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Three-Dimensional Printing of Carbamazepine Sustained-Release Scaffold

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ABSTRACT

Carbamazepine is the first-line anti-epileptic drug for focal seizures and generalized tonic-clonic seizures. Although sustained-release formulations exist, an initial burst of drug release is still present and this results in side effects. Zero-order release formulations reduce fluctuations in serum drug concentrations, thereby reducing side effects. Three-dimensional printing can potentially fabricate zero-order release formulations with complex geometries. 3D printed scaffolds with varying hole positions (side and top/bottom), number of holes (4, 8, and 12), and hole diameters (1, 1.5, and 2 mm) were designed. Dissolution tests and high performance liquid chromatography analysis were conducted. Good correlations in the linear release profiles of all carbamazepine-containing scaffolds with side holes (R^2 of at least 0.91) were observed. Increasing the hole diameters (1, 1.5, and 2 mm) resulted in increased rate of drug release in the scaffolds with 4 holes (0.0048, 0.0065, and 0.0074 mg/min) and 12 holes (0.0021, 0.0050, and 0.0092 mg/min), and the initial amount of carbamazepine released in the scaffolds with 8 holes (0.4348, 0.7246, and 1.0246 mg) and 12 holes (0.1995, 0.8598, and 1.4366 mg). The ultimate goal of this research is to improve the compliance of patients through a dosage form that provides a zero-order drug release profile for anti-epileptic drugs, so as to achieve therapeutic doses and minimize side effects.

Introduction

Carbamazepine is the first-line anti-epileptic drug (AED) for generalized tonic-clonic and focal seizures in the guidelines proposed by the International League Against Epilepsy and National Institute for Health and Care Excellence. It was the most prescribed AED in the UK from 1993 to 2008,[1] the second most prescribed AED in Singapore's largest pediatric hospital (Kandang Kerbau Women's and Children's Hospital) from 2000 to 2009,[2] and the third most prescribed AED (20.2%) in Germany from 2010 to 2012.[3]

The conventional therapeutic range for carbamazepine is narrow (4-12 mg/L).[4,5] Above the therapeutic range, central nervous system (CNS) side effects such as dizziness, diplopia, nausea, headache, and light headedness manifest[4] in approximately 40% of patients on carbamazepine.[6] These side effects have a negative impact on patient compliance, which result in poor seizure control, leading to problems associated with seizures, such as burns and fracture accidents.[7] Side effects also impact seizure control directly as they limit the AED dose which can be given to patients.[8] These side effects are transient or episodic, partially reflecting oscillations in individual AED concentrations in the blood—even minor fluctuations above a threshold concentration are reported to produce these side effects.[6] On the other hand, sub-therapeutic serum drug concentrations result in an increased risk of breakthrough seizures.[9]

Sustained-release carbamazepine has been shown to decrease CNS-related side effects.[6] The conversion of immediate-release carbamazepine to its sustained-release dosage forms (Tegretol-XR and Carbatrol) has shown to significantly decrease the incidence of CNS side effects from 49% to 20% ($p = 0.001$).[6] Furthermore, a 3-month prospective study demonstrated significant improvements in Quality of Life in Epilepsy Inventory-31 (62.8 vs. 68.3; $p < 0.001$) and Adverse Events Profile (37.2 vs. 31.7; $p < 0.0001$) of adults when switched from immediate-release to sustained-release carbamazepine.[10] Sustained-release carbamazepine can also reduce seizure breakthroughs associated with trough concentrations[11] and may improve patient compliance by reducing dosing frequency.[11]

Abbreviations used: 3DP, three-dimensional printing; ABS, acrylonitrile butadiene styrene; AED, anti-epileptic drug; CIJ, continuous inkjet printing; CNS, central nervous system; DoD, drop on demand; DM, fused deposition modeling; PBS, phosphate buffered saline; RP-HPLC, reverse-phase high performance liquid chromatography; SDS, sodium dodecyl sulfate; UV, ultraviolet.

Conflicts of interest: The authors have no conflicts of interest directly related to this study.

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However, fluctuations above the threshold therapeutic range, which predisposes patients to the drug's side effects, still exist with current sustained-release dosage forms. Several studies have reported a correlation between carbamazepine peak concentrations and side effects.[12] *In vitro* studies investigating the release profile of Tegretol-XR and Carbatrol have shown that there is an initial burst of drug release, despite both being sustained-release formulations.[13,14] Thus, undesirable peak effects in serum drug concentrations can result. A dosage form that can release carbamazepine in a linear manner is therefore desirable to reduce or eliminate side effects, so as to improve patient compliance, and eventually to reduce occurrence of seizures.

Several strategies have been employed to achieve linear or zero-order release kinetics in drug formulation research. However, many of these approaches are difficult to achieve and have not progressed to commercialization.[15] One strategy to achieve zero-order release kinetics is to formulate the drug in the form of a donut-shaped tablet.[16] By having a central hole in the middle of the tablet, when the outer circumference of the tablet erodes and decreases, the inner circumference of the tablet erodes and increases. This constant erosion on both the inner and outer circle of the doughnut tablet results in a constant surface area in contact with the drug dissolution environment throughout the entire period of drug release. However, the conventional process of making such coated donut-shaped tablets is complex, time consuming,[17] and requires a discontinuous manufacturing process involving multiple steps of tableting, drilling, and coating.[18] A processing technique that is simplified, feasible, and practical in the pharmacy setting does not yet exist.

