Melt-extruded polyethylene oxide (PEO) rods as drug delivery vehicles: Formulation, performance as controlled release devices and the influence of co-extruded excipients on drug release profiles

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Introduction

The utility of controlled release medication formulations lies in their ability to keep drugs at steady levels in the blood plasma of recipients and within the termini of the maximum and minimum effective therapeutic levels. This avoids the "ups" and "downs" of medication levels within the body which would have been the result had conventional immediate release tablets been administered instead. In the veterinary field, controlled release medications are essential[1] because of the logistical difficulties of administering drugs on a regular (e.g., daily) basis to animals. The chief advantages of controlled release veterinary medications lie in the ease with which they can be administered; decrease in stress for animals, owing to less need for rounding up and frequent dosing; and, most importantly for farmers, the reduced cost of treatment relative to that for a multiple dosage regime.

Polyethylene oxide (PEO) is considered a valuable material in controlled release drug delivery science in the human field of medicine because drugs can diffuse through the viscoelastic mass that PEO forms upon gelation by water. In addition to this important property, PEO can also be used as a flocculent, viscosity-inducing agent, as a lubricant as well as a dispersant and water retention agent.[2] The basic structural unit of the PEO polymer is the ethylene glycol skeleton, which can be written as $HO-(CH_2-CH_2-O)_n-H$. PEO grades (and the nomenclature for these) are determined by the molecular weight of the polymer. Below 25,000 Da, PEOs are termed polyethylene glycols or "PEGs".

The use of PEOs and PEGs in pharmaceutical products is increasing because of their widening acceptance by pharmaceutical regulation agencies. This is attributed to PEOs and PEGs having good physical and chemical stability, dissolving easily in water over time, and possessing the ability to be compressed. Owing to their relatively low melting point (*ca.* 70 ºC) , the higher molecular weight PEO polymers like PEO-303 (as supplied by DOW Chemicals), which has a molecular weight of approximately 7,000,000 Da, are amenable to hot melt extrusion (HME) to produce cylinders or tablets which can incorporate other materials like the active drug and excipients. Pharmaceutical hot melt extrusion (HME), a widely used method in the plastics processing industry, involves the physical mixing of a drug and carrier at the fusion temperatures of the carrier (usually a polymer). Several publications have focussed on this use.[3-8] Some reports involving HME focus on addressing the challenges of increasing the dissolution rate of poorly water-soluble drugs in developing dosage forms[6]. Other reports discuss the advantages of HME being a more efficient and cost effective method for manufacturing various dosage forms.[7] A previous study looked more at manufacturing issues, such as the pursuit of uniform cylindrical shape and homogeneous density.[8] It also looked at additives which could influence mechanical and dissolution properties of the extruded substance which have a bearing on its usefulness as a controlled release drug delivery device.

In the present study, we have sought generally to investigate the innovative use of melt-extruded PEO rods containing commonly used drug substances, with a view to its potential application in extended release drug delivery for the treatment of bovine mastitis in the veterinary sector. Mastitis is an intramammary infection common in lactating cows[9] which is of particular concern in the agricultural sector of countries with major dairy farming-based economies. In New Zealand, this is particularly so because the clinical and subclinical forms of mastitis can bring about significant financial losses caused by lower milk production (from rejected milk), lower milk quality (leading to lower value due to degradation), loss of valuable bovine breeding stock (owing to the need to eliminate infected animals), as well as the associated medical and labour costs with treatment or management of the condition in a commercial dairy herd.

Teat treatment options have been widely reported in the science literature. For example, patents from the mid 1970s[10] have described "bovine teat dip" or "aqueous compositions to aid in the prevention of bovine mastitis". "Teat seals" are contemporarily used and are usually applied to cows that have dried off. In such a treatment, the teat of the cow is infused with two syringes: one which contains an antibiotic like cloxacillin and the second containing some inorganic salts in an oily base which serve to seal the teat so blocking off access to the udder by mastitis bacteria during the dry period. Teat seals containing either reduced antibiotic levels or no antibiotic levels have been reported to be successful at combating the incidence of mastitis in dairy herds in past studies.[11] The drive for reducing the antibiotic levels has emerged from concerns for the overuse of antibacterials in combating mastitis.[11] The use of viscoelastic gels such as PEO or PEG for teat

seals has obvious advantages in that not only can the gel function as a physically soft barrier seal but also it potentially provides a matrix for the extended release of various medications such as antibiotics or other types of medication into the mammary gland. In particular, the melt extrusion process can produce lengths of PEO/drug rods directly that could possibly be used for teat sealing purposes by direct insertion into the teat channel.

It is thus of interest to investigate the conditions under which such extruded PEO rods can be produced, and the factors influencing the release of drugs from such matrices when they are placed in or exposed to aqueous, though physiological-mimicking, milieu. In the present work, we have thus conducted a feasibility study of the manufacture of the extruded rods using simple benchtop extruders from dry drug/PEO mixtures and the carrying out of a UV-based assay of drug release from the rods into an aqueous alcoholic medium. Studies focussed initially on the general behaviour of release from PEO rods containing drug alone. They were then extended to probe the effect of excipients co-extruded with the PEO and drug to determine if a significantly greater extent of controlled release could be achieved. Note that this aim, qualitatively assessed by inspection of the UV-measured drug release profiles over a 24 hour period (see later), was the primary focus of this study rather than an in-depth assessment of the kinetics of release from these particular rods, which should only be attempted in a carefully designed and considered study involving larger data sets for release of drug than have been used in the present study.

In the course of the work some important manufacturing issues were also identified when certain excipients were incorporated. These have also been covered, as they were regarded as useful observations for future development of this field. A wide range of excipients was considered for inclusion in the PEO/drug extrudates with the express intention of creating a useful material from a veterinary point of view (i.e., a device that could offer controlled release over many hours or even days if possible), com-

pared to several hours. In attempting to cover all feasible options to achieve this goal, a wider range of excipients than might have been considered in earlier literature on PEO HME-related topics had to be employed. This has led to some useful observations on their actual or apparent effects in trying to retard PEO gelation, with one aspect not directly discussed in this publication but covered in a presentation in the 2011 NZIC conference held in Hamilton,[12] being studied further for commercial application.

