Journal of Drug Delivery Science and Technology 101 (2024) 106217

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Dexamethasone-releasing PLGA films containing sucrose particles as porogens

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ARTICLE INFO

Keywords:
Biodegradable drug delivery systems
poly(lactide-co-glycolide)
Polymeric films
Porogens
Sucrose

ABSTRACT

The objective of this study was to investigate the use of sucrose particles as a porogen for preparing porous poly (lactide-co-glycolide) (PLGA) films containing dexamethasone by solvent casting technique to modulate PLGA degradation and drug release. Increasing the sucrose content up to 30 % decreased PLGA degradation and extended the drug release duration, a further increase to more than 60 % shortened the release duration. Sucrose created cavities and increased the internal pore surface area for the exchange of degraded acidic oligomers and monomers. This process decreased the autocatalysis within the PLGA matrix, resulting in slower drug release at lower sucrose content. At higher sucrose content, the interconnectivity of the PLGA matrix increased, accelerating the drug release of the entrapped drug. Decreasing the particle size of sucrose has a similar impact on PLGA degradation and drug release as increasing sucrose content. Smaller sucrose particles formed more cavities and a larger overall acidic exchange surface areas. Only 20 % nanosized sucrose resulted in a quasi-linear release profile with interconnected sucrose particles, while 60 % micronized or 100 % non-micronized sucrose particles were necessary to achieve the same effect. In conclusion, modifying the content and particle size of sucrose effectively altered PLGA degradation and drug release, with nanosized sucrose being the most effective porogen. The data obtained with PLGA films could be potentially applied to other PLGA drug delivery systems such as microparticles or implants.

1. Introduction

PLGA is a biodegradable and biocompatible polymer that is increasingly used in tissue engineering and controlled drug delivery [1–4]. Upon implantation, PLGA hydrolyzes into poly (lactic acid) and poly (glycolic acid), which are further broken down into lactic and glycolic acid. These byproducts are then eliminated via the tricarboxylic acid cycle [5,6]. PLGA can be easily processed into desired structures and its physical, chemical and mechanical properties can be tailored to fit a particular need. For instance, PLGA can be used to coat stents, allowing for the slow release of drugs as the coating gradually degrades. Typically, these coatings are made with thin films containing active ingredients that are released from the coating to provide a local therapeutic effect in the vicinity of the coated stent and have been shown to be valuable for the treatment of various medical conditions, in particular those conditions involving diseases of the cardiovascular system. These thin films generally have very low porosities and after the initial burst of the surface bound drug, further drug release occurs primarily through the degradation of the polymer [7–10]. Most of the drug in these thin films is released via the more unpredictable bulk degradation phase, having a late stage burst (quick release). Between the initial burst and quick release phases, a slow release phase often occurs due to the intrinsic properties of PLGA. This slow phase may not provide an effective drug concentration at the target site. However, continuous drug release is crucial for the efficacy of certain medications, such as the anti-inflammatory drug dexamethasone, in minimizing foreign body response [11,12]. To obtain a more continuous release, various methods have been proposed, including the addition of additives (magnesium carbonate, magnesium hydroxide, polyoxyethylene–polyoxypropylene block copolymer, poly (ethylene glycol) (PEG), and hydroxypropyl methylcellulose) [13], a change in drug physical state [14], the use of PLGA blends [15] and PLGA-PEG copolymers [16], and the development of porous films [8,17].

Porous thin films can be prepared using various methods such as particulate leaching [18,19], gaseous foaming [20], and mixing with more hydrophilic polymers [21,22]. Particulate leaching is a straightforward technique that allows effective control over pore size and porosity by adjusting the size and quantity of the porogen. Commonly

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https://doi.org/10.1016/j.jddst.2024.106217
Received 17 July 2024; Received in revised form 17 September 2024; Accepted 19 September 2024
Available online 25 September 2024

