furthermore, most peptides have a short half-life within the circulation and must be gradually released into the bloodstream to have a sustained effect (Kurtzhals et al, 1995).

The expanding field of preclinical and clinical drug applications and developments uses albumin as a protein carrier to improve the pharmacokinetic profile of the drug or to target the drug to the pathogenic site (Elsadek & Kratz, 2012).

II. Brief outline about diabetes mellitus

Diabetes mellitus is a metabolic disease caused by a lack of insulin production in the islets of Langerhans in the pancreas (type 1 diabetes) or insulin resistance (type 2 diabetes) (Elsadek & Kratz, 2012).

In healthy individuals, endogenous insulin secretion can be classified as basal, which provides basal glucose homeostasis, and stimulated, as a response to a meal (Mitrovic et al, 2006). In a subject with a healthy pancreas, basal insulin is continuously released at low levels in response to hepatic glucose output, while prandial insulin is released intermittently in response to elevated glucose levels following a meal. Within seconds of food ingestion, there is an initial release of insulin, which peaks in 1 to 2 minutes and lasts about 10 minutes. In a second phase, which lasts 1 to 2 hours, until normoglycemia is restored, insulin is released of newly manufactured insulin (Freeman, 2009).

The type 1 diabetes mellitus results from the autoimmune destruction of insulin-producing β-cells of the pancreas. There is no cure for type 1 diabetes mellitus, only insulin therapy. Injectable insulin preserves life but perfect glucose control is difficult to achieve and chronic hyperglycemia-associated systemic damage takes its consequences (Holz & Chepurny, 2003). In this context fast-acting analogues are essential for the management of type 1 diabetes mellitus (Berenson et al, 2011).

Type 2 diabetes mellitus is characterized by progressive loss of pancreatic β-cell function and insulin resistance that usually occurs with advancing age, inactivity, and weight gain. The disease accounts for substantial morbidity and mortality from adverse effects on cardiovascular risk and disease-specific complications (Nam et al, 2012). Achieving tight glycaemic control remains an unmet need for many patients with type 2 diabetes (Ahren & Burke, 2012). In type 2 patients, controllable by either prandial or basal analogues alone, basal regimens are preferred to their simplicity and reduced risk of weight gain (Berenson et al, 2011).

Insulin is normally secreted into the blood from the pancreatic β-cells ate low basal rate in the fasting state and at a higher rate in response to the postprandial increase in the blood glucose level. To mimic the normal pattern of insulin release, a combination of rapid-acting and long-acting insulin preparations is used in the most intensive treatment of diabetes (Kurtzhals et al, 1995). Therefore, products in current clinical fall into two classes, rapid-acting analog formulations, intended for bolus injection before meals, and basal analog formulations, intended for once-a-day injection (Berenson et al, 2011).

The final goals of an insulin therapy are the achievement of glycemic control and minimization of hypoglycemia and weight gain risks (Freeman, 2009).

GLP-1 and glucose-dependent insulinotropic peptide (GIP), two incretin hormones, exert important effects on β-cells to stimulate glucose-dependent insulin secretion and to regulate their proliferation and cytoprotection. Also, GLP-1 inhibits gastric emptying, glucagon secretion and food intake (Drucker, 2003). Moreover, GLP-1 exerts additional glucose-lowering actions in patients with diabetes mellitus already treated with metformin or sulfonylurea therapy (Baggio & Drucker, 2002).

However, native peptide, GLP-1, is rapidly degraded by the enzyme DPP-IV after parenteral administration. Hence, degradation-resistant, long-acting GLP-1 receptor agonists are preferable agents for the chronic treatment of human diabetes. Alternatively, inhibition of DPP-IV-mediated incretin degradation represents a complementary therapeutic approach (Drucker, 2003).

The potential for GLP-1 therapy to prevent deterioration of β-cell function or DPP-IV inhibitors therapy to potentiate incretin action is exemplified by studies. Demonstrations show that GLP-1 analogues stimulate proliferation and neogenesis of β-cells and DPP-IV inhibitors prevent degradation of GLP-1 and glucose-dependent insulinotropic peptide (Baggio & Drucker, 2002). Hereupon, considerable efforts toward the development of GLP-1–based agonists, for pharmaceutical administration, have been made (Kim et al, 2003).

