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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