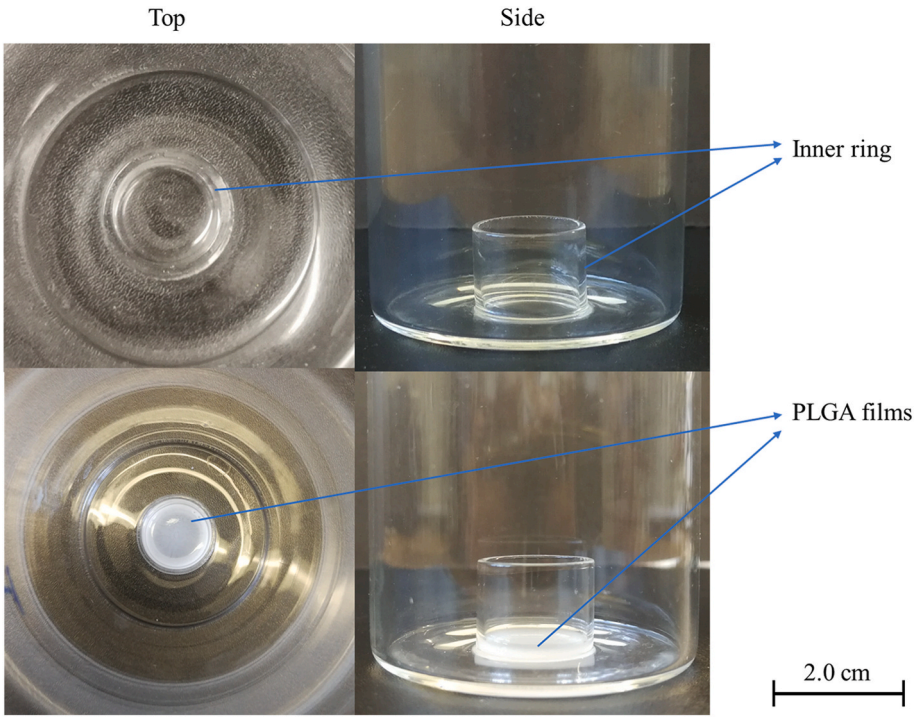


Fig. 1. Top and side views of blank release container and PLGA films incorporated container.

used particulate leaching porogens include inorganic salts like sodium chloride and sugars like sucrose [23–26]. These porogens are favored due to their low cost, biocompatibility, and the convenience of using water as a leaching medium. Although porous scaffolds and films were prepared using leaching of salt or sugar particles (100–250 μm) [25,27–30], there is limited data on the preparation of porous films using porogens smaller than 5 μm or even nanosized porogens. While small porogens create small pores unsuitable for cell implantation, these pores are beneficial for medium transportation and drug release. Nano-porous structures have been found to favor the deposition of proteins and biomolecules, creating a more favorable microenvironment for cell attachment and growth [31,32]. Small porogen particles increase the number of pores and enhance connectivity, impacting polymer degradation and drug release [16].

In previous research, the introduction of nanosized/micronized sugar particles into PLGA microparticles resulted in porous structures with high drug encapsulation efficiency, designed porosity, and adjustable in vitro drug release [33]. This was achieved by selecting the appropriate particle size and weight fraction of the nanosized/micronized sugar particles. The current study fully characterizes the use of sucrose particles with varying content and particle sizes in the degradation of PLGA films and monitors the release of dexamethasone from these films. Parameters such as wet mass change, dynamic pH change, and morphological changes were investigated to elucidate the mechanisms of drug release and polymer matrix degradation in films containing sucrose particles. It is hypothesized that a low content of nanosized sugar particles is a promising porogen for producing highly tunable thin PLGA films.

2. Materials and methods

2.1. Materials

Micronized dexamethasone (D50 = 6.2 μm; Caesar & Loretz GmbH, Hilden, Germany); sucrose (D50 = 20.4 μm; VWR International GmbH, Darmstadt, Germany); poly (lactide-co-glycolide) (Resomer RG 503H, acid end groups; Evonik Industries AG; Darmstadt; Germany); dichloromethane (Merck KGaA, Darmstadt, Germany); NaH_2PO_4, Na_2HPO_4, HCl, NaOH and sodium chloride (Carl Roth GmbH & Co. KG, Karlsruhe, Germany); yttrium oxide-stabilized zirconia oxide beads (0.1–0.2 mm, Sigmund Lindner GmbH, Warmensteinach, Germany) were used as received. Water was purified by a Milli-Q-apparatus (Millipore GmbH, Darmstadt, Germany).

2.2. Methods

2.2.1. Preparation of micronized and nanosized sucrose

The original sucrose powder was jet milled with Spiral Jet Mill 50 AS (HOSOKAWA ALPINE Aktiengesellschaft, Augsburg, Germany) to prepare micronized sucrose. The inlet pressure was 6 bar and the feed rate was kept constant at 0.5 g/min.

Nanosized sucrose was produced by non-aqueous wet bead milling as described previously [34]. 15.0 g milling beads, 250.0 mg micronized sucrose, 5.0 g dichloromethane and a magnetic stirrer were added to a 15 ml glass bottle with a polypropylene cap. For every milling trial, the sealed glass bottle was put in an ice bath and the milling speed was set to 1500 rpm. Samples were milled for 8 h. The nanosuspensions were separated from the beads by filtration through a 10 μm stainless sieve.