Materials and Methods

Most chemicals (polyethylene oxide-303, molecular weight of 7,000,000 (PEO-303, DOW), the individual drugs, buffer salts, excipients and ethanol) were sourced from commercial suppliers as either Analytical grade or laboratory grade reagents. Diazepam, hydrochlorothiazide, naproxen sodium, and chlorpheniramine maleate) were kindly donated by Douglas Pharmaceuticals, West Auckland, New Zealand) and were used without further purification.

Determination and testing (for adherence to Beer's Law behaviour) of candidate drugs that could be co-extruded with PEO for release studies

By consulting pharmacopoeia,[13] a range of drugs was decided upon for incorporation into PEO by melt extrusion. These are summarised in Table 1. After sourcing the drugs, they were checked for their solubility in either water (initially for some drugs) or in 40% (v/v) AR grade (Rhone Poulenc) ethanol, and accurately known concentrations of them were prepared and then scanned using a Biochrom Libra S12 UV spectrophotometer. This was done to determine: 1) the characteristic UV/Vis spectrum of the drug over 200-400 nm to check if it conformed with that shown in the pharmacopoeia and 2) to check that a reasonably linear Beer's Law plot of UV absorbance (at a chosen absorption maximum in the drug's spectrum) versus concentration of the drug was obtained within certain concentration limits. The results of 2) also led to a graphical slope value which could be

Table 1. Drugs used in the release studies from extruded PEO rods[13].

Drug	UV absorption maximum (λ_{max}) / nm in 40% EtOH	Melting point/ °C	Therapeutic use
Sodium Salicylate	296	300 °C ,	Analgesic
Progesterone	246	126-131 °C	Progestational steroid
Hydrochlorothiazide	271	268 °C (decomposes)	Diuretic
Diazepam	254	131-135 °C	Tranquilliser
Chlorpheniramine Maleate	263	130-135 °C	Allergy treatment
Methyl Paraben	257	125-128 °C	Preservative
Ethyl Paraben	257	115-118 °C	Preservative
Propyl Paraben	257	95-98 °C	Preservative
Bromazepam	235, 260	247 °C	Tranquilliser
Metoprolol Succinate	222, 274	120 °C	β-Adrenoceptor blocking agent
Naproxen Sodium	226, 263, 267, 271, 317, 331	156 °C	Analgesic

used in future studies for calculating concentrations of the drug in receptor media in which it had been released from gelled PEO extruded rods.

A list of the drugs used in this study together with their melting points and UV absorption maxima is given in Table 1. Although this research was done with a view to applying it to the manufacture of teat seals and for the treatment of mastitis in cows, the drugs chosen for study were not ones which would be considered for treating mastitis. This was because we wanted to know in general the extent to which the gelation chemistry of melt-extruded PEO could be modified to influence release. Hence the choice of drugs used in the study was chiefly based on their different molecular characteristics (e.g., difference in polarities), with the main aim being to test how well they were released from the rods into a receptor medium when they were co-extruded with PEO either on their own or with various excipients. They were also chosen on the basis of their solubilities in the 40% v/v ethanolic release solvent used (see later).

Manufacturing of the Extruded Rods

It was important for this research to develop a reliable bench scale manufacturing method for the melt extruded rods from polyethylene (oxide). This was achieved using a small bench-sized (in-house manufactured) extruder which had a heating unit wrapped around a stainless steel augur screw that was heated through a programmable ATHENA temperature controller (Fig.1)
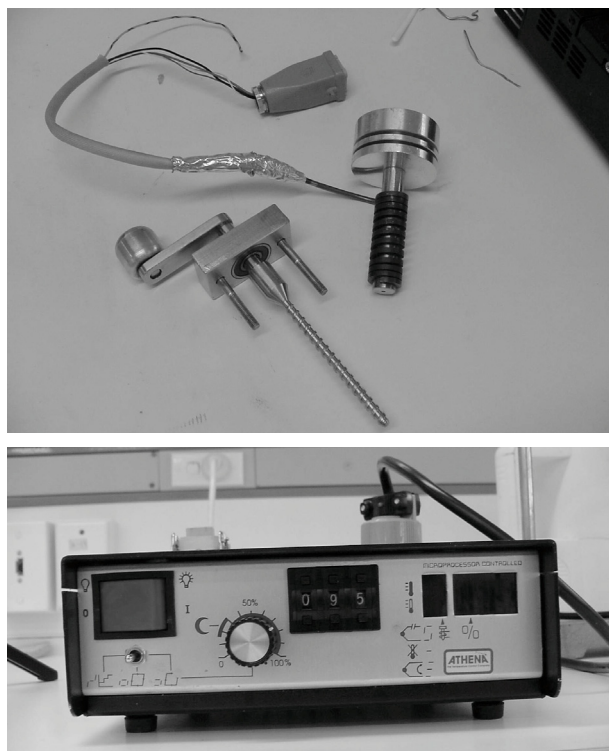

Fig.1. *Upper:* The extruder and heating jacket (dark-coloured screw attached to barrel with wires). *Lower:* The ATHENA extruder temperature control unit.

The methodology for using the extruder to form the extruded rods was as follows. By means of a vice clamped to the edge of a lab bench, the augur screw and heating unit shown in the upper part of Fig. 1 was assembled by inserting the augur screw into the cylinder shaped barrel with heating jacket and held firmly in place with the clamp. The heating jacket was plugged into the heating unit (with heating initiated by setting to 80-100 ºC) and a well-mixed powder consisting of PEO (plus drugs and any excipients) was introduced via a spatula at the top of the barrel in which the augur screw had been inserted. The "crank handle" attached to the augur screw was then turned vigorously clockwise. This action caused the powder to be carried down into the screw and beyond into the heated barrel where the PEO melted and was extruded as a thin rod (Fig. 2) through the small exit point at the end of the barrel. The residence time of the powder mix in the augur screw was thus brief, being less than a minute.
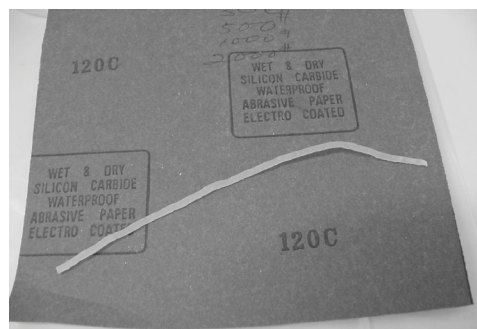

Fig. 2. Typical appearance of a PEO extruded rod. The width of the rod was *ca.* 2.1-2.4 mm. These were initially extruded limp to the touch, but hardened rapidly on cooling to the firmness of a hard plastic rod.

