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# The application of co-melt-extruded poly( $\epsilon$ -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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## ABSTRACT

Eight bioactive drug compounds (abamectin, amoxicillin, dexamethasone, dexamethasone valerate, ketoprofen, melatonin, oestradiol 17 $\beta$ , 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( $\epsilon$ -caprolactone) (PCL) membrane using Valia-Chien side-by-side cells. Permeation rates were mostly low and found to range from 0 to 122  $\mu\text{g h}^{-1}$  with only ketoprofen, melatonin, and progesterone displaying rates exceeding 20  $\mu\text{g h}^{-1}$ . 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  $\mu\text{g cm}^{-2} \text{h}^{-0.5}$  with dexamethasone, dexamethasone valerate, ketoprofen, melatonin, and progesterone giving values exceeding 100  $\mu\text{g cm}^{-2} \text{h}^{-0.5}$ . 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.

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## 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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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 plastyd device, CIDR, Cue-mate, intelligent breeding device, INVAS, PCL, PRID, Rajamehndran 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( $\epsilon$ -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- $\beta$ , 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- $\beta$  (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 (HP $\beta$ CD) 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<sup>a</sup> of the drug candidates considered for melt extrusion into PCL.

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

<sup>a</sup> Values are obtained from Refs. [36–39].

<sup>b</sup> Decomposes on melting.

**Table 2**

UV  $\lambda_{\max}$  (nm) and extinction coefficient ( $\epsilon$ ) values identified for the eight selected drugs of interest that were used in the assaying of the drugs in addition to progesterone.

| Drug                   | $\lambda_{\max}$ (nm) | $\epsilon$ (mL cm <sup>-1</sup> $\mu$ g <sup>-1</sup> ) |
|------------------------|-----------------------|---|
| Abamectin              | 244                   | 0.0792  |
| Amoxicillin            | 228                   | 0.0239  |
| Dexamethasone          | 242                   | 0.0326  |
| Dexamethasone valerate | 242                   | 0.0301  |
| Ketoprofen             | 258                   | 0.0580  |
| Melatonin              | 223                   | 0.1036  |
| Oestradiol 17- $\beta$ | 217                   | 0.0255  |
| Oestradiol benzoate    | 232                   | 0.0439  |
| Progesterone           | 244                   | 0.0474  |

## 2.2. Drug UV $\lambda_{\max}$ identification

A 1.0 mg mL<sup>-1</sup> stock solution of each drug (0.0500 g of drug in a 50 mL volumetric flask) in SDA (Specially Denatured Alcohol) was prepared. Standards of 20  $\mu$ g mL<sup>-1</sup> (1.0 mL aliquot of stock solution made up to 50 mL in a volumetric flask) in HP $\beta$ CD/PBS (pH 5.0 phosphate buffer solution (PBS) containing 9.2 g sodium dihydrogen orthophosphate 1-hydrate with 0.0946 g di-sodium hydrogen orthophosphate and 5% w/v hydroxypropyl- $\beta$ -cyclodextrin (to aid dissolution) in 1.0 L of distilled water) were used to analyse for each drug's UV  $\lambda_{\max}$  value by performing a wavelength scan from 200 to 300 nm (Biochrom Libra S12 UV spectrophotometer) and identifying the peak of maximum absorbance. The  $\lambda_{\max}$  values (Table 2) obtained for the nine drug compounds of interest all occurred in the 220–250 nm region [17,18]. All nine drug compounds (which includes progesterone) gave linear Beer's law plots which were used to measure drug concentrations for the permeation and Hanson dissolution studies (see later).

## 2.3. PCL membrane manufacture for drug permeation studies

The PCL membranes were manufactured by heating PCL polymer spheres (3–6 mm diameter) at 125 °C in a bench-top oven for 30 min on two aluminium plates, with removal from the oven and pressing together (using a vice) with feeler gauges to set the final thickness to 150  $\pm$  10  $\mu$ m. For the purposes of standardising their manufacture in terms of the rate of solidification, the membranes were allowed to cool for 30 min with the assistance of an electric fan while they were pressed together.

## 2.4. Side-by-side diffusion cells for drug permeation studies

A Valia-Chien side-by-side diffusion cell [19] was connected to a circulating waterbath (supplying the heat jackets) set at 37  $\pm$  2 °C with a PCL membrane (150  $\pm$  10  $\mu$ m) placed between the donor and receptor cells. The donor cell (3.4 mL volume) contained the saturated drug in a HP $\beta$ CD/PBS solution with the receptor cell (3.4 mL volume) initially containing only the HP $\beta$ CD/PBS solution. Both cells were mixed with magnetic stirring fleas to ensure homogeneity. Samples (1.0 mL) were taken from the receptor cell at times ranging from 0.5 h to 24 h (depending on the permeation rate initially observed for each drug) and analysed by UV spectrophotometry, via an appropriate calibration curve, at the drug's  $\lambda_{\max}$  value. A fresh 1.0 mL solution of HP $\beta$ CD/PBS was added to the receptor cell after each sample had been removed to maintain a constant volume of 3.4 mL (the dilution effect and volume changes were factored in when calculating total receptor cell  $\mu$ g permeated).

