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Comparison of the properties of implantable matrices prepared from degradable and non-degradable polymers for bisphosphonate delivery

Tamás Sovány*, Anna Csüllög, Ernő Benkő, Géza Regdon Jr., Klára Pintye-Hódi

Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, H-6720, Eötvös u. 6, Szeged, Hungary

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ABSTRACT

The aim of the present study was the development of directly compressed tablets for implantable delivery of risedronate sodium for osteoporosis treatment and the comparison of the mechanism and kinetics of drug release from biogradable (chitosan) and non-degradable (PVC) polymer matrices.

The compositions and process parameters were optimized in accordance to a mixed 2 and 3 level full factorial design. Critical Quality Attributes (CQA), such as diametral breaking hardness, porosity and speed of drug dissolution were investigated.

The results revealed significant differences between the behaviours of the two polymers. Chitosan exhibited poor compressibility, which resulted in poor mechanical properties and the fast disintegration of chitosan based tablets. Nevertheless, despite the fast disintegration, the chitosan based matrices exhibited one-week-long continuous drug release, which can be due to a strong drug-carrier interaction. The presence of intermolecular hydrogen bonds was confirmed with FT-IR and NIR measurements.

In contrast, PVC based compositions exhibited excellent compressibility, good tablet hardness and low porosity. The tablets remained intact during the dissolution and exhibited a slower release rate than what was measured in the case of chitosan based matrices. There was no sign of intermolecular association on NIR spectra, suggesting that the dissolution rate is basically determined by the porosity of tablets, but FT-IR measurements revealed some details of the molecular background of drug release mechanism.

1. Introduction

Bisphosphonates are widely used drugs for osteoporosis treatment, but have poor (approx. 0.4–0.7% of iv.) oral bioavailability and severe side effects, such as irritation and necrosis of the gastrointestinal mucosa (Cadarette et al., 2009). Some experimental results suggest the effect of bisphosphonates on gastric mucosa is based on the modification of the hydrophobicity of the phospholipid bilayer surfaces. The strength of this effect was different amongst the investigated bisphosphonates and risedronate exhibited the lowest effect (Lichtenberger et al., 2000). This result was in accordance with the findings of Thomson et al. (2002), who confirmed that risedronate exhibits considerably higher safety over alendronate from the aspect of mucosal irritation applied in the regularly used 5 or 10 mg doses in daily oral administration. Based on these results, the use of risedronate may be generally considered as safe also in alternative routes.

Numerous investigations confirm that the long term local delivery of bisphosphonates has a great advantage in bone regeneration after injuries (Hur et al., 2016) or implantation of hip or femoral neck prosthesis (Peter et al., 2005; Mazurkiewicz et al., 2013). In these studies, the drug was mixed into the bone cement (Mazurkiewicz et al., 2013), the hydroxyapatite coating of the titanium implant (Peter et al., 2005) or into the modified chitosan coating of a commercial bone platelet (Hur et al., 2016), which ensured the targeted local delivery of the drug to the injured bone parts. Under these conditions a 4 μg daily dose may be enough to ensure successful bone remodelling under a 2-month treatment period, without any sign of adverse reactions or cytotoxic effect. The lack of cytotoxicity in the case of extended release local delivery suggests that the adverse reactions related to the irritative effect of bisphonates are dose dependent and the use of controlled release implants may help to overcome the limitations and risks of oral, intravenous or intramuscular injection use, offering a good way for the systemic delivery of these drugs in osteoporosis, where localized therapy cannot be used due to the generalized nature of the disease (Perugini et al., 2001).

There are numerous methods for implantable delivery of drugs using passive (degradable or non-degradable reservoir or

* Corresponding author.
E-mail addresses: t.sovany@pharm.u-szeged.hu, sovanytamas@gmail.com (T. Sovány).

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monolithic matrix systems, micro- or nanospheres) or active (osmotic or programmable pump systems) release and delivery of drugs (Anselmo and Mitragotri, 2014; Kleiner et al., 2014). Although the use of pump systems may ensure a better control on drug release, the production of reservoir or monolithic systems is easier and cheaper, therefore they are currently of greater interest from the industrial aspect. Although the use of degradable (chitosan, polylactide (PLA), poly(lactide-*co*-glycolide) (PLGA) or polythiourethane) polymers is considerably more advantageous as compared to non-degradable (polyvinylchloride (PVC), poly(dimethyl siloxan), polyurethanes (PU), polyethylene (PE), poly (ethylene-co-vinyl-acetate) (PEVA), poly(methyl methacrylate (PMMA)) ones because the removal of the device after the complete release of the drug is not necessary, it is a major drawback that the release rate is concurrently determined by diffusion, erosion and the degradation rate of the polymers. In comparison, the release from non-degradable matrices is completely diffusion determined (Avgoustakis and Nixon, 1991; Krier et al., 2014; Campiñez et al., 2015).

