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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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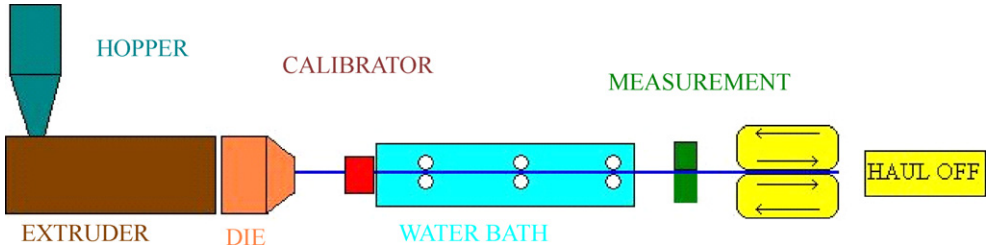


**Fig. 1.** Schematic of compounding process.

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) | $\Delta H$ (100%) crystalline material (J g$^{-1}$) | Density $\rho$ (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 |