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Analysis of *in vitro* drug dissolution from PCL melt extrusion

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ABSTRACT

This study investigated the *in vitro* release of a model API (Nalidixic Acid) from a PCL bulk extrudate and determined how the extent and rate of drug release are affected by the addition of a pore former (PEG) and of a copolymer (PLLA) within the polymer matrix. Drug release and dissolution is a mass transport operation and therefore can rely on both molecular and bulk diffusion. Typical drug delivery systems are made up of three components; a matrix structure (which does not diffuse and hence, its diffusion coefficient is zero), solution (coming in from the external environment and moving inside the matrix structure) and drug (that usually diffuses from the inner matrix into the external release environment). The release from blends produced by both crash cooling and controlled cooling were considered, alongside those processed via both Single and Twin Screw Extrusion. From analysis of the extrusion process it was found that the polymer crystal size was smaller in blends prepared using a 100 °C/min cooling rate than those prepared using a 30 °C/min cooling rate. Furthermore, the solubility of NA in PCL was improved by a factor of 2 by increasing cooling rate which was attributed to higher percentage of amorphous regions. Moreover, a higher degree of NA release was observed in the faster cooling rate due to the increased solubility. The experimental kinetic drug release data were modelled using a number of simple approaches, and it was found that the Kosmeyer–Peppas model was best at describing the experimental data, with $r^2 \geq 0.993$. Finally, the hydrolytic degradation of the extrudates at 37 °C (under static aqueous conditions over the period of 6 months) was also analysed to determine degradation rates.

1. Introduction

The aim of this study was to determine and control the release profile of the antibacterial Nalidixic Acid from the slow biodegrading polymer Polycaprolactone. To aid the release of the drug and the degradation of the PCL, several co-polymers where used; PEG and PLLA for their lubricating and increased degradation effects, respectively (Fig. 1, Table 1).

1.1. Bioactive Extrusion

The dispersive mixing of drugs involves breaking up agglomerates of the minor active phase and dispersing these smaller particles in the major polymer phase. In order to break up these agglomerates, a critical amount of stress must be applied. In the case of extrusion a dispersive extruder should possess a high stress mixing section within the screw. All fluid elements would then pass through this high stress region many times in order to achieve good dispersive mixing and also the same number of times to ensure uniform mixing [1]. Thus dispersion processes require a higher energy input and this is provided by the Twin Screw Extruder due to its either co-rotating or counter rotating screws, as Single Screw Extruders are design to minimise energy input and maximise pumping efficiency [2].

The major role of extrusion in the pharmaceutical industry is in the preparation of granules or pellets of uniform size, shape and density containing one or more drugs [3], a process known as extrusion-spheronisation. The importance of having high-quality pellets or granules for processing into pharmaceutical dosage forms was recognised by Gamlen [4] as well as by Lindberg et al. [5,6].

It was also shown that slower rates of drug release could be achieved with extrusion than with direct compression or wet granulation methods [7] due to increased encapsulation of the active agent. Hot melt extrusion received limited attention in the pharmaceutical literature until recently, with the reporting of hot melt extrusion being used to manufacture matrix drug delivery systems [8].

The technique offers many advantages over traditional techniques. The process is anhydrous and therefore any potential degradation of the drug due to hydrolysis is avoided. As such, extruded effervescent tablets can also be produced [5,6]. Extrusion also has fewer processing steps, no requirements for the compressibility of the active ingredients, de-aggregation of the suspended drug particles in the molten polymer due to intense mixing and

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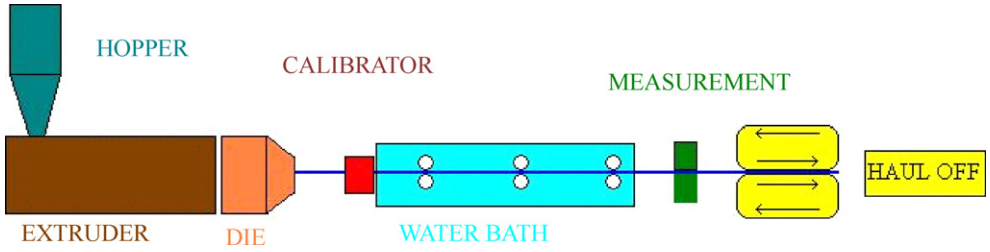

Fig. 1. Schematic of compounding process.

agitation, resulting in a more uniform dispersion and finally the improvement of the bioavailability of the drug when it is solubilised or dispersed at the molecular level [9].

In order to produce granules or tablets via hot melt extrusion, a pharmaceutical grade thermal polymer or lipid material is selected that can be processed at a relatively low temperature due to the thermal sensitivity of most drugs. This limitation of hot melt processing with respect to drug thermal stability was recognised by Follonier et al. [10,11]. As with traditional dosage forms, other excipients are added in order to improve processability and improve uptake within the body. These functional excipients can be broadly classified as matrix carriers, release-modifying agents, bulking agents and lubricants and these affect the drug release rates from melt extruded dosage forms, which are highly dependent on the carrier matrix.

In some cases a plasticizer may be added in order to reduce the processing temperature of the desired carrier material to suit a specific low temperature drug but selection of these are dependent on polymer compatibility and plasticizer stability. Examples of these are PEGs and citrate esters [11–14]. Also pore forming additives and hydrophilic polymers can be added to the formulation to improve the release rate by increasing the porosity of the pellet during dissolution, alongside viscosity inducing agents which are known to limit the burst effect seen in matrix systems [15]. The burst effect which occurs at the beginning of release is due to the non-encapsulated polymer-surface located active agent diffusing into the surround media.

Another factor determining the release of the drug is the physical state of the drug, i.e. either crystalline or amorphous particles, or dissolved in the polymer matrix. In the latter case, the drug is an intrinsic part of the matrix, thus influencing its wettability and release characteristics [16].

1.2. Drug release

The rate of drug release from a polymeric environment is dependent on the solubility of the drug in the polymer, the permeability of the drug through the polymer matrix and in some cases the biodegradability of the polymer. The first two of these determine the flux of the systems and as such the diffusion coefficient of the drug and these factors can be used, alongside biodegradability data to manufacture a polymeric device for controlled drug delivery. As like attracts like, hydrophilic actives have a greater degree of solubility in a hydrophilic polymer and lipophilic actives have better solubility in hydrophobic polymers. Therefore, increasing solubility of an active in an incompatible polymer can be achieved by the addition or copolymerisation with a hydrophilic/phobic polymer if necessary [17].

Many studies over the past few decades have proposed various mathematical models for the determination of drug release from monolithic (having a single and massive structure) dispersion devices [18–25]. In monolithic dispersions, the system consists of a dispersed solid active agent in a rate-limiting polymer matrix, with three main types existing depending on the volume fraction of the agent in the matrix. At low loadings (0–5 vol%) the release of the compound involves the dissolution of the agent in the polymer medium followed by diffusion to the surface of the device. This is known as *simple monolithic dispersion*.

At slightly higher loadings of active (5–10 vol%), the release mechanism is more complex, since the cavities remaining from the loss of material near the surface are filled with fluid imbibed from the external environment, and these cavities provide pathways for the escape of the material remaining in the device. At these loadings the cavities are not connected to form continuous pathways to the surface, but they can increase the overall permeability of the agent and are called *complex monolithic dispersions*.