The aim of present study was therefore the comparison of the potential of biodegradable (chitosan) and non-degradable (PVC) polymers as directly compressed, polymer based monolithic matrices for the implantable delivery of risedronate sodium based on the evaluation of mechanical properties and mechanism and rate of the drug release.

PVC is a widely used polymer for fabrication of medical and drug delivery devices, and was maybe first polymer used for compression of non-degradable, "inert" polymer matrices, despite of the various compressibility depending of the grade used (Rime et al., 1997). Due to its chemical inertness, the drug release is determined by the physical parameters (e.g. pore size and volume distribution) of the matrix, and is not affected by drug-polymer interactions. In contrast, the free amino side chains of chitosan are highly capable to form various physico-chemical interactions (e.g hydrogen bonds or polyelectrolyte complexes) with drugs or polymers, which may significantly influence the drug release rate from chitosan matrices (am Ende and Peppas, 1997; Puttipipatkhachorn et al., 2001; Szakonyi and Zelkó, 2016). The formation of polyelectrolyte complexes is common in chitosan nanoparticles or films, where the free amino groups of the chitosan are undergoing protonation during the dissolution in diluted acids (Phaechamud et al., 2000; Khunawattanakul et al., 2011), but not evident in the case of matrix tablets, where the chitosan is in mostly deprotonated form during preparation (AlKhatib et al., 2008; Sogias et al., 2012). Under these circumstances the formation of polyelectrolyte complexes may be expected only in the GI tract, if the deprotonation of the jellified chitosan in the small intestine is slower as the dissociation of the drug (Li et al., 2013, 2014, 2015; Shao et al., 2015). Therefore, in present study where the dissolution medium is slightly alkaline, the formation of drug-polymer interactions is unexpected (Rege et al., 2003).

2. Materials and methods

2.1. Materials

Risedronate sodium was kindly gifted by TEVA Pharmaceuticals Plc. (Debrecen, Hungary). This drugexhibits excellent (10,4 mg/ml) aqueous solubility its strongest acidic pKa is −0.68. These properties are resulted in an extremely low permeability (logP = −0.75), which may explain its poor oral bioavailability. The non-degradable Halvic PVC powder (MW: 60–150 kDa) and the lubricant calcium stearate were supplied by Gedeon Richter Plc. (Budapest, Hungary). Biodegradable, 1000 cP average viscosity and 80% deacetyled chitosan (MW: 400–600 kDa) was purchased from Heppe Medical Chitosan GmbH (Halle an der Saale, Germany).

The chemical structures of the compounds may be seen in Fig. 1.

2.2. Methods

2.2.1. Preformulation studies

The flow properties (flow time, angle of repose, bulk density) of the powders were studied with a Pharmatest PTG-1 (Pharmatest GmbH, Germany) powder rheological tester.

The plasticity of materials and mixtures was determined with a computer-connected Korsch EK0 eccentric tablet press (E. Korsch Machienenfabrik, Berlin, Germany), instrumented with strain gauges on both punches and a displacement transducer (Micropulse, BTL5-A11-M0050-P-532, Balluff, Germany) on the upper punch. The strain gauges were calibrated with a Wazau HM-HN-30kN-D cell (Kaliber Ltd., Budapest, Hungary). The transducer distance accuracy was checked by using five measuring pieces of accurately known thickness (1.0, 2.0, 5.0, 7.5 and 10.0 mm) under zero load (Mitutoyo, Tokyo, Japan). The materials were filled into the die and compressed manually (to ensure similar conditions for the well- and poorly-compressible materials) in the compression

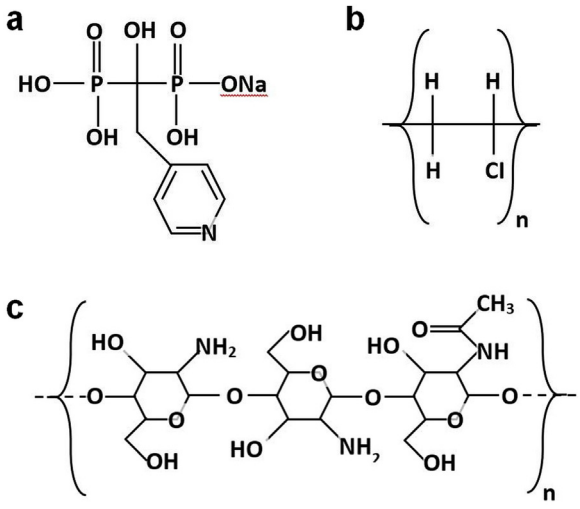

Fig. 1. Chemical structures of risedronate sodium (a), PVC (b) and chitosan (c).

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