## 2.5. Manufacture of the melt extruded drug/PCL devices for Hanson dissolution studies

Manufacture of the drug/PCL devices (for the nine drug candidates selected) was achieved by mixing PCL powder with drug at a loading of ca.10% w/w, then heating to 80 °C in a syringe (100 cc volume, 8 mm nozzle diameter) for 2 h, and finally extruding the melted mix from the syringe. The mixture was then cooled and chipped to 10 mm lengths. In this sense the material used to form the discs for later study can be considered as being formed from a process which approaches a melt extrusion process. This chipped material from the initial extrusion process containing the PCL and the drug was then remelted and subsequently fabricated into a disc by placing it on two aluminium plates in an oven at 80 °C for 1 h, removing and pressing (using a vice) together at room temperature to cool for 30 min with the assistance of an electric fan (feeler gauges on the plates determined the final thickness to be ca. 0.250 mm). The discs were then cut into 28 mm by 28 mm ( $\pm$  1 mm) square shapes to give a final total surface area of 1600  $\pm$  100 mm<sup>2</sup> (when both sides and the edges are factored in to the surface area calculation). In forming these discs, the remelting of the chipped material allowed homogenisation of the drug and PCL prior to pressing into discs.

## 2.6. Hanson dissolution testing of the extruded PCL/drug matrices

Preliminary Hanson dissolution release rate assessment for the progesterone/PCL devices was adapted from the principles defined in USP 23 NF18, January 1995, section 724, page 1793 [20] (see Table 3). The "Apparatus 2" procedure was used with the following modifications. A release media volume of 500 mL of 15% v/v SDA:water (degassed) at 37  $\pm$  0.5 °C with no adjustment for pH or ionic strength was placed into the Hanson dissolution flasks. This choice of release medium was dictated by the intended target receptors of such devices namely the bovine vaginal membrane for which aqueous alcohol mixes are a good simulation of the membrane. The devices remained completely submerged in the release media (they sank on introduction), were unattached, and free to move about once the paddles began to rotate (100  $\pm$  2% rpm set 25 mm above the bottom of the test flask). This ensured that the total surface area of the devices was exposed throughout the release test. The time intervals for manual sample collection (1.0 mL) and immediate analysis (to prevent evaporation) were 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 9.0, 15.0, and 24.0 h after starting. To monitor drug release from the matrices, the concentration of the drug (e.g. progesterone) was

**Table 3**

Hanson dissolution standard method operating conditions.

| Condition                  | Setting  |
|----------------------------|--|
| Stirring element           | Paddle   |
| Release media <sup>a</sup> | 15% v/v SDA:water (de-ionised), placed in the ultrasonic bath for 40 min to remove air   |
| Media volume               | 500 mL   |
| Temperature                | 37.0 $\pm$ 0.5 °C  |
| Ionic adjustment           | None   |
| pH adjustment              | None   |
| Rotation speed             | 100 $\pm$ 2% rpm   |
| Sampling times             | 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 h   |
| Device                     | A square shaped (28 by 28 $\pm$ 1 mm, $\approx$ 0.240 mm thick) 10% w/w drug/PCL tab with a surface area of 1600 $\pm$ 100 mm <sup>2</sup> |
| UV wavelength              | 244 nm   |
| Sampling                   | 1.0 mL manually taken  |

<sup>a</sup> 15% v/v SDA:water was judged to be the optimal level of aqueous alcohol that gave minimal UV interference from dissolved PCL polymer itself.

determined by UV analysis at 244 nm. A plot of the cumulative amount of drug (e.g. progesterone) released per unit area of device versus the square-root-of-time was performed to give a linear relationship, the slope of which equated to an *in vitro* drug release rate.

