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Research paper

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

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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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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.

2.2. Polymerization procedures

To prepare the polymer systems, a 250-mL three-neck glass flask equipped with a heating mantel, a digital mechanical stirrer, a thermometer, and a nitrogen gas inlet system were used. The process of suspension polymerization was carried out as previously described by Villanova et al. [32]. Briefly, the PAA and sodium sulfate were dissolved in water and homogenized reactor. The initiator (BP) was dissolved in the monomer mixture, which was added to the reactor. Vigorous stirring was maintained (750 rpm) and temperature controlled to the maximum of 90 °C. At the end of the reaction and after washing with excess water (under vacuum), spherical beads were collected, free of agglomeration. The beads were dried at room temperature and designated pure beads (PB). Beads containing 0.1% w/w cellulose nanowhiskers were designated NWCB beads. Those containing 2%w/w modified pectin were designated PECB beads. The proportion of monomers used was 60:20:20 (BMA: MMA:EA). The recipes for the preparation of PB, CNWB, and PECB are shown in Table 1.

The method used to modify pectin by GMA was adapted from that described by Souto-Maior et al. [21]. A solution of pectin in deionized water at a concentration of 2.5% w/V was prepared under constant mechanical stirring. The pH of the colloidal dispersion was adjusted to 3.5 using 0.1 N HCl solution. After, 4.8 mL of GMA was added. The agitation was maintained for 24 h at 50 °C. The newly prepared Pec_GMA was incorporated into the formulation of the beads.

Two types of polymers, designated A and B, were prepared by emulsion polymerization. First, a mixture of monomers and water containing the surfactants (pre-emulsion 1) was submitted to 15 min of pulsed sonication (5.0 s on, 5.0 s off) at 50% amplitude with a sonifier (model W450 Digital, BRANSON ULTRASONICS Co., Danbury, USA). The obtained pre-emulsion was transferred to a kettle, to which the initiators were added under slow agitation (250 rpm). After a few minutes, the temperature began to rise until it reached 90 °C. Next, the batch was cooled to about 20 °C. Simultaneously, the second stage (pre-emulsion 2) was submitted to 15 min of pulsed sonication (5.0 s on, 10.0 s off) at 40% amplitude. Pre-emulsion 1 was added to pre-emulsion 2. The entire mass was shaken, and the initiators were introduced. Shortly thereafter, the temperature began to rise until it reached 85 °C, starting from 20 °C. When the process finished and the temperature dropped to 40 °C, the set of initiators was added to polymerize the free monomers. The total solid content of the polymer latexes was determined by gravimetric method, the values of which were 54.70% and 52.40% for polymers A and B, respectively. Finally, the polymers were frozen in liquid nitrogen and freeze-dried for 24 h to obtain the excipient in solid form using the lyophilizer (Terroni, model LT 600, TERRONI, São Carlos, Brazil). The recipes for the preparation of polymeric dispersions A and B are shown in Table 2.

Table 1
PB, CNWB, and PECB bead formulations (all values in grams/100 g total).

Ingredient	PB	CNWB	PECB
Deionized water	60.0	60.0	60.0
PAA	0.2	0.2	0.2
Sodium sulfate	0.2	0.2	0.2
BMA	24.0	24.0	24.0
MMA	8.0	8.0	8.0
EA	8.0	8.0	8.0
BP	0.2	0.2	0.2
CNW	–	0.04	–
Pec_GMA	–	–	0.80

Table 2
Formulations of polymers A and B (all values in grams/100 g total).

Reagents	First stage	Second stage
Polymer A		
MMA	13.53	19.47
BA	4.20	6.79
EA	4.20	6.79
SDS (25% w/v)	1.75	0.88
Renex® 300 (70% w/v)	0.17	0.41
Span® 85	–	0.58
Deionized water	29.12	11.59
Ferrous sulfate	0.009	0.002
Ammonium persulfate	0.047	0.064
Sodium dithionite	0.047	0.064
Cumene hydroperoxide	0.058	0.197
Ascorbic acid	–	0.032
Polymer B		
MMA	10.60	15.89
BA	6.36	9.54
EA	4.28	6.31
SDS (25% w/v)	1.69	0.845
Renex® 300 (70% w/v)	0.112	0.563
Span® 85	–	0.45
Deionized water	28.21	14.65
Ferrous sulfate	0.009	0.002
Ammonium persulfate	0.045	0.062
Sodium dithionite	0.045	0.062
Cumene hydroperoxide	0.056	0.187
Ascorbic acid	–	0.032

2.3. Characterization of polymers

2.3.1. Fourier transforms infrared (FTIR)

A spectrometer FT-IR (Thermo Nicolet, model 6700, THERMO SCIENTIFIC, Madison, USA) with a Centaurus microscope was used to characterize the chemistry of the films from polymer emulsions and from beads dissolved in tetrahydrofurane. The films were cast on polyethylene plates and dried in an oven at 40 °C for 24 h to form thin films (about 1 mm thick). Micro-FTIR–ATR spectra of the films in the region of 650–4000 cm^{-1} were obtained using a germanium crystal in the absorption mode with dry a nitrogen purge at a resolution of 4 cm^{-1}; 64 scans were recorded and averaged.

