Fabrication and in-vitro experimental study on an implantable controlled drug delivery system with micro-hole for zero-order release

Yang Gao¹, Lei Chen¹, Yaguang Huo², Chao Xu⁰, Suli Li¹ and Laixia Yang¹

¹ School of Mechanical Engineering, Xi’an University of Science and Technology, Xi’an, 710054, People’s Republic of China
² Modern Engineering Training Center, Chang’an University, Xi’an, 710018, People’s Republic of China

E-mail: Chaoxu@xust.edu.cn

Keywords: controlled drug delivery system, zero-order release, hot-press shaping, in-vitro experiments

Abstract

Drug delivery is essential for effective therapy. Implantable controlled drug delivery systems (ICDDS) have become a research focus due to the associated advantages of continuous, long-duration, sustained delivery and the reduced side effects associated with this form of drug release. ICDDS can be designed to release drugs in accordance with different demands. Zero-order drug release, which involves a theoretically linear relationship between the cumulative amount of released drug and the amount of time taken for the release, is an important drug release rule for the control of chronic diseases. However, the release process is influenced by various parameters and zero-order drug release is therefore difficult to achieve. In this study, to achieve zero-order drug release, an implantable controlled drug delivery system with micro-hole (ICDDSM) was designed and fabricated with degradable polymer. Based on micro electromechanical systems (MEMS) technology, ICDDSM matrixes with circular and honeycomb structures were fabricated using the hot-press shaping method at a temperature of 75 °C, 30 N of force which were maintained for 150 s. A micro-hole with a diameter 100 μm was formed using a femto-second laser. 5-fluorouracil was loaded into the ICDDSM and in-vitro experiments were conducted in 37 °C normal saline solution. The experimental results showed that the 20 mg of loaded 5-fluorouracil was released in 720 h with the relationship between the cumulative amount of released drug and the drug release time tending predominantly toward linearity. Zero-order drug release was thus achieved. This study proposed a new degradable ICDDS structure to achieve zero-order drug release, and the hot-press shaping process proved feasible for the efficient fabrication of the lower-cost polymer structure.

1. Introduction

The most common routes of administering drugs are oral and intravenous administration several times per day. However, these routes result in drug concentration fluctuations which are affected by drug dosage and absorption. The varying drug concentration leads to reduced efficacy and an increase in side-effects. This is particularly important for patients with chronic conditions that are on long term repeat doses of medication [1]. Hypertension, Parkinson’s disease, and chemoprevention are just some examples of medical conditions that would greatly benefit from controlled and sustained long-term drug delivery, which is difficult to achieve using conventional means. An implantable controlled drug delivery system (ICDDS) that would control drug delivery with continuous, sustained release, and reduce the associated side effects has been explored as a solution to this challenge [2–5].

In an ICDDS, drugs are normally loaded into the matrix material. The loaded drugs are capable of sustained release near to the nidus for drug delivery durations ranging from several minutes to months. Multiple structures have been designed to control drug release and prolong the release time [5–7]. Degradable polymer
can degrade into water and carbon dioxide to avoid unnecessary surgery after the drug is exhausted. Many ICDDS have been designed and fabricated based on degradable materials such as nanospheres [8], multi-layer capsules [9], micro-caged porous devices [10], hollow polymeric nano capsules [11], shell-core tablets [12], and other structures for multi-drug delivery [13, 14].

Degradable ICDDSs help in terms of avoiding subsequent surgery to remove the implanted systems due to the use of biocompatible and biodegradable polymers. However, there are also some associated problems. The first problem is the control of the drug release rule. To achieve the expected drug release rule, researchers have studied several aspects of the ICDDS, including matrix materials [15, 16], drug release mechanisms [17], drug release models [18], and structural design [19]. Because the drug release rules of an ICDDS are influenced by various factors, the control of these rules is also a research focus. The second problem is the ICDDS fabrication method. The fabrication methods used in current research vary from chemical processes to mechanical technology, including such methods as the solvent evaporation method [20], the micro electromechanical systems (MEMS) method [21, 22], and 3D printing [23]. The solvent evaporation method is often used in micro-particle synthesis, while matrixes with a macroscopic structure are mainly fabricated using MEMS and 3D printing. However, these methods are usually only fit for the small-scale production of samples used in studies. The methods of fabrication, which are low cost, high quality and efficiency in process, are the fundamental in ICDDS clinical application, so the fabrication and corresponding parameters require a further study.