### 3. Results and discussion

#### 3.1. Data analysis from the work involving side-by-side diffusion cells for drug permeation studies

From the Valia-Chien side by side diffusion cell work, the plotting of cumulative permeation ( $\mu\text{g}$ ) of drug into the receptor cell versus time (hours) at steady state was confirmed to produce a linear relationship (Fig. 1). The slope of this graph can be related to the permeation rate ( $\mu\text{g h}^{-1}$ ) of the drug through the PCL membrane. Using the measured surface area ( $A$ ) of the membrane and the value of the saturated concentration ( $C_d$ ) of the drug in the donor cell containing HP $\beta$ CD/PBS, the permeability coefficient ( $P$ ) can be calculated in accordance with

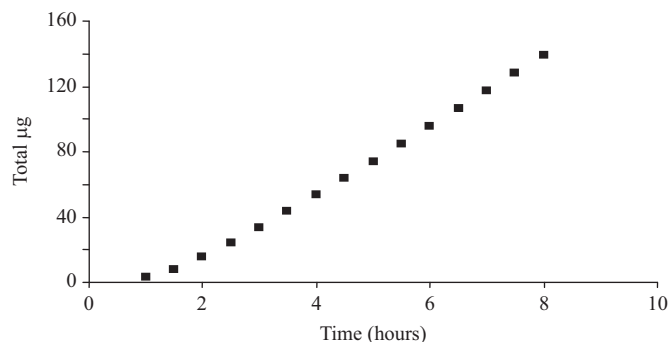
$$P = \frac{\text{Slope}}{AC_d} \quad (1)$$

In the permeability experiments performed using the Valia-Chien side-by-side diffusion cells, the principal factors known to determine  $P$  were the permeation rate and the  $C_d$  of the drug in question as surface area,  $A$  of the membrane remains constant throughout. At the start of the plot, an artefact known as the lag time ( $t_l$ ) (see Fig. 1), occurs due to the physical restraints of the initial diffusion of solvent and drug to permeate into the “dry” membrane resulting in a non-linear response. According to the literature [21] the  $t_l$  can be extrapolated by taking the intercept of the steady-state line (ignoring the non-steady-state at the start of the experiment) on the time axis which gives a value of approximately 1.5 h in the example shown in Fig. 1.

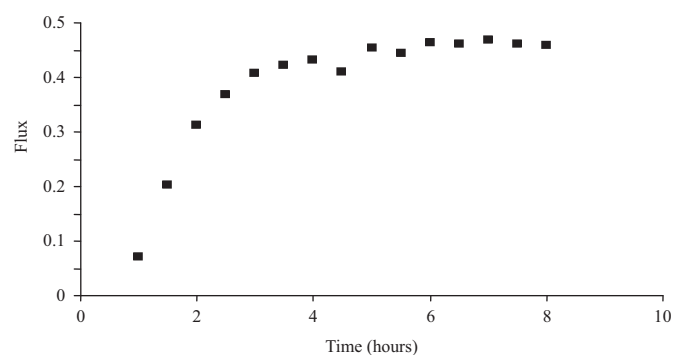
Calculations of the flux values ( $J$ ) to assess the variability associated with permeation over time for drug candidates were performed using Fick's first law (Eq. (2)) [22]

$$J = \frac{Q}{At} \quad (2)$$

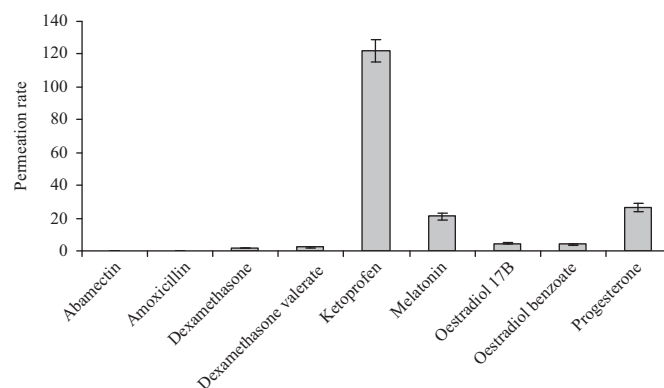
where  $Q$  is the quantity of drug crossing the membrane ( $\mu\text{g}$ ),  $A$ , the total exposed membrane area ( $\text{cm}^2$ ), and  $t$  the time of exposure (minutes). Analysis of the flux ( $J$ ) throughout the experiments done with the Valia-Chien cells clearly showed the initial permeation rate changes over time until a constant value was achieved (Fig. 2).



**Fig. 1.** A typical permeation profile for melatonin obtained using the Valia-Chien side-by-side diffusion cells (total  $\mu\text{g}$  melatonin permeated versus time) with the slope (permeation rate,  $\mu\text{g h}^{-1}$ ) equal to  $PAC_d$  where  $P$  is the permeability coefficient,  $A$  the surface area of the PCL membrane in  $\text{cm}^2$ , and  $C_d$  the value of the saturation concentration of the drug in HP $\beta$ CD/PBS solution.