When the actual drugs and/or excipients (added to delay the onset of PEO gelation) were co-extruded with the PEO to form the rods, PEO powder mixes containing these were prepared in 30 g batches on a % (w/w) basis by accurate weighing to give *ca.* 1% (w/w) drug/PEO rods. When mixes were formulated with excipient inclusion in particular, this was done with either 5% or 20% (w/w) excipient. In experiments where the influence of %(w/w) excipient on drug release was being investigated, 10% (w/w) NaCl was included as an additional excipient. Before extrusion, the drug and/or excipient components of the powder mix were well pre-mixed by shaking in a pottle or a large plastic bag to maximise homogeneity. In using this simple extrusion methodology, the physical form of some of the excipients (e.g. chunky sodium chloride or calcium chloride, lumps of paraffin, etc) often provided a challenge to achieving homogeneous PEO/drug/ excipient powder mixes (see later discussion). However, the methodology was maintained because the % cumulative concentration versus soaking time plots generated (see later) tended to be independent of the different relative loadings of drugs across samples, and it was the gross trends in drug release that were of main interest in this study for assessing the drug release behaviour from the extruded PEO rods with or without the addition of the various excipients.

Samples were also prepared in which a randomly selected melt-extruded PEO/drug rod system (i.e., 1% metoprolol succinate) was also subjected to physical barrier coating treatments for controlling the rate of PEO gelation in the 40% alcohol/water release medium. A barrier coating sys-

tem containing a 25 % (w/w) combination of SPAN80 (sorbitan mono-oleate), an excipient used for orally taken medical preparations, together with a tabletting excipient called hexaglycerol distearate or "HGDS", was prepared. Coating of the co-extruded PEO/metoprolol succinate drug rods involved the brief dipping of the rods into the hot SPAN80/HGDS melt followed by air cooling until the coating solidified. Samples were generated where completely coated rods were generated but also samples where the bottom only or the bottom and top parts of the rod were left exposed (by scratching off the soft coating after application at ends of the rods). This led to a sub-set of 4 samples for this particular experiment, i.e., fully coated, coated with one end of rod exposed, coated with both ends exposed and uncoated rods. Two samples per coating permutation were prepared. These systems were assessed for drug release in the receptor medium follow-ing the same methodology described below.

In vitro *drug release test methodology*

For assessing the release of drugs from the extruded PEO/drug/excipient rods, the extruded rods were cut into approximately 2-cm lengths and weighed on a 3-decimal place balance (Mettler). They were then affixed using superglue (and a wire to keep the rod approximately straight) to the ends of plastic spikes that had previously been threaded through the centre of plastic 100 mL pottle lids and glued in place with hotmelt-gun glue (see upper part of Fig. 3). The lids with attached spikes plus affixed rods could then be screwed onto the accompanying plastic 100 mL pottle where fresh receptor medium (in most cases 40% (v/v) A.R. (Rhone-Poulenc) ethanol/water) was added and made up to the 100 mL mark on the pottle. This particular solvent medium was chosen in this study not only to act as a "sink" but also to simulate a biological membrane,[14] which would possess both hydrophobic and hydrophilic character (such as the inside of a cow's teat or a bovine vaginal membrane) so that an implant such as a melt-extruded rod of PEO could, in practical veterinary treatment situations, be pressed against for release of drugs across that membrane.

When rods containing a certain formulation of PEO/drug or PEO/drug/ excipient were assessed for release, the test was done in duplicate using two separate samples made from the same rod. The pottles with rods and receptor medium were then placed inside sample holders on a 37.5 °C shaker water bath which moved from side to side (see lower part of Fig. 3).

A total of four withdrawals of 10 mL of release medium per replicate sample from pottles for each replicate was done with a syringe to assess release. These were done roughly at one hour (1 h), two hours (2 h), three hours (3 h) and twenty four (24 h) hours after initiation of soaking. The 10 mL withdrawn at each time point was then replaced with an equivalent volume of solvent (40% ethanol) to keep the volume at a constant 100 mL during the release experiment. Owing to the number of samples being processed (i.e., withdrawn and replaced by an equivalent volume of fresh release medium) at a given time period, it was challenging to sample at exact times

Fig. 3. *Upper:* Mode of attachment of extruded PEO rods to release media pottle lids. *Lower:* Pottles in the water bath for testing release of drug from PEO extruded rods into 40% (v/v) ethanol/water.

such as 1 h, 2 h and 3 h for exposure time for each sample so these times are nominal only. The 1 h, 2 h, 3 h, and 24 h soaking times could be thought of as the first, second, third and fourth sampling points for testing release of drug from the extruded rods. The first three sampling points (1 h, 2 h, 3 h), for instance, correspond in practice to soaking times of between 1 and 5 hours after exposing the rods to the release media. The final time point corresponds to an exposure of the sample to the release medium for at least 24 hours.

All 10 mL portions of withdrawn samples were placed into separate sealable pottles, allowed to cool and then analysed by UV/Vis spectrophotometry by taking absorbance readings at the λ_{max} values of the particular drug released from the PEO/drug/excipient rod. The whole spectrum of the receptor medium containing the drug from 200-400 nm was usually scanned before measurements to ensure there were no significant spectral interferences from excipients or PEO etc. Drug concentrations in mg/L (ppm) were then calculated using the relevant Beer's Law plot measured for the drug being tested and % cumulative concentration release profiles were then plotted. The % values were based on the 24 h release concentration which was taken to be the time by which 100% release of the drug from the extruded rods might be expected to have occurred. This assumption was justified by the observation that the PEO portion of the extruded rods had completely disintegrated after immersion for 24 hours in the release medium used, i.e., 40% ethanol/water (see later). Often this 24 h release

value was used as a benchmark to assess how much the rod had released relative to the calculated 100% release value into the 100 mL release medium which was determined from the weight and % (w/w) of drug incorporated in the rod.

