European Journal of Pharmaceutics and Biopharmaceutics 79 (2011) 664–673

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Design of prolonged release tablets using new solid acrylic excipients for direct compression

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ARTICLE INFO

Article history:
Received 18 June 2011
Accepted in revised form 22 July 2011
Available online 29 July 2011

Keywords:
Direct compression
Acrylic solid excipient
Inert matrices
Micromeritic properties
Polymerization techniques
Tablets

ABSTRACT

The design of new excipients that extend the release of drugs from tablets over prolonged periods is essential in reaching enhanced therapeutic performances. In this sense, the objective of this study was to develop new excipients, based on acrylic monomers (ethyl acrylate, methyl methacrylate, and butyl methacrylate) for use in direct compression (DC). The polymeric excipients were prepared by suspension and emulsion polymerization reactions and were characterized by FTIR to confirm the polymerization reaction. For the success of direct compression, excipients must present good flow and compactability properties. Therefore, excipients were submitted to analysis of morphology (SEM), particle size and size distribution by laser diffraction, and powder density (bulk density and tapped density). The Carr index, Hausner ratio, flow ratio, and cotangent of the angle α were determined. Thereafter, the polymeric excipients were used to prepare inert matrices by DC using propranolol hydrochloride (PHCl) as a model drug. The tablets were evaluated for average weight, breaking force, and friability tests. The release profiles were determined, and the dissolution kinetics was studied. The results indicated that matrices prepared from excipients obtained by suspension polymerization (NWCB and PECB) presented a release of PHCl for a period exceeding 12 h, most likely due to the higher micromeritic properties. The results suggested that the increase in the percentage of polymers, as well as in the compression time, resulted in a higher hardness of the matrix with a reduced rate release of the PHCl. Finally, *in vitro* preliminary tests showed that the polymeric excipients produced were non-toxic for the gingival fibroblasts.

1. Introduction

Historically, the oral route is the most frequently prescribed for drug administration. Tablets are considered to be the most desirable dosage form for drug delivery, since it is preferred by patients and industry [1–6]. Tablets consist of a mixture of powder components in which all contribute to the final properties of the product.

Manufacturing tablets, especially directly compressed tablets, is straightforward, and the manufacturing process involves low cost, which is attractive to pharmaceutical laboratories [7]. The term 'direct compression' (DC) is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved. Thus, the DC passes through three manufacturing steps to produce the final dosage form: the powder mix, lubrication, and compression. The direct compression is a process more economical, reduces the cycle time of the products, and is straightforward in terms of requirements of good manufacturing practices. Since with a small number of steps, without water and temperature, the stability of the final product can be increased and, finally, the direct compression is friendlier to the environment [7–9].

The majority of oral tablet formulations represent the so-called immediate release dosage forms. Conventional dosage forms containing drugs with a short elimination half-life must be administrated several times a day to maintain an effective plasma level of the drug, which represents a major drawback in terms of patient compliance. As such, to improve the therapeutic efficacy of oral drug administration, with effective plasma levels for prolonged periods, Pharmaceutical R&D has focused on the development of oral drug delivery systems (sustained, extended, slow action, prolonged, controlled, delayed, pulsed, etc.) [4].

Excipients for DC must have adequate physical properties for the compact of process. Flowability is needed in high-speed rotary tablet machines to ensure homogeneous and rapid flow of powder for uniform die filling. Other important processing parameters include high capacity for compression and consolidation of powders, *i.e.*, the relationship between compression force, compaction, and

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doi:10.1016/j.ejpb.2011.07.011

reduction in bulk volume. Moreover, the tablet must remain in the same shape once the compression force is removed. Few excipients can be compressed directly without elastic recovery. A directly compressible excipient should have a high dilution potential, so that the final dosage form has a minimum possible weight. Also, the directly compressible excipient should not exhibit any physical or chemical change on storage and must be chemically inert [1–3,10,11]. In recent years, scientists have recognized that certain excipients do not always provide the requisite performance to the drug to be formulated or manufactured adequately [8,12–16].

Most commercially available sustained release dosage forms employ hydroxypropyl methylcellulose (HPMC) as matrix-forming agents. The HPMC presents a low cost and easy to manufacture, offers little risk of release of the total drug dose (dose dumping effect), provides appropriate release kinetics, and has been extensively studied. However, the mechanism that controls the release of these systems is the gelling of HPMC, which is not always ideal for controlling the release of highly soluble drugs. Often, large amounts of HPMC are required. Another problem is that HPMC is poorly compactable and poor flow characteristics making it unsuitable for direct tabletting, and wet granulation can generate rigid particles [17]. The present work proposes the development of polymers capable of forming inert matrices by direct compression, based on acrylic and methacrylic monomers. The monomers are highly reactive and are able to form polymers and copolymers alone or in combination with other molecules, including natural macromolecules, enabling the control of chemical and physical properties of materials according to the specific application [18–22].