**Fig. 2.** A typical flux ( $J$ , ( $\mu\text{g cm}^{-2} \text{min}^{-1}$ )) profile (melatonin) associated with the permeation of a drug through the PCL membrane.



**Fig. 3.** Permeation rates ( $\mu\text{g h}^{-1}$ ) for the eight selected drugs of interest in addition to progesterone.

For all drug compounds studied the  $t_l$ , which may be evaluated in similar manner via this method, was clearly observed and was found in contrast to be 2.5 h (i.e. the time where the curve flatlined), after which time the  $J$  values became constant. Hence, there is a difference in the measured  $t_l$  value of 1 h between the two plots although the prescribed method for determining  $t_l$  is the steady-state time intercept method as embodied in Fig. 1. Knowledge of  $t_l$  is useful in determining some initial formulation parameters (for example drug load, device size, and shape) when investigating a matrix delivery system as it is known to vary from drug to drug as well as between different systems [23].

Fig. 3 is a summary of the drug permeation rates, as calculated from the slope of the total  $\mu\text{g}$  versus time plot, over the entire permeation profile plot (due to the variation in  $t_l$  between different drug compounds resetting to zero was not performed). These data were obtained from two (for dexamethasone valerate and progesterone), four (for abamectin, amoxicillin, dexamethasone, ketoprofen, melatonin, and oestradiol benzoate), and six (for oestradiol 17 $\beta$ ) duplicate tests. The linearity of the plots as indicated by  $R^2$  values of 0.980 or greater for most compounds indicated good reproducibility in the data measured. However, in contrast, the plot obtained for amoxicillin gave an  $R^2$  value of only 0.762. This inferred that this particular drug was unstable under the conditions of measurement employed (i.e. 37 °C and 48 h) as over this period, a yellow colouration developed in the initially colourless solution indicating a possible degradation of the amoxicillin [20].

In general, most drugs studied apart from ketoprofen displayed low to zero permeation rates through the membranes. Progesterone and melatonin displayed similar, albeit low permeation rates. Calculations of the permeability coefficient ( $P$ ) for the drugs gave values ranging from  $1.04 \times 10^{-5}$  to  $4.94 \times 10^{-9} \text{ cm s}^{-1}$  with most values below  $1 \times 10^{-7} \text{ cm s}^{-1}$  including progesterone (see Table 4).



**Table 4**

Permeability coefficients ( $P$ ) of the eight selected drugs of interest and progesterone compared against the solubility of each drug ( $C_d$ ) in aqueous solution and in HP $\beta$ CD/PBS solution.

| Drug                   | Permeability coefficient ( $P$ ) <sup>a</sup> (cm s <sup>-1</sup> ) | $C_d$ aqueous <sup>b</sup> (μg mL <sup>-1</sup> ) | $C_d$ HP $\beta$ CD/PBS (μg mL <sup>-1</sup> ) |
|------------------------|---|---|--|
| Abamectin              | $5.73 \times 10^{-6}$   | 3   | 8  |
| Amoxicillin            | $4.94 \times 10^{-9}$   | 4385  | 12699  |
| Dexamethasone          | $1.71 \times 10^{-7}$   | 108   | 3036   |
| Dexamethasone valerate | $2.89 \times 10^{-6}$   | 12  | 282  |
| Ketoprofen             | $1.02 \times 10^{-5}$   | 284   | 427  |
| Melatonin              | $1.12 \times 10^{-6}$   | 3273  | 6615   |
| Oestradiol 17- $\beta$ | $8.08 \times 10^{-6}$   | 7   | 1997   |
| Oestradiol benzoate    | $1.04 \times 10^{-5}$   | 1   | 142  |
| Progesterone           | $2.50 \times 10^{-6}$   | 16  | 3711   |

<sup>a</sup> Permeability coefficient ( $P$ ) calculated by dividing the final permeation rate (μg s<sup>-1</sup>) by the product of the PCL membrane's area and the drug's solubility in HP $\beta$ CD/PBS, i.e. " $C_d$  HP $\beta$ CD/PBS" (μg mL<sup>-1</sup>).

<sup>b</sup> " $C_d$  aqueous" is defined as the solubility of the drug in aqueous solution.

Given the evaluation of an injected moulded PCL intravaginal insert containing progesterone has been carried out and shown to be as clinically effective as the currently available commercial products on the market [14], it is appropriate to compare the permeation results of progesterone through PCL with those of the other drug compounds investigated in this study. The results in Fig. 3 are interesting in that only melatonin and ketoprofen have similar or better permeation rates when compared to progesterone. The oestradiol drugs display a rate approximately one fifth that of progesterone, and both the dexamethasone candidates less still (approximately one tenth) with abamectin and amoxicillin indicating almost zero permeation. According to these results only melatonin and ketoprofen "appear" to display permeation rates that would make them suitable for incorporation into a PCL matrix. This assessment however ignores any consideration of the drug dosage requirements as well as a number of other pharmacokinetic or physicochemical parameters important in controlled drug delivery. To assess whether or not potential applications exist with the drug compounds tested the factors that influence the drug/PCL permeation rate need to be considered.