III. Albumin and its characteristics

Albumin has the greatest abundance among plasma proteins in the blood stream, which is the main reason for its role as the most versatile transport protein in the blood circulation (Elsadek & Kratz, 2012).

The human serum albumin as the most abundant protein in the body with approximately 1/2 kg being distributed between the blood circulation, the lymphatic system and the extracellular as well as intracellular compartments already represents a blockbuster drug (Elsadek & Kratz, 2012). This protein has also a $t_{1/2}$ of nineteen days in humans, which is much greater than the $t_{1/2}$ of some short-lived regulatory peptides (Dennis et al, 2002; Kim et al, 2003).

Albumin is quantitatively the most important transport protein in plasma and can act as a submajor antioxidant in extracellular fluids (Galliano et al, 1998). It serves to maintain plasma pH, contributes to colloidal blood pressure, functions as carrier of many metabolites

and fatty acids, and serves, as already mentioned, as a major drug transport protein in plasma (Dennis et al, 2002).

This versatile protein carrier for drug delivery has been shown to be nontoxic, non-immunogenic, biocompatible and biodegradable. Therefore, it is the ideal material to fabricate nanoparticles for drug delivery (Elzoghby et al, 2012). Moreover, because albumin is a multifunctional transport protein that binds reversibly a wide variety of endogenous substances and drugs its binding property can also be exploited to develop a method of attaining a longer half-life for small proteins and peptides (Kurtzhals et al, 1995). This latest strategy consists in binding a therapeutic peptide or protein covalently or physically to albumin to enhance its stability and therefore its $t_{1/2}$ (Kratz, 2008).

IV. The impact of albumin on drug delivery

Over the past decades, albumin has emerged as a versatile carrier for therapeutic and diagnostic agents, primarily for diagnosing and treating diabetes, cancer, rheumatoid arthritis and infectious diseases (Elsadek & Kratz, 2012).

Albumin is playing an increasing role as a drug carrier in the clinical setting. Principally, three drug delivery technologies can be distinguished: coupling of low-molecular weight drugs to exogenous or endogenous albumin, conjugation with bioactive proteins and encapsulation of drugs into albumin nanoparticles (Kratz, 2008).

Noncovalent association with albumin has been shown to extend the $t_{1/2}$ of short lived proteins, therefore the binding property of albumin can be exploited to develop a method of attaining a longer $t_{1/2}$ for small proteins and peptides (Dennis et al, 2002). This can be achieved by the administration of a prodrug which is then allowed to bind to albumin in the circulation. The therapeutic efficacy of albumin-protein conjugates, via covalent and noncovalent attachment, has been demonstrated for a number of proteins (Choi, 2007). Accordingly, peptide binding to albumin has been used to improve the PK properties of several smaller proteins, including insulin (Kim et al, 2003).

Although the covalent linkage of peptides or protein drugs to HSA greatly prolongs their lifetime in vivo, is pharmacologically irrelevant when it irreversibly inactivates them. Therefore is crucial to retain the drug bioactivity (Shechter et al, 2005).

Albumin is also an ideal material to fabricate nanoparticles for drug delivery. For this reason albumin nanoparticles have gained considerable attention owing to their high binding

capacity of various drugs and being well tolerated without any serious side-effects (Elzoghby et al, 2012).

In addition, albumin is an always-found component in the plasma protein corona, formed as a result of the competition between proteins for the nanoparticle surface. It is shown that the preformed albumin corona, serving as a protective coating for NPs, is able to inhibit the plasma proteins adsorption, prolong the circulation time and reduce the toxicity (Peng et al, 2013).

V. Albumin *proprieties* on therapeutic strategies for diabetes treatment

a) Nanoparticulate carrier for oral insulin delivery

Protein nanoparticulate systems are of advancing importance owing to their modifiable functionalities and potential applications in various biological fields. The customizable nature of proteins also makes them outstanding carriers as target-specific delivery systems. Protein nanoparticles prepared using albumin is one covered area (Yewale et al, 2013).