In addition to soaking of extruded rods from all PEO/drug/excipient combinations studied, an experimental release trial was carried out to test homogeneity of powder mixing of PEO/drug mixes with and without excipients added. The drug tested for release for this experiment was sodium salicylate which was added to give a value of ca. 1% (w/w) in powder mixes of PEO combined with either "cellulose CMC", paraffin or no excipients (i.e., PEO alone with the drug) . Accurately weighed amounts (0.1-0.6 g)of these powders (i.e. they were not extruded into rods) were added to pottles into which 100 mL of 40% EtOH/H2O was then added. These were sealed and left to stand in the dark at room temperature for 48 hours. At the conclusion of this experiment the solutions were subjected to a single UV analysis at 296 nm after shaking to homogenise the contents of the pottles. To ensure complete dissolution of the powders in the release medium, soaking for 48 h was used instead of for 24 h.

Results

Initial Experiments involving the extrusion of PEO (alone) with a wide range of drugs and soaking in 40% EtOH to determine release behaviour

Initial experiments involving the extrusion of PEO(alone)/1% (w/w) drug powder mixtures involving diazepam, hydrochlorothiazide, sodium salicylate, naproxen sodium, bromazepam, methyl (as well as ethyl and propyl) paraben, metoprolol succinate, chlorpheniramine maleate and progesterone gave favourable results with all extruding well at 80-95 ºC. The lengths of rod tested for release were generally in the range of 1.98 to 2.08 cm, width 0.20 to 0.24 cm and weighing from 0.081 to 0.140 g. The glue used to affix the rods to the pottle caps was confirmed not to dissolve in the 40% EtOH release solvent used to give any background in U.V./Vis. spectra.

Generally by the first sampling point ("1 h"), the PEO/drug rods were observed to go limp and progressively dissolve over the next two sampling points, albeit while still being attached to the pottle lids. By the time more than 24 hours of soaking had elapsed, the rods had dissolved and deformed to such an extent that they had become detached from the pottle lid with a diffuse mass of PEO in the approximate form of the rod observed to be lying on the bottom of the release pottle. This approximately 24 hour sampling point was where the highest UV absorbance due to the released drug was usually observed. In fact, the concentration detected was visually levelling off in % cumulative concentration *vs.* soaking time graphs plotted of the release at that point (see later). It was this point (owing to the degraded and dissolved state of the extruded rod) that the cumulative concentration % release plots were calculated (the last point at which is invariably "100%"). The use of this time point at the 100% release was deemed mostly justifiable because a significant pro

portion of the drug co-extruded into the rod had released after only the third time point for measuring release (i.e., up to 90 % of the expected amount based on the % (w/w) of drug in the extruded rod for some drugs). Hence there is likely to be less than 10% of the original drug amount still resident in the diffuse mass of PEO gel lying at the bottom of the release pottle after 24 h of soaking.

Graphs of cumulative % concentration of drug released vs. soaking time for drugs co-extruded solely with PE.

A wide range of commonly used drugs (as shown in Table 1) were co-extruded with PEO alone at a loading level of approximately 1% (w/w). Two cumulative concentration % vs. time and % release vs. time plots for drugs with differing solubility properties in aqueous solutions are shown in Fig. 4, namely diazepam, which is largely insoluble; and Naproxen sodium, which is soluble. Both drugs, however, dissolved in the 40% EtOH/water release medium to produce UV-analysable solutions. Two curves per drug are shown in Fig. 4 for the diazepam/PEO system and serve to show the consistency of release behaviour for each of the two replicates per drug tested. The shape of the curve, to which a logarithmic trend-line is best fitted, is strongly representative of the typical drug release behaviour observed throughout this study from the extruded rods, namely, a steep increase in drug release at the first, second and third time (sampling) points followed by a plateauing or leveling off by the "24 h" timepoint. This release behaviour is obviously dominated by the fact that the rods swell rapidly via hydration to the point that they drop off the pottle lids to rest at the bottom of the sampling containers.[15] The same curve shape is observed when the actual UV measured concentration data from each replicate rod are plotted *vs.* the time of soaking, implying that this shape is not an artefact of using cumulative concentration as a unit. Hence, the speed at which gelation occurs for PEO co-extruded for drugs without any added excipients is leading to rapid loss of drug from the rods. Indeed in a study where a related polymer PEG6000 was co-extruded with a poorly soluble drug, 17β-estradiol hemihydrates,[16] the PEG6000 (and other polymers co-extruded in separate samples) were found to be facilitating the transport of this relatively insoluble drug into solution.

In the present study, although the cumulative concentration % release versus time plots gave very similar appearances over all drugs trialled, the actual cumulative concentration % release values at the first three sampling points did exhibit some variation, depending on which drugs were tested. The range of release concentrations is illustrated in Fig. 5 for all replicates tested of the drugs studied. This shows the wide variation in concentrations at the 1h, 2h and 3h sampling points. Progesterone, sodium salicylate and naproxen sodium exhibit the highest release over that time period, probably because of their higher solubilities in the release media. Values for the % cumulative concentration range for all the drugs tested range from the about 45% to 70%.
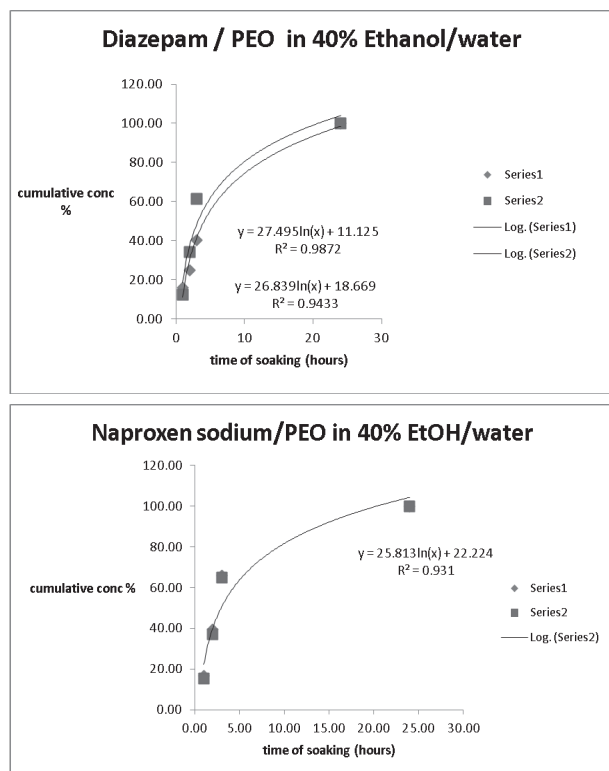
Visually the PEO extruded rods went limp very quick