The nine drug compounds investigated displayed a range of molar mass ( $M$ ), solubilities (as dictated by  $\log K_{ow}$  used to measure the hydrophilicity/hydrophobicity factors in a molecule that influence partitioning between a polar and non-polar solvent) and saturation concentrations ( $C_d$ ). Each of these parameters is known to influence the diffusion coefficient and hence final permeation rate. The combination of a low  $M$ , high  $C_d$ , and low  $\log K_{ow}$  for ketoprofen favoured diffusion through the solvated regions of the polymer resulting in the high final permeation rate observed. Conversely the large  $M$  and  $\log K_{ow}$  of abamectin along with its poor solubility in aqueous solution did not favour regional diffusion through the PCL polymer. The final permeation rates do not relate to one, two, or three principal factors but a combination of these factors favouring diffusion through the solvated PCL polymer. Table 5 provides an assessment of the least squares regression ( $R^2$ ) values of the physicochemical property parameters  $M$ ,  $pK_a$ ,  $\log K_{ow}$ ,  $C_d$  for water, and HP $\beta$ CD/PBS-based media, permeation rates, and permeability coefficients ( $P$ ) versus each other in all the combinations noted in the table. For instance, the  $R^2$  value for values of molecular weight of candidate drugs used in this study versus the permeability rates observed for the same drugs from PCL is 0.2038. Some physicochemical parameters which are closely related were seen to have good correlations such as the solubilities of the drug in water and HP $\beta$ CD/PBS media (i.e.  $C_d$  water and  $C_d$  HP $\beta$ CD/PBS)

**Table 5**

Least squares regression correlations ( $R^2$ ) of the drug physicochemical properties  $M$ ,  $pK_a$ ,  $\log K_{ow}$ ,  $C_d$  (in water and HP $\beta$ CD/PBS solution), permeation rate, and permeability coefficient ( $P$ ) for the bioactive compounds studied.

|                           | $pK_a$           | $\log K_{ow}$ | $C_d$ (aqueous) | $C_d$ (HP $\beta$ CD/PBS) | Rate   | $P$    |
|---------------------------|------------------|---------------|-----------------|---------------------------|--------|--------|
| $M$                       | 0.0319           | 0.2845        | 0.0346          | 0.0999                    | 0.2038 | 0.0092 |
| $pK_a$                    | 1.0 <sup>a</sup> | 0.3901        | 0.2587          | 0.5486                    | 0.2199 | 0.0412 |
| $\log K_{ow}$             | - <sup>b</sup>   | 1.0           | 0.5284          | 0.6924                    | 0.0294 | 0.3839 |
| $C_d$ (aqueous)           | -                | -             | 1.0             | 0.8223                    | 0.0123 | 0.2887 |
| $C_d$ (HP $\beta$ CD/PBS) | -                | -             | -               | 1.0                       | 0.0073 | 0.2737 |
| Rate                      | -                | -             | -               | -                         | 1.0    | 0.2030 |
| $P$                       | -                | -             | -               | -                         | -      | 1.0    |

<sup>a</sup> Correlations of "1.0" are expected when you are calculating the coefficient of plots of parameters against themselves.

<sup>b</sup> '-' Represents mirrored results so not repeated. If repeated this value would be 0.3901.

as well as the  $\log K_{ow}$  when correlated to  $M$  and  $pK_a$  but no particularly strong correlations were seen for permeation rate or permeability coefficients correlated versus the physicochemical properties (the best of these were 0.22 with  $pK_a$  versus permeability rate and 0.38 with  $\log K_{ow}$  versus permeability rate).

Earlier reported studies on the permeation of three oestrogens (oestrone, oestradiol, oestriol) and dexamethasone across cellulose acetate [24] showed that an increase in permeation was correlated with increased temperature and  $\log K_{ow}$ , decreased polarity and fewer attached hydroxyl groups. That research implied that diffusion (for these steroids) occurred through aqueous channels within the membrane and that obstruction and polar interactions were a limitation to permeation.