Three-dimensional printing (3DP) is a novel technique that is different from the traditional subtractive or formative methods of manufacturing. It uses an additive or layer-by-layer-based approach to create a complex 3D geometry for a variety of applications.[19,20] Its ability to customize and fabricate complex structures[21-25] has prompted its use in many health care applications, such as for bone and cartilage replacements, customized dental implants, antimicrobial drug-eluting implants, hearing aids, and surgical guides, among others. 3DP also offers the advantages of speed, low cost, availability of a wide range of printing materials, accuracy, and reproducibility.[16] Despite these advantages, 3DP has not yet been used in dosage formulations in the practice setting. 3DP can simplify the process of making dosage forms with complex geometries by eliminating the need for multistep manufacturing sequences.[16] Therefore, compared to other manufacturing technologies, 3DP is a feasible option to produce scaffolds that can achieve zero-order drug release kinetics.[25] In addition, 3DP has the potential to individualize drug therapies for different patients,[21,25,26] for example, by combining different AEDs into one scaffold, thus reducing polypharmacy and improving adherence to AED therapy.

Several 3DP techniques for the customization of 3D printed oral tablets exist. They can be classified accordingly to the deposition techniques used, namely, printing-based inkjet systems, laser/ultraviolet (UV)-based writing systems, and nozzle-based deposition systems.[19] Printing-based inkjet systems[27] can be divided into 2 main types—continuous inkjet printing (CIJ) and drop on demand (DoD) inkjet systems. CIJ dispenses a continuous stream of droplets, while DoD ejects precise droplets at high speed when necessary. In both CIJ and DoD systems, a precise controlled volume of solution is jetted to the desired location on the substrate by an electric charge induced on the droplet and an electrostatic field.[27] However, a substantial amount of pre-formulation studies have to be performed for these inkjet systems to ensure that the drug solutions have suitable properties for jetting. Furthermore, the control of viscosity and surface tension is vital. The small volumes and low concentrations needed to prevent clogging of the ejector also imply that inkjet printing is only suitable for printing high potency drugs.[28] These disadvantages suggest that inkjet printing is still a distance away from the actualization of personalized medicine for the general public.

Laser/UV light-based writing systems are widely used in medical fields, especially in tissue engineering.[29] It works on the basis of the solidification of a photosensitive liquid resin by photopolymerization using either a laser (stereolithographic apparatus) or light-emitting diode high-definition projector (digital light processing).[30] These 2 techniques are largely similar, except for the source of light that polymerizes the resin. Laser/UV light-based systems offer high precision and accuracy for the print out and does not require extensive pre-formulation work. However, there is a substantial amount of post-fabrication processing, such as additional UV curing. Moreover, the use of photoinitiators for photopolymerization induces free radicals, of which its safety has been questioned.[31]

Nozzle deposition system, commonly represented by fused deposition modeling (FDM), is a 3DP technique where a molten thermoplastic polymer filament is extruded by 2 rollers through a high temperature nozzle and thereafter solidifies into the desired pattern on the build plate. The precision and accuracy is not as high as laser writing systems. However, FDM is often the cheapest among all 3DP techniques and is therefore more affordable for the general public.[30] Furthermore, the materials used are often inert polymers that offer great mechanical strength.

In order for 3DP to achieve personalization of therapy on a large scale, the technique used would have to be cost-effective and widely available. FDM appears to be a suitable choice for this purpose. Therefore, this study tests the hypothesis of whether 3DP (FDM) can be used to make a zero-order drug release dosage form for carbamazepine. The objective of this study is to design and investigate 3D printed scaffolds with different hole parameters in order to find out the optimal parameters that can release carbamazepine in a zero-order manner.

Materials and Methods

Active Ingredient and Other Materials

Rhodamine B (drug surrogate) and sodium dodecyl sulfate (SDS, 99%; used for the dissolution medium) were obtained from Alfa Aesar (Massachusetts, MA). Phosphate buffered saline (PBS, 10×, Ultra Pure Grade; used for the dissolution medium) was obtained from Vivantis (Selangor Darul Ehsan, Malaysia). Analytical grade carbamazepine was obtained from Sigma-Aldrich (St. Louis, MO). Tegretol 200 (carbamazepine) tablets were obtained from Novartis (Basel, Switzerland).

Design of 3D Printed Scaffolds

In this article, "scaffold" refers to a drug container printed with a 3D printer and is used to hold the drugs and excipients specifically. Prior to using carbamazepine, in order to select the best scaffold design, rhodamine B was used as a drug surrogate to visualize the drug release kinetics. The scaffolds were designed to have a cup-shaped body, with a lid to cover it after packing the drug within (Fig. 1). The 3D model of the scaffolds was created using AutoCad 2015 (Autodesk, San Francisco, CA). Ledges on the scaffolds were constructed to secure the lid onto the scaffold body. The purpose of this design was to allow the scaffold to be capped after packing rhodamine B into the scaffold body, so that the only way for drug release into the environment would be through the holes, thus ensuring a constant surface area for

