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Review

Casein-based formulations as promising controlled release drug delivery systems

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ABSTRACT

Casein, the major milk protein, forms an integral part of the daily diet in many parts of the world. Casein possesses a number of interesting properties that make it a good candidate for conventional and novel drug delivery systems. This article reviews approaches aimed to associate bioactive molecules to casein and analyze the evidence of their efficacy in modifying the release and/or improving the bioavailability of the associated molecules. The ability of casein to modify drug dissolution from compacts was reported. The high tensile strength of casein films, favors its use as an acceptable film-coating for tablets. Naturally occurring genipin and a natural tissue enzyme, transglutaminase, were used as crosslinkers to prepare novel casein-based hydrogels for the controlled release of bioactives. Casein floating beads were developed to increase the residence time of drugs in the stomach based on its emulsifying and bubble-forming properties. Casein-based microparticles entrapping bioactive molecules were prepared via emulsification-chemical crosslinking with glutaraldehyde, enzymatic crosslinking by transglutaminase, simple coacervation and electrostatic complexation. Casein nano-formulations were also prepared to deliver nutraceuticals and synthetic drugs via enzymatic crosslinking, graft copolymerization, heat-gelation and polyelectrolyte ionic complexation. It can be concluded that casein-based formulations are promising materials for controlled drug delivery.

Contents

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1. Introduction

Over the past decade the use of biodegradable polymers for the administration of pharmaceuticals and biomedical agents has increased dramatically. The most important biomedical applications of biodegradable polymers are in the areas of controlled drug delivery systems [1,2]. Biodegradable polymers can be either natural or synthetic. In general, synthetic polymers offer greater advantages than natural ones in that they can be tailored to give a wider range of properties. However, toxicity is more likely to be associated with these synthetic polymers. Therefore, a safer carrier has been demanded. Natural polymers may generally be considered safer than synthetic polymers. Thus, natural polymers have certain advantages as drug delivery carriers [3].

Drug delivery systems based on food proteins hold much promise because of their high nutritional value and excellent functional properties, including emulsification, gelation, foaming and water binding capacity as well as their applications as ingredients in the food industry [4–7]. Food protein networks have the ability to interact with a wide range of active compounds via functional groups on their polypeptide primary structure, thus offering a variety of possibilities for reversible binding of active molecules and for protecting them until their release at the desired site within the body [8,9].

In addition, proteins are metabolizable; hydrolysis of food proteins by digestive enzymes generates bioactive peptides that may exert a number of physiological effects in vivo, for example, on the gastrointestinal, cardiovascular, endocrine, immune and nervous systems [10,11]. Generally, proteins represent good raw materials since they have the advantages of absorbability and low toxicity of the degradation end products. Moreover, it has been reported that some exogenous proteins (e.g. gliadin from wheat gluten) are able to interact with epidermal keratin by means of weak but numerous bonds [12–16].

Systems based on proteins including gelatin, collagen, casein, albumin and whey protein have been studied for delivering drugs, nutrients, bioactive peptides and probiotic organisms. A wide variety of protein-based delivery system formulations have been described, including films [17], hydrogels [18], microparticles [19–21] and nanoparticles [22,23].

Milk proteins are natural vehicles for bioactives. They are widely used in the food industry for their nutritional and functional properties. Casein, the major milk protein, is inexpensive, readily available, non-toxic and highly stable. As a natural food product, this GRAS (generally recognized as safe) protein is biocompatible and biodegradable. Studies based on ingestion by patients allergic to milk found that 62% of the patients reacted to β-lactoglobulin (β-lg), 60% to casein, and 53% to α-lactalbumin. β-lg having the highest allergic response was due to its relative resistance to acid digestion. Caseins, in particular, have evolved to be easily digestible [24].