An acceptable ICDDS will release a drug at the desired rate, accommodate a large loading quantity of the drug appropriate for long-term treatment, be of small size, be stable in terms of fabrication quality, and will be low cost. The zero-order release [24–26] of a drug is one of the fundamental rules for sustained drug delivery and theoretically involves linearity of the relationship between the cumulative amount of released drug and drug release time. In other words, the concentration of the released drug should be constant. In this study, an ICDDS with micro-holes (ICDDSM) based on biodegradable polymer Poly (lactic-co-glycolic acid) (PLGA) was proposed in order to realise zero-order release. The ICDDSM release mechanism involved a combination of diffusion and the degradation of the polymer matrix. PLGA has been certified by the United States Food and Drug Administration (FDA) as a safe, biocompatible material [27]. Moreover, PLGA degradation and swelling properties have been studied and a drug release model was established in our previous work. The drug release simulation results showed that the ICDDSM performed the controlled drug release in approximately 50 days [28]. In comparison with micro-needle structures [29] and multi-layered structures [30], the arrays of micro-cavities used in this study can allow the loading of large drug doses and prolong the drug release duration.

In this study, high quality samples of the ICDDSM were fabricated based on Ultraviolet Lithographie, Galvanoformung, and Abformung (UV-LIGA) and hot-press shaping technology. In-vitro experiments were carried out and the results showed that the ICDDSM could release the drug in accordance with a zero-order drug release rule.

2. Materials and methods

2.1. Materials

The novel ICDDSM comprised the following three parts: the drug loading matrix, the loaded drug, and the bonding membrane containing micro-holes. The structural prototype of the ICDDSM is shown in figure 1. The matrix contained several micro-depot arrays for drug storage. The maximum size of the ICDDSM was 10 mm × 10 mm and the depth of the drug-depot was between 400 μm and 500 μm. The number of the micro-holes was at least one and the diameter of the micro-holes in the bonding membrane was in the micron range and varied from 100 μm to 300 μm.

The matrix and the bonding membrane were fabricated with degradable copolymerisation polymer PLGA, which is classed as an FDA-approved biodegradable polymer. PLGA is suitable for use in various medical applications because of its controllable degradation rate, fine biocompatibility, and its associated convenient manufacturing process. PLGA particles were purchased from DURECT® (USA). The monomer ratio (PLA/PGA) was 50/50, intrinsic viscosity was 0.55–0.75 dl g⁻¹, and the weight-average molecular weight was 43 KDa. The loaded drug, 5-fluorouracil (5-Fu), is used extensively in clinical applications for cancer chemotherapy. This was obtained from the Shandong Qilu Pharmaceutical Co., Ltd (Shandong, China). The 5-Fu purity was over 98%.

2.2. The fabrication of matrix for drug loading

The PLGA matrix was fabricated using a polydimethylsiloxane (PDMS) soft mould based on the hot-press shaping method. The PDMS mould was produced by using the UV-LIGA technique. The fabrication process is shown in figure 2. Steps 1 to 4 show the SU-8 insert-mould fabrication, which was based on the photolithography method. Steps 5 and 6 show the PDMS mould fabrication process. The PDMS was coated...
onto the SU-8 micro patterns and solidified in a vacuum drying oven at 65 °C for 2 h. Steps 7 and 8 show the formation of the PLGA matrix. The glass transition (Tg) temperature of the PLGA was 50 °C–55 °C. Therefore, in order to ensure that the PLGA fully filled the PDMS mould, the temperature of the forming process was set at 75 °C and a force of 30 N was exerted on the PDMS mould for 150 s. The temperature was then reduced below the Tg temperature to cool the PLGA down to the stiff glassy state. Due to the flexibility of the PDMS, it could easily be removed from the stiff PLGA without causing deformation of the PLGA structures. The PLGA drug-loading matrix was thus obtained. The fabrication equipment included the hot-press machine, which had a positional accuracy of ±1 μm and a temperature range that could be varied from standard room temperature to 150 °C.