When the loading of the dispersed agent exceeds 20 vol%, the cavities left by the loss of material are sufficiently numerous to form a continuous channel to the surface of the matrix. In this case the majority or the entire active is released by diffusion through these channels. This type of device is known as a *monolithic matrix system*. The solubility and diffusivity of the dispersed agent in the fluid filling the channels determines the rate of release and can be described by Percolation Theory [26].

The release profiles used here can be categorised into three types [27,28]. In the simplest of these, known as *zero order release*, the release rate remains constant until the active is exhausted in the device.

$$M_t = kt \tag{1}$$

where k = constant; t = time (s); M_t. = mass of active released (μg).

The second type of release kinetics is Kosmeyer–Peppas. The rate in this case is proportional to the mass of active contained within the device. The release rate is given:

$$M_t = M_0 k t^n \tag{2}$$

where M_0 = mass of active (μg) at t = 0 s; n = release exponent.

The rate declines exponentially with time, approaching a release rate of zero as the device nears exhaustion. In many experimental situations, including the case of drug release the mechanism of dif-

Table 1
Physical properties of materials.

Materials	Molecular weight (g/mol)	Melt temperature (°C)	Glass transition temp (°C)	ΔH (100%) crystalline material (J g^{-1})	Density ρ (g cm^{-1})
PCL	50,000	58–64	−60	139	1.1
NA	232.23	227–230	–	117.9	–
PEG	8000	68	−23	197	1.1
PLLA	280,000	201	68	92.7	0.83

fusion deviates from the Fickian equation and follows a non-Fickian (anomalous) behaviour [23].

The third release pattern, referred to as the *square root of time* or $t^{1/2}$ release, in which the rate is proportional to the square root of time. In contrast to first order release, the rate remains finite as the device approaches exhaustion. The rate is given:

$$M_t = kt^{0.5} \quad (3)$$

The empirical equation represents an extension of the short time solutions for Fickian and non-Fickian diffusional release from a thin film [24].

The above equations are used here in order to provide the best comparison with published data.

2. Materials and processing

2.1. Materials

2.1.1. Poly(ε–caprolactone)

PCL is a semi-crystalline biodegradable polymer. It has a low melting point of between 58 and 64 °C, depending on the degree of crystallisation and molecular weight [29]. The material was supplied by Solvay Caprolactones with grade number 6500.

The values for the molecular weight and ΔH 100% crystalline for each of the polymeric materials are taken from literature. (PCL and PLLA from literature) [30,31]. All other values were determined experimentally by DSC, DMTA and a densimeter, respectively.

2.1.2. Nalidixic Acid

Nalidixic Acid (NA) is a synthetic chemical that has antibacterial activity against gram-negative bacteria. The bacteria are so classified from the colour they appear after staining (in this case pink due to the Safranin). Nalidixic Acid's chemical formula is $C_{12}H_{12}N_2O_3$ and is also known as 1,4-dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthridine-3-carboxylic acid. The NA used in this study had a molecular weight of 232 and a melting temperature of 227–230 °C (Merck) and was supplied by Tyresk Chemicals with a 98% purity.

2.1.3. Polyethylene glycol

Polyethylene glycol (PEG) is a hydrophilic low molecular weight polymer (oligomer) and is the basis for many surfactants which when added to hydrophobic structures, reduces the contact angle of water by absorbing the air–water interface. In this study a molecular weight of 8000 was used which was supplied from Sigma–Aldrich in a soft flake form. It has a melting temperature of 68 °C, is non toxic and is a Newtonian fluid.

2.1.4. Poly l-lactic acid

Poly l-lactic acid (PLLA) supplied by Sigma–Aldrich is a well known biodegradable polymer which has a wide range of applications in the biomedical field and can easily be used as an alternative to the conventional non-degradable polymers. The chirality of the lactic acid unit provides a means to adjust degradation rates, as well as physical and mechanical properties. PLA is a semi-crystalline polymer with a melting range of 178–182 °C and crystallinity of approximately 70%. The high crystallinity of this polymer is the main reason for its relatively slow hydrolysis rate.

2.2. Sample preparation

2.2.1. Extrusion and pressing

Prior to compounding, all materials in powder form were blended into their respective compositions in a high speed mixer at 1800 ± 5 rpm for 5 min (Rondol DAC150, UK). The PLLA was provided in pellet form and therefore was subjected to cryogenic grinding in 10 ± 0.1 g batches at 3000 ± 5 rpm for 30 min. This produced a powder with an average particle size of 200 ± 10 microns. Table 2 shows the compositions produced. The varying concentrations of NA were based on the small but effective quantities of drug used in the pharmaceutical industry (5–10%, w/w) to the larger and excessive loadings used for research (25–35%, w/w).

Table 2
Blends produced in the Twin Screw Extruder.

Batch number	Composition (w/w%)			
	PCL	NA	PEG	PLA
1	100	–	–	–
2	95	5	–	–
3	90	10	–	–
4	75	25	–	–
5	65	35	–	–
6	95	–	5	–
7	90	5	5	–
8	70	5	25	–
9	95	–	–	5
10	75	–	–	25
11	90	–	5	5
12	85	5	5	5

These mixtures were then fed into a 25 mm Twin Screw Extruder (Dr Collin Z25, Germany), to produce a continuous strand of each blend using a gravimetric feeder. The extruder operating speed was 120 ± 1 rpm with an increasing temperature of 80–90 ± 2 °C across the barrel. On exiting the single rod 4 mm die, the strand was quenched in a water bath, at a temperature of 20 ± 0.5 °C, and then passed through a pelletiser. Each 300 ± 0.01 g powder batch produced 80 ± 1 g of waste, thus producing 220 ± 1 g of pellets. The residence time in the barrel from entering the extruder to exiting the die was 2.0 min.

Thermogravimetric analysis carried out on the NA (i.e. heating 5 mg of NA from 30 to 90 °C at 10 °C/min and holding for 2 min and measuring the % mass loss of NA), showed no significant degradation in the 2.0 min residence time during extrusion. The pellets then formed the feed for the second pass through the extruder, to ensure complete dispersion.

Batch numbers 1–5 were also extruded from a Killion KN150 38 mm Single Screw Extruder, fitted with a Davis–Standard barrier screw (L/D 30, 3:1 compression ratio) attached to a 4 mm diameter single rod die. The extruder was run at a constant speed of 119 rpm using the same temperature profile as the Twin Screw Extruder.

The pellets from each blend were placed into a Platen Press (Dr Collin, Germany) to produce plaques of 1 ± 0.1 mm thickness.

The samples were covered with PTFE (Teflon) sheet in order to avoid contamination of the plaques, before being placed onto aluminium plates inside the press. From these plaques, samples were cut and the various analyses undertaken.

The running cycle of the press was divided into three heating stages and one cooling stage, which was controlled by separate cooling plates. Table 3 shows the running cycle for the press.

The effects on extrusion melt temperature and pressure can be seen in Fig. 2. The addition of NA up to the maximum quantity studied (35%, w/w) had little effect on the processing conditions, whereas the addition of PEG produced a significant decrease in the

Table 3
Platen Press Cycle for blends.

