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Gliadin films. I: Preparation and in vitro evaluation as a carrier for controlled drug release

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Abstract

A method for the preparation of soft capsules (Gl.C) and chewable gums (GCG) of the hydrophobic wheat protein, crude gliadin, is reported. Gliadin films were found to be more hydrophilic than comparable gelatin films. The release of paracetamol was significantly sustained, indicating drug delivery. Drug release profiles in 0.1 M hydrochloric acid media consisted of three regions for Gl.C: these were an initial latency period, followed by a low release region and essentially constant rate; and one region for GCG with very slow release of paracetamol. A mechanism of drug release is proposed involving hydrophobic interaction between gliadin and non-polar ligands. These results are discussed and based on this study, gliadin appears to be a highly promising, low-cost, bioacceptable protein for the manufacture of drug formulations with a very interesting controlled released potency.

Keywords: Gliadin; Capsule; Chewable gum; Paracetamol; Controlled release

The hydrophobic properties of wheat gluten proteins, along with H and S-S bonds, make an important contribution to the structure and viscoelasticity of gluten (Khan et al., 1980; Tatham et al., 1984). Nevertheless, our knowledge of the hydrophobic properties of gluten proteins and their function as drug carriers is incomplete. The surface hydrophobicities of purified α-, β-, γ- and ω-gliadins have been investigated by hydrophobic interaction chromatography and have revealed a considerable capacity for interaction between gliadins and non-polar ligands (Popineau and Pineau, 1987), when the interaction of gelatin with small organic molecules (Ofner and Schott, 1987) and anionic compounds (Gautam and Schott, 1994) is considered. The increasing interest in efficient and selective delivery of therapeutic agents to the site of action is derived from the use of microspheres as controlled release targeting agents for drugs (Goldberg, 1983). Even though many biodegradable materials are used for the preparation of controlled release tablets or microspheres as carriers, there are several limitations such as high temperature, use of surfactants and solvents. Among the various drug delivery systems investigated in order to achieve this goal, proteins such as albumin (Morimoto and Fujimoto, 1985; Gupta and Hung, 1989a,b;

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Ohya et al., 1991), gelatin (Yan et al., 1991), cross-linking gelatin (Digenis et al.; 1994), or casein (Jayakrishnan et al., 1994), polysaccharides such as cellulose derivatives (Benita and Donbrow, 1982; Ghorab et al., 1990) and other polymers (Avgoustakis and Nixon, 1993a,b) have received considerable attention. The surface characteristics of polymers play a significant role in their controlled drug release. Davis and Illum (1988) used coatings of absorbed or grafted copolymers to create more hydrophilic polystyrene particles; Kim and Oho (1988) reported on the development for hydrophilic human albumin and Narayani and Panduranga Rao (1993) methotrexate linked covalently to gelatin using carbodiimide as the coupling agent. The hydrophobicity of polymers has thus been shown to be important for controlled drug release. Crude gliadin from common wheat shows interesting hydrophobic properties permitting on the one hand the substitution of gelatin as the polymer for hard-gelatin and soft-gelatin capsules of a polymer matrix, and on the other, the regulation of drug release from the pharmaceutical form.

Prolamines are characterized by their solubility in aqueous alcohol mixtures or in aqueous mixtures of extreme pH (less than pH 2 or greater than pH 10) and, therefore, most of the applications of prolamine films are from solutions of prolamines in alcohol and other solvent mixtures or water-based solutions having extreme pH values. The disadvantage of these coating systems in foods or in pharmaceuticals, and hence the reluctance of the industry to use prolamine film systems, is that the solvents and/or pH levels are often incompatible with and difficult to remove from the finished product. Ethanol was preferred because of its ready availability in food grade quality and because it is quickly evaporated.