2.2.2. Preparation of PLGA films

Solvent casting technique was used. 45 mg PLGA was dissolved into 0.25 g dichloromethane with different content of sucrose particles (w/w, based on the weight of PLGA and dexamethasone). 5 mg dexamethasone powder was added to the PLGA solution/suspension. Then, this PLGA suspension was mixed (1 min and 8000 rpm; Ultraturrax, IKA®-Werke GmbH & CO. KG, Staufen, Germany). Subsequently, the polymer phase was transferred to the inner ring of the release bottle (Fig. 1). After 48 h solvent evaporation air-drying, hardened films were further put into a vacuum oven to remove solvent residual (room temperature and 48 h; Heraeus VT 5042 EKP, Heraeus Germany GmbH & Co. KG, Hanau, Germany).

2.2.3. Particle size analysis

The particle size of nanosized sucrose after diluting 100 times in 1 %

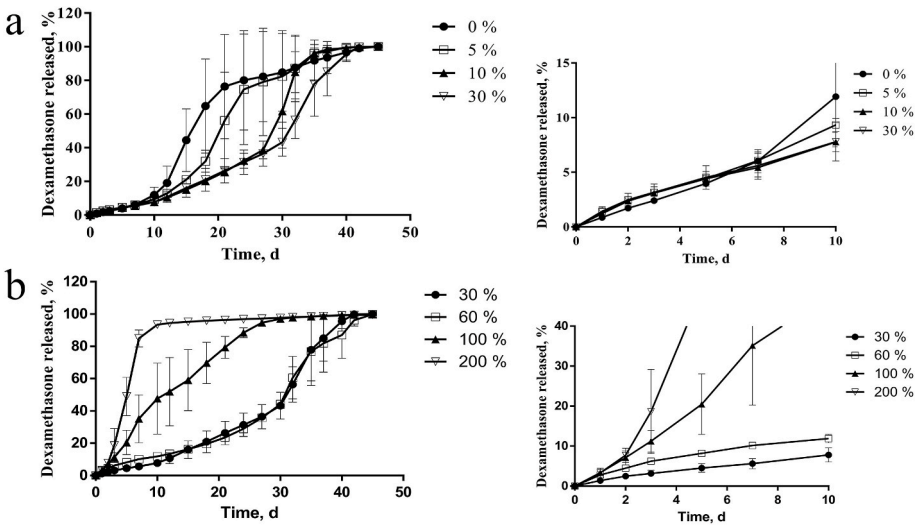


Fig. 2. *In vitro* drug release from dexamethasone PLGA films containing different content of original sucrose particles: (a) 0–30 % and (b) 30 %–200 %. Magnifications of the first 10 days are shown on the right.

Table 1
Burst, slow-release time and slow-release drug amount of dexamethasone PLGA films containing different content of original sucrose particles.

Sucrose content, %	Burst, %	Slow-release time, d	Slow-release amount, %
0	0.87 ± 0.15	10	11.92 ± 4.61
5	1.22 ± 0.22	12	12.8 ± 0.83
10	1.38 ± 0.48	27	38.64 ± 5.21
30	1.43 ± 0.31	30	43.23 ± 8.32
60	2.78 ± 0.10	30	44.12 ± 2.58
100	3.34 ± 1.16	5	20.46 ± 7.57
200	3.32 ± 0.77	2	7.71 ± 1.77

PLGA 503H dichloromethane solution was determined in triplicates by photon correlation spectroscopy using a Zetasizer® Nano ZS (Malvern Instruments Ltd., Malvern, UK). The z-average and the polydispersity index (PDI) are displayed (n = 3).

The particle size of original and micronized sucrose particles was observed under an optical microscope (Axioskop, Carl Zeiss Jena GmbH, Jena, Germany). Diameters of more than 300 particles were measured in the photomicrographs using an image processing program (Image J 1.53a, National Institutes of Health, Maryland, USA).

2.2.4. Morphology

Scanning electron microscopy (SEM) was used to image the morphology of the original, micronized and nanosized sucrose particles. Samples were sputtered under an argon atmosphere with gold (CCU-010 HV, Safematic GmbH, Zizers, Switzerland) and observed with a SU8030 (Hitachi High-Technologies Europe GmbH, Krefeld, Germany).