Stage	Temperature (°C)	Pressure (bar)	Rate (°C/min)	Time (min)
1	90	0	–	1
2	90	50	–	2
3	90	100	–	2
4	20	50	150	1

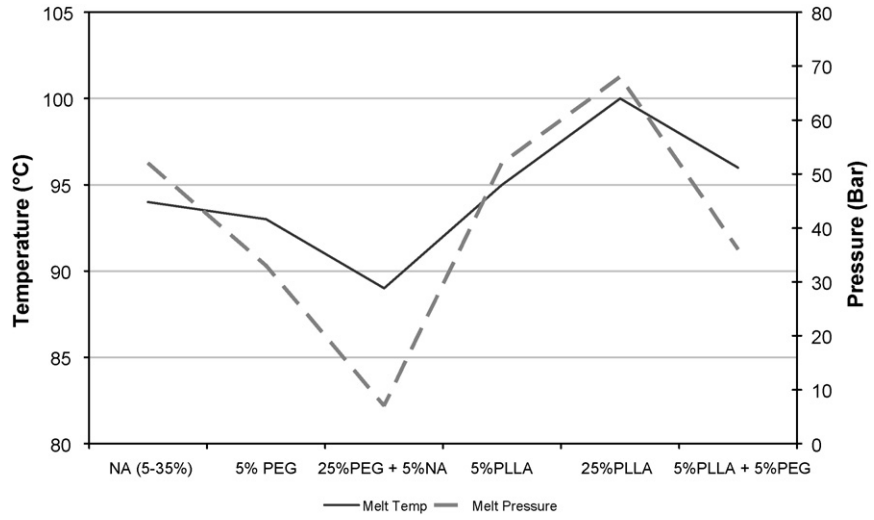

Fig. 2. Polycaprolactone extrusion variables.

melt temperature and pressure, this was due to the PEG's Newtonian behaviour once melted, caused by its low molecular weight. Increasing amounts of PLLA caused the melt temperature and pressure to increase within the extruder, thus making compounding more difficult as the PLLA remained in the solid state during processing.

2.2.2. Drug release

Tris buffer (pH 9) of concentration 0.01 M and ionic strength 0.1 M was prepared by dissolving tris(hydroxymethyl)aminomethane base (60.57 ± 0.001 g) in deionised water (4500 ± 1 ml). Sodium chloride (43.122 ± 0.001 g) was added and following dissolution the solution was titrated to pH 9.47 at 20 ± 1 °C with 2 M hydrochloric acid. The volume was then made up to 5000 ml with deionised water. This pH was chosen as the Nalidixic Acid has increased solubility in alkaline solutions and maximum release was required for the study.

McCartney bottles were filled with 10 ± 0.01 ml volumes of the buffer solution and placed in an incubator at 37 °C and 60 rpm, giving a pH 9. The drug release samples were prepared by punching 10 mm diameter discs from the 1 mm thick plaques made in the Platen Press. These discs were suspended in pre-heated buffer solutions and placed in a dynamic environment i.e. shaking water bath at 50 rpm. After designated time intervals, the blends were removed and immersed in fresh pre-heated buffer solution in order to mimic a sink condition, defined here as the presence of the analyte at less than 10% of its maximum solubility in the media, and the samples retained for analysis by UV–visible spectroscopy (Labform Spectrophotometer, UK) The frequency of sampling was determined by the amount of drug released in the previous sample but continued for a period of 180 days.

2.2.3. Degradation

Degradation was measured as a percentage weight loss from the polymeric matrix over period of 180 days. The pre-cut 10 mm diameter, 1 mm thick discs were weighed and placed into pre-heated 50 ml buffer solution. The samples were then placed in a static environment in an oven at 37 ± 0.1 °C for the duration of the test. Every 30 days the samples were dried and their weight recorded. The samples were placed back into the oven in fresh pre-heated buffer solution.

The true weight loss was calculated by subtracting the weight lost due to drug release from that obtained by measuring the weight of the above samples.

2.2.4. Statistics

All experiments were carried out in at least triplicate and results are expressed as a mean ± standard deviation. Statistical analysis was performed using Analysis of Variance (ANOVA) software. Post hoc comparisons of individual mean values were preformed using the Fisher PLSD test with a probability less than 0.05 denoting significance.

3. Results and discussion

3.1. NA release from PCL–NA blends produced by Single Screw Extrusion at various cooling rates

3.1.1. Solubility and crystal size

The blends were prepared using a Killion 25 mm diameter Single Screw Extruder due to the large batch size required, under the same conditions with respect to residence time and temperature, as those for the Twin Screw. The shear rate within the extruder was calculated as 31 rpm. This is lower than that experienced in Twin Screw Extrusion. The resultant pellets were then formed into plaques in the Platen Press with cooling regimes of 30 °C/min and 100 °C/min. The total melt time of 5 min before cooling begins in the press ensures the removal of the thermal history from the blends. Solubility of the NA in the PCL was calculated using the Saunders method and the Hyper DSC, with values of 76.9 and 31.2 μg/cm^3 for the 100 and 30 °C/min cooling rates, respectively, as illustrated in Fig. 3. A higher amorphous content (which is provided by the

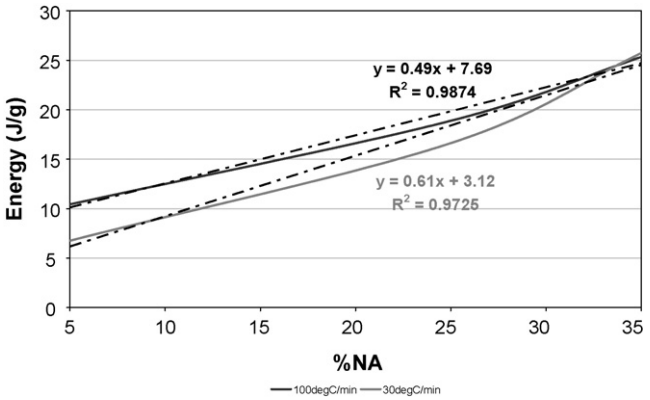

Fig. 3. Solubility of NA in PCL determined by hyper DSC.

Table 4
Crystal properties of PCL–NA release blends.

Cooling rate (°C/min)	Blend	% Crystallinity	Slope of cooling exotherm	Crystal size (μm) from microscopy*
100	5%NA	60	12	61
	10%NA	54	7	58
	25%NA	45	8	51
	35%NA	36	8	45
30	5%NA	58	12	193
	10%NA	53	11	187
	25%NA	44	12	146
	35%NA	37	9	103

* Crystal size measured using Lucia software supplied by Nikon and using a 10 mm graticule.

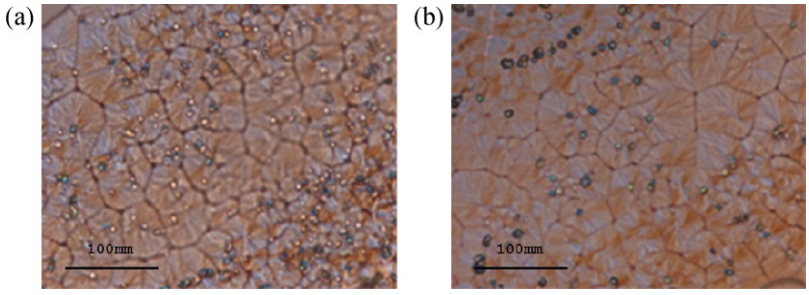

Fig. 4. Optical micrographs of PCL crystals and NA distribution – 5%NA blend ×200, (a) 30 °C/min and (b) 100 °C/min.

Table 5
% NA released from PCL.