2.4. Micromeritic studies of the excipients

2.4.1. Morphology by scanning electron microscopy (SEM)

The morphology of beads and freeze-dried polymers was investigated using scanning electron microscopy (SEM) (model JSM 5410, JEOL, Tokyo, Japan). Prior to investigation, the samples were sputter-coated with gold.

2.4.2. Particles size and size distributions

The particle size and size distributions were analyzed by laser diffraction using a granulometer (CILAS, model 1064, CILAS Co., Orleans Cedex, France). First, samples were passed through sieves, dispersed in water, and then ultrasonicated for 60 s.

2.4.3. Determination of bulk and tapped densities of the beads

Apparent density (d_0) and tapped density (d_f) were measured indirectly through the apparent volume, as described in the British Pharmacopoeia [45]. The tests were performed using an automatic compactor (Volumeter Tapped, model SVM, ERWEKA, Heusenstamm, Germany). The bulk density was determined by slowly pouring the samples into a 100-mL graduated glass cylinder to complete 60% of the container volume. The mass related to the occupied volume (60 mL) was weighed on an analytical balance.

The bulk density was measured by the relation between the weight (g) and the apparent volume (mL).

The tapped, derived from the tapped density, was determined by tapping a graduated glass cylinder containing a known weight of samples. The volume was recorded after 10 taps (V_{10}), 500 taps (V_{500}), and 1250 taps (V_{1250}). In cases where the difference between V_{500} and V_{1250} was greater than 2%, another cycle of 1250 taps was performed until variations were less than 2% [45]. The tapped density (g/mL) was calculated from the mass (g) and the final volume of solids (mL).

2.4.4. Determination of Hausner ratio and Carr's Index

The Hausner ratio (HF) is the relationship between D_f and D_0 and is related to interparticle friction. As such, it can be used to assess the properties of powder flow. The Carr index (CI%) is the quotient between the apparent and compact densities expressed as a percentage. The compressibility percentage indirectly gives an idea of the cohesion, size uniformity, and surface area of powders or their mixtures [3].

2.4.5. Analysis of the rate flow and the cotangent of angle α

The flow rate of the excipients was studied using a flow tester (Granulate Flow, model GWF, ERWEKA, Heusenstamm, Germany) and was determined from the flow time of the sample. The excipients (44 g) were poured through the funnel (12 mm) coupled to the equipment in non-vibration mode. The funnel was opened, and the time taken to discharge the samples was measured [46].

2.5. In vitro cytotoxicity test

Preliminary tests to evaluate the possible toxicity of the excipients were performed using the test of cell viability by MTT method, using cells from human gingival fibroblasts. The culture and isolation of the cells was described in detail by Villanova et al. [32] according to methodology developed by Carvalho et al. [47]. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) is a water-soluble tetrazolium salt that is converted to an insoluble purple formazan by cleavage of the tetrazolium ring by succinate dehydrogenase within the mitochondria. The formazan product is impermeable to the cell membranes and, therefore, accumulates in healthy cells. The MTT assay was tested for its validity in various cell lines. In the test, the amount of formazan that is produced can be correlated with the number of living cells in the sample [48].

Samples were sterilized by UV radiation. Briefly, 1×10^4 cells/mm^3 were previously seeded in 24-well plates and cultivated for 24 h. After 24 h, the entire medium was aspirated and 210 μL of culture medium together with fetal bovine serum (FBS) was placed in each well, to which was added 170 μL of MTT (5 mg/mL), followed by incubation of the plates for 4 h in an oven at 37 °C and 5% CO_2. The formazan salts were solubilized for 12 h with 10% sodium dodecyl sulfate (SDS)–HCl, and the metabolic activity was determined from the optical density at 595 nm by using a spectrophotometer (ADAP 1.6). The cell viability was determined by comparing the optical densities of samples and controls of cultures with a standard curve of 10^3–10^6 cells/mm^3. The controls used included (1) cells and Dulbecco's modified Eagle's medium (DMEM) with 10% of FBS; (2) cells and DMEM medium without FBS; (3) phosphate-buffered saline solution (PBS) as the positive control; and (4) 10 mg/ml of orthodontic wire as the negative control. All experiments were performed using triplicate assays ($n = 3$), and the data were presented as means ± standard deviation. Statistical comparisons were performed using one-way analysis of variance (ANOVA) and Bonferroni's post hoc test (GraphPad *Prism 3.0*, GraphPad *Software*, San Diego, *USA*). Differences were considered statistically significant for $p \leqslant 0.05$.