2.2.5. In vitro release

PLGA films were immersed in 50 ml of 10 mM phosphate buffer (pH

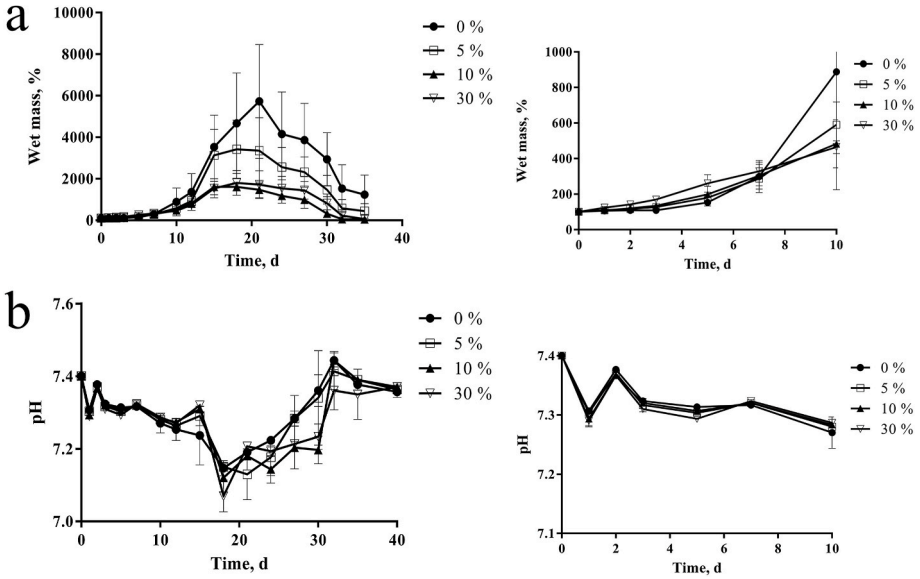


Fig. 3. Dynamic (a) wet mass and (b) release medium pH changes of dexamethasone PLGA films containing 0 %, 5 %, 10 % or 30 % original sucrose particles. Magnifications of the first 10 days are shown on the right.

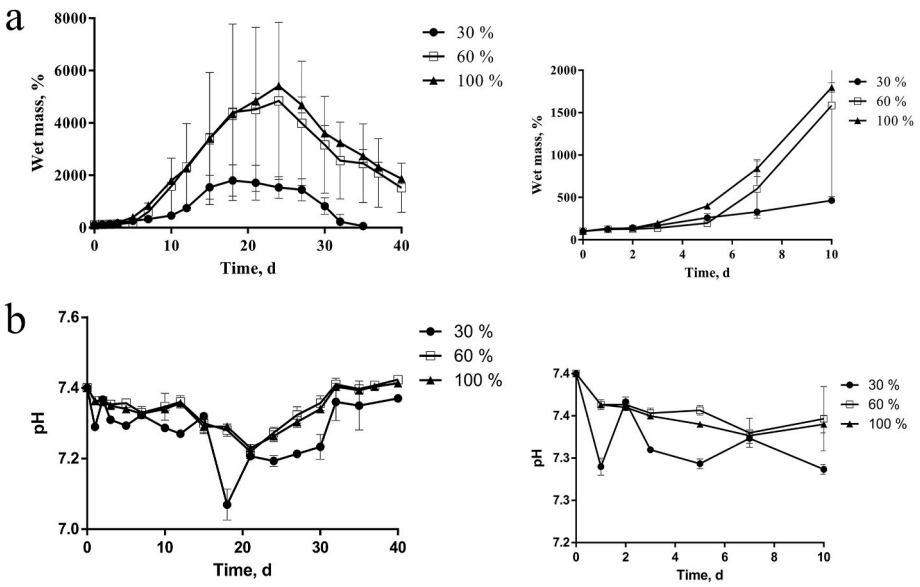


Fig. 4. Dynamic (a) wet mass and (b) release medium pH changes of dexamethasone PLGA films containing 30 %, 60 % or 100 % original sucrose particles. Magnifications of the first 10 days are shown on the right.

7.4) and incubated in an incubator shaker (37 °C and 80 rpm, New Brunswick Scientific Co. Inc., Connecticut, USA). Glass container was covered by glass lids and sealed by a parafilm membrane (Bemis Company Inc., Wisconsin, USA). At pre-determined time points (1, 2, 3, 5, 7, 10, 12, 15, 18, 21, 24, 27, 30, 32, 35, 37, 40, 42 and 45 d), all release media was removed and replaced with 50 ml fresh media. The samples were passed through 0.45 μm syringe filters and the concentration of drug in each sample was determined spectrophotometrically (242 nm, Agilent HP 8453, Agilent Technologies Inc., Santa Clara, US).