Blend	Initial amount of NA encapsulated (μg)	% Released after 42 days	
		100 °C/min	30 °C/min
5%NA	5.0×10^3	11	8
10%NA	9.9×10^3	10	6
25%NA	25×10^3	6	4
35%NA	35×10^3	9	6

faster cooling rate) typically results in higher drug solubility, as the drug molecules are soluble in the amorphous regions of the polymer [32]. For the 100 °C/min cooling rate the solubility of the NA is given as 7.69% (w/w) which corresponds to 0.0769 mg/cm^3, and for 30 °C/min is 3.12% (w/w) corresponding to 0.0312 mg/cm^3.

As shown in Table 4, the amorphous content of the PCL remains relatively unchanged regardless of the cooling rate. A significant difference is noted with the crystal size at both cooling regimes, with crystal size for 100 °C/min being at least half that of those measured for 30 °C/min. It is therefore postulated that the decrease in crystal size which allows for a less tortuous pathway through the matrix alongside an increased cooling rate is the main cause of the increased solubility and therefore increased drug release into the surrounding buffer. The slope of the cooling exotherm from the onset of crystallisation until peak crystallisation in a DSC trace is an indication of the rate of crystallisation. A higher gradient indicates slower crystallisation kinetics, as the time taken to reach 50% available crystallisation is longer.

Higher gradients in the cooling exotherm were determined for the blends cooled at 30 °C/min than for those at the faster cooling rate, confirming the presence of larger and more regular crystals being present within the matrix.

The NA was released into phosphate buffer solution at a pH of 9 at 37 °C under dynamic conditions. The initial burst effect which takes place in the first few hours of the release investigation is the rapid expulsion of the NA from the PCL surface (Fig. 4).

It is the increased solubility as determined previously which accounts for the difference in drug released from blends prepared by both cooling systems. As illustrated in Table 5 and Fig. 5 the amount of drug released is greater for the 100 °C/min system than for the 30 °C/min. At the end of 42 days, the amount of drug released had begun to slow significantly, especially for those prepared using crash cooling, and therefore maximum release was assumed at this time.

With only a small percentage of total NA incorporated into the PCL being released, the remaining NA is completely encapsulated by the PCL to account for the plateau in the release profile. Also with increasing drug content the overall percentage released decreases. This is contrary to what is usually observed; increasing the concen-

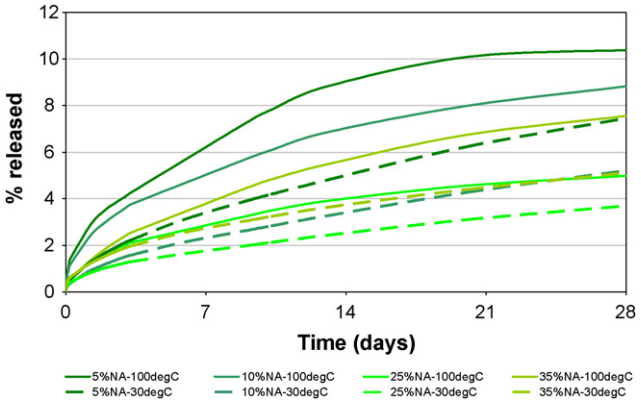

Fig. 5. Release profiles of NA from PCL formulations produced under both cooling regimes.

Table 6
Statistical analysis for crash cooling regime.

Drug release at 100 °C/min				
% (w/w) NA	5	10	25	35
5		S	S	S
10			S	S
25				S

Table 7
Statistical analysis for 30 °C/min cooling regime.

Drug release at 30 °C/min				
% (w/w) NA	5	10	25	35
5		S	S	S
10			S	S
25				S

tration increases release as the drug has higher deposition at the device surface and pathways of drug can be found from the centre to the device core. The decrease noted here may be caused by the lipophilic NA becoming incorporated into the lipophilic PCL and thus partitioning into the aqueous channels of the PCL becomes the rate-limiting step.

Kumar et al., using Glycerol Monooleate (GMO)/water cubic phase systems, discovered that the location of the drug within the matrix is an important parameter affecting the release and kinetics [33]. This phenomenon is supported by studies undertaken by Lara, who released salicylic acid from GMO/water cubic phase systems [34].

The maximum solubility of the NA in the buffer solution was determined as 1853 μg/ml. Therefore it was assumed that equilibrium between the NA and the buffer was never reached (as concentration of NA released at any time never exceeded 10% of this maximum solubility), and the system remained under sink conditions. Also placing the NA release formulations into fresh buffer at each time interval ensured sink conditions.

The ANOVA carried out for each of the cooling regimes on the raw data, is given in Tables 6 and 7 indicate that all the blends were statistically different from each other. This provided the confidence in the data when applying various drug release models.

3.1.2. Release models

The ideal release type is that of zero order; i.e. a constant release rate over the life of the device. However, due to various parameters within the devices, e.g. drug location, polymer crystallinity and device shape, a combination of diffusion and convection processes can occur which makes zero order mechanisms invalid [27].

The release models applied to the data are the; zero order model, square root of time model, and the Kosmeyer–Peppas power law model. During these investigations the zero order release model was shown to be an invalid representation for most of the blends. This is confirmed in Table 8 which illustrates the low r^2 values. An r^2 value of 0.999 indicates an excellent fit of the model to the experimental data; with larger inexactness in the model shown as the r^2 value decreases.

In the monolithic slab PCL–NA devices, an excess of NA is available (at the loadings greater than the solubility level of 7.69%) so that a NA depletion zone forms at the surface of the device. This leads to the diffusional ($t^{1/2}$) release kinetics. Applying the square root of time model to the experimental data (which describes drug release that is linear with the square root of time) to the experimental data presents a reasonable fit with r^2 values now increasing to 0.979 and 0.993 for 10% (w/w) NA at 30 and 100 °C/min, respectively.

This model assumes that the release rate remains finite as the device approaches exhaustion and is described by the diffusion coefficient (D) of the NA through the PCL matrix, which is a function of the solubility calculated previously. Permeability values were determined and are presented in Table 9. Permeability is calculated from Eq. (4) [34].

$$P = SD \tag{4}$$

where P = Permeability or flux (mg cm^{-1} day^{-1}); S = Solubility (mg cm^{-3}); D = Diffusion coefficient (cm^2 day^{-1}).

Varying the sample shape has considerable impact on the diffusion coefficient, with values of 0.5, 0.4 and 0.35 being typical representations of release controlled by Fickian diffusion in spheres, slabs and cylinders, respectively [35]. Diffusion coefficient values which are less than or greater than these, predict that release is controlled anomalously (e.g. by a combination of diffusion and convection). Also, the diffusion coefficient is a function of the release dimension mathematics of the device.

The typical values quoted are for one-dimensional systems, whereas in this study three dimensional release was measured, with the data modelled on a one-dimensional equation. Therefore, the values calculated for diffusion coefficient throughout are considered subjective but reliable due to the high r^2 values. The mathematics of a three dimensional model was not considered in this study.

Due to the increasing NA solubility and higher diffusion coefficients with increasing amorphous content in PCL, the permeability values of the blends are higher for those prepared by crash cooling.

Changing the release model applied to the experimental data from the square root of time to that of a power law described by Kosmeyer and Peppas [23], resulted in increased exactness of the fit. This model give r^2 values of 0.999 for the release from the 10% (w/w) NA blend and little variation in the r^2 values was noted between the cooling regimes. Kosmeyer–Peppas have described a model for which the rate declines exponentially with time, approaching a release rate of zero as the device approaches exhaustion using the condition of $M_t/M_\infty < 0.6$.

Table 8
Release models for both cooling regimes.