2.6. Preparation of tablets by direct compression from the synthesized polymers

A preliminary assessment of the ability of the polymers to form inert matrices by direct compression was undertaken. Tablets containing 160 mg of propranolol hydrochloride (PHCl) in a total weight of 500 mg were prepared. Polymers A and B were milled using a mortar and pestle before being incorporated into the different formulations. Tablets were prepared at a laboratory scale. Initially, all the powders were weighed and passed through 80 mesh sieves. The blend was mixed during 10 min in a mixer (model Y, POWDERMIX, Santos, Brazil), and the Aerosil® was added and blended for a further minute. Finally, the tablets were compressed in an automatic eccentric press (model CIOLA, CIOLA, Mogi das Cruzes, Brazil) using a round flat-faced punch and die set 11 mm. The compression force was 60 kN, and the compression time was varied from 30 s to 2 min. The compositions and sample designations of the tablets are shown in Table 3.

2.7. Physical evaluation of tablets

The physical properties of the tablets were evaluated according to official specifications. To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (model H15, METTLER, Toledo do Brasil, São Bernardo do Campo, Brazil). In a weight variation test, the percentage deviation for tablets of more than 300 mg is ±5%. Breaking force was measured in 20 tablets using a portable digital tablet tester (model 298/DGP, NOVA ÉTICA, São Paulo, Brazil). A tablet breaking force of about 50–60 N is considered adequate for mechanical stability. Friability was determined on 10 tablets by measuring the average weigh lost after 100 revolutions in a friabilometer (model 300.1, NOVA ÉTICA, São Paulo, Brazil). The weight loss should not be more than 1%w/w [44,45,49].

2.8. Analysis of the release profiles and kinetics of dissolution

The propranolol hydrochloride content was determined using a validated spectrophotometric procedure, at 319 nm in a spectrophotometer (model UV-1601, SHIMADZU, São Paulo, Brazil). The analytical curve in water for PHCl (chemical reference substance) was determined in the concentration range of 40–80 μg/mL. Prior to this, the potential interference in the quantification of PHCl was assessed by making physical mixtures of the drug and excipients, with subsequent acquisition of UV spectra in water, after centrifugation.

Dissolutions studies were carried out according to the method given for "Delayed Release Articles" from USP 32 [44]: pH 1.2 saline buffer solution was used in the first 2 h and then was replaced by a pH 6.8 phosphate buffer solution for 10 h. Dissolution tests were carried out with a dissolution tester (model Q850, QUIMIS, São Paulo, Brazil). The dissolution test conditions used were baskets, rotation speed of 100 rpm, 900 mL of dissolution medium

Table 3
Qualitative and quantitative composition of the tablets (all values in%w/w).

Composition	Formulation no.							
	1	2	3	4	5	6	7	8
Propranolol hydrochloride	32	32	32	32	32	32	32	32
Microcel® PH102	35	19	3	–	19	3	3	3
NWCB	32	48	64	67	–	–	–	–
Polymer A	–	–	–	–	64	–	–	–
Polymer B	–	–	–	–	–	64	–	–
PECB	–	–	–	–	–	–	48	64
Aerosil®	1	1	1	1	1	1	1	1

Table 4
Mathematical models to determine dissolution kinetics.

Model/kinetic	Relationship established
Zero-order	Amount of undissolved drug *versus* the time ($t \times$ %ND)
First-order	Natural logarithm (ln) of the undissolved drug amount *versus* time ($t \times \ln$%ND)
Higuchi model	Square root of time *versus* dissolved percentage ($t \times$ %Q)
Korsmeyer–Peppas	Natural logarithm (ln) cumulative percentage of drug released *versus* log time ($\ln Mt/M \times \ln t$)

From: Siepmann and Peppas [51]; Grassi and Grassi [52].

(37.0 ± 0.5 °C), for 12 h. Ten-millilitre aliquots were withdrawn at predetermined intervals and replaced with fresh medium pre-warmed at 37 ± 0.5 °C. Samples were centrifuged, diluted in water, and analyzed by UV spectrophotometry at 319 nm, using a 1-cm cell and water as a blank. The amount of drug released was determined from a correlation curve of PHCl (chemical reference substance) in water.

To elucidate the drug release mechanism, the dissolution data were analyzed using zero-order, first-order, Korsmeyer–Peppas, and Higuchi equations with linear regression. The Korsmeyer–Peppas model describes the drug release from a polymeric system and can be used to analyze the first 60% of drug released from the curve. The most appropriate model was selected taking into account the proximity to the linearity and considering only those points that corresponded to the ascendant phase of the curves [50–53]. The mathematical models used in this study are described in Table 4.

3. Results and discussion

3.1. FTIR spectroscopy

Polymerization of acrylic and methacrylic monomers can be characterized by the absence of peaks in the region near 1630 cm^{-1}, associated with the breaking of C=C double bond and its conversion to C—C. The absence of the 1635 cm^{-1} band (Fig. 1) suggests that the polymerization reaction was successful. A sharp intense band at 1702–1738 cm^{-1} is due to the presence of ester carbonyl group stretching vibration. Furthermore, two strong C—O stretching bands at 1238 and 1140 cm^{-1} characterize the ester groups. Other prominent bands include 1447 cm^{-1} (CH_2 symmetric bending, CH_3 asymmetric bending), 1386 cm^{-1} (CH_3 symmetric bending), and 748 cm^{-1} due to rocking CH_2 [54,55].