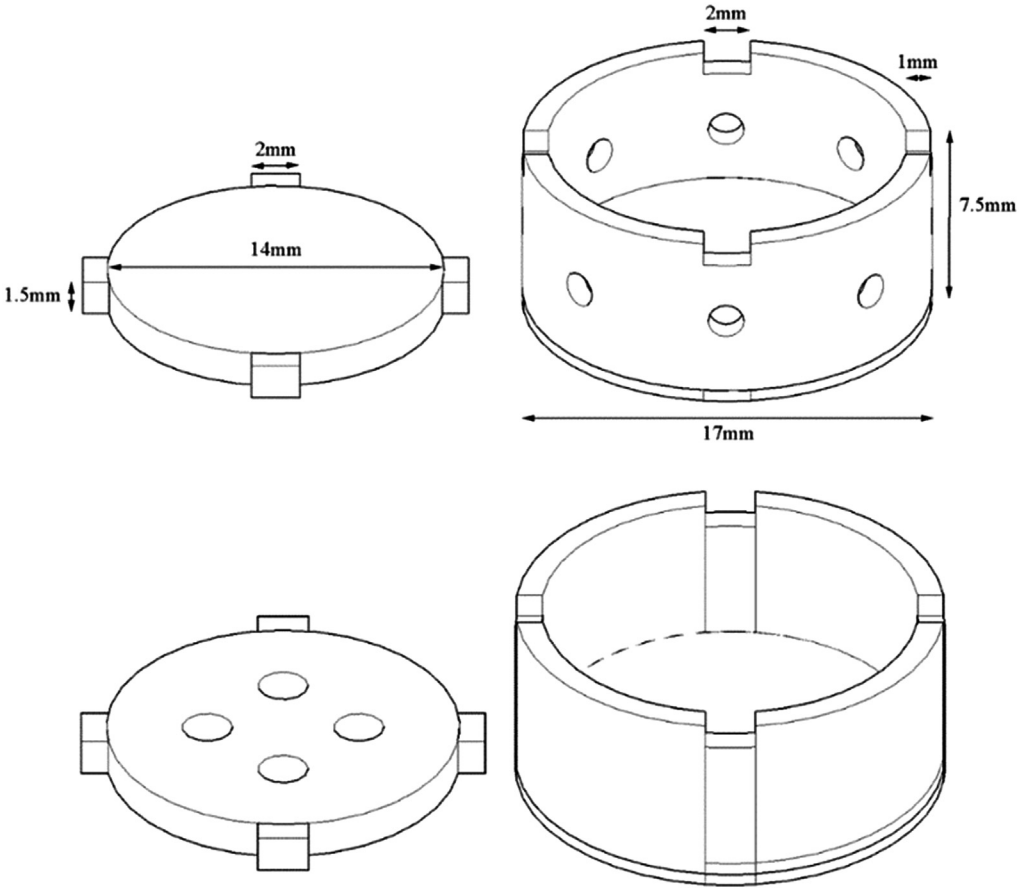

Figure 1. 3D model of rhodamine B containing tablets. Top: lid and tablet body with holes at the side. Bottom: lid with holes and tablet body. Both tablets have the same dimensions.

interaction. The 3D models were printed using a Da Vinci 1.0 3D printer and the XYZware software (XYZprinting, CA). The printing filament used by the 3D printer was a 1.75 mm diameter acrylonitrile butadiene styrene (ABS) filament. The print settings used were of the highest density setting (90%), the thinnest layer height (0.1 mm) for the highest resolution, and "standard" printing speed as defined by the software.

Two scaffold designs were 3D printed with ABS as the material—one with the holes positioned at the side and another with holes positioned at the top/bottom (Fig. 1). Both designs had a diameter of 17 mm, a wall of 1 mm thick, and a base of 1.5 mm thick. To account for the printing resolution of the 3D printer, the lid of the scaffold was designed with a diameter of 14 mm to fit the scaffold body exactly. The thickness of the lid was 1.5 mm. A thin layer of paraffin film was used to cover the small gaps between the lid and the scaffold body so as to ensure that the drug release into the medium would only be through the holes that were designed. All lengths were measured from the 3D model of the scaffolds. 3D models of scaffolds with varying positions (side vs. top and bottom), hole diameters (1.5 and 2 mm), and number of holes (4, 5, 8, 12) were constructed (Table 1).

Design of Scaffolds Containing Rhodamine B, In Vitro *Dissolution Methods, and Methods of Analysis*

Two hundred milligrams of rhodamine B was used for packing into each scaffold. One liter of 1× PBS was used as the dissolution medium for the drug release study. The dissolution medium was contained in a 1 L beaker, placed on top of a Thermo Scientific Cimarec Digital Stirring Hotplate set to "4" on the stirring speed dial and maintained at room temperature. One milliliter samples of the dissolution medium were taken and replaced with 1 mL of PBS at 5, 15, 30, 60 min, and then at regular intervals of 1 h. All the dissolution tests were carried out for at least 6 h.

Table 1
Coefficient of Determination (R^2) of Total Amount of Rhodamine B Released Versus Time Curve of Rhodamine B Containing Tablets Fitted to a Linear Regression Model and Rate of Release (μg/min)

Position of Holes	No. of Holes	Hole Diameter (mm)	Length of Dissolution Test (h)	Coefficient of Determination	Rate of Release (μg/min)
Lid	5	2	8	0.776	7.9
Lid and bottom of tablet	5; 5	2	6	0.808	0.3
Side of tablet	4	2	6	0.917	0.4
Side of tablet	8	1.5	8	0.733	0.5
Side of tablet	12	1.5	24	0.975	50.2
Side of tablet	12	2	8	0.819	12.6

Standard rhodamine B solutions at 2, 1, 0.5, 0.25, 0.1, 0.05, 0.025, and 0.005 μg/mL in PBS were prepared by serial dilution. The standard solutions and sample solutions were analyzed using an Infinite® M200 fluorescence spectrophotometer (Tecan, Zürich, Switzerland) set to an excitation wavelength of 555 nm and an emission wavelength of 580 nm. PBS was used as the blank solution. The standard curve of rhodamine B was a plot of rhodamine B concentration as a function of fluorescence intensity. The cumulative amount of rhodamine B released was plotted against time. The points were fitted to a linear equation using linear regression analysis. The linearity of the drug release profiles of the scaffolds was evaluated based on their coefficient of determination (R^2) of the best-fit linear curve.

