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Poly(lactic acid) Microparticles for Drug Carriers in Enhancement of Controlled Release Systems towards 3D Printing

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Abstract

The aim of this work was the synthesis and characterization of biocompatible and biodegradable microspheres based on poly(lactic acid), containing methyl orange; a hydrophilic substance. Poly(lactic acid) microspheres were fabricated via the double emulsion water-oil-water (W1/O/W2) technique. More than 10 repetitions of the experiments were conducted for the optimization of the synthetic process, using the same materials. The morphology and size, as well as the structure, of the produced materials were determined via scanning electron microscopy and Fourier transformed infrared spectroscopy, respectively. The study of the active substances release profile from the polymeric matrix, in buffer solutions that stimulate blood and stomach pH, proved that the aforementioned synthetic process could be suitable for the production of materials that could be used for drug delivery and release systems.

Keywords: Nanotechnology; Nanomedicine; Emulsions; Poly(lactic Acid); Three Dimensional Printing

Introduction

Importance of Present Work

Advances in drug delivery and release systems focus on controlling the pharmacological effect of the drug, with the ultimate goal to optimize treatment. Pharmacokinetic profile can be influenced by the release rates of the drug, as well as the specific drug mechanism of action and drug pharmacodynamics, thus affecting patient's treatment. An optimal drug delivery system ensures that the drug is distributed at the site of action for a precise duration and effect, in order to allow for an effective, safe and reliable application [1,2].

As far as personalized medicine is concerned, the use of three-dimensional printing (3DP) technology is supposed to be of utmost importance, being distinguished from conventional manufacturing techniques, because it is appropriate for creating pharmaceutical complexes and innovative dosage forms, such as pellets and drug loaded micro/nanospheres. This fabrication technology can build three-dimensional objects layer by layer, by using an appropriate digital model, so that medication can be tailored to individual patient's needs.

The benefits of using this technology, in personalized medicine, and especially for the fabrication of ready-to-use tablets, involve a) the control of temporal and spatial distribution of the active substance, b) the option of achieving very low pharmaceutical ingredient deposition; c) control the porosity, d) the hardness, e) the infill percentages and many other formulation parameters [3]. In terms of industrialization and commercialization, the benefits include the reduction of waste, the elimination of expensive and massive supply chains and the optimization of products quality by achieving high control of the manufacturing processes.

Nanotechnology includes scaled-up, reliable, and cost-effective manufacturing of nanoscale materials, structures, devices, and systems. It leads to the production of improved materials and new products and allows for the control, manipulation, study, and manufacture of structures and devices in the "nanometer" size range that could be combined with the novel properties of 3D printing techniques expanding the abilities of personalized medicine [2]. Polymeric biocompatible and biodegradable micro and nanoparticles have drawn the attention due to their stability and ease of surface modification. Studies have demonstrated that nanoparticles outweigh microparticles [4] because they affect drug loading efficiency, delivery and release. Furthermore, nanospheres can overpass the Blood-Brain Barrier (BBB), can be easily absorbed by cells, can offer equivalent drug distribution in the polymer and also improve patient-compliance [5].

Microparticles are being produced under controlled conditions, using state-of-the-art manufacturing processes such as spray-drying, electrospinning, solution blow spinning, emulsion cross-linking, precipitation polymerization [6]. As far as emulsion technique, that has been used at this work, is concerned, different types of formulations such as double emulsion Water-Oil-Water (W/O/W) have been employed, whereas traditionally small-molecular weight surfactants have been used as stabilizing agents. The combination of emulsion cross linking process for creating stable micro drug loaded spheres, along with the three-dimensional printing technology, could improve the release profiles, bioavailability and loading efficiency of pharmaceutical tablets.