Many of the structural and physicochemical properties of caseins facilitate their functionality in drug delivery systems [23]. These properties include binding of ions and small molecules, exceptional surface-active and stabilizing properties, excellent emulsification and self-assembly properties together with superb gelation and water binding capacities. The pH-responsive gel swelling behavior renders casein useful for programmable release. Casein can also interact with other macromolecules to form complexes and conjugates with synergistic combinations of properties. In addition, casein has various shielding capabilities, essential for protecting sensitive payload, enabling to control the bioaccessibility of the bioactive and promote its bioavailability. For example, casein could serve as a shield against radiation, particularly UV light, utilizing its strong UV absorbance properties, around 200–300 nm [23,25,26]. With its unique physicochemical properties, this natural polymeric surfactant is a good candidate for the preparation of conventional and novel drug and nutraceutical delivery systems. However, the limitations of casein may include its possible immunogenicity/allergenicity. This review gives an account on the systems that make use of casein as a drug carrier with a special emphasis on casein-based micro and nanoparticles as promising drug delivery vehicles.

2. Casein structure

Casein comprises about 94% protein and 6% low molecular weight compounds collectively called colloidal calcium phosphate. Mainly four casein phosphoproteins, αS_1-, αS_2-, β-, and κ-casein, exist approximately in proportions of 4:1:4:1 by weight respectively in cow milk. Their molecular weights are between 19 and 25 kDa and their average isoelectric point (pI) is between 4.6 and 4.8. All of the four caseins are amphiphilic and have ill-defined structures [27,28]. Casein may be used in pharmaceutical products either in the form of acid casein which has a low aqueous solubility or sodium caseinate which is freely soluble except near its isoelectric point [29–32].

Caseins are proline-rich, open-structured rheomorphic proteins as they assume any one of several energetically favorable conformations in solution. The proline peptides in the casein structure tend to interrupt alpha-helix and beta strands and disulphide bridges are absent in their structure. As a result, casein has relatively little secondary or tertiary structure, therefore caseins are quite heat stable. Moreover, the open structure of the caseins, due to their high proline content, makes them readily accessible for proteolytic cleavage. This characteristic along with the acid-soluble calcium–phosphate bridging, makes an excellent target-activated release mechanism for unloading the drug in the stomach [22,23].

Caseins are amphiphilic proteins which self-assemble into stable micellar structures in aqueous solutions. Casein micelles are composed of the four previously mentioned phosphoproteins held together by hydrophobic interactions and by the bridging of calcium phosphate nanoclusters (colloidal calcium phosphate, CCP) that are bound to phosphorylated serine residues of the casein side chains [33]. CCP plays a crucial role in maintaining micellar integrity. Three of the caseins (αS_1-, αS_2- and β-casein) contain centers of phosphorylation (at least three phosphoserine residues in close proximity) that can bind to the amorphous calcium phosphate cluster. Both αS_1- and αS_2-casein contain more than one phosphate center and can thus act as linking agents between nanoclusters [34]. The surface of the micelles is primarily covered with κ-casein providing a hydrophilic, charged surface layer which stabilizes the micelles through intermicellar electrostatic and steric repulsion [35,36]. Nanocluster and Horn models for casein micelles are illustrated in Fig. 1 [37].

Casein proteins have distinct hydrophobic and hydrophilic domains. αS_1-casein has a strongly acidic peptide of 40 amino acids that contains seven of the eight phosphate groups, twelve carboxyl groups and only four positive groups. The highly charged N-terminal region of β-casein contains four of the five phosphates of the molecule, seven carboxyl groups and only two positive groups. The sialyated glycoprotein κ-casein has only one phosphate and fourteen carboxylic acid groups located in the hydrophilic C-terminal region called the glycomacropeptide [38,39].

3. Casein film coatings

Although cellulose or acrylic based polymers have been utilized for many years as extremely good film formers or coating agents [40], there is a growing interest in polymers of natural origin which possess high levels of biodegradability and aqueous solubility [41]. Whilst proteins seem to be an obvious choice, the current literature is extremely limited regarding the use of proteins for the coating of pharmaceutical dosage forms. The most common example is zein, an alcohol soluble protein obtained from corn, which has been used as an effective film former and coating agent [42]. Although proteins provide a suitable bioalternative to commonly used synthetic and semi-synthetic polymeric film coats, a major issue prohibiting their widespread use is their limited mechanical strength. This has been addressed in several investigations describing the use of cross-linking to significantly alter these mechanical properties [43].

Protein cross-linking can be achieved through the use of chemical agents such as formaldehyde or glutaraldehyde [44], or through the