Design of Scaffolds Containing Carbamazepine and In Vitro *Dissolution Methods and Methods of Analysis*

The 3D printed scaffolds used to contain carbamazepine were similar to the rhodamine B containing scaffolds but smaller in size, to better simulate the actual size of an oral tablet to be swallowed. The differences in scaffold sizes did not affect the results as there was no comparison between rhodamine and carbamazepine. The carbamazepine scaffolds had a diameter of 15 mm, 6 mm height, a wall 1 mm thick, and a base 1.5 mm thick. The lid was designed with a diameter of 12 mm to fit the scaffold body exactly. In order to find out the optimal geometry of the scaffold, each scaffold designed had a different permutation of the hole diameter (1, 1.5, and 2 mm) and number of holes (4, 8, and 12 holes).

Commercially available Tegretol 200 tablets contain 200 mg of carbamazepine, and aerosil 200, microcrystalline cellulose, Nymcel ZSB-10, and magnesium stearate as the excipients. Tegretol 200 tablets were ground to fine powder using a pestle and mortar. One hundred milligrams of the powder was used for packing into each scaffold. Paraffin film was used to cover the gaps between the lid and the scaffold body. For the drug release study, the scaffolds were contained inside a hemispherical basket suspended approximately 2.5 cm from the bottom of the beaker. The dissolution medium used was 1 L of 1% wt/wt SDS, as specified in the United States Pharmacopeia XXII National Formulary XXII (1990) for dissolution testing of carbamazepine tablets.[32] The dissolution medium was constantly stirred using a magnetic stirrer at 100 rpm and equilibrated at 37°C. Aluminum foil was used to cover the dissolution apparatus to prevent evaporation. One milliliter samples of the dissolution medium were taken and replaced with fresh 1% SDS at 5, 15, 30, 60 min, and then at regular intervals of 1 h for up to 8 h. Triplicates were carried out for each permutation of number and diameter of holes.

The standard and sample solutions for carbamazepine were analyzed using reverse-phase high performance liquid chromatography (RP-HPLC). Sample solutions were centrifuged at 8000 rounds per minute for 5 min before analysis of the supernatant by RP-HPLC. The HPLC machine used was a L-2000 (Hitachi, IL) equipped with a pump (Hitachi L-2130), an auto-sampling system (Hitachi L-2200), column oven (Hitachi L-2300,) and an UV detector (Hitachi L-2400). Separation was done using a 4.6 × 75 mm Zorbax SB-C18 reverse-phase column with an average particle size of 3.5 μm (Agilent Technologies, Santa Clara, CA). The column was maintained at room temperature. Methanol water in 50:50 ratio was used as the mobile phase. The pump was set to isocratic mode and flow rate was set as 1 mL/min. The column effluent was analyzed using UV at a wavelength of 285 nm. Data analysis was done using the EZChrom Elite program (Agilent Technologies).

Standard carbamazepine solutions at 40, 20, 10, 5, 1, 0.5, 0.1, and 0.05 μg/mL were prepared by serial dilution on each day of the experiment. The standard curve for carbamazepine was a plot of carbamazepine concentration as a function of the carbamazepine peak area of the UV absorption × retention time curve from RP-HPLC analysis. A cumulative approach of calculating drug released at each sampling time was also used for the carbamazepine scaffolds.

Results

Dissolution Tests Using Rhodamine B Containing Scaffolds

For the scaffolds with holes at the side, increasing the number of holes resulted in an increase in the rate of release of rhodamine B (Table 1). In scaffolds with the 1.5 mm hole diameter, the one with 12 holes had a higher rate of release (50.171 μg/min) compared to the one with 8 holes (0.524 μg/min). The scaffolds with 12 holes at the side also had the highest rate of rhodamine B release (50.171 and 12.608 μg/min). The scaffold with holes on the lid had a higher rate of release (7.910 μg/mL) than the scaffold with holes on both the lid and bottom.

In general, the scaffolds with holes at the side produced more linear dissolution profiles than scaffolds with holes at the top and/or bottom. The scaffold with holes on both the lid and bottom produced a more linear dissolution ($R^2 = 0.808$) compared to the scaffold with holes only on the lid ($R^2 = 0.776$). On the other hand, the scaffolds with 4 and 12 holes (with 1.5 mm hole diameter) at the side produced the most linear dissolution profiles ($R^2 = 0.917$ and 0.975, respectively). Based on the overall results, scaffolds with holes on the side were chosen for further investigation using carbamazepine. Scaffolds with holes on the lid and bottom were discontinued from the study and the contradictory results were not examined.

Dissolution Test of Carbamazepine Zero-Order Release Scaffolds

All the scaffolds containing ground Tegretol 200 tablet exhibited good linear release profiles of carbamazepine (Figs. 2-4) for all variations of the hole diameters and number of holes. The scaffold with 12 holes and 1 mm hole diameter had the most linear dissolution profile ($R^2 = 0.9985$), followed by the scaffold with 4 holes and 2 mm hole diameter ($R^2 = 0.9980$), and then the scaffold with 12 holes and 1.5 mm hole diameter ($R^2 = 0.9969$). The least linear dissolution profile was observed in the scaffold with 4 holes and 1 mm hole diameter ($R^2 = 0.9139$). There was no general trend in the R^2 of the dissolution profiles.

Most of the scaffolds had a small burst of drug release between 0 and 5 min (Table 2). There was a positive correlation between the initial burst of carbamazepine with hole diameters. The carbamazepine amount released initially in the scaffolds with 8 holes (0.4348, 0.7246, and 1.0246 mg released initially) and 12 holes (0.1995, 0.8598, and 1.4366 mg released initially) increased as the hole diameters increased (1, 1.5, 2 mm). However, there was no observable trend between the number of holes (4, 8, 12) and the amount of carbamazepine released initially.