According to a number of preformed studies it is shown the benefits of using albumin as a drug delivery system.

In one performed study, surface-modified albumin nanoparticles were prepared from two poly(ethylene glycol)-HSA conjugates. Compared with unmodified nanoparticles, the slower release of Rose Bengal (the model drug used for encapsulation) from the surface-modified HSA nanoparticles in the presence of the enzyme suggested that the existence of a steric hydrophilic barrier on the surface of the nanoparticles made digestion of the nanoparticles more difficult (Lin et al, 2001).

In one other example, the effect of nanoparticulate delivery system on enhancing insulin permeation through intestinal membrane was evaluated using multilayered nanoparticles encapsulating insulin within a core coated with albumin. Albumin was applied to the nanoparticles as outermost coat to protect insulin through shielding from proteolytic degradation. Outcomes showed that albumin layering is important toward improving insulin transport across the intestinal membrane, possibly by stabilizing insulin in the intestinal conditions. Transcellular permeation was evidenced by internalization of independently labeled insulin and nanoparticles into enterocytes, in which insulin appeared to remain associated with the nanoparticles (Woitiski et al, 2011).

Another preformed study had the aim to characterize and evaluate a novel oral insulin nanoparticulate system based on alginate-dextran sulfate core, complexed with a chitosan-polyethylene glycol-albumin shell. Nanospheres showed to increase insulin plasma level and to improve glycemic response to an oral glucose overload. They strongly adhered to villus apical enterocytes and markedly labeled Peyer's patches. The outcome allows to conclude that nanospheres preserve insulin and exert an antidiabetic effect after oral administration, which is explained by the protective effect against proteolytic enzymes by the albumin coating, by the mucoadhesive properties of chitosan-polyethylene glycol and by the possibility of chitosan reversibly altering tight junctions leading to an improved absorption of insulin (Reis et al, 2008b).

In another example of produced insulin albumin-chitosan-coated alginate nanospheres, outcomes showed a reduction of glycemia to approximately 72% of basal values. Albumin served as an important enteric coating providing acid and protease protection enabling uptake of active drug following oral dosage (Reis et al, 2008a).

Finally, in a different preformed study nanoparticles with 396 nm mean diameter were coated with albumin. They resulted in negatively charged nanoparticles which retained insulin bioactivity and enhanced pharmacological availability by shielding insulin from enzymatic degradation and through chemical and physical facilitation of permeation through the intestinal membrane (Woitiski et al, 2010).

b) New era of insulin analogues and incretin-based therapies

GLP-1 analogues are a new class of oral glucose-lowering drugs that mimic the endogenous peptide hormone, GLP-1 (Waugh et al, 2010).

Due to the susceptibility of therapeutic peptides to degradation by peptidases, lack of bioavailability and distribution to the target site, recent efforts have concentrated on improving their PK profile making use of the albumin-binding strategies (Elsadek & Kratz, 2012).

To meet the requirement for a constant basal supply of the hormone, diabetic patients receive daily subcutaneous injections of long-acting insulin suspensions (Kurtzhals et al, 1995). However, once daily injection of existing intermediate/long-acting insulin preparations does not provide a 24-hour basal insulinemia in most patients. High variability, pronounced insulin peaks, and a high risk of nocturnal hypoglycemia only poorly simulate normal physiology. Therefore the modification of the insulin molecule to modulate its PK

and pharmacodynamic properties represents a pioneering triumph of rational protein design (Berenson et al, 2011; Rosskamp & Park, 1999).

As mentioned before, albumin is an abundant natural drug carrier that has been used to improve the $t_{1/2}$, tolerability and efficacy of a number of bioactive agents. In this sense albumin technologies are being used to prolong duration of action of therapies for diabetes (Ahren & Burke, 2012). The protraction of action of insulin analogues is due to its binding with serum and interstitial albumin and subsequent slow release (Brunetti, 2001).