Blend			Release models						
			Zero order		$\sqrt{t}$ Higuchi		$k't^n$ Kosmeyer–Peppas		
			K	r^2	D	r^2	k'	n	r^2
Rate (°C/min)	100	5%NA	0.018	0.535	0.099	0.937	0.240	0.440	0.991
		10%NA	0.031	0.658	0.172	0.979	0.210	0.440	0.998
		25%NA	0.043	0.662	0.242	0.979	0.200	0.460	0.997
		35%NA	0.091	0.802	0.494	0.996	0.150	0.530	0.999
	30	5%NA	0.014	0.851	0.673	0.995	0.150	0.520	0.999
		10%NA	0.020	0.860	0.937	0.993	0.140	0.530	0.999
		25%NA	0.036	0.772	0.172	0.997	0.190	0.430	0.997
		35%NA	0.070	0.683	0.345	0.993	0.210	0.420	0.999

Table 9
Permeability of NA in PCL at various cooling regimes.

Cooling rate (°C/min)	Solubility (mg/cm^3)	Blend	Diffusion (cm^2 day^{-1})	Permeability (mg cm^{-1} day^{-1})
100	7.69	5%NA	0.099	0.764
		10%NA	0.172	1.321
		25%NA	0.242	1.861
		35%NA	0.494	3.797
30	3.12	5%NA	0.673	0.211
		10%NA	0.937	0.292
		25%NA	0.172	0.579
		35%NA	0.345	1.076

3.2. NA release from PCL–NA blends produced by Twin Screw Extrusion

3.2.1. Twin Screw release blends

In contrast to Section 3.1 where only PCL–NA blends were produced, the Twin Screw Extruder was used to produce batches for drug release analysis from all the materials in the study containing NA, i.e. in addition to 5–35% (w/w) NA, was those with pore former PEG and copolymer PLLA incorporated into the PCL–NA. These blends were all subjected to a cooling rate of 100 °C/min.

As before, the blends containing the larger concentrations of the NA, released less of their total % incorporated, than the smaller concentrations, with the 35% (w/w) NA blend releasing only 44% of its total in comparison with the 68% released by the 5% (w/w) NA blend. A clear representation of this is illustrated in Fig. 6. This is again caused by incorporation of the NA into the PCL at higher loadings that reduced the partitioning of the NA into the buffer. Equilibrium of the NA in the buffer was never attained as the maximum NA solubility in the buffer (1853 μg/ml) far exceeded that released from the blends.

It was noted that a second burst of NA release occurred between 65 and 85 days under dynamic conditions. This may be due to the samples swelling in the buffer and causing an increase in NA diffusion into the ingressed buffer, as the PEG leached from the blend. The addition of the PEG and the PLLA also act to decrease the time taken to exhaustion significantly with 90% of incorporated drug being released after only 4 days in the blend containing 5% (w/w) each of NA, PEG and PLLA, and 20 days with that of 25%PEG–5%NA (Table 10).

With the addition of the PEG pore former and the PLLA copolymer, NA release of 109% was noted alongside shorter sample exhaustion times illustrated in Table 11. This clearly highlights the inaccuracy of using the theoretical quantity of NA for calculating release amounts. However, the theoretical value shown in Table 2 can still be used as a comparison tool as it does not affect the time taken for exhaustion of the sample. An absolute value could

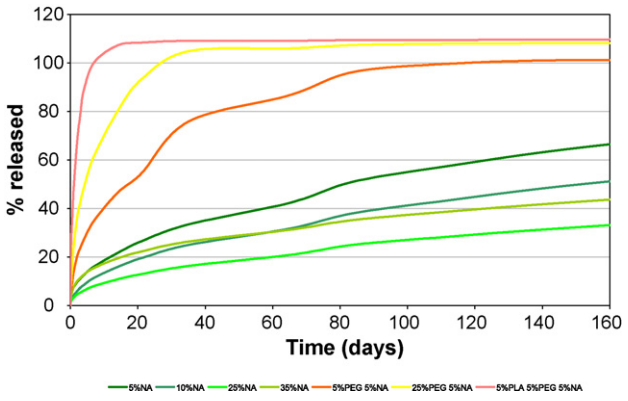

Fig. 6. Release profiles for all blends containing NA over 160 days.

Table 10
Statistical analysis on Twin Screw Extruded blends.

% NA	5	10	25	35	5–5%PEG	5–25% PEG	5–5%PEG–5%PLLA
5		S	S	S	S	S	S
10			S	S	S	S	S
25				S	S	S	S
35					S	S	S
5–5%PEG						S	S
5–25% PEG							S

be determined using the Back Extract technique with High Performance Liquid Chromatography. Due to time constraints it was not possible to determine the absolute mass of NA within each release sample, and therefore the theoretical value was used.

The faster drug release from the PCL–PEG–PLLA blend may be due to the phase separation within the blend as the buffer would penetrate into the amorphous PLLA with greater ease than into the PCL. A similar result was found by Cai et al., in their work with 5-Fluorouracil loaded into blends of PLLA–PCL and PLLA–PEG. They also found that the drug release behaviour depended more strongly on the morphology of the system than on the hydrophilicity of the drug carrier [37].

During NA release, pores are produced in the PCL matrix as shown in Fig. 8. The pore size and number is dependent on drug loading and addition of release aids. The release of the NA saw numerous pores formed on the surface of the PCL (illustrated in Figs. 7 and 8), and on increasing magnification, channels throughout the PCL are visible.

With the addition of PEG and PLLA into the release blends, the number and diameter of the pores increased dramatically from nanometers to microns due to the leaching of the PEG, thus accounting for the faster release rate (illustrated in Figs. 9–11). This even distribution of the pores indicates good dispersion of the PEG throughout the PCL matrix.

The white powder substance visible on all the micrographs after NA release was analysed in a mass spectrometer for a compositional trace (illustrated in Fig. 12), and it was found to be a salt from the buffer solution.

Applying the previous models; zero order, square root of time and Kosmeyer–Peppas, to the Twin Screw release data, a similar trend to that found with the Single Screw was observed, i.e. the model that describes the best fit is the Kosmeyer–Peppas as illustrated in Table 12. Although r^2 values appear to be high for the zero

Table 11
Release blend characteristics.

Blend	NA released (%)	Time to exhaustion (days)
5%NA	68	168
5%NA–5%PEG	102	107
5%NA–25%PEG	107	20
5%NA–5%PEG–5%PLLA	109	14

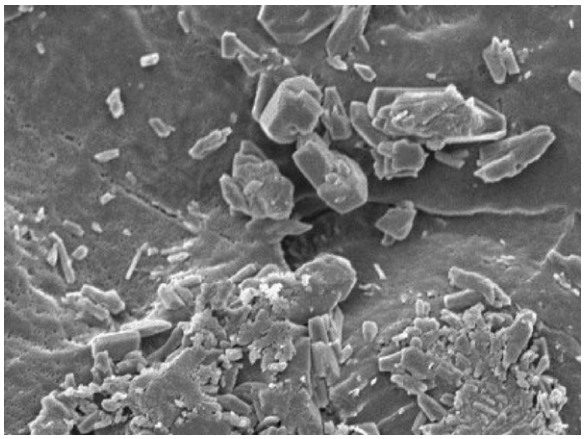

Fig. 7. PCL–NA blends before release ×1000.