Similarly, there was an increasing trend in the rate of carbamazepine release with increasing hole diameters (Table 2). The rate of release in the scaffolds with 4 holes (0.0049, 0.0065, 0.0074 mg/min) and 12 holes (0.0021, 0.0050, 0.0092 mg/min) increased as the diameters increased in the order of 1, 1.5, and 2 mm. In the scaffolds with 2 mm diameter holes, the rate of release (0.0074, 0.0090, 0.0092 mg/min) increased with the number of holes (4, 8, 12).

Discussion

This study identified the dissolution profiles of 3D printed scaffolds containing rhodamine B (as drug surrogate) and

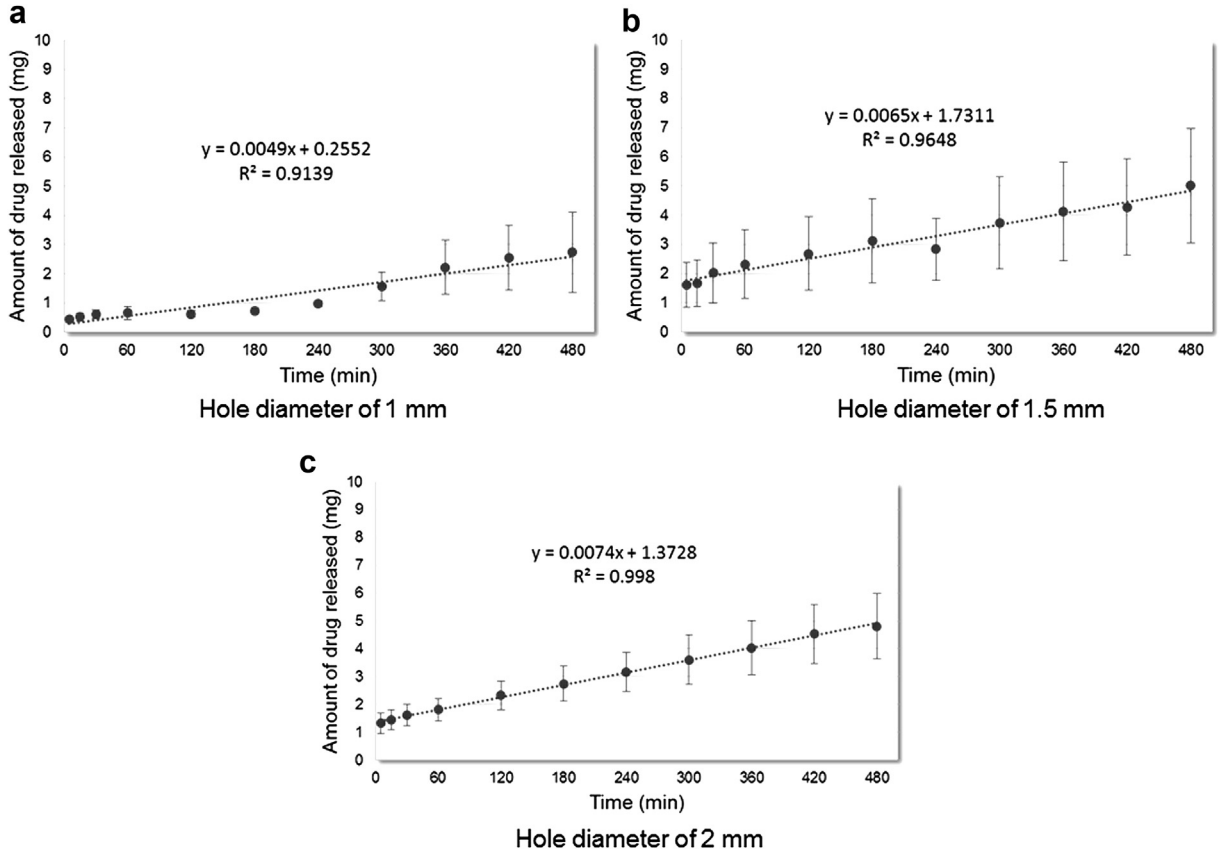

Figure 2. Amount of drug released versus time of sampling for dissolution testing of carbamazepine tablets with 4 holes and varying hole diameters of 1, 1.5, and 2 mm.