Previous Works-Use of Poly(lactic Acid) (PLA) and 3D Printing of Controlled Released Systems

Over the past few decades, there has been a growing interest in controlling the release of drugs in accordance with the pharmacological properties of active substances, in order to improve the effectiveness of

drug therapy. Such systems often used polymers as drugs carriers, while the idea dates back to the 1960s through the employment of silicone [7]. Controlled release systems aim to distribute the appropriate amount of the active substance in the area of interest, at a predetermined rate for a systemically or specified period. Such delivery and release systems outmatch conventional dosage forms providing improved efficacy, safety ratio, more uniform drug effect, reduced toxicity, and better patient compliance and convenience.

There is a variety of such formulations, whose release patterns are divided into two categories. The first one includes those that release the sustained component at a slow zero or first order rate, and the second, those that dispense a small amount (burst effect), followed by slow zero or first order release [8].

The main principle of drug release lies on the encapsulation of the active substance in a soluble membrane, the progressive membrane dissolution and creation of micro tracts, the permission of aqueous medium entrance into the membrane, continued by drugs dissolution. Finally, the dissolved drug is diffused out of the system. The factors affecting the drug release rate, include the structure of the matrix where the drug is contained, the chemical and physical properties associated with the polymer, such as solubility, temperature and pH sensitivity, and the active substance [9]. In literature, the advantages related with controlled release- smart systems is demonstrated, such as small programmable devices in the field of microfabrication [10], drug release from delivery systems based on hydroxypropyl-methylcellulose (HPMC) [11], thermosensitive poly(N-isopropylacrylamide) (PNIPAAm) hydrogels with an interpenetrating polymer network structure [12], etc.

Among biodegradable polymers, PLA is one of the most extensively studied materials for this application [13]. It undergoes scission in the body to monomeric units of lactic acid, which is a natural intermediate in carbohydrate metabolism. PLA is therefore suitable for further uses such as resorbable sutures, implants for orthopedic surgery or blood vessels, which finally can be replaced by the body's tissues. As to the sustained release, PLA has been used for delivery of anti mycobacterial drugs [14], quinolones [15], antimalarial and anti inflammatory drugs [16], antitumor agents [17], hormones [18] and fluoride containing tablets for oral use [19].

The ability to develop and manufacture dosage forms, utilizing 3DP techniques, provides new opportunities on controlled-release layers. Fabrication of pharmaceutical products can be achieved through a number of techniques, such as fused deposition modelling, inkjet based fabrication and thermal inkjet printing, while offers a lot of advantages. Some of them refers to patients in need of extremely low amounts of drug or drug applied in small doses, patients in treatment of chronic illnesses with high frequency of dosing couples with side effects and amenability to broad types of pharmaceutical active ingredients as well as drugs with narrow therapeutic windows.

Three-dimensional printing of tablets offer lots of advantages including high production rates due to its fast operating systems, reduction of materials used which can reduce the cost of production, thus gaining an added value. This principle has been demonstrated to tablets containing fluorescein 4-aminosalicylate and 5-aminosalicylate [20] and prednisolone [21]. The application of these technologies into the field of drug delivery systems has been established by the development and FDA approval of Levetiracetam (SPIRTAM®) tablets, the first 3 dimensional printed orodispersible tablets [17]. An additional potential benefit, concerning 3D printing and affecting drug release profile, is that this technology can be used to fabricate tablets of any geometry [22]. Moodley et al. [23] created donut-shape polymer matrices in order to obtain zero-order drug release, while Bayomi et al. [24], used parabolic shapes to achieve the same. Also, there have been studies on different tablet shapes in drug release, ranging from triangular, cylindrical and half-spherical tablets of the same formulation. Drug release kinetics, resulted from different shapes of printed tablets showed no dependence on the surface area but rather on surface to volume ratio, indicating that geometrical shape and volume plays an important role on drug release profile [19].

In this work, a tablet compression machine was used, in order to create tablets consisting of the biocompatible polymer PLA which has been pre-modified into micro spheres containing the active substance.