Cyclodextrins are known permeation enhancers [25–27] for poorly soluble drug compounds through biological and synthetic membranes. It has been stated that cyclodextrins enhance permeation by carrying the drug through the aqueous diffusion layer (a barrier to diffusion) from the bulk solution towards the membrane surface. At the membrane surface the drug partitions from the drug-cyclodextrin complex into the membrane (often lipophilic as is the case for PCL). This illustrates the importance of the solubility and  $\log K_{ow}$  parameters in determining the permeation rate. The interaction between the drug and cyclodextrin (assuming equilibrium) counteracts the partition process but remains necessary in order to obtain a significant chemical potential gradient for diffusion to occur. This is but one interaction that describes why no particular parameter ( $M$ ,  $pK_a$ ,  $\log K_{ow}$ ,  $C_d$  (water and HP $\beta$ CD)) is dominant in determining drug permeation through PCL.

### 3.1.1. Studies of drug release from drug/PCL devices by Hanson dissolution studies

A summary of the melt extruded PCL/drug samples manufactured for this study are summarised in Table 6. It was acknowledged that the introduction of different drug compounds into the polymer could potentially alter the nature of drug/polymer interactions as well as the pharmaceutical properties of the final drug/PCL device. With the aim of making physically uniform melt extruded materials, the manufacturing methodology was kept as consistent as possible although proving this using a technique like scanning electron microscopy (SEM) was difficult because it was challenging to distinguish on the basis of EDX spot analyses the difference between PCL or drug-originating features such as crystals. This is because both the PCL and the drugs tested only

**Table 6**

The number of individual devices (*N*) manufactured from the drug load per cent (%) w/w chipped material with the average surface area (mm<sup>2</sup>) of each drug device analysed.

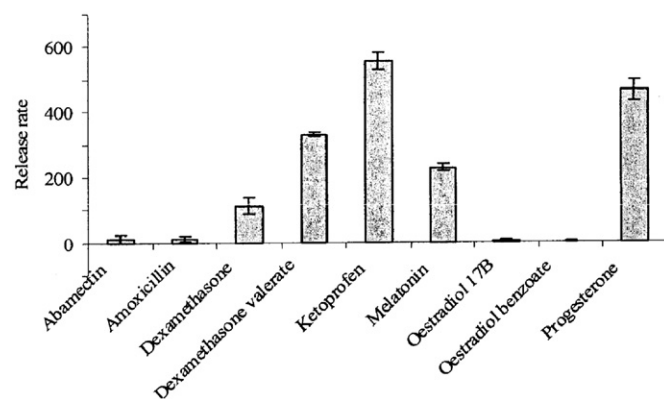
| Drug                   | N               | Drug load (%) w/w | Area (mm <sup>2</sup> ) |
|------------------------|-----------------|-------------------|-------------------------|
| Abamectin              | 3               | 10.5              | 1575 ± 4                |
| Amoxicillin            | 3               | 10.3              | 1556 ± 26               |
| Dexamethasone          | 3               | 10.1              | 1603 ± 15               |
| Dexamethasone valerate | 3               | 10.1              | 1489 ± 32               |
| Ketoprofen             | 3               | 10.3              | 1611 ± 32               |
| Melatonin              | 3               | 10.3              | 1669 ± 10               |
| Oestradiol 17-β        | 8               | 10.5              | 1523 ± 58               |
| Oestradiol benzoate    | 8               | 10.2              | 1535 ± 49               |
| Progesterone           | 63 <sup>a</sup> | 10.0              | 1602 ± 50               |

<sup>a</sup> Includes all of the PCL devices manufactured for method development and validation of the standard Hanson dissolution test method which explains the large number produced.

have C,H,O-containing functional groups and structures which would not provide characteristic signals for each component. Hence the different drug/polymer interactions that could result over the range of compounds melt extruded with PCL must still be considered as a factor when attempting to compare the final release rates of the nine drugs of interest when measured by Hanson dissolution. The other factor to be borne in mind when comparing the Hanson dissolution results with the permeation studies is that a different release medium was used for this purpose, namely a 15% v/v SDA/water solution employed to simulate the bovine vaginal membrane which will behave like a typical amphiphilic biological membrane and have both hydrophobic and hydrophilic characteristics.