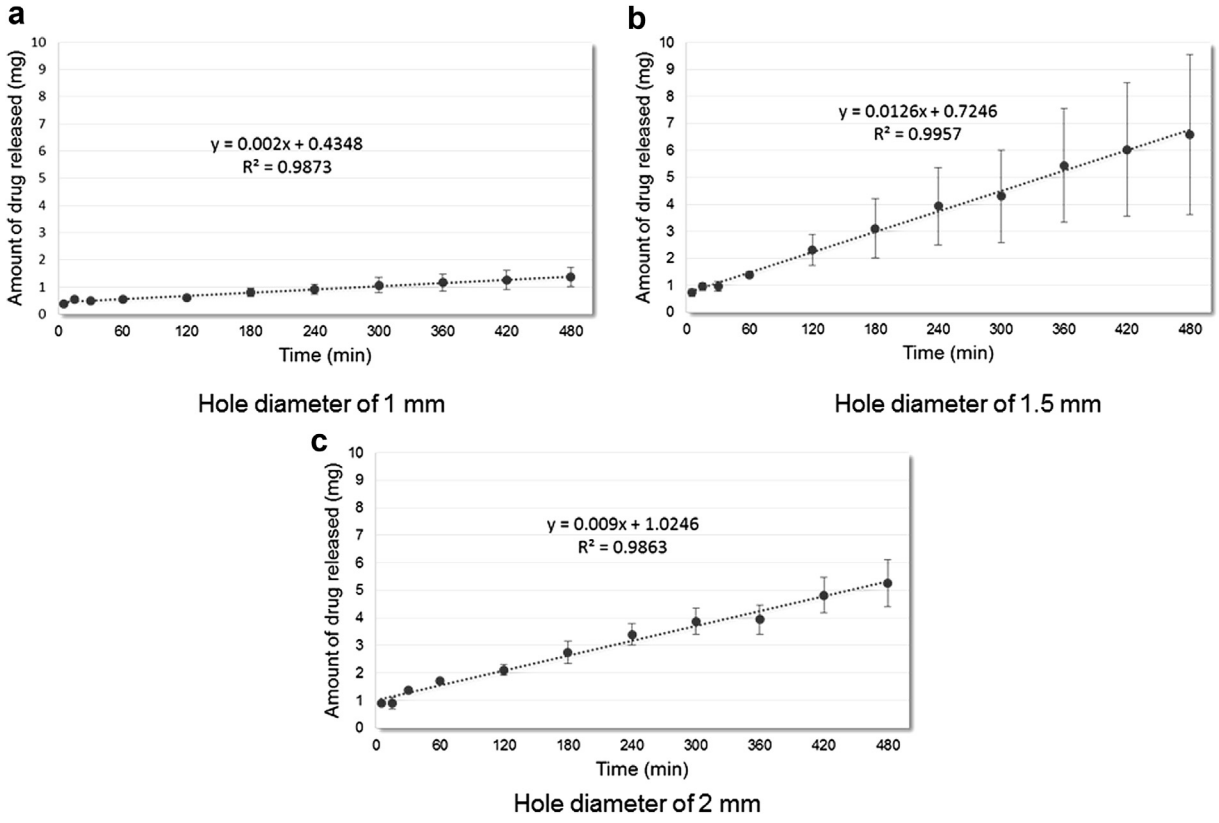

Figure 3. Amount of drug released versus time of sampling for dissolution testing of carbamazepine tablets with 8 holes and varying hole diameters of 1, 1.5, and 2 mm.

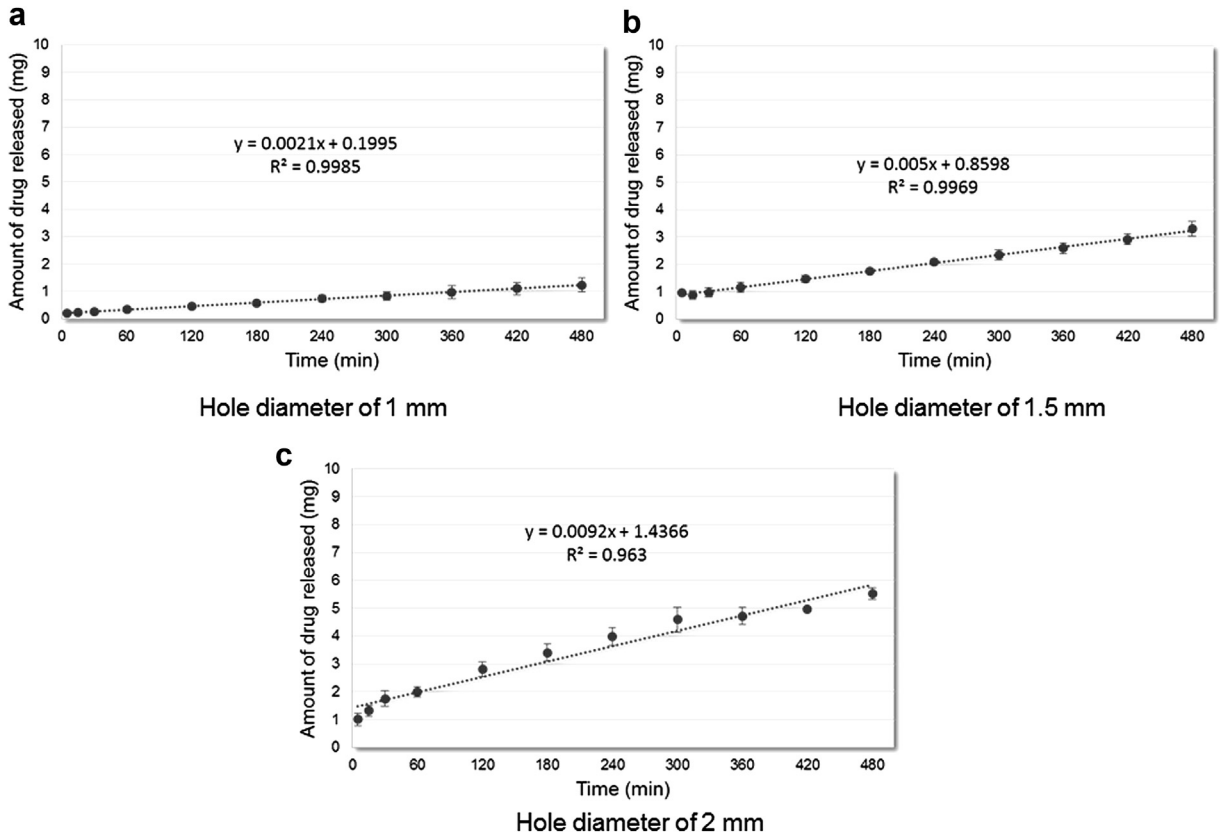

Figure 4. Amount of drug released versus time of sampling for dissolution testing of carbamazepine tablets with 12 holes and varying hole diameters of 1, 1.5, and 2 mm.

carbamazepine through various scaffold designs (based on varying number of holes, size of holes, and position of holes). To our knowledge, our scaffold design is novel and has not been studied. Scaffolds with holes at the side exhibited zero-order dissolution kinetics representative of a sustained-release tablet. The results showed that scaffolds with 12 holes and 1 mm diameter holes produced the most linear profiles. The scaffold design was able to release drugs reproducibly at a constant rate after 5 min. The linearity of drug release for the individual scaffolds was likely due to the constant surface area of the drug powder in contact with the environment throughout the dissolution test.