2.2.6. Monitoring of dynamic changes in the film mass

At pre-determined time points, excess water was carefully removed using Kimtech Science precision wipes (Kimberly-Clark GmbH, Koblenz, Germany) and the whole container was weighed. The mass change in percent was calculated using the following formula:

$$\text{mass change } (\%)(t) = \frac{\text{mass (t)-mass (t = 0)}}{\text{mass (t = 0)-mass (container)}} \times 100$$

where mass (container) is the weight of the container, mass (t = 0) is the initial weight of the formulation and container, and mass (t) refers to the weight of the wet formulation and container.

2.2.7. pH measurement

pH measurements were conducted at room temperature using an 827 pH lab benchtop pH meter (Metrohm AG, Herisau, Switzerland) equipped with a primatrode electrode. The pH of the release medium was measured at pre-determined time intervals to determine any changes in the pH.

2.2.8. Dynamic changes in the film morphology

At pre-determined time points, excess water is carefully removed using Kimtech Science precision wipes (Kimberly-Clark GmbH, Koblenz, Germany). Top and side pictures were taken with a light macroscope (Inteq® Informationstechnik GmbH, Berlin, Germany).

2.2.9. Statistical analysis

All results were depicted as the mean value ± standard deviation (SD) from at least three measurements. Statistical analyses were performed using Prism (GraphPad Software, Inc., San Diego, USA).

3. Results and discussion

3.1. Effect of sucrose concent

Dexamethasone-loaded PLGA films were fabricated using the solvent casting method incorporating varying amounts of sucrose as porogen to adjust the film structure and then the corresponding drug release. These films were prepared directly in a container with an inner glass ring of a fixed diameter (1.5 cm) and similar thickness (approximately 0.250 mm). The top and side views are shown in Fig. 1. The films formed a uniformly spread opaque layer at the bottom of the container. Sucrose particles are commonly employed as porogens to create surface pores and internal cavities within the PLGA matrix through leaching. Typically, sucrose particles of about 200 μm generate 100–400 μm pores suitable for cell seeding and other applications. Additionally, the ratio of sucrose to PLGA greater than 3 is usually used to ensure the interconnectivity of the porous structure. However, limited research has explored the effects of lower sucrose amounts on the PLGA structure. Dexamethasone has been used as an anti-inflammatory drug in various scaffolds, but strategies for adjusting its release are not well investigated. In this study, different amounts of original sucrose (20 μm) were mixed into the PLGA films. The sucrose contents were 5 %, 10 %, 30 %, 60 %, 100 %, and 200 % based on the weight of PLGA and dexamethasone, which is relatively low compared to the sucrose content typically used in tissue engineering.

Interestingly, the modulation of dexamethasone release was significantly influenced by varying the sucrose content in the PLGA films. As the sucrose content increased from 0 % to 30 %, there was a notable increase in drug release within the first 5 days, an extension of the quick release phase onset, and a prolongation of the overall release period (Fig. 2a). Specifically, on the first day, the burst release increased from 0.87 % to 1.22 % with the addition of 5 % sucrose, and further to 1.38 % and 1.44 % with the addition of 10 % and 30 % sucrose, respectively (Table 1). The initiation of the quick release phase was delayed progressively from day 10 (0 % sucrose) to day 30 (30 % sucrose). The time required to release more than 80 % of the drug extended from 24 days (0 % sucrose) to 27 days (5 % sucrose), 32 days (10 % sucrose), and 35 days (30 % sucrose). However, further increasing the sucrose content from 30 % to 200 % led to a higher initial drug release within the first 5 days, an earlier onset of the quick release phase, and a reduction in the overall release period (Fig. 2b). The burst release increased from 1.44 % (30 %