### 3.2. Hanson dissolution test

The validation of the standard Hanson dissolution test method showed that the particular test parameters adopted for the progesterone/PCL devices were appropriate even though, progesterone does have some significant physicochemical differences from the other eight selected drug candidates studied, in particular, the absence of a p*K*<sub>a</sub> value. After developing an appropriate drug release test using the progesterone/PCL devices (by investigating the influence of a number of different method parameters with this system) the release rates of the eight drugs of interest (plus progesterone for comparison reasons) were assessed. A relationship is known to exist between dissolution and bioavailability [28] but given the number of contributing factors able to influence the dissolution process it is unlikely that a single test method can be applied to all drug compounds. The ultimate aim of an *in vitro* dissolution assessment is to provide information on the drugs' absorption potential *in vivo* via determination of the kinetics of the dissolution process (the rate limiting step in bioavailability). Most models focus on the *in vitro* dissolution data to assess bioavailability ignoring the influence of *in vivo* dissolution following administration. This limitation arises because of the difficulty in assessing *in vivo* dissolution [28]. As a result the release rates for the nine drugs investigated (Fig. 4) do not indicate whether or not, following dissolution, they are actually bioavailable only that on administration they become potentially bioavailable. The other important factor to note is that this will apply only to dissolution rate limited drugs and not to those which are permeation-limited for which increased dissolution will not lead to increased availability by absorption through membranes. Ranking different drug release rates according to a single Hanson dissolution test procedure thus gave a simplistic but useful comparison that was used to assess the viability of



**Fig. 4.** Hanson dissolution data showing the average release rates ( $\mu\text{g cm}^{-2} \text{h}^{-0.5}$ ) in 15% aqueous alcohol determined from the slope of the release versus the square-root-of-time plot for the nine drug/PCL devices investigated. Error bars represent variations for 3 duplicates of each compound tested.

different drugs that had not been previously considered for incorporation into a PCL matrix delivery device.

Fig. 4 provides a summary of the average release rates of the nine drugs of interest when measured using the standard Hanson dissolution test method. It is clear from the figure that the drugs, dexamethasone, dexamethasone valerate, ketoprofen, and melatonin exhibited release rates exceeding  $100 \mu\text{g cm}^{-2} \text{h}^{-0.5}$  which compared favourably with release behaviours exhibited by an existing commercial intravaginal device that incorporates progesterone [14]. The drugs with release rates approximately one tenth this limit or less (*viz.*, abamectin, amoxicillin, oestradiol 17-β, and oestradiol benzoate) would require the methodology by which they are incorporated into the PCL matrix (*i.e.* drug load, co-polymer addition or different polymer for co-extruding, additional excipients, etc.) [2,29–32] to be modified if they ever were to be part of a viable controlled release PCL matrix delivery device. There are clearly limitations with using these drugs with the present scenario of testing. Based on the release rates obtained from the Hanson dissolution experiments alone, dexamethasone, dexamethasone valerate, ketoprofen, and melatonin, appear to show the greatest potential for adaptation into a matrix delivery device, with the results observed for progesterone reaffirming its expected suitability as a candidate when based on past experiences from other researchers. Abamectin and amoxicillin, on the other hand, did not exhibit high release rates and furthermore had earlier showed very poor permeability which renders them as unfavourable candidates for PCL matrix devices given the present methodologies used in this study. In the case of amoxicillin this had been due to the possibility that it was unstable under the experimental conditions used.

From the drug permeation rate studies shown earlier, ketoprofen, melatonin, oestradiol 17-β, and oestradiol benzoate, gave the appearance of being suitable for potential adaptation into a PCL delivery device. However, the poor Hanson dissolution release rates of both oestradiol-based drug species (17-β and benzoate) precludes them as possible device adaptation candidates. Possibly better device manufacture or a different mode of Hanson dissolution methodology may be needed to explore the utility of PCL/oestradiol drug matrices. Dexamethasone and dexamethasone valerate though giving visibly poor permeation rate results gave more encouraging release rates via Hanson dissolution and this contrasting behaviour may highlight a possible limitation to drug delivery for these drug species via a PCL matrix device if permeation, alone, was to be relied upon as a major part of the drug delivery.

Finally in seeking to understand the release results provided by the Hanson dissolution study, it is of value to calculate some *R*<sup>2</sup>

correlation values of the Hanson dissolution release data plotted versus physicochemical properties of the drugs used. It was also of interest to determine if any correlations could be seen between the sets of permeation rate and Hanson dissolution rate data. It is known that a variety of factors can influence dissolution rate *in vitro* with six main classes identified according to the literature [33,34]. These relate to method and instrumental variations, drug dosage and formulation, other miscellaneous factors and also physicochemical properties of the drugs themselves. These were expected to have an impact on the release properties of the drugs test [28,35] but when least squares regression correlations of the physicochemical properties ( $M$ ,  $pK_a$ ,  $\log K_{ow}$ , and solubility of the drugs in aqueous solution) against release rate for the nine drugs analysed were calculated, these were not strong (0.1621, 0.1039, 0.0407, and 0.0380, respectively). This suggests that no one factor is responsible for controlling the dissolution process but rather a number of factors operating simultaneously to influence the final release rate observed. Secondly, when the permeation rate data from earlier are plotted against the release rate data (determined using the standard Hanson dissolution test method), for the nine selected drug candidates, an  $R^2$  correlation of 0.5675 is obtained. This value suggests that a moderate relationship exists between permeation rate and release rate for the nine selected drugs. Hence one can say that the processes involved in drug permeation through a PCL membrane and the dissolution (release) of a drug out of a PCL matrix device are diffusion controlled and/or influenced by a combination of the drug physicochemical properties.