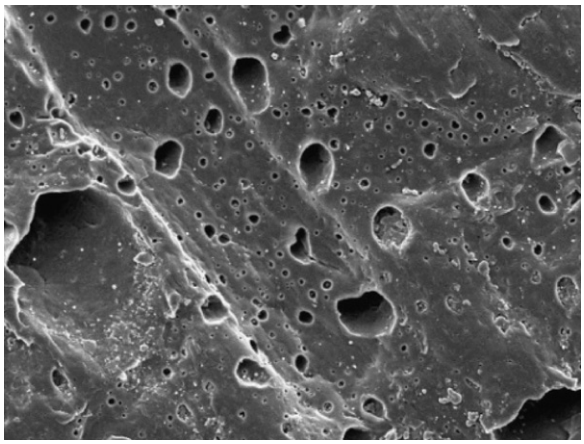

Fig. 9. PCL–NA–PEG after release ×1000.

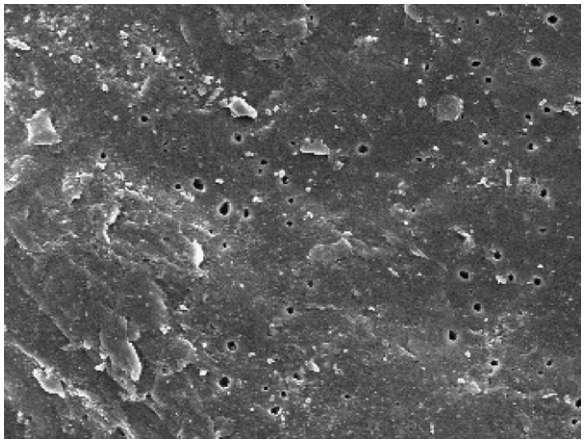

Fig. 8. PCL–NA blends after release ×1000.

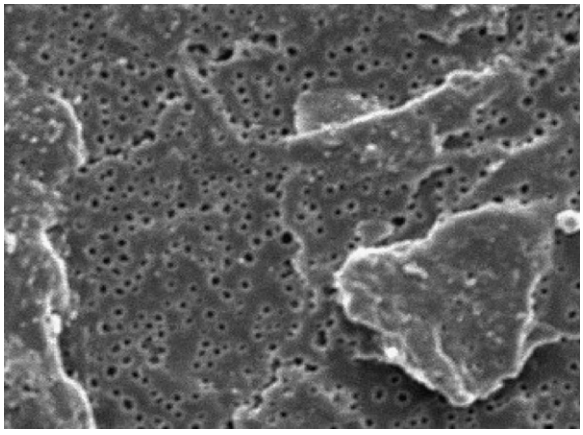

Fig. 10. PCL–NA–PEG–PLLA after release ×1000.

order and square root of time models for the blends containing only NA, the models provide poor representation of the experimental data at higher loadings when PEG and PLLA are added. The values of the diffusion coefficient (D) indicate that again the release mechanism is anomalous as it ranges widely around the ideal 0.4 ($cm^2\ day^{-1}$) for Fickian diffusion. In contrast with the other models, the Kosmeyer–Peppas maintains a good fit for the data regardless of NA content and the incorporation of PEG and PLLA. Fig. 13 shows the models applied to the experimental data for the 25% NA blend (Fig. 14).

The flux, or permeability, from Eq. (4), was also determined. However, it is only correct where r^2 values are high, as this increases confidence in D. Also, in order to correctly calculate the permeability of the blends containing PEG and PLLA, the solubility of the NA in each PCL mix would have to be determined separately. As regards the PCL–PEG blend it can be assumed that the solubility of the hydrophobic NA would be unaffected by the PEG due to its highly crystalline and hydrophilic nature, however, the NA would be soluble to a degree in the PLLA as it has an amorphous content of approximately 67%.

3.2.2. Comparison NA release from Single and Twin Screw Extrusion

In order to determine the most effective method of distributing NA throughout the PCL matrix, and subsequently its release characteristics, a comparison of the PCL–NA blends prepared using both the Single and Twin Screw Extrusion at 100 °C/min was undertaken. Both methods have similar crystallinity but differing rates of crystallisation as seen in Table 13. The blends prepared by Twin Screw

Table 12
Release models for Twin Screw Extruded blends.

Blend	Release models							Permeability ($mg\,cm^{-1}\ day^{-1}$)
	Zero order		$\sqrt{t}$ Higuchi		Kosmeyer–Peppas			
	k	R^2	D	R^2	k'	n	R^2	
5%NA	0.024	0.807	0.269	0.993	0.123	0.365	0.991	0.021
10%NA	0.036	0.851	0.393	0.999	0.088	0.461	0.998	0.030
25%NA	0.061	0.825	0.675	0.996	0.104	0.426	0.999	0.052
35%NA	0.114	0.605	1.300	0.939	0.163	0.386	0.996	0.100
5%NA–5%PEG	0.041	0.612	0.472	0.938	0.139	0.466	0.996	0.036
5%NA–25%PEG	0.047	0.169	0.576	0.721	0.222	0.546	0.997	0.044
5%NA–5%PEG–5%PLLA	0.044	−0.81	0.559	0.091	0.489	0.431	0.997	0.043

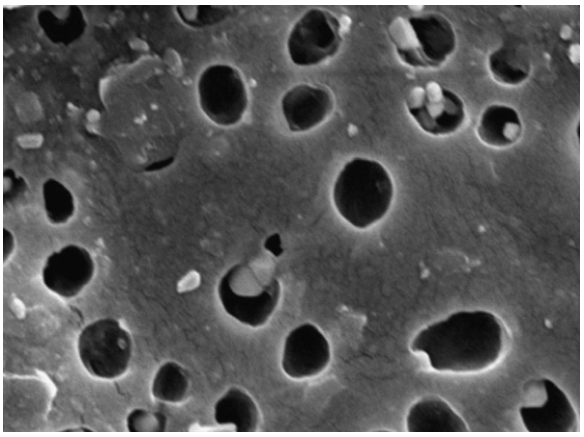

Fig. 11. PCL–NA–PEG–PLLA after release ×15000.

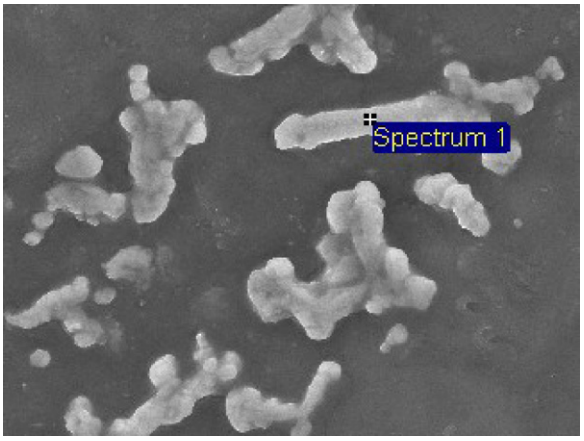

Fig. 12. Buffer salt ×15000.

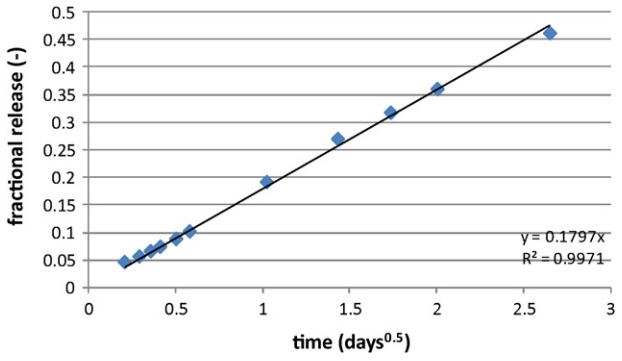

Fig. 13. Higuchi model applied to 5%PEG 5%NA blend experimental drug release data.

