Results in Pharma Sciences 1 (2011) 80–87

Contents lists available at SciVerse ScienceDirect

Results in Pharma Sciences

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

The application of co-melt-extruded poly(ε-caprolactone) as a controlled release drug delivery device when combined with novel bioactive drug candidates: Membrane permeation and Hanson dissolution studies

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ARTICLE INFO

Article history:
Received 21 July 2011
Received in revised form
17 November 2011
Accepted 18 November 2011
Available online 25 November 2011

Keywords:
Melt extrusion
Permeation
Release
Poly(ε-caprolactone) (PCL)
Bioactive drugs

ABSTRACT

Eight bioactive drug compounds (abamectin, amoxicillin, dexamethasone, dexamethasone valerate, ketoprofen, melatonin, oestradiol 17β, and oestradiol benzoate) were combined via melt extrusion and disc pressing processes with a polycaprolactone (PCL) matrix and were then evaluated and compared via membrane diffusion and Hanson dissolution studies. This investigation was to determine the potential of this matrix to act as a controlled release drug delivery vehicle for a number of drugs not previously combined with PCL in a melt extrusion mix. The inclusion of the progesterone/PCL system, for which the drug release behaviour has been well studied before was intended for comparison with the PCL systems incorporating drugs that have received little research attention in the past. Initial studies centred on an evaluation of the permeation ability of the bioactive drugs dissolved in aqueous cyclodextrin solutions through a poly(ε-caprolactone) (PCL) membrane using Valia-Chien side-by-side cells. Permeation rates were mostly low and found to range from 0 to 122 $\mu g\ h^{-1}$ with only ketoprofen, melatonin, and progesterone displaying rates exceeding 20 $\mu g\ h^{-1}$. Hanson dissolution release profiles in aqueous alcohol were subsequently measured for the 9 melt extruded PCL/drug combinations and led to Hanson release rates of 0–556 $\mu g\ cm^{-2}\ h^{-0.5}$ with dexamethasone, dexamethasone valerate, ketoprofen, melatonin, and progesterone giving values exceeding 100 $\mu g\ cm^{-2}\ h^{-0.5}$. A number of drugs such as the dexamethasones probably performed better than they did in the permeability rate measurements because of the less polar aqueous alcoholic solvent used. In searching for useful correlations between the drug physicochemical properties and release rate, only a moderate correlation ($R^2 = 0.5675$) between Hanson dissolution release rate and permeation rate was found. This suggests that the release rate and the permeation are both controlled by the rate of drug diffusion through the PCL with release rate involving an additional dissolution process (of the drug) before permeation occurs accounting for the moderate correlation. In general, of the eight drugs considered, it was clear that the oestradiol-based drugs, abamectin, and amoxicillin were generally not suited to drug delivery via PCL under the conditions used. However, ketoprofen was found to be very suitable as a drug candidate for melt extrusion with PCL with dexamethasone valerate, dexamethasone, and melatonin also showing potential as candidates though to a much lesser extent.

1. Introduction

Physical approaches to drug delivery involve the incorporation of the drug with some form of synthetic polymer. Examples include melt-extruded drug-bearing films, capsules, or particles (inert or bio-erodible) that can be applied to the skin, taken orally, implanted subcutaneously, injected, or inserted into various body cavities [1–5]. The kinetics of release for the system becomes a property of the polymer matrix (physical attributes) [6] and drug used (physicochemical properties) [7]. Physical approaches of drug delivery are good for sustained drug action throughout the body or for maintaining high levels within a particular body compartment (example, intravaginal). The principle behind physical drug delivery systems is a sustained drug level through balancing the pharmacokinetic processes and the drug-release

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doi:10.1016/j.rinphs.2011.11.002

characteristics of the polymer used [8,9]. It is in this category that a great deal of work has been carried out to investigate the possibility of oestrus control (examples, progesterone and oestradiol) via an intravaginal drug delivery system in both humans and livestock [10].

The need for developing the intravaginal drug delivery route has been driven by the inability of existing routes to achieve the clinical requirements desired by the animal industry (veterinary and farming). From its infancy in the 1960s, that saw the first trials using polyurethane sponges for delivering progesterone, has evolved an industry whose potential is far from reached. Animal, veterinary, and plastic engineering scientists [10] initiated an explosion in design concepts with little input from formulation scientists, the outcomes of which were some inherent pharmaceutical problems (drug load, excessive vaginal discharge). Too rapid development of these delivery systems led to commercial availability within two years of conception, another contributing factor to the inherent problems [10]. Only recently has a more rigorous pharmaceutical science approach been applied to investigate the viability of the intravaginal route and already many innovations have resulted especially in the field of oestrus control (examples include the active delivery device, C-shaped plasthyd device, CIDR, Cue-mate, intelligent breeding device, INVAS, PCL, PRID, Rajamehendran rubber tubing, Ring, Rod, and Sponges) [11–14]. Many of these devices are expensive, difficult to manufacture, or persist in the environment, the noticeable exception being poly(ε-caprolactone) (PCL), a simple, relatively inexpensive and biodegradable polymer [15]. The successful melt-extrusion of progesterone and PCL for the oestrus control of cattle has shown that sustained drug delivery from this simple matrix device is commercially viable. The manufacture of these devices also is relatively cost effective with the added benefit that the biodegradation products have been shown to have a low impact on the environment [14].