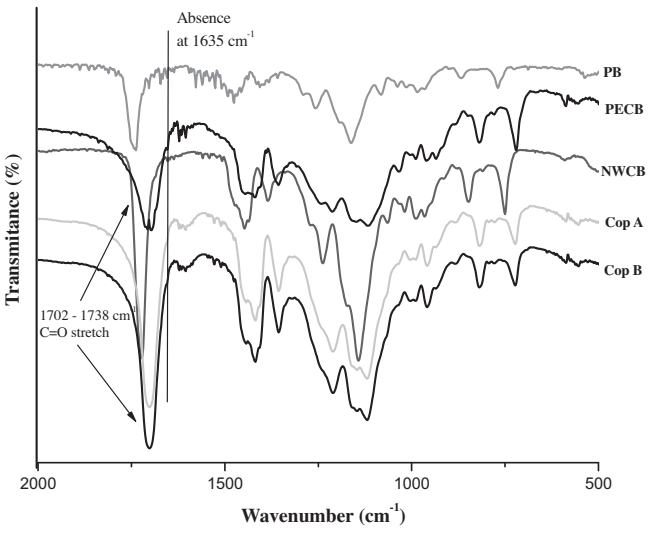

Fig. 1. FT-IR spectra of PB, CNWB, PECB beads, and polymers A and B.

3.2. Evaluation of micromeritic properties of excipients

Particle morphology is of great importance to the pharmaceutical industry. It is well known that morphology affects the flow behavior in the mixing and tablet machine equipment [32]. The scanning electron micrograph (SEM) of the CNWB beads showed that the excipient was obtained as spherical and submicron particles. SEM of the PECB beads revealed agglomerates, and this material was passed through 120 mesh before further testing (Fig. 2). Moreover, the emulsion polymerization technique and freeze-drying of the latex generated laminate materials with irregular shape and size distribution (Fig. 3).

Powders of similar particle sizes but dissimilar shapes can have markedly different flow properties owing to differences in interparticle contact areas. For example, spheres have minimum interparticle contact and generally optimal flow properties, whereas flakes or dendritic particles have a very high surface-to-volume ratio and poorer flow properties [3]. Spherical particles exhibit better flowability due to less friction between particles and between particles and equipment surfaces. In addition, spherical particles have a superior compressional behavior during the tabletting [3,5,56].

Assessment of particle morphology by SEM can be positively correlated with the results obtained from the determination of the flow through direct and indirect methods. CNWC and PECB beads exhibited higher bulk densities than other samples, most likely due to sphericity and small particle size, which favored the closer packing.

Polymeric excipients showed good packing and flowability, indicated by Hausner's ratio value and Carr's index. The Carr's compressibility index can to predict the flow properties that are used to give an indication of the ability to produce a uniform blend. CI values between 5% and 15% are indicative of excellent flow, and values between 12% and 16% represent good flow. On the other hand, values of greater than 23% and up to 35% are attributed to materials whose flow is poor. The HF given by the ratio between the bulk density and compacted density of powders is related to the cohesion and adhesion forces between particles. Hausner showed that powders with low interparticle friction, such as coarse spheres, had ratios of approximately 1.25, whereas more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.5. Therefore, it is accepted that values below 1.25 are related to a good flow, while values above 1.25 are related to a poor flow, since flow and cohesive capacity are inversely proportional [3,57].

According to the results presented in Tables 5 and 6, it is possible to conclude that CNWB and PECB beads have flow properties and compaction behavior suitable for pharmaceutical applications. Polymers A and B presented higher CI% and HF values, which can be attributed to the greater particle size and irregular morphology when compared with the beads with smaller size, spherical shape, and smooth surface, factors that favor flow. However, the flow of materials with CI% values between 18% and 35% and intermediate HF (1.25–1.5) may be improved by adding lubricants and glidants [3,11]. The results obtained in this work are consistent with the idea that the more successfully a material is consolidated during the tapped density test, the poorer its flow properties tend to be [11].