Therefore, crude gliadin was extracted from fat-free wheat flour with 65% (v/v) ethanol. After agitation (1 h), settling (8 h), filtration (0.45 μm Millipore filter) and evaporation in vacuo at 40° C, the protein was freeze-dried ($P = 750$ μmHg, $T = -55$° C). Paracetamol was a gift sample from Rhône-Poulenc-Rorer (Paris, France). Sorbitol and glycerol were purchased from Prolabo (Paris, France). All other chemicals used were of analytical grade. Paracetamol capsules (Dafalgan™) and paracetamol tablets (Doliprane™) were purchased from UPSA Laboratories (Paris, France) and Theraplix Laboratories (Paris, France), respectively.

The gliadin mass was prepared by adding accurately metered chilled 50% ethanol and edible plasticizers (sorbitol and glycerol) to freeze-dried gliadin. These ingredients were mixed until a fully hydrated, pasty mass had been achieved. The mass consists of 18–36% (w/w) gliadin, 9–18% (w/w) plasticizers (sorbitol/glycerol, 2:1, w/w) and 46–73% (w/w) 50% (v/v) ethanol. It may be used as is or coloring agents, preservatives, opacifiers, flavors or drugs may be added by means of a high-speed mixer. The mass must be deaerated by sonication in order to maintain its uniformity. Removal of oxygen is also important for product stability.

The gliadin mass was coated onto Teflon® slides and cured into a film using heat radiation. The heat lamp was located 20 cm above the film for a few hours (2–10 h within the gliadin concentration). The heat lamp resulted in a curing temperature of about 37° C. The films were uniform.

The gliadin films were cut as thin ribbons and transformed on stainless-steel mold pins. The gliadin films were then removed from the mold pins and cut to the correct length.

The method of filling corresponded to the indirect type: 500 mg of paracetamol were measured in a chamber completely independent of the capsule body. Such soft, elastic gliadin capsules were readily sealed by heating ($T = 37$° C, R.H. = 70%). Hence, in our study the shells are not, as is usually the case, formed, filled and sealed in a combined operation. Shells are preformed and the shell material contains an active ingredient.

As previously carried out, the gliadin films containing paracetamol were cut as thin ribbons to the correct length (each piece had to contain 500 mg of paracetamol). The ribbons were folded and the gums formed by heating the folded ribbons ($T = 37$° C, R.H. = 70%).

Pharmacopoeias require that capsules are tested in the same apparatus as tablets even though they have different properties. Gliadin is

an adhesive material and tends to block the wire meshes that form part of the standard equipment. Disintegration complied with the disintegration test for tablets and capsules (Appendix XIIA of USP XXV). 0.1 M hydrochloric acid was used as the liquid and a disc was added to each tube. Methods of testing dissolution based on flow-through cells have been proposed as the most suitable for testing of modified-released capsules due to the closer control of hydrodynamic conditions and ease of pH adjustment of test media.

The release profile of paracetamol from Gl.C, tablets, gelatin capsules and GCG was determined in 0.1 M hydrochloric acid media. The experiments were carried out using a Dissolution Test Apparatus (Hewlett-Packard) at 37° C and 100 rpm. The release medium was periodically sampled (every 5 min for 1 h and every 10 min until 3 h), filtered using a 0.45 μm Millipore filter and assayed spectrophotometrically at 280 nm.

Major medical conditions are best treated by administration of a pharmaceutical or other active substance in such a way as to sustain its action over an extended period of time. This type of administration is useful, for example, for treating chronic pain, such as that associated with inflammatory disease. Controlled-release drug-delivery devices are designed to limit or slow the rate of drug release of fast-release systems containing the same drug. With a few exceptions, the primary method for achieving this delayed drug release is via the use of biodegradable polymers which slowly degrade, erode or dissolve via non-degradable polymers that limit the dissolution and diffusion of the drug within the device. In the case of gliadin, the controlled drug delivery is the consequence of the hydrophobic interaction between gliadin and paracetamol and of its biodegradation. This biodegradation involves processes such as hydrolysis and oxidation and is catalysed by enzymes.