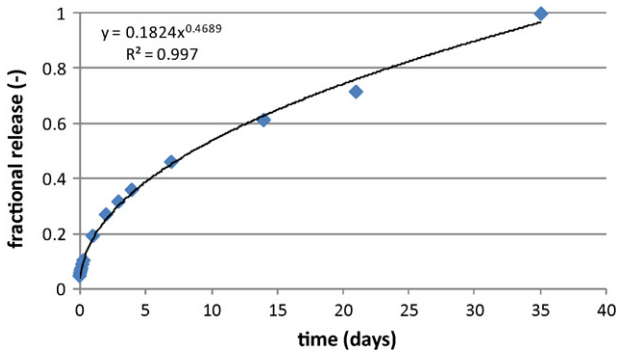

Fig. 14. Kosmeyer–Peppas model applied to 5%PEG 5%NA blend experimental drug release data.

Table 13
Crystalline properties of Single and Twin Screw Extruded PCL–NA blends.

Extrusion method	Blend	% Crystallinity	Gradient of cooling exotherm
Single Screw	5%NA	60	12
	10%NA	54	7
	25%NA	45	8
	35%NA	36	8
Twin Screw	5%NA	69	2
	10%NA	54	2
	25%NA	52	1
	35%NA	33	1

Extrusion had much slower rates of crystallisation at the same crash cooling rate and may further improve NA release.

Fig. 15 outlines the release profiles of the two types of extrusion, and it is clear that using the Twin Screw method provides blends with the ability to release not only a larger quantity of their NA loading but also release an equivalent amount quicker. This is demonstrated in Fig. 15 where 10% release from a 10% (w/w) NA blend takes approximately 5 days from the Twin Screw (TS) blend compared with 35 days from the Single Screw (SS) blend. This indicates better distribution and more homogeneity of the NA throughout the PCL using the Twin Screw.

It can therefore be postulated that the dispersion of the NA incorporated into the PCL prepared by Twin Screw Extrusion is better than that prepared by Single Screw Extrusion, as a larger amount of drug is released (by bulk diffusion from pores), both in the initial burst effect stage of 1–4 h and also over the entire release period. This is useful in determining the life span of the device.

DSC analysis indicated that the NA had a nucleating effect on the PCL (indicated by the higher crystallisation temperatures of the PCL–NA blends). However, with excessive NA concentration (>25%, w/w) the overall percentage crystallisation achievable within the PCL was reduced, due to an interference in the crystallisation process. This was supported by the reduction in the crystallisation rate (shown in Table 13) as the reduction in the gradient of the cooling exotherm with increasing NA concentration.

Regarding the effect on the extrusion method on the crystallisation, it was postulated that since Twin Screw Extrusion is more shear intensive than the Single Screw, this would cause a break up of NA agglomerates within the PCL alongside improved dispersion. This increased dispersion would result in greater nucleation and kinetics, and therefore a faster crystallisation rate. However, as the results in Table 6 show, the crystallisation rate slows dramatically when using the Twin Screw Extrusion system, indicating the NA is being subjected to excessive mechanical attrition caused by the higher shear forces. This attrition of the NA then leads to a change

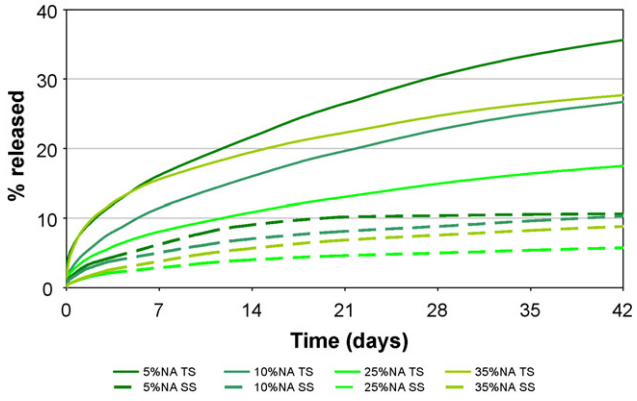

Fig. 15. NA release – comparison between Twin and Single Screw Extrusion.

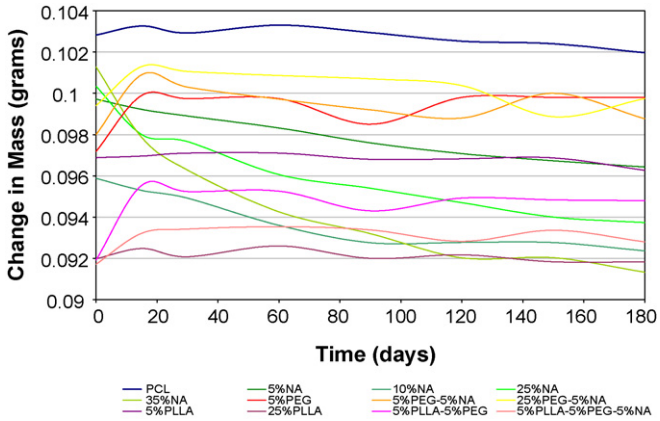

Fig. 16. Weight changes in blends over hydrolytic degradation period.

in the order of the crystallisation kinetics and slows the rate of crystallisation.

This could be further investigated using transmission electron microscopy (TEM) to determine the size, dispersion and aspect ratio of the NA in the PCL matrix, and its subsequent effects on the crystallisation kinetics.

3.3. Hydrolytic degradation

The ingress and egress of the buffer solution on the blends over the 6-month hydrolytic degradation period is illustrated in Figs. 16 and 17.

It is clear that due to the relatively long hydrolytic degradation time (PCL degrades in excess of 2 years and PLLA hydrolytically degrades within 2 years) that no hydrolytic degradation occurs within the blends. The test period for the hydrolytic degradation (as with the drug release testing period) was 6 months derived from ISO 10993-1 used to determine the biocompatibility of a medical device prior to study. Over the 6-month period the weight of the PCL and PCL–PLLA blends remain relatively constant. The decrease in weight in the PCL–NA blends is therefore that of the NA release. As *in vitro* hydrolytic degradation occurs in four stages; hydration, strength loss, loss of integrity and mass loss in that order, it is not surprising that no significant change is noted in the weight [38].

Where blends contain PEG, a small sharp ingress of buffer is observed as the blends begin to swell. This increase in weight may be due to; swelling, which counteracts the decrease in weight due to NA release or equilibrium within the pores, being reached halting NA release, giving an overall weight increase. Since the PEG dissolves out of the PCL (as it acts as a pore former), a larger volume

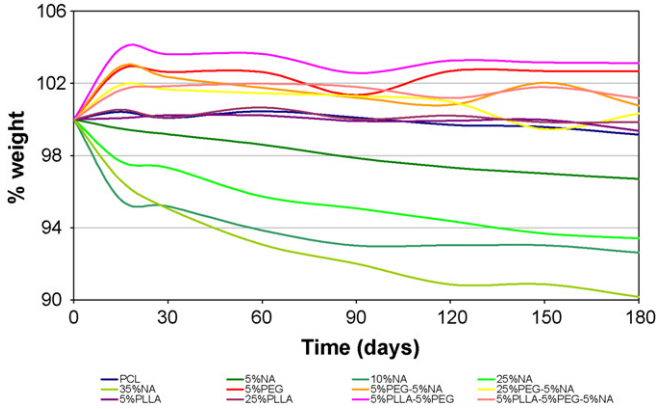

Fig. 17. Weight changes over hydrolytic degradation period.