Fig. 4. Cumulative concentration versus time of soaking for (upper) Diazepam/PEO (plots for both replicates shown), and (lower) Naproxen sodium/PEO co-extruded rods in 40% ethanol at 37ºC.
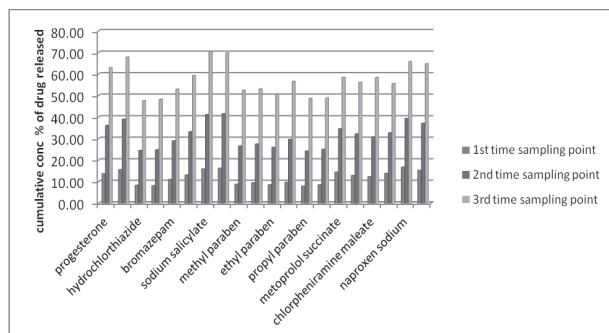

Fig. 5. UV-assayed % cumulative concentrations measured at 1 h, 2 h and 3 h soaking times (in 40% EtOH/H$_2$O at 37 ºC) for release of drug from melt extruded rods of PEO (alone) with various drugs. Sampling points for each group of 3 bars per replicate sample for drugs should be read from left to right.

ly when immersed in the release medium, as is evident in Fig. 6. In terms of how "accurate" the 100% release assumption at 24 hour sampling was concerned, Fig. 7 shows a plot of the comparison of observed 24 hour release concentrations (in ppm) for all replicates of drugs illustrated in Fig. 5, with their calculated 100% release value based on the weight of the rod and weight percent of drug inside each rod and, furthermore, assuming 100% release of that into the 100 mL of release solvent. As is evident, there is a large variation of agreement between the calculated 100% and observed release values. Most of the % variance in agreement was positive, so larger concentrations than expected from calculated 100% release concentrations were actually observed. Some systems like PEO/chlorpheniramine maleate and PEO/metoprolol succinate gave extremely large positive variances, while a few like PEO/bromazepam and PEO/ethyl paraben gave

negative variations for their concentrations at 24 hour sampling periods. The many reasons for these variations include inhomogeneities in drug concentration throughout the PEO/drug extruded rod, sampling technique or dilution errors building up in the values calculated for the concentration with time owing to the need to correct the observed concentrations for dilution. However, with most %variance between -20 and +20 %, the results were seen as indicative. With the exception of bromazepam, the replicates for each extruded drug/PEO combination behaved consistently with each other.
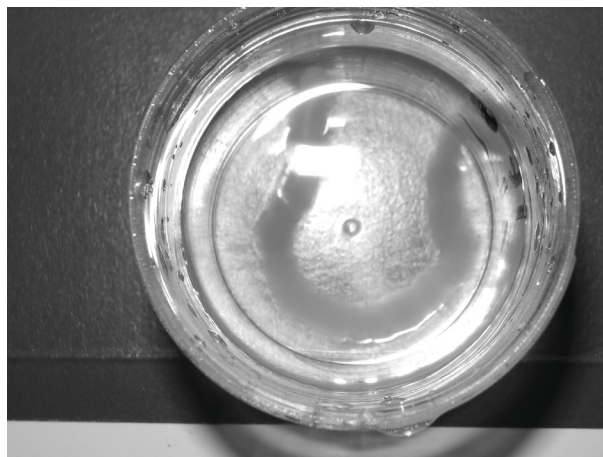

Fig. 6. A melt-extruded PEO rod (U-shaped shadow) and its appearance after soaking in 40% EtOH/H$_2$O for 1 hour. Lengthening and swelling of the rod as illustrated occurs rapidly within the first hour of soaking.
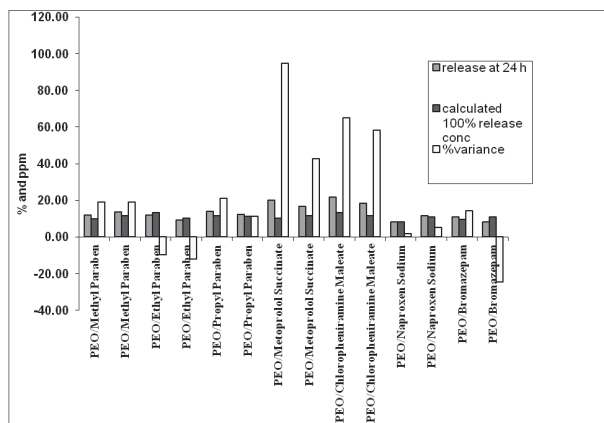

Fig. 7. Comparison of the UV-assayed release profiles of drugs from extruded PEO(alone)/drug rods soaking in 40% EtOH/H$_2$O solutions at 37 ºC with the concentrations for the calculated 100% release of drugs from rods into 100 mL of release solvent. Release at 24 h, calculated 100% release of drug concentrations and % variance should be read from the left to right columns respectively per replicate sample tested for the drugs.

Experiments in which PEO is co-extruded with sodium salicylate and excipients to achieve a greater extent of controlled release

It was obvious from experiments involving extrusion of drugs with PEO alone that the level of release into the 40% EtOH/H$_2$O medium was very rapid, to the extent that its use as a controlled release material for delivering a drug over a matter of days would be limited, owing to rapid dissipation from the gelating PEO matrix which

visibly leads to its rapid disintegration. PEO forms a hydrogel in aqueous solution. Hydrogels are well known for producing networks which can release drugs rapidly over periods of hours or days. Much work has been done with molecularly based strategies for limiting release such as through crosslinking.[17] However, given that there is an interest in finding simpler ways to do this for veterinary applications where the veterinary industry supplying these pharmaceuticals and the clientele using them prefer lower unit cost of materials utilized for such purposes, physical methods for delaying drug release from the PEO hydrogel were sought instead. Various strategies along these lines have been tried in the past, such as charge interactions between ionic type polymers and charged drugs (not applicable with PEO) and surface diffusion control, where a reduced permeability film resides at the surface along with a thermosensitive switch that may facilitate diffusion given changes in temperatures. The approach taken in this study was simpler in concept and concentrated more on the use of excipients co-extruded with the PEO and drug. Historically, excipients were defined[18] as additives to a pharmaceutical that ensured it had the correct weight, consistency and volume so that administration could proceed in the way intended. This was the role expected of an excipient when the drug delivery vehicle was restricted to the traditional tablet or pill. Nowadays, with more diverse forms of drug delivery vehicles available, the traditional definition has been extended with excipients often performing multiple roles when included in a pharmaceutical formulation. In the present study, it was desired to rein in the fast release characteristics of the PEO when it, alone, was extruded along with the drug. Hence, excipients were chosen so that they might compete with the PEO for water after immersing the extruded rods in the release medium (see Table 2). This, it was envisaged, should then slow down the rate of gelation of the PEO, hence slowing the release of drug from the rods.