The Carr's index and Hausner ratio only reflect the potential for consolidation of powders based on the cohesiveness between the particles. To know the ease and speed of flow, it is important to determine the flow rate by mean of the time and cotangent of α

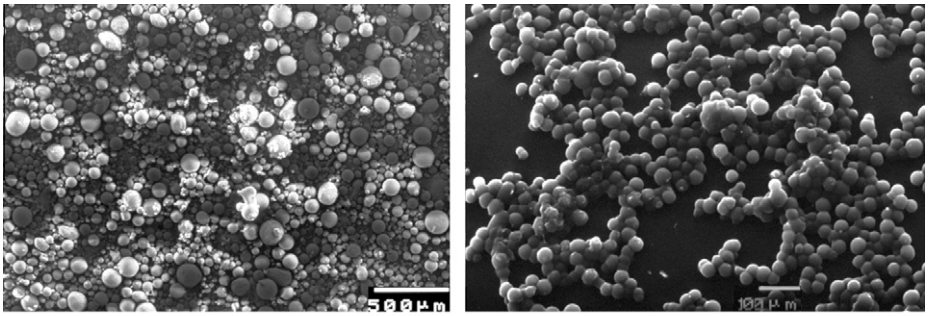

Fig. 2. SEM of NWC (a) and PECB (b) beads (magnification of 35×).

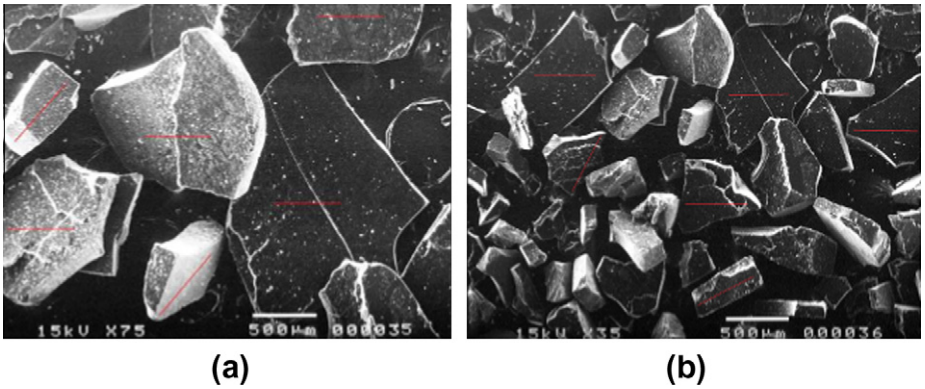

Fig. 3. SEM of polymer A (a) and polymer B (b) (magnification of 35×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

angle. The results show that all the polymeric excipients exhibit good flow, since the values of flow time and cotangent of angle α were less than 10 s and 0.1, respectively (Table 6).

It is known that both particle size and morphology affect flow behavior in blending and compression. Particle size and particle size distribution play significant roles in flowability and other properties, such as bulk density and consolidation of bulk solids. Even a small change in particle size can cause significant alterations in the resulting flowability. Reduction in particle size often tends to decrease the flowability of a given granular material due to the increased surface area [58]. Particle size also plays an important role in the consolidation of powders. Reduction in size increases the contact area between the particles, thereby increasing the cohesive forces and lowering the flow rate. An increase in particle size generally leads to an increase in consolidation (and thus volume reduction). The finer the particle size and greater the range of particle sizes, the greater the cohesive strength and lower the flow rate [59].

Fine powders and particles with irregular shape tend to exhibit reduced flow. On the other hand, coarse granules (>250 μm) are not suitable for pharmaceutical application. Powders of pharmaceutical interest should, preferably, have a particle size of less than 250 μm [2,3,11,56] or 200 μm, according to other authors [60]. The

Table 5
Apparent volumes in milliliters for the excipients.

Sample	Mass (g)	V_0	V_{10}	V_{500}	V_{1250}	V_{2500}
CNWB	36.46	60.0	57.0	55.0	55.0	–
PECB	38.35	61.0	58.0	57.0	57.0	–
Polymer A	44.90	86.0	74.0	69.0	60.0	59.0
Polymer B	43.63	87.0	77.0	69.0	64.0	62.0

Table 6
Values of tapped density (D_0), bulk density (D_f), Carr's Index, Hausner ratio, flow time, and cotangent of α angle for the excipients.

Parameters	CNWB beads	PECB beads	Polymer A[a]	Polymer B
d_0 (g/mL)	0.608	0.629	0.522	0.501
d_f (g/mL)	0.663	0.673	0.761	0.704
CI (%)	8.30	6.54	23.90	20.30
HF	1.091	1.069	1.465	1.405
Time flow (s)	0.64	1.01	1.59	0.91
α angle	0.021	0.034	0.051	0.029

[a] Vibration mode of the Erweka Granulate Flow tester was triggered.

size and particle size distribution were evaluated by laser diffraction. PB, polymer A, and polymer B were not subjected to the laser diffraction analysis due to the high proportion of particles larger than 500 μm, which is the upper limit for the equipment used.

For CNWB beads, 10% of the particles had a diameter of less than 58 μm and 50% below 145 μm. The average diameter was found to be approximately 200 μm. For PECB beads, 10% of the particles had a diameter of less than 21.8 μm, 50% below 35 μm, and the average diameter was found to be approximately 87.5 μm. The cumulative particle size distribution analysis indicated a heterogeneous size of beads for both samples, although the polydispersity index was 2.54 and 1.44 from CNWB and PECB respectively, which were considered small in the context of the analysis. Chen and Davis prepared microspheres of poly(hydroxybutyrate–hydroxyvalerate) containing diazepam and considered a polydispersity index of close to 2 as being satisfactory [61].