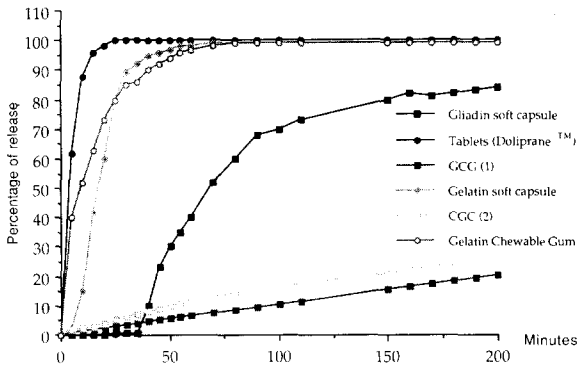

Fig. 1. Plots of paracetamol release from gliadin and gelatin matices containing 500 mg of active paracetamol.

The ease with which the films (as Gl.C or GCG) were degraded is governed by the enzyme protease. Proteolysis was measured using a turbidity method; a direct relationship exists between the gliadin concentration and the ease of degradation, i.e., the lower the gliadin concentration of the film, the faster is the rate of degradation of the protein matrix.

This suggests that the residence time of the gliadin film in the bowel might be controlled by changing the gliadin concentration of the film. Moreover, the disintegration time of gliadin is twice as long as that of gelatin in intestinal medium.

The quantity of paracetamol in each therapeutic unit was 500 mg. The gliadin and plasticizers concentrations used for the formulation of gliadin mass prepared for this study were approx. 36 and 18 wt%, respectively. In vitro release profiles of the drug from paracetamol containing oral forms are shown in Fig. 1 (relative standard deviations $< 5\%$, $n = 10$). Three types of drug release profiles are identified.

For paracetamol tablets (Doliprane™), paracetamol gelatin capsules (Dafalgan™) and gelatin chewable gums (manufactured as GCG by substituting gliadin with gelatin), the drug release profiles consisted of two regions: an initial stage of high release rate, probably due to the rapid leaching of drug from the pharmaceutical form which was almost complete after 2–3 h of immersion in the dissolution medium (burst effect) which was followed by an extended region of essentially constant release rate (steady-state release region).

For Gl.C the drug release profile consisted of three regions; an initial latency period (about 8 h) which was followed by a region of lower release rate and a constant release rate. These results

suggested an interesting interaction between paracetamol and gliadin which generated a slower release of paracetamol.

For GCG the paracetamol release profile is dramatically different from the other formulation. Interestingly, the rate of release from Gl.C and GCG was not identical which suggested that the hydrophobic interaction between gliadin and paracetamol was stronger in GCG and thus that this interaction is the reason for drug release. This very slow release was considered to be the determining factor for the greater potency observed per unit amount of the drug with a protein system. The slower paracetamol release reported may be due to the hydrophobic interaction and/or the morphology of the gliadin cross-linking matrix. It has previously been proposed to produce formulations which will release the active substance therein at a controlled rate such that the amount available in the body to treat the condition is maintained at a therapeutic level over an extended period of time.

Particularly suitable periods are 12 and 24 h, since such formulations need only be taken once or twice a day to maintain an effective treatment of the conditions. Such formulations can be designed and are generally known as 'sustained-release formulations'. Many sustained-released formulations are already known, but there is no generally applicable method by which such formulations can be designed.

Generally speaking, each sustained-released formulation is dependent on the particular active substance incorporated therein. In designing a formulation, it is generally necessary to take into account many factors, including the rates of absorption and clearance of the active substance, the interaction of the active substance with excipients and/or coating to be used in the formulation, the solubility of the active substance and of the excipients and/or coatings, and the effects on the bioavailability of the active substances, which may be caused by the excipient and/or coatings.

Thus, gliadin, which is readily available, inexpensive, and from plant origin, appears to be a highly promising carrier and substitute for gelatin in future investigations of drug carrier systems, all the more because of the facile buccal disintegration of gliadin films which is of considerable interest when the patient is an infant, young child, elderly person or a more mature person who is unable to ingest easily charge tablets or capsules. The challenge is increased exponentially when for such persons the active compound, which is to be delivered such as an anti-inflammatory agent, is most effective and less toxic when protected from acidic gastric juices and is desired to be gradually released over a period of time. These challenges are met by the gliadin systems for the delivery of active substances which has been discussed herein.

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