The integral nature of the structure was the basis of the drug control. Although drug loading cavities may possess different shapes, the convenience associated with demoulding and the integrity of PLGA matrix during the formation process was taken into consideration. An obtuse-angle-based honeycomb structure (figure 3(a)) and a smooth arc-based circular structure (figure 3(b)) were thus used in this study. The honeycomb structure consisted of an array of hexagons with side length of 1 mm, edge thickness of 100 μm, and depth of 300 μm. The
A femto-second laser method was used to fabricate the micro-hole in the bonding membrane. The laser was a Ti:Al₂O₃ solid-state laser with a wavelength of 800 nm, pulse duration of 120 fs, and a repetition frequency of 1 kHz.

The cross-sectional area and the depth of the micro-hole were important factors influencing the drug release rule. A drug release model and associated numerical simulation to achieve zero-order drug release in an ICDDSM has previously been studied [28]. In order to simplify the influence of the micro-holes distribution on the drug release rule, only one micro-hole was incorporated into the design in the middle of the structure. The results indicated that with a micro-hole depth of 200 μm and a micro-hole diameter of 100 μm, 20 mg of loaded 5-Fu could be released in 30 days at a rate that approximated zero-order release.

The thickness of the bonding membrane and the depth of the micro-hole both represent the same parameter. Firstly, the 200 μm thick PLGA bonding membrane was formed in the hot-press machine at 70 °C temperature, 50 N force which were maintained for 30 s. Then, based on the femto-second laser method, a 100 μm diameter micro-hole was formed in the bonding membrane.

To decrease the deformation of the matrix and the micro-holes during the bonding process, the melt bonding method was selected for use in this study. To test the bonding effect, bonding experiments were carried out without drug loading at a bonding temperature of 55 °C which was maintained for 30 s. The bonded devices are shown in figure 4. The structure of the drug carrier and membrane were integrated in such a way as to ensure that the interface had no obvious gaps. The PLGA membrane and drug carrier proved to be adequately bonded.
Based on this fabrication process, 20 mg 5-Fu was weighed using electronic scales (ShangHai LiChen, 0.1 mg) and loaded into the drug carrier. The structure of the micro-hole in the bonding membrane was integrated as shown in figure 5. The shape of the micro-hole was intact and the wall of the micro-hole was smooth.

2.5. In-vitro drug release experiments

To verify the ICDDSM drug release rule, in-vitro drug release experiments were carried out at 37 °C using normal saline for simulating the body fluid. The concentration of the released drug was detected using the high performance liquid chromatography (HPLC, SPD10A, Shimadzu). The wavelength that the chromatograph was set to detect was 270 nm.

The honeycomb ICDDSM samples were incubated in 20 ml of normal saline at 37 °C. The bottles were then tightly capped and placed inside an incubator maintained at 37 °C and shaken at 100 rpm in order to study the 5-Fu release profiles. At specific time intervals, the solution was removed and then replaced with fresh normal saline solution at 37 °C to maintain the release conditions. The concentration of the released 5-Fu was detected using the HPLC.

To study the effect of the different drug loading structures on the drug release rule, the circular structure ICDDSM samples were also put through the experimental process. In order to verify the availability of the micro-hole in the membrane, an ICDDS was fabricated with the same structural parameters of the ICDDSM.
except for the lack of a micro-hole in the bonding membrane. Comparative *in-vitro* experiments were then conducted with the ICDDS and the ICDDSM to verify the availability of the micro-hole.