Materials

Sodium 4-{[4-(dimethylamino) phenyl] diazenyl}benzene-1-sulfonate (Methyl Orange, Fisher Scientific), Poly(vinyl alcohol) (86-89% hydrolyzed, low molecular weight, Alfa Aesar) and poly(lactic acid) (2003D, Nature Works) namely. Citric Acid Monohydrate (99.5%, Sigma Aldrich) and Sodium Phosphate Dibasic Dehydrate (99%, Sigma Aldrich) were A. R. grade and used as received without further purification.

Synthesis Technique-Case study: PLA microspheres as drug carriers

Poly(lactic acid) exhibits ideal properties of delivery and controlled release of active substance inside the body. This biocompatible and biodegradable material facilitates adjusting characteristics on its structure, such as the size and shape of its derivatives. Poly(lactic acid) particles are commonly prepared by single- or double-emulsion, a method that provides the ability to customize particle characteristics such as size, encapsulated agent, and surface properties [1]. The technique performed to create micro spheres as far as the encapsulation of hydrophilic active substance inside them, was that of the double emulsion water-oil-water (W1/O/W2).

The active substance was dissolved in water (the first water phase, W1) and added dropwise to the PLA-dichloromethane solution (organic phase, O) under ultrasonic irradiation in order small water droplets-active agent surrounded by the polymer to be formed (Figure 1). The resulting emulsion was added to water (second water phase, W2), in which a stabilizer and surfactant agent [poly(vinyl alcohol), PVP] had been prior dissolved, under vigorous stirring to facilitate solvents evaporation and to completely stabilize the spheres. The final step was the centrifugation of the emulsion, the collection and washing of the micro structures, and the lyophilization for water removal. The final product gathered in a form of powder that consisted of spherical polymer structures including methyl oranges droplets.

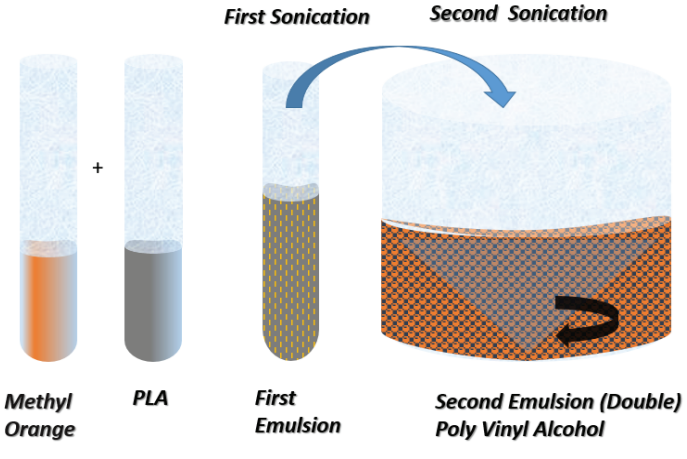

Figure 1: Schematic of PLA Microparticle Fabrication

The following step included the tableting of the produced, micro structured powder. The tablet compression machine (MINIPRESS MII, 186) was used in order to create pills as dosage forms. This tableting formation takes place by the combined pressing action of two punches and a die, where the basic principle is the hydraulic pressure. The powder was placed in the compressing tool punch-dye cavity which includes the punch die and the lower punch. During compression stage, the top punch tents to meet the lower one while the distance between the two punches determines the thickness and the hardness of the produced tablet. Six identical tablets that consisted of 0.238 gr of the powder were created. The tablets breaking force was measured by Tablet Hardness Tester TBH 125, at a range from 80N to 100N. In order to determine the tablets breaking force, 10 similar tablets were broken in the hardness tester machine Table 1.

Characterization Techniques

The microstructure and elemental analysis of the spheres were studied by Scanning Electron Microscopy (SEM), in combination with Energy Dispersive X-Ray Spectroscopy (EDS). A PHILIPS Quanta Inspect (FEI Company) microscope with 149 W filament 25 KV equipped with EDAX GENESIS (AMETEX PROCESS & 150 ANALYTICAL INSTRUMENTS) was used for the characterization. To determine the average diameter of each formation, measurements were taken directly from the SEM images using Image J software. A minimum of 600 measurements of the diameter of particles selected randomly from the field of view, from 5 different areas of the sample, to acquire a representative size distribution.