Therefore, the main objective of this work was to prepare inert matrix prolonged released tablets by direct compression, employing new acrylic solid polymers prepared by using different methods of polymerization. The excipients were obtained by the suspension and emulsion polymerization process from the monomers, ethyl acrylate (EA), methyl methacrylate (MMA), and butyl methacrylate (BMA), in aqueous media. From an environmental standpoint, the preparation of acrylic polymers by processing in suspension and emulsion in water is advantageous, since they are free of volatile solvents. In the body, the absence of organic solvent residues reduces the risk of toxicity. The choice of monomers was based on prior knowledge of the composition of commercially pharmaceutical polymer dispersions listed in Pharmacopeias.

In the suspension polymerization technique, a monomer or mixture of monomers is dispersed by strong mechanical agitation into droplets suspended in a second liquid phase in which both monomer and polymer are essentially insoluble. The monomer droplets are then polymerized, while dispersion is maintained by continuous agitation. Polymerization initiators or catalysts soluble in the monomer phase are generally used. Depending on the particular monomer used, hard or soft beads are formed, which normally separate easily from the aqueous phase when stirring is discontinued [23,24]. The main difficulty of the suspension process is the tendency during polymerization for the viscous and adhesive droplets and pearls to agglomerate or to stick to each other, which leads to heat build-up and coagulation. The control of size and size distribution of particles can be achieved by adjusting the reaction parameters, such as stirring speed, reaction temperature, type of reactor system, composition, the addition of suspending agents, and the addition of stabilizers and co-stabilizers [25–31]. In the first part of this study, we tested the addition of nanofibers of cellulose as a co-stabilizer for the formulation of the polymer [32].

Several natural polymers have been widely used in pharmaceutical drug delivery systems, either as natural materials or as derivatives compounds, because of their low toxicity, specific biodegradability, high stability, and low cost. However, these macromolecules have swelling capacity and solubility in water, which can result in premature release of drug from the DDS [21,33–35]. In this work, low-methoxylated pectin was chemically modified with glycidyl methacrylate (Pec_GMA), aimed at reducing its solubility in water and in an attempt to improve its mechanical properties, since pure pectin exhibits resistance to consolidation due to their high elastic recovery during the compression process and ejection of the tablets [36–38]. Pectin was chosen because it is a polysaccharide whose use is associated with the development of colon-specific DDS and is mucoadhesive [39,40]. Later, the Pec_GMA was included in the formulation to obtain beads through the suspension polymerization process.

Emulsion polymerization was also used to prepare the acrylic polymer as polymer dispersions. Many commercially available acrylic excipients are liquid dispersions with low solid content (about 40%), which leads to the need to use the wet granulation that is not always successful due to the need to use large quantities of the polymer dispersion since a higher percentage of polymers is necessary to reduce the permeation of water inside the granules and thus to produce slower release [41]. In conventional emulsion polymerizations, the main ingredients are monomer(s), water, surfactant, and initiator. The emulsion polymerization is a complex process governed by the nucleation, growth, and stabilization of polymer particles from the formation of free radicals, combined with stabilization of colloidal phenomena [42]. An important difference between the polymerizations in suspension and in emulsion is that, in the latter, the initiator used is soluble in the aqueous phase [43].

In this work, excipients were prepared by both suspension and emulsion polymerization of acrylate monomers. The suspension polymerization process can provide polymeric materials in the form of solid pearls or beads. The polymers prepared by emulsion polymerization were dried by freeze-drying to obtain a solid excipient, suitable for DC. Physical tests called micromeritics were performed to study the suitability of the solid particles to be used as a pharmaceutical excipient. To investigate the safety issue, we performed a preliminary cytotoxicity to evaluation of the polymeric excipients using an *in vitro* method. Finally, the synthesized excipients were used to prepare DC tablets with propranolol hydrochloride (PHCl) as a model drug. The release profiles were studied using methods adapted from the United States Pharmacopeia 32th edition [44].

2. Experimental

2.1. Materials

Ethyl acrylate (EA), methyl methacrylate (MMA), butyl methacrylate (BMA), polyacrylic acid (PAA), glycidyl methacrylate (GMA), ammonium persulfate, sodium dithionite, ascorbic acid, cumene hydroperoxide, and phosphate-buffered saline (PBS) solution were supplied by Aldrich, USA. All monomers were used as received without prior purification. Dulbecco's modified Eagle's medium and fetal bovine serum (FBS) were purchased from Gibco, USA, and (3-(4,5-dimethylthiazol-2-yl) 2,5-diphenyl tetrazolium bromide) was provided by Chemicon, USA. Benzoyl peroxide (BP), Span® 85, ferrous sulfate, sodium dodecyl sulfate (SDS), isopropanol, hydrochloric acid solution (HCl solution) 0.1 N, sodium chloride, sodium sulfate, citric acid monohydrate, and sodium phosphate dibasic anhydrous, with analytical purity, were purchased from Vetec and Synth, Brazil. Pectin GENU® LM 104 AS was donated by CP Kelco, Brazil. Propranolol hydrochloride, Aerosil®, and microcrystalline cellulose PH 102 (pharmaceutical grade) were donated by Magistral Pharma Ponte Pharmacy. Cellulose nanowhiskers were produced in the Department of Chemistry, UFMG.