The particle size of polymers A and B can be estimated by the images obtained by SEM (Fig. 3). The freeze-drying process

resulted in particles with irregular and laminar shape. The size remained close to 500 μm and was larger for polymer A compared with B. The particle size of polymers may be reduced by, e.g., as grinding in a mortar and pestle or ball milling in an attempt to homogenize the particle size distribution. Consequently, parameters such as flow and compressibility can be optimized [2,3,11].

3.3. Results of average weight, breaking force, and friability

Changes in weight can cause problems during the production of solid oral dosage forms, in addition to the non-equivalence of doses. The main reasons for non-compliance of the average weight are the inadequate flow of the material to be compressed and the large size of the particles, which can lead to inadequate filling of the dies. Tablets with widely different masses tend not to be uniform in dosage, which can cause fluctuations in plasma concentrations in the drug. Another drawback may occur during packaging on automated equipment controlled by the weight of the tablet, causing delays [2,3,62]. As can be seen in Table 7, only formulations 2 and 5 did not meet the USP specifications, since more than one unit in each batch had weight variations above 10% [44].

Tablets must be able to withstand the rigors of handling and transportation in the manufacturing plant, in the drug distribution system, and in the hands of the end users. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured. One commonly employed test of the ability of tablets to withstand mechanical stress determines their resistance to chipping and surface abrasion by tumbling them in a rotating cylinder. The percentage weight loss after tumbling is referred to as the friability of the tablets. Another measure of the mechanical integrity of tablets is their breaking force (so-called hardness), which is the force required to cause them to fail in a specific plane [44].

Hardness is an attribute of interest to both the compression process, which can be used as a parameter for equipment adjustment and calibration, and the quality of the finished product. In general, the higher the compression force and the greater the consolidation and deformation of the powder in the die, the greater the contact points in the material being compacted and the lower the porosity of the tablet. There is a tendency to increase the hardness and disintegration time. On the other hand, low hardness values can be considered an indirect measure of the inefficiency of the process of consolidation and compaction of the powders in tablets. Harder tablets may be more difficult to eject from the press, but they will have lower friability [3,11,62,63].

Results showed that the samples presented a hardness of greater than 100 N, except for formulations 1 (41 N) and 5 (62 N). During compression of these latter two samples, capping and lamination were observed, indicating the occurrence of relaxation of the compact, which resulted in a higher porosity of the tablets and the highest friability values (1.54% and 3.12%, from 1 and 5, respectively). The short compression time for formulation 1 (30 s), and the large size of the particles of polymer A used in the manufacture of formulation 5, may explain the low hardness and high friability. This fact may also explain high weight variation of the tablets of formulation 5, as the flow into the die may have been irregular.

Table 7
Results of tests for quality control performed on the formulations.

Formulation	Average weight (mg) (CV%)	Hardness (*N*) (CV%)	Friability (%)
1	512.40 (5.51)	41.00 (14.54)	1.54
2	534.79 (2.19)	111.50 (10.54)	0.13
3	516.83 (4.42)	128.50 (10.60)	0.13
4	515.58 (3.24)	164.50 (8.70)	0.11
5	542.61 (3.81)	62.00 (11.90)	3.12
6	518.49 (3.85)	100.00 (12.45)	0.31
7	500.25 (5.23)	170.80 (8.90)	0.09
8	512.08 (6.22)	184.50 (7.60)	0.03

CV% = coefficient of variation.

3.4. In vitro release studies

The analytical curve of PHCl in water and the linear equation was calculated by the linear regression method ($y = 0.005x + 0.0019$). The coefficient of correlation (r) was equal to 0.99, suggesting the existence of good linear correlation between concentration and absorbance. The UV–VIS spectra were obtained in water at 319 nm – wavenumber in accordance with the literature for the PHCl [64].

To evaluate the drug release, the sink condition was initially assured by checking the solubility of the PHCl (160 mg) in 300 mL of HCl solution at buffer pH 1.2 and pH 6.8. The results indicated that the volume of dissolution medium used was appropriate. The dissolution profile is a useful tool in formulation development and can show differences in the dissolution caused by factors related to the drug, excipients, and manufacturing process. According to the results, formulation 1 showed that almost a 100% release occurred within 4 h, suggesting poor matrix integrity with a release profile equivalent to an immediate release product. The fact can be corroborated by the low hardness found for this specific sample. An increase in compression time, coupled with the increase in the amount of excipient, changed the release profiles. For sample 2 (ratio drug/excipient equals 1:1), it took 7 h for the release of approximately 95% of the drug, whereas for sample 3 (1:1.5), the same amount was released in 10 h. However, the increase in compression time for formulation 4–2 min produced 90% release of the drug after 12 h of testing [32].