3. Result analysis and discussion

3.1. The ICDDSM drug release rule

To verify the availability of the micro-hole in terms of the drug release rule, comparative experiments were carried out with ICDDSs both with and without a micro-hole, with all other parameters being identical. The results are shown in figure 6, which shows the drug release results for the circular structure ICDDSM. From figure 6, it can be seen that when the ICDDS samples without micro-holes were immersed in 37 °C normal saline solution, very little of the 5-Fu was released in the first 120 h, clearly showing that a time lag was present. That was due to the PLGA matrix not being sufficiently eroded within this time. The release mechanism is thus mainly the diffusion. Therefore, the texture of the PLGA matrix remained intact and the packaged 5-Fu was hardly released from the PLGA matrix.

After micro-hole was prepared in the bonding membrane, the ICDDSM samples were immersed in 37 °C normal saline solution for drug release. The drug in the loaded cavities was released easily through the micro-hole, even when the PLGA had not degraded sufficiently. A diagrammatic sketch of the ICDDSM drug release mechanism is shown in figure 7. The micro-hole in the bonding membrane connected the drug cavity to the solution around the ICDDSM. On the drug cavity side of the micro-hole, the drug concentration was at saturation level, while the drug concentration on the solute side of the micro-hole was zero. A concentration gradient was thus formed and maintained at the micro-hole. Therefore, the loaded drug could be diffused through the micro-hole in the bonding membrane, driven by the concentration gradient. Early during the drug release period, the drug release mechanism was mainly diffusion. As time elapsed, the PLGA polyester chains were fractured and gradually separated into the solution. The texture of the PLGA became loose and more of the

![Figure 6.](image1.png)  
*Figure 6. The relationship between the cumulative amount of released drug and the drug release time.*

![Figure 7.](image2.png)  
*Figure 7. The mechanism of drug release from the biodegradable ICDDSM.*
drug was released through the PLGA material. The drug release mechanism was thus a combination of degradation and diffusion.

In this case, the time lag was clearly eased. The cumulative amount of released drug increased consistently and steadily. In figure 6, it can be seen that the 20 mg of 5-Fu that was loaded in the ICDDSM was released in approximately 720 h (30 days). The relationship between the cumulative amount of released drug with respect to time tended towards linearity over the whole release period. The time-delay at the beginning of the drug release period was eliminated and the drug release rule approached zero-order release.

3.2. Influence of the structure of the drug loading cavity
Two types of the ICDDSM with different drug loading cavities were designed and fabricated: circular and honeycomb structures. The results of the in-vitro drug release experiments are shown in figure 8. The drug release rule trends were homologous as a whole, neither of the drug release trends demonstrated an associated time lag, and the cumulative amount of released drug increased steadily. In the first 300 h of drug release, the relationship between the corresponding cumulative amount of released drug and the drug release time for the circular and honeycomb structures was almost consistent. After the first 300 h, the discrepancy between the two relationships clearly increased. In other words, the circular structure ICDDSM released the drug faster than the honeycomb structure. The main reason was considered to be the osmotic pressure inside and outside of the ICDDSM. There was a drug concentration gradient between the inner and outer sides of the bonding membrane, allowing the loaded drug to be released under the influence of the concentration gradient. The inner osmotic pressure was higher than the outer pressure at the bonding membrane. This osmotic pressure caused the fracture of the polymer matrix, especially in the later stages of drug release due to the low intensity and inflexibility of the drug container. The drug cavities of the circular structure ICDDSM were larger than those of the honeycomb structure, so the osmotic pressure of the circular structure ICDDSM was larger than that of the honeycomb structure. The fracture probability was thus increased which will cause the increased rate of drug delivery. The problem associated with osmotic pressure could be solved in terms of design and optimisation of the drug container.

3.3. A comparison of experimental and simulation results
The circular structure drug release in-vitro experiments were carried out using the same parameters as used in the simulation study [28], and a comparison of the results is shown in figure 9. From figure 9, it can be seen that the trend of the curves is analogous, especially at the beginning of the drug release. Deviation began occurring after 120 h of drug release.