Table 14
Changes in crystallinity of the blends during degradation.

Blend	% Crystallinity @ t = 0 days	% Crystallinity @ t = 180 days
PCL	58	59
5%NA	73	75
10%NA	60	63
25%NA	69	70
35%NA	51	54
5%PEG	62	65
5%NA–5%PEG	74	78
5%NA–25%PEG	63	67
5%PLLA	61	64
25%PLLA	46	50
5%PEG–5%PLLA	67	69
5%NA–5%PEG–5%PLLA	62	65

is available within the PCL for buffer ingression, which therefore equilibrates the weight at above 100%.

Cai et al. found that during hydrolytic degradation high water sorption was closely related to the mechanism that caused penetrant water to remain in the interface of the PLLA–PCL phase due to phase separation. Therefore, the hydrophilicity of the blends was increased significantly in comparison with the bulk PLLA and PCL due to the phase separation structure and drug release rates accelerated [37]. Coupled with this, ingression of buffer could also be the lack of motion (static environment) within the degradation solution due to a stationary water bath. Wada et al. reported that in order to optimise drug release the surrounding media should be kept in constant motion in order to aid diffusion [39]. It would seem probable that a similar approach should be adopted during hydrolytic degradation studies. In this study the samples were subjected to motion only on the days of weighting in order to get an accurate measurement, however, constant motion may be required for a more detailed analysis.

Analysis of the crystallinity over the entire hydrolytic degradation period (shown in Table 14) confirms some hydrolytic degradation of the blends as a small percentage increase in crystallinity was observed. These results however, could be due to experimental error. In order to confirm hydrolytic degradation was taking place, an extended testing period should be considered—at least 1 year. Should hydrolytic degradation have been occurring in bulk then a large increase in the crystallinity of the blends would have been expected. This increase in crystallinity is caused by polymer chain scission resulting in a decrease in the amorphous content. Similar results have been found by Weir et al. who found that during hydrolytic degradation of PLLA crystallinity increased from 35% to 72% over an 18-month period [40].

The chain scission which causes a decrease in the chain length also increases the mobility of the macromolecules that result in increased probabilities for the drug molecules to jump from one cavity to another. Thus the diffusion coefficient of the drug is not constant, but varies with average polymer molecular weight of the degrading matrix making long term release rate dependent on the degradation kinetics [41,42]. This result also found by Siepmann et al., who studied the effect of biodegradable P(LA–GA) microparticles on 5-Fluorouracil drug release and successfully predicted drug release kinetics from a formulated model which took into account the drug diffusion with non-constant diffusivities [36].

The small increase in crystallinity occurs in all blends and may indicate some degree of hydrolytic degradation over the relatively short testing time.

4. Conclusions

Release from Single Screw Extruded blends

- Crystal size was smaller in blends prepared using the 100 °C/min cooling rate than those prepared using the 30 °C/min cooling rate.
- The crystallisation kinetics was slower in the 100 °C/min cooled blends as there was limited amount of time for crystal growth.
- Solubility of NA in PCL was improved by a factor of 2 with increasing cooling rate due to higher percentage of amorphous regions.
- Larger NA release was observed in the faster cooling rate due to the increased solubility.
- The Kosmeyer–Peppas model was the best at describing the experimental release data, with r^2 values $\geq$0.993.

Twin Screw blend release

- Increasing the NA loading resulted in a decrease in the maximum percentage drug released from each blend due to larger quantities of NA being encapsulated by the PCL.
- The addition of PEG and PLLA into the blends resulted in increased NA release and faster exhaustion times.
- Again the Kosmeyer–Peppas model gave the best fit to the experimental data.

Twin Screw vs. Single Screw NA release

- The crystallisation kinetics in the Twin Screw blends was slower than those of the Single Screw, due to possible excessive mechanical attrition of the NA during Twin Screw Extrusion.
- A more efficient and larger quantity of NA release was found using blends prepared by Twin Screw Extrusion, due to the improved homogeneity of the PCL–NA blends.

In blends prepared by Single Screw Extrusion, the crystal size was smaller and crystallisation kinetics was slower in the crash cooled blends than those with controlled cooling at 30 °C/min. This was a result of the shorter time available for crystallisation in the crash cooled blends. The net result of this was the increased solubility of the NA in the crash cooled PCL; the solubility was almost twice that of the controlled cooled samples, which further increased the quantity of NA release.

The power law model proposed by Kosmeyer and Peppas to describe drug release was fitted to the experimental data. Release from the PCL–NA blends prepared by Twin Screw Extrusion and crash cooling resulted in larger NA release than those produced via Single Screw Extrusion. This was due to the improved dispersion of the NA in the PCL produced by the counter rotating screws in the extruder.

Increasing the concentration of the NA in the blends gave an overall percentage decrease in the drug release for each PCL–NA blend, and was attributed to increased NA encapsulation by the PCL matrix. When added to the NA containing formulations, PEG and PLLA promoted further release of NA and lead to faster device exhaustion times. Again, the Kosmeyer and Peppas model provided a precise fit to the experimental data; however, this was empirical, as the model is based on a mathematical description of one-dimensional release, whereas the experimental drug release was occurring three dimensionally. Also the release modelled here was produced from a single rod extrudate and formed into slabs, moulding the blends into complex devices would change the release kinetics and could result first order release as opposed to the power law model.

Hydrolytic degradation

- No significant changes were observed in the hydrolytic degradation of the blends due to the short testing period.
- The burst effect of the drug release was notable as a decrease in weight was observed for the PCL–NA blends.
- Improved hydrolytic degradation measurements may have been obtained if samples were kept in constant motion during testing period.
- A small increase in the percentage crystallinity of the blends was noted at the end of the 6-month testing period indicating a small degree of hydrolytic degradation was taking place.

With the short testing period given to hydrolytic degradation in terms of the total hydrolytic degradation cycle, it was un-surprising that no significant mass loss was observed in the blends due to hydrolytic degradation. The only mass loss noted was that of the NA release and PEG leaching. However, a small degree of hydrolytic degradation was noted in all the blends over the 6-month period as a small increase was observed in the crystallinity of the blends, however, this may be due to experimental error.

The best formulation is that containing 5% (w/w) levels of NA, PEG and PLLA with 85% (w/w) PCL. This formulation produced the larger NA release levels and fastest exhaustion time and would be suited for use in the Twin Screw tube extrusion of, or as coatings for catheter tubes were dwell time in the body can be up to 5 days. This would eliminate biofilm formation and urinary tract infections. However, for catheters that are required for extended periods of time (in long term intensive care patients where bacterial resistance and skin cell attachment is likely to occur) lower concentrations of drug released are required with longer device exhaustion times. Therefore, tailoring of the base materials would be required, i.e. decreasing concentration of PEG to limit NA release.

As the NA was used as a model drug, other applications could be considered for use i.e. internal sutures for use during surgery (due to the PCLs advantageous extensional properties allowing for production of the sutures by fibre spinning), with more potent antibacterial agents incorporated into the PCL matrix, in order to eliminate infection. Also since the mechanical integrity of the PCL is unaffected by the addition of the NA and PLLA, its use as a tissue engineering material for bone scaffolds could be improved. Incorporation of an antibacterial would reduce infection and also tailoring the addition of a Polylactic Acid would increase degradation rates *in vitro*.

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