Taking into consideration Figure 2, it can be mentioned that the morphology of the produced materials is spherical. However, the fabricated spheres are not uniform in size, their diameter ranges from 800 nm up to 20 micrometers. More specifically, regarding Figure 3 that demonstrates the PLA microspheres size distribution, it may be remarked that the diameter of the highest spheres population ranges from 1 μm up to 5 μm. (Figure 4) illustrates the SEM image of PLA microspheres loaded with methyl orange together with the EDS analysis and the corresponding EDS mapping of N element. The EDS analysis confirms that the loaded microspheres consist of carbon and oxygen due to the PLA and methyl orange and N that is ascribed to methyl orange. Considering the EDS mapping it may be remarked that the methyl orange has been adsorbed into the microsphere due to the fact that the presence of N element-that comes from methyl orange-covers entire the microsphere.

Fourier Transform Infrared Spectroscopy (FTIR) method was also performed in order to evaluate the structure of the produced materials (Figure 5). The peaks at 574 cm^{-1} and at 693 cm^{-1} are assigned to C–C_{l2} stretching vibration of CH_2C_{l2}, and the bands at 816 cm^{-1} and 846 cm^{-1} are referred to C=CH vibration of PVA. The peak at 1753 cm^{-1} is assigned to C=O stretching vibration of PLA and the band at 1607 cm^{-1} is due to C=C vibration of PVA. Moreover, the band at 1088 cm^{-1} is due to C–O–C a stretching vibration of PLA ester groups and the peak at 1032 cm^{-1} is attributed to N-N stretching vibration of methyl orange. Also, the peak at 1193 cm^{-1} is ascribed to R-SO_2-OR' bonds vibrations of methyl orange. A band at 1436 cm^{-1} is assigned to CH_2Cl vibration of dichloromethane. Finally, the peak at 2922 cm^{-1} is attributed to CH_2 stretching of PVA [25].

A dissolution study of the tablets was performed using two different media buffer solutions; the first simulated pH of human blood (7.4) and the other one (5.4) simulated human stomach environment. In order to maintain a constant temperature at 37.0 ± 0.2°C, a stable low stirring rate at 20 rpm and an automated sampling was conducted, during the methyl oranges release, using the Dissolution Test Instrument PT-DT70. Each tablet was immersed into 500 mL of buffer solution. The samples spectrum was analyzed in a UV-IR (Jasco V-630) spectrophotometer in order to identify the concentration of methyl orange into the solution, at different times.

Applications

From the release profile, a biphasic manner was evidenced, with an initial fast release phase followed by a slower release. The initial fast release is clearly associated with the "burst effect", i.e., very fast release from the surface. During the second phase, the release of drug can be explained by a combination of diffusion through the film and its hydrolytic degradation. The initial fast release is due to diffusion of the drug incorporated at or near the surfaces of the tablets and is independent on the pH value since it is not related with polymer degradation. The second release phase is a combination of two mechanisms, diffusion through the films and hydrolytic degradation of PLA, respectively.

Figure 6 indicates that the prepared material is in accordance with the criteria in drug release mechanisms, while the methyl oranges release profile from PLA matrix corresponds to 'power law'-semi-empirical equation which describes drugs released amount from polymeric systems [11]:

$$\frac{M_t}{M_\infty} = Kt^n \qquad (1)$$ (Equation 1)

Where M_t and M_∞ show the amount of the active substance at time t and infinite time respectively, n stands for the release exponent where (n=0.5 indicates controlled diffusion release and n=1.0 controlled swelling release) and k is a constant that depends on geometric characteristic of the device.