Formulations 5, 6, 7, and 8 were compressed for 2 min. The release profiles are presented in Fig. 4. In formulation 5, containing polymer A as a matrix, the entire drug was released in within 6 h, and the tablets suffered total breakdown during the test. For formulation 6, produced with polymer B, the release time was approximately 10 h. Formulations 7 and 8, both prepared with the polymer BPEC beads in proportions of 48 and 64% w/w, respectively, showed adequate release profiles. For formulation 7, 85% of PHCl was released after 12 h, while for formulation 8, 67% of the drug was released after 12 h. The tablets remained intact during the test.

In addition to the compression force, the duration of the compression cycle and the duration of the compression time are parameters that influence the tablets final properties. At low compression forces, a longer period of time is required for the consolidation and rearrangement of the matrix material. Modern tablet machines, especially rotary, work in two stages (a pre-compression followed by compression itself) and exert forces that can exceed 100 kN. One advantage of the rotary tablet machine is that it operates at high speed and applies pressure on both sides of the tablets, promoting more homogeneous densification [3,11,65,66]. In this study, an eccentric device was employed, which explains the increase in compression time from 30 s to 2 min (time that the material stayed about compression force). From the analysis of the dissolution profiles, the increase in compression time contributed to the formation of matrices that released the drug for longer periods of time.

Although hardness is not an attribute that can be directly correlated with drug release, a higher hardness value may be advantageous to maintaining tablet integrity and controlling drug delivery. From a comparison of the release profiles, tablets with a greater hardness showed a more prolonged release of PHCl, most likely because the tablets were less porous, limiting the rate of

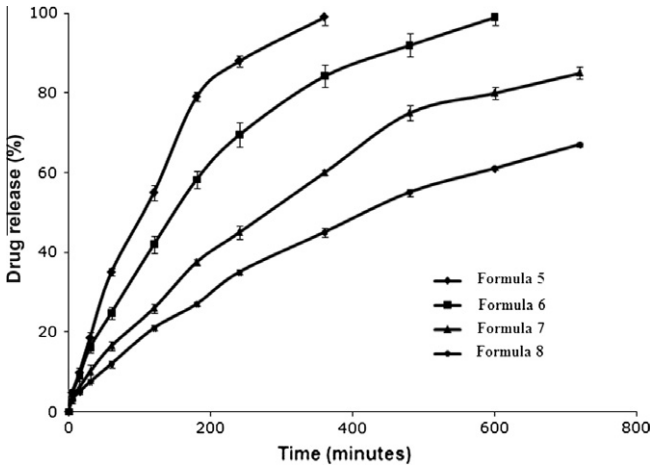

Fig. 4. Release profiles of PHCl in tablets containing polymer A (5), polymer B (6), and PECB beads 48 and 64%w/w (7 and 8, respectively) as excipient matrix forming ($n = 6$).

penetration of the dissolution medium and reducing the rate of drug release. These results are consistent with those obtained by other authors who used acrylic polymers in the preparation of matrices [59,67,68]. As can be seen in Fig. 5, the tablets remained intact at the end of the dissolution test, without showing erosion of the matrices.

Knowledge of the kinetics of tablets dissolution is a fundamental step in the development of modified release dosage forms [69–71]. The mathematical models applied *in silico* are an option for the optimization of formulations; therefore, they can provide information concerning the mass transport involved in the drug release, considering factors such as geometry, type of polymer, and porosity. The kinetic models can be subdivided into two categories: (1) diffusion models that involve a transport mechanism by diffusion with components of degradation and (2) models that combine diffusion with theories such as erosion, dissolution, and leaching, among others [72–75].

To understand the drug release mechanisms from these formulations, data were treated according to zero-order, first-order, and Higuchi and Korsmeyer–Peppas equations. The calculated values for the correlation coefficient (r) are presented in Table 8. The obtained results showed that the models that best fit the formulations followed the Higuchi and Korsmeyer–Peppas equations, indicating that diffusion was the main component of release. These results are in accordance with several authors who have studied drug release from inert matrices [41,76–78]. As formulation 1 broke down during the first hours of testing, its kinetics was not evaluated.

The release exponent (n) characterizes the release mechanism. For geometrical cylinder shapes, values of n can range between 0.45 and 0.89. Values of $n \leqslant 0.45$ indicate the Fickian diffusion mechanism. Values of $0.45 < n < 0.89$ indicate non-Fickian diffusion, whether or not coupled with diffusion/polymer relaxation. Finally, values of $n > 0.89$ indicate transport mechanism type II. Since the form of tablets obtained was cylindrical and the values of n for the formulations 4, 7, and 8 were $\leqslant 0.45$ (0.382, 0.412, and 0.256, respectively), it may be suggested that for these formulations, the release of PHCl occurred by a Fickian diffusion mechanism, since there was no swelling and polymer relaxation, as would be expected in cases of anomalous transport [79]. The n values for the other formulations were not determined because the release profiles were not considered appropriated for sustained release formulations.