The viability of incorporating bioactive drug compounds into a melt-extruded matrix system like PCL polymer can be achieved without costly animal trials through some relatively inexpensive *in vitro* methods. Side-by-side cell permeation trials can indicate any innate potential for the drug to diffuse through the polymer before incorporation through, for instance, melt-extrusion with the polymer can be considered. Dissolution experiments with the melt-extruded drug/polymer matrix may then be carried out to show the relative release rates of the drug from the polymer indicating the potential therapeutic levels possible. SEM analysis of the morphology of a matrix system can also highlight features as a result of the combining of the drug and polymer.

Currently the principal commercial applications of intravaginal drug delivery are in providing end users (veterinary professionals, farmers) a convenient means of oestrus control in production animals (dairy, meat, and equine) [10]. Little is known about the use of this pathway to administer *other* drugs such as antibiotics or anthelmintics. Presently, a successful PCL device [14] is available for the controlled delivery of progesterone regulating the oestrus cycle of cattle and PCL as a vehicle has been studied before (along with other melt extrudable matrices) in the delivery of various drugs [16], but there is sparse drug delivery-associated literature available for PCL melt extruded with other potentially useful bioactive drug compounds such as abamectin, amoxicillin, dexamethasone, dexamethasone valerate, ketoprofen, melatonin, oestradiol 17-β, and oestradiol benzoate The aim of this research, therefore, was to investigate the melt extrusion of these particular drugs with a PCL platform for the controlled release delivery of these bioactive drug compounds. It was also the aim of this paper to correlate release rate from (and permeation rate through) PCL with the physicochemical properties of the drugs tested to gain insights into drug delivery behaviour. The progesterone/PCL system was included in this study for comparison as this has been studied extensively before [14]. The intended target receptors for devices containing such drugs could be, among others, the vaginal mucosa of cattle and this has dictated the release medium used for the Hanson dissolution work carried out in this study (namely aqueous alcohol mixtures) which are intended to simulate the amphiphilic nature of the vaginal and other biological membranes with respect to dissolution of drug from the drug-containing PCL matrices.

2. Materials and methods

2.1. Materials

Table 1 lists the drugs considered in this study together with their medical application and melting points.

Abamectin (94.3%) was supplied by Ancare NZ Ltd, New Zealand, with amoxicillin (99.2%) being supplied by Biochemie, Austria. Ketoprofen (100.1%) was supplied by Bidachem, Italy while melatonin (99.0%) was supplied by Flamma, Italy. Oestradiol 17-β (99.4%) and oestradiol benzoate (100.0%) were supplied by Gedeon Richter Ltd, Budapest, and progesterone (99.5%) was supplied by DEC manufacturing (NZ) Ltd. Dexamethasone (99.0%) and dexamethasone valerate (101.0%) were supplied by Crystal Pharma, Spain and were regarded as two differently behaving drugs in this study because of the presence of the valerate functionality in the latter drug. Results from these two dexamethasone drugs are hence reported as separate substances. PCL powder (Capa 6806, Batch #003046/2C) was sourced from Solvay caprolactones, UK. Hydroxy propyl beta cyclodextrin (HPβCD) was from Sigma-Aldrich, Australia. All chemicals and reagents were used as received from the various suppliers. All water used was doubly distilled on a glass still.

Table 1
The bioactive class and melting points[a] of the drug candidates considered for melt extrusion into PCL.

Bioactive compound	Bioactive class	mp (°C)
Abamectin	Anthelmintic	155–157
Amoxicillin ((6*R*)-6-[α–D-(4-hydroxyphenyl)glycylamino]penicillanic acid)	Anti-biotic	194
Dexamethasone (Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16α)-)	Hormone	255 D[b]
Dexamethasone valerate (Pregna-1,4-diene-3,20-dione,9-fluoro-11β,17,21-trihydroxy-16α-methyl-, 17-valerate)	Hormone	192
Ketoprofen (2-[3–benzoylphenyl] propionic acid)	Anti-inflammatory	94
Melatonin (*N*-acetyl-5-methoxytryptamine)	Hormone	117
Oestradiol 17-β (estra-1,3,5(10)-triene-3,17β-diol)	Hormone	173
Oestradiol benzoate (estra-1,3,5(10)-triene-3,17β-diol 3-benzoate)	Hormone	191–198
Progesterone (pregn-4-ene-3,20-dione)	Hormone	126–130

[a] Values are obtained from Refs. [36–39].
[b] Decomposes on melting.