In this study, the dissolution media entered the 3D printed scaffold only through the holes, because ABS itself was impermeable to the media. All scaffolds were observed to have remaining drug and excipients after 8 h of testing, hence we extrapolated that the disintegration and dissolution process lasted for at least 8 h. The proposed mechanism of drug dissolution was similar to the concept of a multi-layered osmotic device where the dissolution media permeated through a membrane (semipermeable to dissolution environment) and wet the scaffold core. The osmotic agent in the scaffold core would swell up, thus causing the drug to escape from the scaffold core through a small passageway, resulting in controlled drug release. The mechanism for our 3D printed scaffold would be the same, except that the dissolution media entered the scaffold core through the same holes that the drug exited from.

Using rhodamine B as a drug surrogate, our study showed that positioning the holes at the side resulted in more linear release profiles than holes at the top and bottom of the 3D printed scaffolds. Of the 3 scaffold configurations (holes on top, holes at the side, and holes on both top and bottom), the scaffolds with holes at the side produced a considerably better linear release profile than the other 2 configurations, with an R^2 of 0.917 compared to 0.776 and 0.808. Further changes to the scaffold with holes at the side, in terms of the number of holes and hole diameters, also demonstrated good linearity, except for the scaffold with 8 holes of 1.5 mm diameter and scaffold with 12 holes of 2 mm diameter. A possible reason for this deviation from the general trend could be due to the random effects of photodegradation of the rhodamine samples resulting from accidental light exposure. Because the use of rhodamine was only a pilot to determine the optimal configuration

Table 2
The Rate of Release of Carbamazepine and Estimated Amount of Carbamazepine Released at Time = 0 for Each of the Tablet With Permutations of 4, 8, and 12 Holes and Hole Diameter of 1, 1.5, and 2 mm

Rate of Release (mg/min)				Estimated Amount Released at Time = 0 (mg)			
Number of Holes	Hole Diameter (mm)			Number of Holes	Hole Diameter (mm)		
	1	1.5	2		1	1.5	2
4	0.005	0.007	0.007	4	0.255	1.731	1.373
8	0.002	0.013	0.009	8	0.435	0.725	1.025
12	0.002	0.005	0.009	12	0.200	0.860	1.437

of the scaffold (holes on lid or body) for our study, the results did not affect the subsequent results of the setup using carbamazepine in the scaffold.

For all scaffolds using carbamazepine, good linear release profiles of carbamazepine were observed, with an R^2 value of at least 0.91. In general, increasing the hole diameters increased the rate of carbamazepine release from the scaffolds, while maintaining the linearity of the drug release profile. Our finding was similar to Kim's report on donut-shaped tablets,[18] where increasing the central hole size increased the surface area exposed and hence the rate of dissolution of diltiazem hydrochloride from the coated donut-shaped tablets. The group of scaffolds with 4 or 12 holes also demonstrated a clear trend of an increased amount of carbamazepine released at time = 0 with the increase in hole diameter. However, for the group of scaffolds with 8 holes, the setup with the hole diameter of 1.5 mm had the highest release rate, followed by the 2 mm, and then 1 mm holes. The high rate of carbamazepine release for the scaffold with 8 holes of 1.5 mm diameter was largely contributed by one of the replicates which had an unusually high rate of release—0.028 mg/min compared to the other two replicates which had a rate of release of 0.005 and 0.004 mg/min. This anomaly could have been due to experimental error where the lid was not capped properly.

Generally, the rate of release of carbamazepine had a positive correlation with the hole diameter of the scaffold. There was no clear association between the number of holes in the scaffold and the rate of release of carbamazepine, except for the group of scaffolds having a hole diameter of 2 mm. This finding seemed to conflict with our expectation that changing the number of holes would affect the surface area and thus the dissolution rate. We postulated that a possible reason could be that the grinding of the Tegretol 200 tablet using a pestle and mortar resulted in varying particle size distributions, which would affect the dissolution rate of the drug according to the Noyes Whitney equation.[33] Future studies could eliminate this confounder by using a standardized size reduction method, such as jet milling, to produce powders of narrow size distributions.[34]

The excipients in the Tegretol 200 tablet could potentially play a role in its drug release profile. Microcrystalline cellulose swells in contact with water through the capillary action of water into the pores, which can force the drug out of the scaffold through the holes. This is the same for croscarmellose (nymcel ZSB-10). However, in our study, the 3D printed scaffolds were not packed to the brim, but only just enough to cover the holes with the grounded powder. Thus, it is questionable whether the swelling actually had an effect on the drug release profile. Furthermore, we assumed that there was no inter-tablet variation in excipient amounts and ratios among the Tegretol 200 tablets. Different brands of carbamazepine tablets could be tested out as future work.

