Journal of Pharmaceutical Sciences 105 (2016) 231–241

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Preparation and Characterization of Amylose Inclusion Complexes for Drug Delivery Applications

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ARTICLE INFO

Article history:
Received 4 May 2015
Revised 21 July 2015
Accepted 22 September 2015
Available online 18 November 2015

Keywords:
inclusion complexes
high amylose
nimesulide
praziquantel
controlled release
solid state NMR
X-ray diffractometry
calorimetry (DSC)
dissolution

ABSTRACT

Amylose complexes with nimesulide (NMS) and praziquantel (PZQ) were prepared by a simple and low cost method, so that high yield (>57%) and drug content (up to 68.16%) were achieved. The influence of drug:polymer ratio, temperature, and presence of palmitic acid on the complexes properties was evaluated. Differential scanning calorimetry, X-ray diffraction, and nuclear magnetic resonance data evidenced the drug–polymer interaction and the formation of inclusion complexes with semi-crystalline structures related to type II complexes. The drug release rates from complexes were lowered in acid media (pH 1.2) and phosphate buffer (pH 6.9). The presence of pancreatin promoted a significant acceleration of the release rates of both drugs, evidencing the enzymatic degradability of these complexes. The highest enzymatic resistance of PZQ1:30PA60°C complex makes the release time longer and the full release of PZQ in phosphate buffer with pancreatin occurred at 240 min, whereas the complexes with NMS and PZQ1:5PA90°C did it in 60 min. According to the Weibull model, the drug release process in media without enzyme occurred by complex mechanisms involving diffusion, swelling, and erosion. In media containing pancreatin, generally, the better correlation was with the first order, evidencing the acceleration of the release rates of drugs in the early stages of the test, due to enzymatic degradation.

Introduction

Among the different routes of drug administration, the oral route is the most used in the therapy because it is a noninvasive and easy route of administration, allowing a greater acceptability of the patient and dose flexibility.[1-5]

Conventional oral dosage forms allow a quick drug release after administration and repeated doses are required, which might lead to the dose fluctuation, increasing the risk of reaching subtherapeutic or toxic levels, which compromise the therapeutic response.[6-8]

Therefore, the temporal and spatial control of drug delivery is of great interest in the research and development of new drug delivery systems, as it represents a valuable strategy to enhance the therapeutic response. Different approaches can be exploited, concerning formulation and/or technologies, such as the controlled release systems that are designed to modulate the release rates over the gastrointestinal (GI) tract, allowing the drug release in a sustained or targeted way.

Starch is of particular interest in the design of innovative drug delivery systems because of its wide availability, low cost, and biodegradability, as it undergoes chemical degradation *in vivo* by enzymatic hydrolysis, resulting in non-toxic products.[9-12]

Starch consists of a mixture of two different polymers, amylose and amylopectin. Amylose has a linear structure composed by units of D-glucose linked together by D-glycosidic bonds (1→4), and amylopectin is a very large, highly branched molecule containing D-glucose units linked by glycosidic bonds α (1→6).[13-15]

The α (1–4) configuration of amylose allows a helical shape, building inclusion complexes with hydrophobic ligands. During formation of inclusion complexes, helical structures are organized so that the hydroxyl groups are disposed on the outer surface of the helix, whereas glycosidic oxygen and methylene groups are faced to the inner core resulting in a more hydrophobic cavity, which provides binding sites with high affinity with hydrophobic ligands.[16-18]

In memory of Raul Cesar Evangelista.

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http://dx.doi.org/10.1002/jps.24702
0022-3549/

The complexes can be organized in different structures, such as type I structures (amorphous or disordered), polymorphs A and B (double helix) and polymorph V, which has been associated with the formation of complex type II (single helix), that provides higher enzymatic resistance.[10,12,17,19-22]

The release of the ligands occurs by enzymatic hydrolysis of the complexes in two steps: initially, a rapid hydrolysis of amorphous areas of the complexes[23,24] and, subsequently, a slow degradation of the crystalline areas of them (influenced by the size of the amylose chain and lipid).[25]

The rate of hydrolysis also depends on the enzymatic activity so that at low enzymatic activity, as presented by salivary enzymes, only the amorphous portions are hydrolyzed and then the more crystalline structures of the complex are hydrolyzed in the small intestine by the action of pancreatin enzyme, firstly, type I complexes and then more crystalline complexes such as complex type II.[17,26]

In this work, high amylose complexes with nimesulide (NMS) and praziquantel (PZQ) were prepared and characterized by analyzes of yield of complexes, content of complexed drug, differential scanning calorimetry (DSC), X-ray diffraction (XRD), nuclear magnetic resonance (NMR), and liquid uptake. The potential as site-specific drug delivery systems was evaluated by *in vitro* dissolution test.