The first reason for this behaviour is that during the in-vitro experiments, tiny fractures occurred in the ICDDSM due to degradation. This is especially due to the efficient degradation behaviour of the PLGA matrix. These tiny fractures are a reason for the increase in drug release rate. The second reason is that in the drug release model, in order to emphasise the main mechanisms of drug release, diffusion and degradation were chosen as the dominant drug release factors. Other factors which could have a small effect on the drug release rate were simplified. However, these factors were present in the in-vitro experiments, so the drug release rate was higher in the in-vitro experiments than in the simulation model.
4. Conclusions

In this study, an ICDDSM was designed and fabricated to achieve the zero-order drug release rule. A micro-hole was formed in the bonding membrane which changed the drug release mechanism to a combination of diffusion and degradation. Based on MEMS technology, samples of the ICDDSM were produced using the hot-press shaping method and laser forming. Furthermore, in-vitro experiments were performed and the drug release from the ICDDSM was verified as tending towards zero-order release. The following conclusions were drawn:

(1) Based on MEMS technology, the hot-press shaping method could be used to fabricate the PLGA polymer matrix at low cost and high efficiency. The hot-press process was conducted at 75 °C and 30 N which were maintained for 150 s.

(2) In-vitro experiments were conducted, and the results showed that the release of 20 mg 5-Fu was controlled over approximately 720 h. No time-delay phenomenon was noted at the beginning of the drug release, and the relationship between the cumulative amount of released drug and the drug release time mainly tended towards linearity. Zero-order drug release was thus achieved.

(3) The circular and honeycomb drug cavity structures demonstrated similar drug release trends. The drug release rule was only slightly influenced by the structure of the drug cavity.

(4) The in-vitro experiments verified the rationality of the drug release model, which provides a basis for further study in terms of structural optimisation.

The ICDDSM serves as a novel structure for drug release in accordance with the zero-order drug release rule. We believe this novel structure has very strong potential for the sustained, targeted and efficient therapy, it may lead a new way for the treatment of chronic diseases.

Acknowledgments

The authors gratefully acknowledge the support of the National Natural Science Foundation of China (No. 51605379), Basic Research Plan of Natural Science of Shaanxi Province (2019JQ-804).