Drugs can either be bound physically or covalently through a ligand or protein-binding group to HSA (Elsadek & Kratz, 2012). Owing to the restricted passage of albumin-drug complexes across membranes, the PK parameters of many drugs can be altered by modification of their affinity for albumin (Kurtzhals et al, 1995).

Market approved products for treating diabetes include fatty acid derivatives of human insulin or the GLP-1 (Levemir® and Victoza®) and an antidiabetic Exendin-4 analog bound to recombinant human albumin (Elsadek & Kratz, 2012).

c) Preformed albumin corona, a protective coating for nanoparticles based drug delivery system

It is well known that the small size of nanoparticles confers it some beneficial properties, like the improved solubility, the lower dose and the enhanced bioavailability. But it is also the small size that confers nanoparticles a very large surface-to-volume ratio and thus leads to some undesired results after entering the body (Peng et al, 2013).

The ability of NPs to adhere and penetrate cell membranes was shown to depend on their physical properties, including size, surface composition and surface charge (Treuel et al, 2013).

In the biological fluid proteins associate with nanoparticles and the amount and presentation of the proteins on the surface of the particles leads to an *in vivo* response. Proteins compete for the nanoparticle surface, leading to a protein "corona" that largely defines the biological identity of the particle (Cedervall et al, 2007). The protein corona that thereafter replaces the original NPs becomes what the organs and cells really see (Peng et al, 2013).

Consequently, the in vivo fate of NPs and the biological responses to the NPs are changed. This is one substantial reason for the two main problems of the nanoparticles

based drug delivery system, i.e. nanotoxicity and rapid clearance of NPs from the blood after intravenous injection (Peng et al, 2013).

The inhibition of plasma proteins adsorption onto the NPs may be an effective strategy to solve the above problems. One optimal protein is needed to interact with nanoparticles and form a pure protein corona in advance (Peng et al, 2013).

Due to its high abundance in the organism, albumin is almost always observed on particles and may be retrieved even if it has relatively low affinity (Cedervall et al, 2007). The preformed albumin corona, serving as a protective coating for NPs, is able to inhibit the plasma proteins adsorption, prolong the circulation time and reduce the toxicity (Peng et al, 2013).

In a preformed study its demonstrated the successful application of the preformed albumin corona in inhibiting the plasma proteins adsorption and decreasing the complement activation, and ultimately in prolonging the blood circulation time and reducing the toxicity of the polymeric PHBHHx (Poly-3-hydroxybutyrate-co-3-hydroxyhexanoate) nanoparticles. Pre-forming albumin corona has a great potential to be a versatile strategy for optimizing the NPs based drug delivery system. The study outcomes show that bovine serum albumin corona has substantial effect on the physicochemical properties of nanoparticles (Peng et al, 2013).

Another existing problem is caused by the alteration of certain proteins' conformation and function following adsorption onto the NPs, finally resulting in the toxicity. Therefore the potential toxicity of nanoparticles is a great issue needing to address for safe drug delivery. In addition, the exposure time of particles to cells also has a substantial influence on the cell viability, which is lower for the longer exposure time in general (Peng et al, 2013). These phenomena occur because NPs are of similar size to typical cellular components and can efficiently intrude living cells by exploiting the cellular endocytosis machinery, resulting in permanent cell damage (Treuel et al, 2013). Hereupon, it is also shown in this study's results that the cytotoxicity difference between NPs and NPs-BSA is significant on various occasions and cytotoxicity of NPs can be substantially reduced in the presence of BSA corona (Peng et al, 2013).

Also, the study outcomes show that blood circulation time of nanoparticles is significantly prolonged in the presence of the BSA corona suggesting that the BSA corona plays an important role in protecting NPs from the rapid clearance. Moreover the NPs-BSA complex shows an enhanced bioavailability compared to the naked NPs (Peng et al, 2013).

VI. Developments and market approved technologies

<u>Levemir®</u>

Insulin detemir - Levemir® - from Novo-Nordisk, is a long-acting insulin analogue indicated for use as basal insulin therapy in patients with type 1 or type 2 diabetes mellitus. This is an albumin-binding derivative of human insulin (Elsadek & Kratz, 2012).