Thus, it was necessary to design experiments where various excipients were added to the PEO/drug powder mix before extrusion, so that rods containing these could be manufactured and trialled for their ability to delay release by subjecting them to the identical protocol used for the systems where PEO alone was co-extruded with drug. In testing this simple physical method for controlling release, it was decided to trial a very wide range of possible candidate excipients ; a total of 10 common and novel compounds were co-extruded with PEO. These were PEG6000, cell CMC, "TONE" brand polycaprolactone, solid paraffin, magnesium stearate, polyvinyl(alcohol), arabinogalactan (oligosaccharide derived from the American Western Larch tree), agarose, calcium chloride and sodium chloride, which was added to a number of these as an additional excipient. At the last stage of this study beeswax was also tried, but was combined with PEO via a different empirical methodology to that used for forming the PEO-extruded rods. Owing to the large number of excipients investigated which would have led to a large number of drug/PEO/excipient permutations/trials, it was decided to concentrate on only one drug to test the ability

Table. 2 The primary function of excipients used as 5% or 20% w/w loadings which were co-extruded with PEO-303 rods containing also ~1% (w/w) sodium salicylate. Rods were also co-extruded with 10 % (w/w) sodium chloride unless otherwise stipulated.

Excipient	Mode of action for slowing PEO-303 gelation in the release medium	Co-extrudability with PEO-303
Agarose (No NaCl added)	Competes with PEO for water to delay PEO gelation	Good
Arabinogalactan (No NaCl added)	ditto	Good
Calcium chloride (No NaCl added)	Competes with PEO for water in similar manner to NaCl but to a greater extent owing to the influence of the divalent Ca2+ ion which results in a more heavily hydrated ion	Good
Carboxymethylcellulose ("cell CMC")	Competes with PEO for water to delay PEO gelation	Good
Lactose	Competes with PEO for water to delay PEO gelation	Extremely poor leading to blocking of the extrusion apparatus
Magnesium stearate	Provides hydrophobic layer to delay gelation of PEO by water	Very poor leading to low quality, non-cohesive rods
Paraffin wax	ditto	Good, though uniformity of mixing of PEO, drug + excipients is problematic
PEG6000	Competes with PEO for water to delay PEO gelation	Good
PVA (polyvinyl alcohol).	ditto	Good
Sodium chloride (not used on its own)	Used as an adjuvant in most excipient-added samples to compete with PEO for water so delaying PEO gelation	Good, although large salt crystal size may not promote the best uniformity of mixing of solid components
TONE polycaprolactone	Temporary encapsulant for PEO rod to delay access of water to PEO	Good

of these substances to delay drug release. Of the drugs trialled and discussed earlier, it was decided to use sodium salicylate because of its rather rapid release rate from the PEO (only) extruded rod as shown in Fig. 5. Hence powder mixes consisting of ~1% by weight of drug, and 5 or 20% by weight of excipient (remainder PEO) were prepared. To provide an additional amount of competition for gelation, it was also decided to include 10% by weight of NaCl in all samples (apart from arabinogalactan, agarose and calcium chloride). The powder mixes were then extruded in the usual manner as described earlier.

Extrusion results involving excipients

Although extruded rods could be successfully prepared from most PEO/Na salicylate/excipient combinations using temperatures of 80-100 ºC in the extruder, a number of combinations exhibited manufacturing issues. In particular, attempts to co-extrude PEO/drug with 20% lactose proved virtually impossible due to the material sticking intractably in the extruder. Only some segments could be obtained, which were insufficient for release testing. Co-extrusion with 20% Mg stearate at 85-90 ºC was also problematic because the material was too "slippery", thereby providing a barrier to extrusion of any rod of substance. Fragile poorly formed and/or filled rods were the result. Lowering the temperature of extrusion led to grainy and brittle rods. Rods containing 20% cell CMC by weight tended to extrude only above 100 ºC and caused some blackening in some parts of the rods produced, which had to be rejected. TONE polycaprolactone, while extruding to produce rods of acceptable quality, was a substance that was difficult to clean out of the barrel of the extruder. Paraffin exhibited issues similar to magnesium stearate. Its slipperiness in the extruder often made it challenging to extrude rods efficiently, especially when present at 20% by weight (which may have been associated with challenges in homogenizing a powder mix containing that high level by weight of paraffin).

The group of samples containing AG or agarose or CaCl$_2$ as excipients without NaCl could also be extruded to produce acceptable quality rods; although for samples containing 20% agarose by weight, blockage of the extruder barrel occurred and the CaCl$_2$-containing mixes led to selective "sieving/separating out" of the CaCl$_2$ granules near the top of powders being introduced into the feed inlet of the extrusion barrel. This raises questions about the uniformity of excipient throughout the extruded rod produced (although the resultant rods were observed to contain speckles of the calcium salt throughout the body of the rod). Given the excipients existed in different physical forms from powders/granules to waxy or oily solid/chunky materials, the issue of how uniform the rods were in composition when extruded from a powder mix needed to be considered.

Results of release experiments.