#### 4. Discussion and conclusions

The combination of side-by-side diffusion cell experiments and Hanson dissolution studies of novel drug combinations with PCL has led to some useful data on the utility of these combinations as drug delivery vehicles. Before discussing these it is important to reiterate that different scenarios are being tested in each of these experiments, i.e. permeation versus Hanson dissolution. One experiment involves permeation of drug from a saturated solution containing cyclodextrin through a thin PCL membrane into an aqueous receptor fluid of similar composition but without any dissolved drug. The other experiment is a Hanson dissolution study of release directly from a PCL matrix containing the drug immersed into an aqueous alcoholic mixture, the release medium. Permeability studies were carried out to shed light on which of the relatively little tested drugs would perform the best if combined into a PCL matrix. With the permeability data obtained to get some initial insights, Hanson dissolution studies were then performed in aqueous alcohol media to finally correlate these release rates with those from the permeability experiments.

In summary, side-by-side diffusion cell experiments, for the nine drugs studied permeating through a PCL membrane, gave permeation rates ranging from 0 to  $122 \mu\text{g h}^{-1}$ . Apart from ketoprofen which demonstrated an exceptionally high permeation rate, other drug candidates displayed relatively lower permeation rates with permeability rate following the trend progesterone > melatonin > oestradiol (both) > dexamethasone (both) > abamectin and amoxicillin. Least squares regression ( $R^2$ ) values obtained by plotting the measured permeation rates against the drug physicochemical properties of  $M$ ,  $pK_a$ ,  $\log K_{ow}$ , and solubility (in water and HP $\beta$ CD/PBS solutions) showed no especially strong correlations, therefore, suggesting that a variety of drug physicochemical factors acting together could influence permeation.

Hanson Dissolution release rates for the PCL-melt-extruded drug matrices tested in 15% aqueous alcohol release media gave numerically higher values than the permeability experiments,

ranging from 0 to  $556 \mu\text{g cm}^{-2} \text{h}^{-0.5}$ . In attempting to compare the two (permeability versus Hanson dissolution) values against each other, the higher values from the Hanson dissolution experiment can be understood in terms of the units used for each experiment. Numerically the Hanson dissolution value unit contains a surface area term  $\mu\text{g cm}^{-2} \text{h}^{-0.5}$  while permeability rate values only have an amount per unit time unit ( $\mu\text{g h}^{-1}$ ). Multiplying the Hanson dissolution value through by the drug device surface area (Table 6) to get an approximate comparison with the permeability data (in terms of  $\mu\text{g h}^{-0.5}$  instead of  $\mu\text{g h}^{-1}$ ) leads to an even larger number so reaffirming the larger numerical values obtained for this particular experiment. The other reason for the observed higher numbers in Hanson dissolution must be attributed to the 15% v/v SDA solvent chosen as the release medium and mimic for an amphiphilic membrane.

Hence in contrast to the permeation results, under the testing conditions used, the Hanson dissolution release rate ranking followed the trend: ketoprofen > progesterone > dexamethasone valerate > melatonin > dexamethasone > abamectin (and) amoxicillin > oestradiols (both). One drug, amoxicillin, performed poorly in both permeability and Hanson dissolution studies due possibly to decomposition issues under the conditions employed leading to the lack of UV detection. The  $R^2$  values obtained when either the permeability rate or average Hanson dissolution release rate of all the drugs tested were plotted against the drugs' physicochemical properties showed numbers considerably < 1 indicating that no strong correlations existed which meant that no one drug physiological property was responsible for trends observed. However, a moderate correlation ( $R^2$  of 0.5675) obtained when Hanson dissolution release rate data were plotted against the permeation rate data suggested that release rate and permeation rate processes are partly influenced by the rate of drug diffusion through the PCL but that drug release involves an additional dissolution process to take place into the release medium (influenced by drug solubility) before diffusion of the drug may proceed out of the PCL.

In conclusion, based on both sets of data obtained in this study, it is evident that the oestradiol-based drugs, abamectin and amoxicillin are generally unsuitable as candidates for drug delivery via PCL under the conditions used. Ketoprofen, on the other hand, was found to be a highly favourable candidate for further development of applications involving melt extrusion with PCL with dexamethasone valerate, dexamethasone and melatonin also being favourable but to a lesser extent.

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