On the other hand, because the scaffolds were not fully packed with powder, there could have been a possibility of the presence of air pockets in the scaffolds. In our experiments, air was observed to escape and trap at the holes of the scaffolds. The trapped air pockets could in turn retard the drug release rate of carbamazepine. For the scaffolds with the 1.5 mm hole diameter, particularly in those with 8 holes, air could have completely escaped from the scaffold in one of the triplicates because of the way it was put into the dissolution media, thus resulting in a higher rate of drug release and higher standard deviation. This might explain the contradictory decrease in drug release rate in the scaffolds with 1.5 mm hole diameter from 0.0126 mg/min (8 holes) to 0.005 mg/min (12 holes). This same reason might also explain the lower rhodamine release rate (0.304 μg/min) from the scaffold with holes in the lid and bottom of the scaffold compared to the scaffold with holes only in the lid (7.910 μg/min).

We envisioned that this setup could potentially be used as a method of personalizing patients' therapies in the retail setting where pharmacists would pack the grounded drug powder into the 3D printed scaffold. Simple tools such as a mini powder compactor might be required to ensure that the drug powder is tightly packed to prevent any trapping of air bubbles. One potential benefit of the 3D printed scaffolds as a dosage form is its feasibility to individualize drug therapies for different patients. AEDs were selected as the drug-of-choice because a significant proportion of epileptic patients would tend to be on poly-therapies.[4] By combining different AED cocktails into one scaffold, it could potentially reduce pill burden and improve the medication adherence of epileptic patients, and thus improve control of epilepsy. Although this study is still at its teething stages, it shows the potential of using 3DP as a method, in small-scale health care systems in hospitals and clinics, whereby extemporaneous (non-commercially available) drug products have to be made. This study provides a basic skeleton for 3DP-enabled medications and future studies should consider carrying out investigations on incorporating multiple AEDs, or even drugs for other chronic diseases into one scaffold using the same, or improved, designs.

Limitations

The 3D printed scaffolds had a small initial burst of drug release between 0 and 5 min, which could be due to the release of the drug through the holes before the scaffolds were fully immersed. This premature release of drug could be circumvented by the introduction of a thin coating material to cover the holes when the scaffold was put into the dissolution medium. A low molecular weight hydroxypropyl methylcellulose and polyvinyl acetate could potentially be used as the coating materials.[35,36]

The usual dose of carbamazepine for epilepsy in adults is 800-1600 mg/day, which is at a release rate of 0.56-1.11 mg/min.[5] The maximum rate obtained in this study was 0.0126 mg/min, which would not be enough to achieve the therapeutic dose. However, this study has demonstrated that an increase in scaffold hole diameter can lead to an increasing rate of drug release. Therefore, future studies can explore the optimal size of the holes that will produce the desirable dissolution rate of the drug. The low rate of drug release can also be circumvented by increasing the amount of carbamazepine in the scaffold.

As we did not compare between scaffolds containing pure carbamazepine powder and powdered Tegretol 200 tablets, we could not elucidate whether the other excipients in the tablets might affect the release profiles of the scaffolds. Future studies should investigate the effect of excipients and other formulations on the release profile. More thorough characterization of the systems, using parameters such as scaffold hardness and uniformity, among others, should be performed as well.

Finally, the material used to design the scaffolds needs to be able to retain its shape throughout the gastrointestinal transit time in order to maintain a constant surface area for zero-order release of carbamazepine. ABS is the most commonly used material for 3D printing and has excellent thermal, mechanical properties and good chemical resistance,[37] which makes it suitable as a material for this dosage form design. To our knowledge, there are no studies that have focused on the use of ABS in pharmaceutical applications. Recent studies show that ABS scaffolds are biocompatible for cartilage and nucleus pulposus tissue regeneration[38] and as ear-shaped scaffolds for skin cell culture.[39] Although ABS is not bioresorbable, it can potentially be used in pharmaceutical applications due to its biocompatibility and strong chemical resistance, and thus it can be passed out of the body safely, as with most foreign bodies.[40] However, more studies

should be performed to address the ongoing concerns about the possible leaching of acrylonitrile monomers, which may be carcinogenic.[41]

Other than ABS, various polymers have also been utilized in the pharmaceutical industry for the 3D printing of drug delivery systems using the FDM technique. An example is the use of polylactic acid as a drug eluting implant for slow and partial drug release of the antibiotics nitrofurantoin and hydroxyapatide.[25,42] Poly(vinyl) alcohol has also been used as a drug carrier for the investigation on the effects of geometry on drug release from 3D printed tablets.[43] In fact, poly(vinyl) alcohol has been used as a drug carrier for aminosalicylate modified-release tablets,[44] prednisolone extended-release tablets,[45] and budesonide modified-release tablets.[46] On the other hand, ethyl vinyl acetate has been used as a novel drug carrier for a 3D printed T-shaped intrauterine drug delivery system for indomethacin.[47] In a similar study, polycaprolactone has also been used to deliver indomethacin in a controlled-release manner in a 3D printed polycaprolactone-based implantable prototype of T-shaped intrauterine system.[48] In consideration of the wide variety of polymers that can potentially be used for drug delivery systems, we encourage future studies to also explore these polymers for the scaffold designs of drugs, such as carbamazepine.

Conclusion

This study has demonstrated that 3DP is a useful technique to design scaffolds that have linear release profiles after 5 min, with carbamazepine as our drug-of-choice. This study has also demonstrated that the hole diameters of the printed scaffolds have a positive relationship with the rate of carbamazepine release, but not with the number of holes. The scaffold design described in this study forms a basis that can be further optimized for a zero-order release dosage form, so as to reduce the dose-dependent CNS side effects of carbamazepine. The ultimate goal of this research is to benefit epilepsy patients by achieving the therapeutic doses required for seizure control through minimizing the side effects of AEDs, and improving the compliance of patients through a dosage form that provides a zero-order release drug profile.

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