All extruded rods produced were tested for release with the usual sampling at the nominal 1 h, 2 h, 3 h and 24 h soaking times in 40% EtOH/H$_2$O at 37ºC. In Fig. 8 and Fig. 9 bar graphs are shown for UV-detected sodium salicylate concentrations measured of all replicates tested

for each PEO/Na salicylate/excipient combination at the 1 h, 2 h, 3 h and 24 h sampling points, with a comparison bar indicating the calculated 100% release concentration (in the 5th column to the right of the columns indicating concentrations at 1 h, 2 h, 3 h and 24 h sampling points from left to right in the bar graph). Data for the excipients used with NaCl included at 10% by weight are shown in Fig. 8, while Fig. 9 shows data for the excipients used without NaCl. For all PEO (only) / sodium salicylate replicates the level of drug detected in the release medium after 24 h of soaking exceeds that of the expected value, assuming total release of all the drug into the 100 mL of release medium.
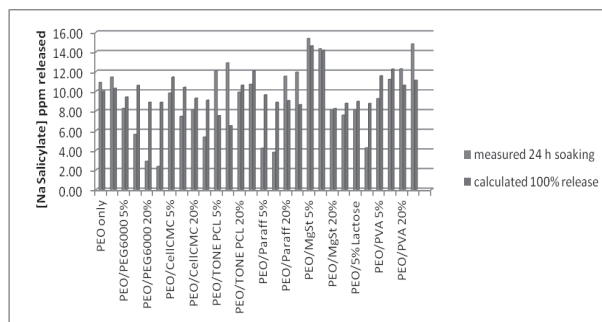

Fig. 8. UV-assayed data for [Na salicylate] released from soaking of extruded rods containing PEO and drug with or without various excipients in 40% EtOH/H$_2$O solution at 37 ºC for 24 h. Columns should be read left to right for measured 24 h soaking and calculated 100% release for each replicate tested.
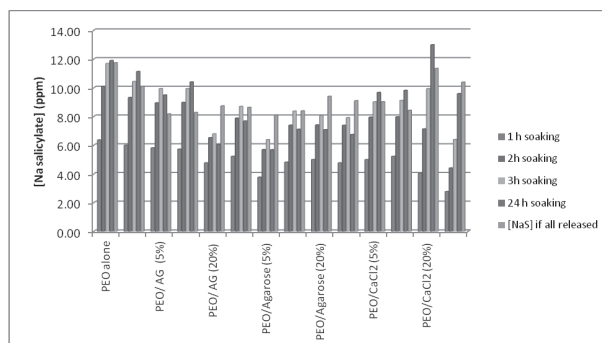

Fig. 9. UV-assayed data for [Na salicylate] released from soaking of extruded rods containing PEO and drug with or without various excipients in 40% EtOH/H$_2$O solution at 37 ºC for 24 h. These extruded rods did not have 10% (w/w) NaCl incorporated into pre-extruded powder mixes. Columns should be read left to right for measured 1 h, 2 h, 3 h, 24 h released [Na salicylate], and calculated 100% release concentrations for each replicate tested.

These data from Fig. 8 and Fig. 9 for the PEO(alone) replicates reflect the rapid release of drug into the release medium as expected of (gelling) PEO and in line with the previously described release trials. The partial non-agreement with calculated 100% release values may also reflect the fact that extrusion of the drug with PEO into rods could be compositionally non homogeneous, so that "1% by weight of drug in the unextruded powder" may not mean 1% by weight in the extruded rod. However, the level of agreement between the 24 h sampled concentrations and the calculated 100% release concentrations expected from the rods were within 1 ppm for the PEO (only)/drug samples and the behaviour of replicates was consistent. There will also be experimental error in the

calculation of the concentrations from UV assay. The most noticeable effect of the excipients on the disintegration of the PEO rod in the release medium was seen in rods observed at the nominal 1 h sampling point, where most of the sample rods containing excipients appeared visually to disintegrate less relative to PEO(alone)/drug extruded rods. Also, in support of this, the measured values for [Na salicylate] at 1 h sampling were all lower than the corresponding value for the [Na salicylate] released from PEO (alone)/drug extruded rods. This suggests a short-term inhibition process of PEO gelation is occurring. However, when rods with excipients were considered in terms of their release behaviour, especially the rods containing magnesium stearate, PVA, 20% by weight paraffin, and TONE PCL, the actual measured release of sodium salicylate at 24 h in relation to the calculated 100% release of drug expected from the rods ranked the systems as ones of similar effectiveness to or less effective than PEO alone in restricting release of drug. Hence, it was obvious that formulation with these particular excipients did little to stem the release of the drug from the soaked extruded rods, and so were limited in any role they might have had as a physical barrier or as components that interfered with PEO gelation. Indeed the PEO/TONE PCL co-extruded rods were a case in point, because outwardly they gave the deceptive appearance of retaining their rod shape when observed at 1 h, 2 h and 3 h soaking times when, in fact, what had actually happened (as borne out by UV assaying) was that the PEO had leached out of the internal parts of the rod into the medium, leaving the TONE PCL-encapsulating shell intact but empty.

Other PEO/excipient combinations for which data are illustrated in Fig. 8 and Fig. 9 gave potentially interesting results: the rods containing PEO/PEG6000, PEO/cell CMC, PEO/ paraffin 5%, PEO/lactose 5% and PEO/agarose (no NaCl) gave measured 24 h sodium salicylate concentrations which were consistently (and for some systems (PEG6000 and 5% paraffin) significantly below the calculated 100% release values expected (for both replicate rod samples tested). Some systems, however, such as the PEO/drug/5% lactose mix did give very different absolute values of measured [Na salicylate] values between the replicates which raises in these samples the spectre of compositional non-uniformity in the extruded rods as discussed above. The consistency of behaviour with respect to lower observed overall 24 h release concentrations than what is expected from calculated 100% release values could, however, also suggest that these particular excipients have indeed had the desired effect of retaining the drug within the PEO gel mass, whether it be through forming a physical barrier to the drug being released or via competing with PEO for water during the gelation process. Possibly, the biggest effect imparted by the excipient is realized in the first hour of soaking, as demonstrated by the visual observations on the delayed disintegration of the rods in the aqueous alcoholic release media relative to the typical, rapid PEO(alone)/drug extruded rod disintegration behaviour.