ORCID iDs

Chao Xu https://orcid.org/0000-0003-2194-0862

References

[1] Yi Y, Buttner U and Foulds I G 2015 A cyclically actuated electrolytic drug delivery device Lab Chip 15 3540–8
[2] Hossen S, Hossain M K, Bashor M K, Mia M N H, Rahman M T and Uddin M J 2019 Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: a review J. Adv. Res. 15 1–18
[3] Eldaious I, Colson Y L and Grinstaff M W 2019 Polymer-drug conjugate therapeutics: advances, insights and prospects Nat. Rev. Drug Discovery 18 273–94
[4] Zhang H, Jackson J K and Chiao M 2017 Microfabricated drug delivery devices: design, fabrication, and applications Adv. Funct. Mater. 27 1703506
[5] Yi Y and Koel J 2017 A remotely operated drug delivery system with dose control Sens. Actuators, A 261 177–83
[6] Yi Y, Huang R and Li C 2019 Flexible substrate-based thermo-responsive valve applied in electromagnetically powered drug delivery systems J. Mater. Sci. 54 3392–402
[7] Pirmonaradi F N, Jackson J K, Burt H M and Chiao M 2011 On-demand controlled release of docetaxel from a battery-less MEMS drug delivery device Lab Chip 11 2744–52
[8] Abid S, Raza Z A and Rehman A 2016 Synthesis of poly(3-hydroxybutyrate) nanospheres and deposition thereof into porous thin film Mater. Res. Express 3 105042
[9] Kaoui B, Lauricella M and Pontrelli G 2018 Mechanistic modelling of drug release from multi-layer capsules Comput. Biol. Med. 93 149–57
[10] Son A L et al 2017 An implantable micro-caged device for direct local delivery of agents Sci. Rep. 7 17624
[11] Raichur A, Nakajima Y, Nagaoa Y, Maekawa T and Kumar D S 2014 Hollow polymeric (PLGA) nano capsules synthesized using solvent emulsion evaporation method for enhanced drug encapsulation and release efficiency Mater. Res. Express 1 045407
[12] Okwouwa T C, Pereira B C, Arafat B, Cieszynska M, Isreb A and Alhnan M A 2017 Fabricating a shell-core delayed release tablet using dual FDM 3D printing for patient-centred therapy Pharm. Res. 34 427–37
[13] Sundararaj S C, Thomas M V, Peyyala R, Dziubla T D and Puleo D A 2013 Design of a multiple drug delivery system directed at periodontitis Biomaterials 34 8835–42
[14] Grayson A C R, Choi I S, Tyler B M, Wang P P, Brem H, Cima M J and Langer R 2003 Multi-pulse drug delivery from a resorbable polymeric microchip device Nat. Mater. 2 767–72
[15] Geng Y H, Ge X H, Zhang S B, Zhou Y W, Wang Z Q, Chen J and Xu J H 2018 Microfluidic preparation of flexible micro-grippers with precise delivery function Lab Chip 18 1838–43
[16] Lee E, Zhang H, Jackson J K, Lim C J and Chiao M 2016 Janus films with stretchable and waterproof properties for wound care and drug delivery applications RSC Adv. 6 79900–9
[17] Kamaly N, Yameen B, Wu J and Farokhzad O C 2016 Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release Chem. Rev. 116 2602–63
[18] Peppas N A and Narasimhan B 2014 Mathematical models in drug delivery: how modeling has shaped the way we design new drug delivery systems J. Controllede Delivery 190 75–81
[19] Pishnamazi M, Hafizi H, Shirazian S, Culebras M, Walker G M and Collins M N 2019 Design of controlled release system for paracetamol based on modified lignin Polymers 11 1059
[20] Kim J E, Cho H J and Kim D D 2014 Budesonide/cyclodextrin complexloaded lyophilized microparticles for intranasal application Drug Dev. Ind. Pharm. 40 743–8
[21] Lee H J, Choi N, Yoon E S and Cho I J 2018 MEMS devices for drug delivery Adv. Drug Delivery Rev. 128 132–47
[22] Yi Y, Buttner U, Carreno A A A, Conchouso D and Fouilh J G 2015 A pulsed mode electrolytic drug delivery device J. Micromech. Microeng. 25 105011
[23] Awad A, Trenfield S J, Gaisford S and Basit A W 2018 3D printed medicines: a new branch of digital healthcare Int. J. Pharm. 548 586–96
[24] Filgueira C S et al 2016 Sustained zero-order delivery of HC-1 from a nanochannel membrane device alleviates metabolic syndrome Int. J. Obesity 40 1776–83
[25] Ferrari S et al 2013 Leveraging nanochannels for universal, zero-order drug delivery in vivo J. Controlled Release 172 1011–9
[26] Liu X, Yang Y, Yu D G, Zhu M J, Zhao M and Williams G R 2019 Tunable zero-order drug delivery systems created by modified triaxial electrospinning Chem. Eng. J. 356 886–94
[27] Fabiennet D, Eduardo A, Joana M S, Régis C, Aude I B and Véronique P 2012 PLGA-based nanoparticles: an overview of biomedical applications J. Controlled Release 161 305–22
[28] Gao Y, Chen T and Wang X 2011 Numerical modeling of a novel degradable drug delivery system with microholes Microsyst. Technol. 17 387–94
[29] Park J H, Allen M G and Prausnitz M R 2005 Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery J. Controlled Release 104 51–66
[30] Ryo W H, Vyakarnam M, Greco R S, Prinz F B and Fasching R J 2007 Fabrication of multi-layered biodegradable drug delivery device based on micro-structurining of PLGA polymers Biomed. Microdevices 9 845–53