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Frontal polymerization as a new method for developing drug controlled release systems (DCRS) based on polyacrylamide

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ABSTRACT

Stimuli-responsive polymers are macromolecular materials that undergo changes in response to small external stimuli in the environmental conditions. Among stimuli-responsive hydrogels are several polyacrylamides. Frontal polymerization is a fast, easy and inexpensive polymerization technique used for the synthesis of macromolecules.

Aim of this work was the evaluation of the Frontal polymerization technique as new method for the preparation of controlled release dosage forms in which drug loading and polymer preparation occur together, as well as the possibility of obtaining more dosage units by a unique preparation. Hydrogels based on polyacrylamide containing diclofenac sodium salt were prepared using the Frontal polymerization and compared with similar systems obtained by the classic batch method. Polymers characterized by three different degree of cross-linking were prepared. The stability of the drug during the sample preparation was evaluated by IR analysis. The obtained samples were characterized in terms of drug content, morphology, in vitro drug release and swelling properties. Samples were studied also divided into disks. The results show that hydrogels based on polyacrylamide can be prepared by Frontal polymerization; these samples show similar properties to those obtained by batch polymerization. The drug is stable in the polymerization reaction conditions. Samples characterized by the lowest degree of cross-linking show drug loading values always higher than samples with the highest one regardless of the preparation method employed. The swelling ratio decreases as the degree of cross-linking increases. Loaded samples swell more than drug free ones. From a single preparation of hydrogel, three disks showing same drug content and in vitro release behaviour can be obtained and thus they can be used as three single dosage units.

1. Introduction

Controlled drug delivery occurs when a natural or synthetic polymer is combined with a drug or other active agent in a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the advantages of using controlled delivery systems can include the purpose to achieve more effective therapies by eliminating the potential for both under- and over-dosing, the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug and increased patient compliance [1]. Controlled release is regulated by various mechanisms such as diffusion, erosion/degradation or swelling. Most of polymeric delivery systems which work by a swelling release mechanism are hydrogels.

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Polymer hydrogels are three-dimensional, hydrophilic, macromolecular networks capable of imbibing large amounts of water or biological fluids [2,3].

Since the employment of hydrogels as soft contact lenses in the 1960s [4], hydrogels have been introduced as novel materials for pharmaceutical and biomedical applications. The work of Lim and Sun in 1980 demonstrated the successful application of calcium alginate microcapsules for cell encapsulation [5]. Later in the 1980s, Yannas and coworkers incorporated natural polymers such as collagen and shark cartilage into hydrogels for use as artificial burn dressings [6]. Recently, such hydrogels have become attractive to the new field of 'tissue engineering' for repairing and regenerating a wide variety of tissues and organs [2,7–10]. Over 30 years of research in this field resulted in the common use of hydrogels as soft contact lenses, wound dressings, drug delivery systems, superabsorbents etc.; with a number of products being commercially available, it seems that their use in the field of medicine and pharmacy may be the most successful and promising. Both natural and synthetic polymers can be used for the production of hydrogels.

In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in their physical properties because of their relatively high water content and soft and rubbery consistency. Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Furthermore, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration [11,12].

Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels' [13]. The smartness of these materials is due to their ability to receive, transmit or process a stimulus and respond by exhibiting changes in their physical or chemical behaviour resulting in the release of entrapped drug in a controlled manner [14,15].

Variations in pH are known to occur at several body sites, such as the gastrointestinal tract, vagina and blood vessels, and these can provide a suitable base for pH-responsive drug release. In addition, local pH changes can be generated by using specific substrates and used for modulating drug release. pH-responsive hydrogels are composed of polymeric backbones with ionic pendant groups. Most commonly studied ionic polymers for pH-responsive behaviour include poly(acrylamide) (PAAm), poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA) and poly(dimethylaminoethyl methacrylate) (PDMAEMA) [16] which are high molecular weight organic polymers that, depending on the difference in molecular structure, can be classified as linear or cross-linked macromolecules. For instance, linear PAAM dissolves in water while cross-linked PAAM absorbs hundreds of times its weight in water without dissolving. PAAM is able to swell and gel when in contact with biological fluids and is therefore used as carrier of drugs [1,17] also in many of its copolymeric forms, which are stimulus-sensitive polymers [18–20].

The chemical and physical properties of PAAM differ significantly from those of the acrylamide (AMD) monomer, which is a neurotoxin to humans. In contrast, PAAM when used at prescribed rates is nontoxic to humans although overexposure can lead to skin irritation and inflammation of mucous membranes.

Frontal polymerization (FP) is a polymerization method that takes advantage of the exothermicity of the reaction for the propagation and self-sustaining of the reaction itself. Indeed, subsequently to an initial ignition (chemical or physical), a hot polymerization front is formed which propagates throughout the reactor in a fashion similar to a reaction wave, thus converting monomer into polymer. After reaching the steady state, no further energy supply is necessary in order for the front to sustain itself.

The first work dealing with FP dates back to the '70s: Chechilo and Enilokopyan frontally polymerized methyl methacrylate under high pressure [21]. After this first work, Pojman et al. applied FP on various typologies of monomers and reagents: epoxy resins [22], ionic liquids [23] and acrylic monomers [24–26]. Crivello et al. focused their attention on the FP of glicidyl ethers [27,28], whereas Chen et al. successfully exploited such a technique with 2-hydroxyethyl acrylate [29], and *N*-methylolacrylamide [30], moreover, they prepared epoxy resins/polyurethane networks [31] and polyurethane-nanosilica hybrid nanocomposites [32]. Our research group synthesized poly(dicyclopentadiene) [33], polyurethanes [34,35], interpenetrating polymer networks [36], unsaturated polyester/styrene resins [37], poly(diurethane diacrylates) [38], and applied FP to the consolidation of porous materials [39]. Recently, we reported on the synthesis of polymer-based nanocomposites with montmorillonite [40] and polyhedral oligomeric silsesquioxanes [41]. Besides, we proposed a new class of initiators based on ionic liquid compounds that resulted to be particularly useful in the frontal radical polymerization in that they allow for lower temperature polymerization fronts [42].

Since the nineties, FP has received a great impetus by Pojman et al. who explored macrokinetics and dynamics [21,22] and new frontally polymerizing systems [23,24].

Since 2000, our research group has been active in this field. Namely, we have studied the application of FP to the synthesis of several kind of polymers [25,27] and polymer nanocomposites [28,29]. Besides, FP was also applied to the consolidation of stone and wood [30,31].

Aims of this work were: (1) the study of the potential application of the Frontal polymerization technique as a new method for the preparation of controlled release dosage forms in which the drug loading and the polymer preparation occur simultaneously; (2) the evaluation of obtaining more dosage units by a unique preparation.

Polyacrylamide has been chosen as the polymer, also because its hydrogels are pH-sensitive and diclofenac sodium salt as a model drug.

The work has been developed by performing the following steps:

- preparation of polyacrylamide samples containing diclofenac sodium salt by Frontal polymerization and by batch polymerization as a comparison. Different poly-