Soaking of PEO/excipient/sodium salicylate powder mixes in 40% ethanol/water for 48 h

In order to determine the uniformity of the PEO/sodium salicylate and PEO/sodium salicylate/excipient powder mixes prior to extrusion, three systems were investigated with two replicate samples per system prepared. The systems chosen were: PEO alone with drug, PEO/NaCl (10% by weight)/cellulose CMC/ (20% by weight) and PEO/NaCl (10% by weight)/paraffin (5% by weight). NaCl is a hard crystalline solid, Cellulose CMC is a powder, while paraffin is a chunky/waxy/oily solid; hence, these materials represented the spectrum of physical dispersion types of excipient that were mixed with PEO in the previous experiments described in this study. The powder mixes prepared were made up identically to those made in previous release experiments except that 0.1-0.6 g of each of the mixed powder systems was pre-weighed into the release pottles used (in duplicate) without extrusion into rods. 100 mL of release medium was then added to these powdered samples and the pottles sealed. To ensure full dissolution and, because soaking was conducted at ambient temperatures, the powders were allowed to remain in the release medium for 48 h as opposed to the customary 24 h for the rods. Furthermore, they were kept in the dark to prevent any spurious light-mediated decomposition of the sodium salicylate over this prolonged soaking time. After this period of time the solutions were all observed to be reasonably clear though viscous with some settling of gel on the bottom. They were shaken prior to taking samples for the single UV analysis. The results are shown for all replicates tested as a bar graph in Fig. 10.
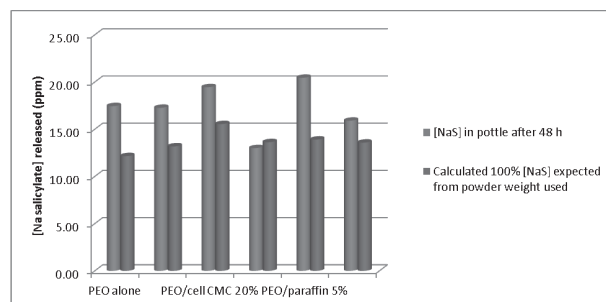

Fig.10. Bar graphs showing the concentration of sodium salicylate released from powder mixes of PEO with sodium salicylate (~1% w/w), cell CMC and paraffin (with each sample also containing 10% (w/w) NaCl) that had been soaked for 48 h in 40% EtOH/H_2O at ambient temperature in the dark. [NaS] = concentration of sodium salicylate. Data are shown for both replicates per system studied. The left hand column in each group is the UV-assayed concentrations and the right hand column is the calculated 100% release concentration expected from the weight of powder sampled in 100 mL of release media.

With the exception of one rod replicate sample (PEO/cell CMC), the pottles gave higher [sodium salicylate] values than expected from the calculated 100% release concentrations for the rods used. Dilution errors would not feature in this data as no samples were withdrawn until the end of the soaking period where they were assayed by a single UV analysis. As a consequence, no solvent was replaced during the 48 h soaking period. Some of the results in Fig. 10 contradict the extruded rod results in Fig. 8 and Fig. 9, where lower concentrations than the calcu-

lated 100% release concentrations for the rods used were observed for 24 h release (e.g., PEO/NaCl/paraffin 5% by weight, see Fig. 8). There could be several interpretations of these results. One is that the powder mixes, especially those containing chunky/ waxy excipients like NaCl and paraffin, exhibit compositional homogeneity issues when a small subset of sample (i.e., 0.1-0.6 g as in this experiment) is taken from a larger prepared powder mix. The other interpretation, or more appropriately caveat, is that it may not be wise to compare results for release of drugs from powdered soaked samples as opposed to extruded rods from the same powders because the act of extruding the mix into a rod is aiding in mixing the excipients, sodium salicylate and PEO intimately, so that beneficial effects like provision of a physical barrier or competing with PEO for water are brought into effect, thereby stemming release of drug into the release medium as intended.

Experiments involving release from PEO/drug extruded rods that had been precoated with physical barrier coatings prior to immersion in the 40% EtOH/H$_2$O release media

The mixed results from the PEO/drug/excipient co-extruded rod studies as discussed above led to consideration of research trials where physical barriers were instead placed on the PEO/drug extruded rods as an alternative strategy to delay release of drug from the gelating rods. By placing a physical barrier via a total or partial encapsulation of the rod itself, it was reasoned that controlled release of the drug might be realized through a slow breakdown or erosion of the barrier film.

In general this was trialled using 1% by weight of metoprolol succinate as the drug with the same release sampling protocol as was used in the previously described studies. Barrier coating systems using SPAN80 and HGDS (applied by dipping rods in molten mixtures of these components followed by rapid cooling) that involved comparison of release of drug from rods which were fully coated, coated with one end of rod exposed, coated with both ends of rod exposed and uncoated rods were prepared and tested. In short, no results from such a system were obtained because the barrier coating completely disintegrated and clouded the release medium, so rendering UV analysis impossible. Another barrier coating (which cannot be mentioned for commercial reasons) was also trialled and applied by dipping in molten mixtures of the barrier coating. This, though not clouding the medium, was found to provide a very weak barrier to the disintegration of the rods through PEO gelation. Parts of the coating were observed to have curled at the end of the soaking period, so providing little protection to the underlying PEO rod. Hence, the "rod coating" approach was not taken any further.

"PEO/beeswax composites"

The research experiences and lack of success associated with controlling release of drug from PEO/drug/excipient co-extruded rods with or without barrier coatings prompted a change in research strategy with respect to achieving a significant (i.e. beyond 1 h of soaking) inhibition of release of drugs in matrices containing PEO.

The change in strategy involved not preparing the extruded rods but instead creating discs of co-melted PEO and beeswax. This work, which was initially done at the end of this study as a brief but successful experiment, showed a significant delay in the release of drug. It was further developed in a summer research project by BSc Tech student Ho Ying Yuen in 2010, who displayed the research as a poster presentation at a Waikato Sustainable Bioeconomy Student Poster conference held at the University of Waikato in May 2010 where she was awarded one of the three poster prizes offered in the competition decided by industrially-based judges. Commercial interest was sparked in this after the conference. As a result, research and development of this system, albeit in a different direction to its original use as a drug delivery agent, are now proceeding with promising applications. Some of the disclosable results of the further study of this system were presented at the recent NZIC conference in Hamilton in November 2011.[12]

In conclusion, this empirical study has demonstrated the practical issues of using PEO in extruded rod systems for drug delivery. Fast gelation of the PEO in aqueous solutions can lead to rapid release of drugs; and, apart from the well known strategies used by earlier workers in this field, simple strategies involving co-extruded excipients and physical barrier coatings as used in this study, may only have limited impact for delaying release. Further work concentrating on the success of the comelted PEO/ beeswax system as a delivery matrix is continuing. Some of the disclosable aspects of this technology will be the subject of a separate publication in the future.

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