3.5. Viability assay

Cellular viability studies showed that gingival fibroblasts were viable in cultures that came into contact with the beads (CNWCB and PECB) and the polymers (A and B). It could be observed that, in the control groups (control and 1 negative control), cell viability was approximately 100% (Fig. 6). However, there was no statistical difference in cell viability in the presence of these experimental excipients when compared with the control groups after 24 h. This result demonstrates that gingival fibroblast viability is not modified in the presence of the samples, which indicates they are likely to be non-cytotoxic. The results of cell viability by MTT were preliminary, and the toxicity of these new excipients should be evaluated in future studies using other techniques.

4. Conclusions

Strategies for success in the design of oral drug delivery systems require the study of the physical properties of the excipients. The excipients prepared by the suspension polymerization, in the form of beads, formed more suitable matrices, possibly due to better flow and compressibility of the bulk when compared with freeze-dried polymers (A and B). The compression time and the type and amount of polymer used influenced friability, hardness, and drug release. The dissolution profiles showed that the proposed formulations produced with 64%w/w of CNWB, 48%w/w of PECB, and 64%w/w PECB formed inert matrices that did not erode and released the PHCl for a period exceeding 12 h. Changes in profiles and release kinetics were most likely due to the difference in nature of the matrices. Acrylic and methacrylic excipients tend to undergo plastic deformation. This led to the formation of harder,

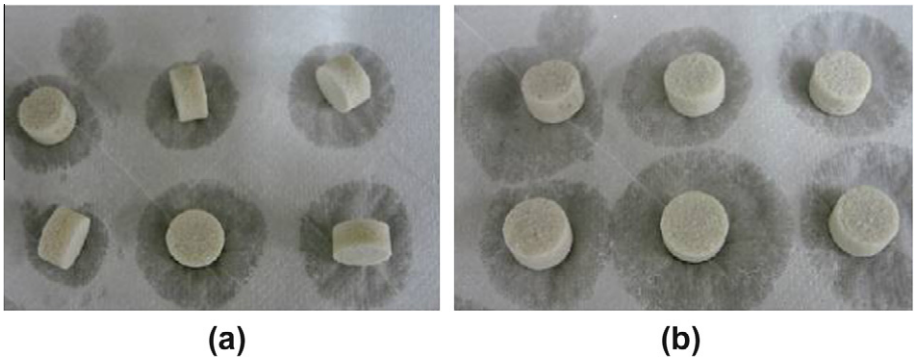

Fig. 5. Photographs of the tablets of formulations 7 and 8 containing 48% (a) and 64% w/w (b) PECB beads as excipient after a 12-h dissolution test. The tablets remained intact.

Table 8
Kinetic assessment: correlation coefficient (r) of kinetics model.

Model	2	3	4	5	6	7	8
Zero-order	0.9632	0.9628	0.9536	0.9578	0.9557	0.9782	0.9841
First-order	0.9551	0.9523	0.9518	0.9456	0.9681	0.9954	0.9989
Higuchi	**0.9997**	**0.9995**	0.9949	**0.9939**	**0.9944**	0.9977	0.9965
Korsmeyer–Peppas	0.9672	0.9546	**0.9987**	0.9888	0.9920	**0.9980**	**0.9990**

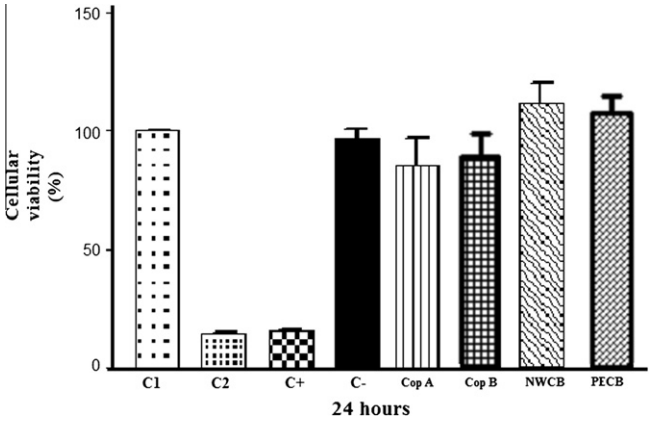

Fig. 6. Cellular viability of excipients obtained by MTT assay after 24 h ($n = 3$; $p \leqslant 0.05$).

less friable tablets with lower porosity, reducing the penetration of the dissolution medium and the release rate of PHCl. It was suggested that the contribution of acrylic polymers in forming the plastic matrix was the limiting factor for drug release. Another advantage that can be associated with the developed excipients was the need not to add other ingredients in the formulations, since the beads acted as filler-binders in the direct compression process. However, the beads (CNWCB and PECB) are hydrophilic and swell slightly in water, but do not significantly change. Thus, they can also be used in the wet granulation process. Finally, the results of the cell viability test indicated that all acrylic polymers produced may be non-cytotoxic and could be biocompatible for pharmaceutical applications.

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