The protracted action of insulin detemir is explained by increased self-association and reversible binding to albumin, which slows its systemic absorption from the injection site (Keating, 2012). The C-terminal amino acid threonine in recombinant human insulin is replaced by a lysine moiety, and myristic acid is then covalently bound to its ε-amino group. This insulin analog stimulates the insulin secretion in pancreatic cells in a glucose-dependent manner (Elsadek & Kratz, 2012).

Determir has been shown to have modest advantages in terms of hypoglycaemia, especially nocturnal (Waugh et al, 2010).

After the subcutaneous injection, the $t_{1/2}$ of Levemir® is extended from 4 to 6 minutes for native human insulin to 5 to 7 hours for Levemir® and one subcutaneous injection per day is sufficient to normalize the blood glucose level.

This is the only long-acting insulin that remains soluble both before and after injection and does not form microprecipitates or crystals (Elsadek & Kratz, 2012).

Levemir® has already developed into a blockbuster since its market approval in 2004 (Kratz & Elsadek, 2012).

<u>Victoza®</u>

Liraglutide is an albumin-binding derivative of GLP-1, developed by Novo-Nordisk, for treatment of type 2 diabetes. The peptide hormone is derivatized in the GLP-1 peptide sequence (Elsadek & Kratz, 2012). Its prolonged effects result from the substitution of lysine for arginine 34 and the addition of a glutamic acid and a 16 carbon fatty acid chain to the lysine 26 residue of native GLP-1 (Nonogaki & Suzuki, 2013).

As already been mentioned, GLP-I is a glucose-dependent hormone, stimulator of pancreatic β-cell function, which favours the efficient control of blood glucose homeostasis (Green et al, 2004).

Liraglutide is stable against metabolic degradation due to albumin binding and has a plasma half-life of 11–15 hours after subcutaneous administration making it suitable for once daily administration (Elsadek & Kratz, 2012).

It targets β-cells, allowing for increased and prolonged insulin secretion concomitantly regulating blood sugar levels. It also lowers body weight and only has mild and transient side effects, mainly gastrointestinal disorders (Elsadek & Kratz, 2012).

<u>Albumin-modified exendin-4 conjugate</u>

ConjuChem Biotechnologies, Inc. is developing an *ex vivo* synthesized albumin conjugate of the peptide Exendin-4, for treatment of type 2 diabetes. This synthetically modified Exendin-4 is derivatized in a lysine residue with an acetamide that is covalently bounded to a cysteine residue of a recombinant HSA (Elsadek & Kratz, 2012).

Exendin-4 is a GLP-1 homolog and an agonist for the GLP-1 receptor which regulates glucose homeostasis, namely direct actions on the endocrine pancreas and indirect activation of the central nervous system that regulates gastric emptying, satiety, and body weight. Exendin-4 binds and activates the GLP-1 receptor, thus inducing insulin release. Exendin-4 is more potent at lowering glucose concentrations than human GLP-1 (Elsadek & Kratz, 2012; Luciani et al, 2013). However to gain a continued effect, the peptide has to be injected twice a day owing to its short plasma half-life $t_{1/2}$ = 2,4 hours (Huang et al, 2008).

Efficacy on glucose reduction in a phase I/II trial supported a once-a-week dosing for this new albumin- conjugated compound (Elsadek & Kratz, 2012).

The conjugated compound showed to retain the ability to mimic a full spectrum of GLP-1-receptor-dependent actions, including improved glucose tolerance, increased levels of glucose-stimulated insulin, decreased HbA1c, and weight loss associated with decreased hepatic triglyceride content (Baggio et al, 2008).

Despite this characteristics Novo-Nordisk already has an albumin-binding derivative of a myristic derivatized glucagon-like peptide approved (Victoza®), so further development of this product is facing a competitive commercial situation (Elsadek & Kratz, 2012).