Table 1: Shape, dimensions and breaking force of tablets

Shape	Diameter (cm)	Height (mm)	Weight (gr)	Breaking force (N)
Flat-faced plain	1.10 ± 0.01	3.00 ± 0.01	0.238 ± 0.001	90 ± 10

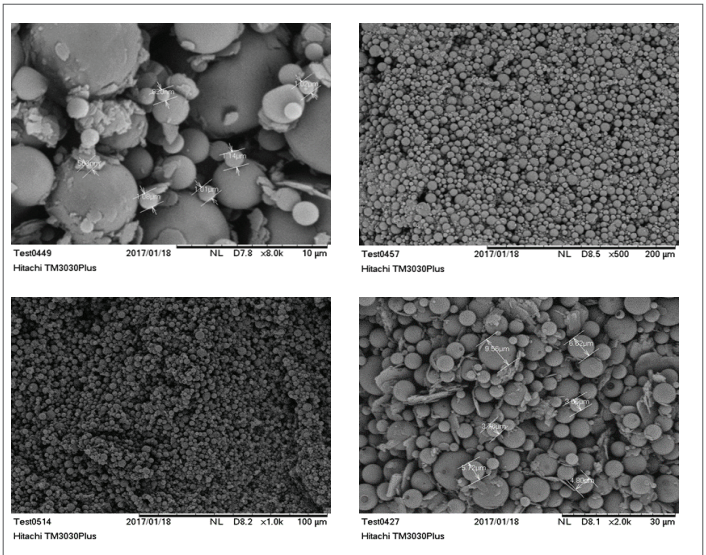

Figure 2: SEM images of PLA Microspheres as Received After the Centrifugation of the Emulsion

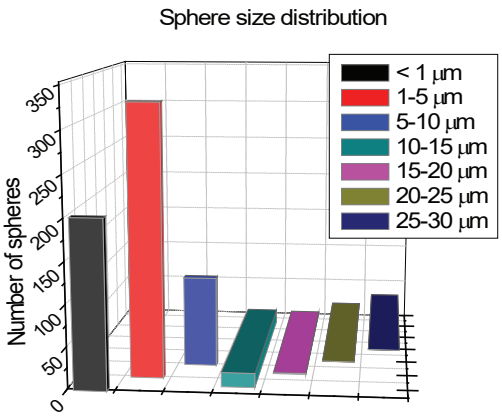

Figure 3: PLA Microspheres Size Distribution

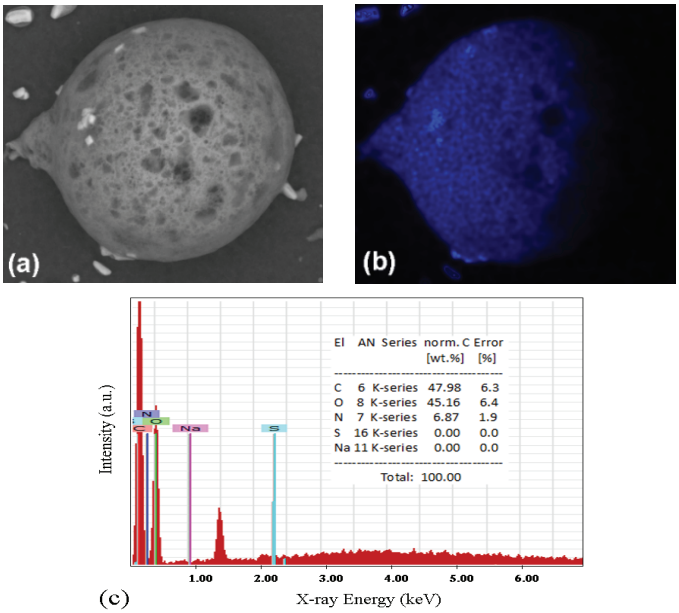

Figure 4: PLA Microspheres Loaded With Methyl Orange: (a) SEM Image, (b) The corresponding EDS mapping of N Element and (c) EDS Analysis