Materials and Methods

Materials

High amylose (Hylon VII, 70% amylose, 30% amylopectin) was obtained from National Starch & Chemical (Bridgewater, NJ); sodium hydroxide (NaOH) was supplied by Synth (Diadema, São Paulo, Brazil); hydrochloric acid was provided by Quimis (Diadema, São Paulo, Brazil); PZQ was obtained from Valdequímica (São Paulo, São Paulo, Brazil), palmitic acid (PA); pancreatin were provided by Sigma–Aldrich (St. Louis, MO); and NMS and sodium lauryl sulfate (SLS) were from Henrifarma (São Paulo, São Paulo, Brazil).

Preparation of Inclusion Complexes

The inclusion complexes of NMS or PZQ with high amylose were prepared based on procedures described by Bhosale and Ziegler[27] and Putseys et al.,[17] with some modifications.

A predetermined amount (5% by dry mass of high amylose) of PA was dissolved in 10 mL of an alcoholic solution of drug (NMS or PZQ) at different concentrations (0.6, 0.2, and 0.1 g/mL). This solution was vigorously mixed with high amylose in a mortar, getting systems at different drug:high amylose ratios (1:5, 1:15, and 1:30). Alcohol evaporation was allowed at room temperature and the systems were dispersed in purified water (10%, w/v) and incubated at 60°C or 90°C, by 2 h. Samples without PA were also prepared according the same procedure, excluding this material.

The samples were labeled according to the drug name abbreviation followed by drug–polymer ratio (1:5, 1:15, or 1:30), presence of PA and temperature of incubation (60°C or 90°C) (Table 1).

Complexes Yield

The yield of the complexes was calculated according to Eq. (1). For the complexes prepared without PA, this term was excluded from the equation.[28]

Table 1
Labels of Inclusion Complexes, Complexes Yield, and Content of Complexed Drug

	Samples	Yield (%)	Content of Drug (%)
NMS temperature 60°C	NMS1:5PA60°C	73.73	2.79
	NMS1:560°C	83.13	8.55
	NMS1:15PA60°C	70.36	28.79
	NMS1:1560°C	74.78	30.16
	NMS1:30PA60°C	75.75	52.16
	NMS1:30 60°C	74.39	43.18
NMS temperature 90°C	NMS1:5PA90°C	74.13	36.45
	NMS1:590°C	77.82	18.89
	NMS1:15PA90°C	86.77	39.55
	NMS1:1590°C	99.06	26.12
	NMS1:30PA90°C	72.98	45.32
	NMS1:30 90°C	82.55	37.13
PZQ temperature 60°C	PZQ1:5PA60°C	62.94	52.18
	PZQ1:560°C	62.60	26.44
	PZQ1:15PA60°C	60.48	56.78
	PZQ1:1560°C	57.31	29.88
	PZQ1:30PA60°C	67.88	68.16
	PZQ1:3060°C	59.42	63.16
PZQ temperature 90°C	PZQ1:5PA90°C	57.86	65.13
	PZQ1:590°C	63.29	23.56
	PZQ1:15PA90°C	84.45	51.15
	PZQ1:1590°C	70.49	53.16
	PZQ1:30PA90°C	64.62	19.89
	PZQ1:3090°C	66.39	43.16

$$\text{Yield } (\%) = \frac{\text{Mass (complexes)}}{\text{Mass (high amylose + PA + drug)}} \times 100 \quad (1)$$

Content of Complexed Drug

A known mass of the complexes (about 15 mg) was incubated in 1 mL of pancreatin solution at 37°C, by 24 h. After the complete digestion of the complexes, the drugs were extracted with ethanol and quantified by spectrophotometry in the UV–vis (NMS—298 nm; PZQ—264 nm). The percentage of complexed drug was determined according to equation (2).[2,10,28,29]

$$\text{Drug complexed } (\%) = \frac{\text{Mass drug quantified in pancretin sol.}}{\text{Theorical mass of drug of the complexes}} \times 100 \quad (2)$$

For preparing the pancreatin solution, 0.177 g of pancreatin was dissolved in 20 mL of phosphate buffer 20 mM (pH 6.9) containing NaCl (0.04%). This solution was centrifuged (352 × g/10 min), filtered and the supernatant was used for the test.

Differential Scanning Calorimetry

Thermal behavior of isolated materials (high amylose, NMS, PA, and PZQ), physical mixtures (NMS PM1:5; NMS PM1:5PA, PZQ PM1:5, and PZQ PM1:5PA) and complexes (Table 1) were analyzed on a DSC1 STARe System-Mettler Toledo. The samples (about 5 mg) were weighed in stainless steel pans (100 μL) and heated from 25°C to 200°C, at 10°C/min under nitrogen atmosphere.

X-Ray Diffraction

The diffractograms of drugs (NMS and PZQ), polymer (high amylose) and the complexes were recorded on a X-ray diffractometer (Siemens®, model D5000) with goniometer speed of 0.02/min, under irradiation of Cu-Kα ($\lambda = 15406$ Å) in a scanning region from 4° to 70° (2θ).