Drug	Composition/ Half-life	Therapeutic applications	Outcomes
Determir (Levemir®)	Insulin analog: -substitution on the C-terminal amino acid threonine by a Lys moiety and myristic acid; -$t_{1/2}$ - 5-7 hours (Elsadek & Kratz, 2012)	Long-acting insulin analogue for basal insulin therapy on type 1 and 2 diabetes (Keating, 2012)	Less weight gain; Less within-patient variation in self-measured fasting plasma glucose; Generally well tolerated. (Keating, 2012)
Liraglutide (Victoza®)	GLP-1 analog: -substitution of Lys for Arg, addition of a glutamic acid and a fatty acid chain to a Lys residue on native GLP-1; -$t_{1/2}$ - 11-15 hours (Nonogaki & Suzuki, 2013)	Long-acting GLP-1 analog, for treatment of type 2 diabetes (Elsadek & Kratz, 2012)	Increased and prolonged insulin secretion; Regulated blood sugar levels and body weight, with minor side effects. (Elsadek & Kratz, 2012)
Exendin-4 conjugate (CJC-1134-PC)	Synthetically modified Exendin-4: -derivatized in a Lys residue and covalently bounded to a cysteine residue of a recombinant HSA; Phase I/II clinical trials, once a week administration (Elsadek & Kratz, 2012)	Long-acting antidiabetic albumin conjugate, for treatment of type 2 diabetes (Elsadek & Kratz, 2012)	Regulated gastric emptying, food intake and body weight. (Baggio et al, 2008)

Table I - Resume of market approved technologies major characteristics.

VII. Discussion

Albumin is emerging as one of the most important drug carriers for therapeutic active peptides and drugs (Elsadek & Kratz, 2012).

Regarding insulin analogues the commercial success of long-acting insulin (Levemir®) and glucagon-like peptide (Victoza®) developed by Novo-Nordisk for treating diabetes by simply attaching myristic acid as the albumin-binding moiety has paved the way for the development of various albumin-binding strategies for improving the PK profile and targeting properties of therapeutic active peptides and antibody fragments (Elsadek & Kratz, 2012). However, because the susceptibility of insulin analogues to chemical and physical degradation correlates with their propensity to undergo conformational fluctuations, structural studies of the rugged landscape of protein folding and misfolding promise to define a new frontier of translational research with application to global health. At this frontier the design of insulin analogues – and their self-organization within a subcutaneous depot – will require the integration of biochemical principles with the emergent perspective of nanotechnology (Berenson et al, 2011).

Concerning albumin-based nanoparticles as drug carriers they have gained considerable attention owing to their high binding capacity of various drugs and being well tolerated without any serious side-effects (Elzoghby et al, 2012). Formulations incorporating albumin demonstrate beneficial effects on diabetic symptoms and will be of interest in the treatment of diabetes with oral insulin (Reis et al, 2008b).

The nature of the nanoparticle coating, in addition to its role in NP stabilization, is expected to control the apparent release of the encapsulated therapeutic agents whilst creating an interface that inhibits nonspecific protein adsorption (Yogasundaram et al, 2012).

It has been also demonstrated the successful application of the albumin corona in optimizing the nanoparticles based drug delivery system. The formation of albumin corona has substantial impacts on the physicochemical properties of NPs. Plus in the presence of the BSA corona the cytotoxicity and blood circulation time of NPs has been shown to be significantly reduced and extended, which is the result of the weakened opsonization and the reduction of phagocytosis (Peng et al, 2013).

VIII. Conclusion

Modification of the insulin molecule to modulate its PK and pharmacodynamic properties represents a pioneering triumph of rational protein design.

Nanospheres are being developed for the oral delivery of peptide-based drugs, such as insulin, in which albumin serves as an important enteric coating.

After the demonstration of the successful application of NPs-proteins interaction in optimizing the nanoparticles based drug delivery system, via pre-forming the stable albumin corona surrounding NPs, it can be concluded that the pre-forming albumin corona could be a versatile strategy for optimizing the nanoparticles drug delivery systems.

Considering the commercial success of products that use albumin as a drug carrier and the ongoing clinical trials, albumin is attracting the interest of various biotech companies as well as of large pharmaceutical companies, and it is likely that the ongoing pipeline development will move further albumin-based drugs into the clinical setting.

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