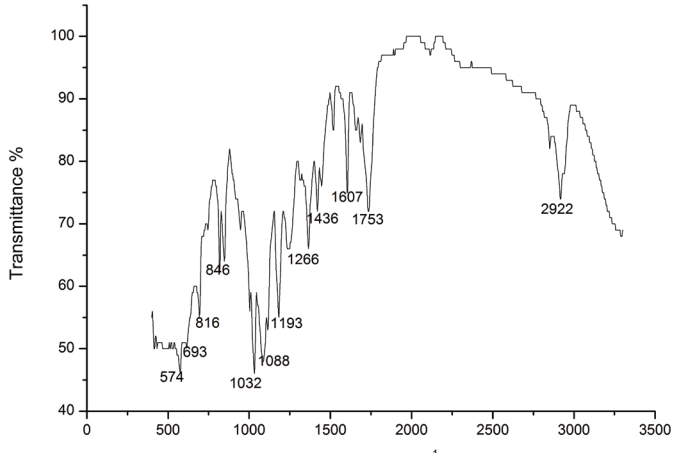

Figure 5: FT-IR Spectrum of the Produced Microspheres

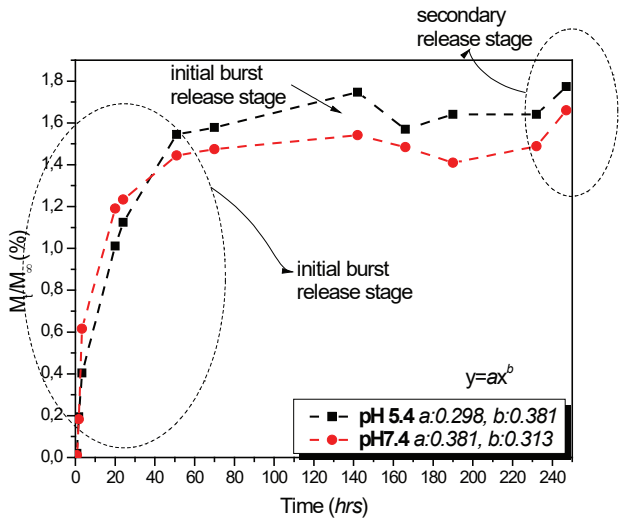

Figure 6: Dissolution Rate Diagrams of the Tablets, as Release Profile

Conclusions and Future perspective

Microspheres containing methyl orange have been prepared by the double emulsion technique W/O/W. Poly(lactic acid) constituted the organic phase and PVA has been used as a surface active agent. The diameter of the highest spherical formation ranged from 1 μm up to 5 μm, thus leading to uniform distribution of methyl orange into the polymer.

The aim of this study is to acquire the release mechanisms and assess the degradation behavior of PLA-methyl orange system, in order to create 3D printed tablets, consisting of the biocompatible polymer PLA, which has been pre-modified into micro spheres containing the active substance. Due to the high surface density of the spheres, a uniform drug distribution into the polymer is achieved. The modified extruded polymer will act as printer filament feedstock material, with the typical diameter of 1.75-1.85 mm, so that the printed dosage form will be, already, drug loaded; for this, a controlled release will be accomplished.

Future perspectives of this research work include the extrusion of the modified polymer filament, with the typical diameter of 1.75-1.85 mm, followed by the 3DP of tablets with different sizes and geometries. Finally, tablets dissolution tests will define the release profile and kinetics of the active substance, from polymer matrix. It is expected that the application of 3DP in pharmaceutical drug delivery and drug release will offer additional benefits, as it paves the way towards progressive drug delivery with built-in flexibility that is suitable for personalized medications. The combination of emulsion cross linking process for creating stable micro drug loaded spheres, along with the three-dimensional printing technology, could improve the release profiles, bioavailability and loading efficiency of pharmaceutical tablets.

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