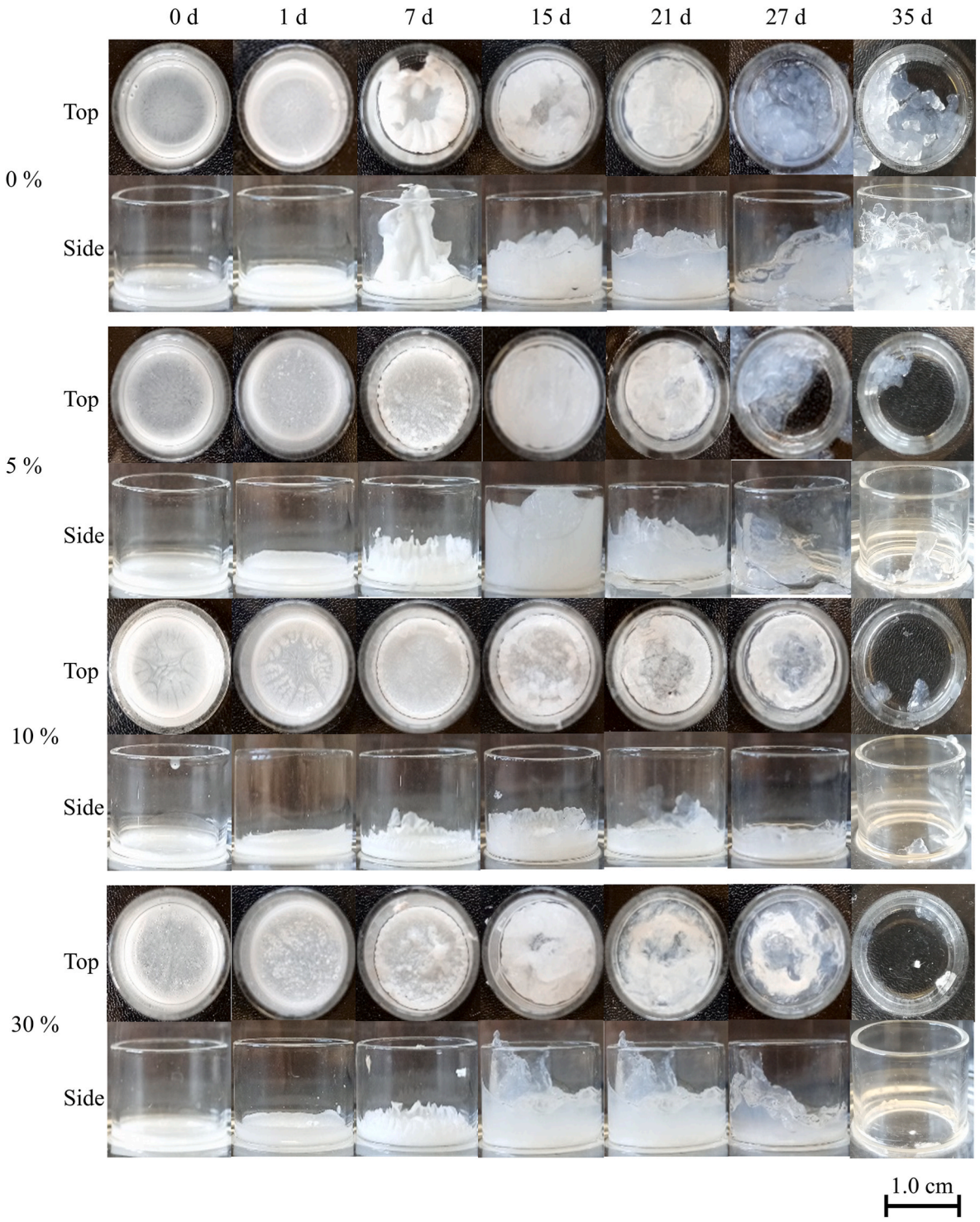


Fig. 5. The top and side views of dexamethasone PLGA films containing 0 %, 5 %, 10 % or 30 % original sucrose particles.

sucrose) to 3.42 % (200 % sucrose). The initiation of the quick release phase shifted from day 30 (30 % sucrose) to day 2 (200 % sucrose). The time to release more than 80 % of the drug decreased from 37 days (60 % sucrose) to 21 days (100 % sucrose) and just 7 days (200 % sucrose).

As described in the introduction section, the porous PLGA structure can be formed by a sugar particle leaching process. The porous structure just generated from the percolated porogen network in the PLAG matrix after the porogen leaching [35]. Leaching sucrose particles increases the surface area available for drug diffusion, leading to enhanced drug release during the initial release phase. Additionally, leaching introduces more release medium into the matrix, which helps to neutralize degraded acidic oligomers and monomers, thereby extending the PLGA degradation period. This delay in degradation postpones the quick release phase and reduces the overall drug release rate.

However, when excessive sucrose particles are leached, the resulting cavities become interconnected. In such cases, drug release is no longer primarily controlled by the degradation of the PLGA matrix. The interconnected structure significantly accelerates drug release due to the increased surface area for drug diffusion and the closer proximity of drug particles to the release medium.

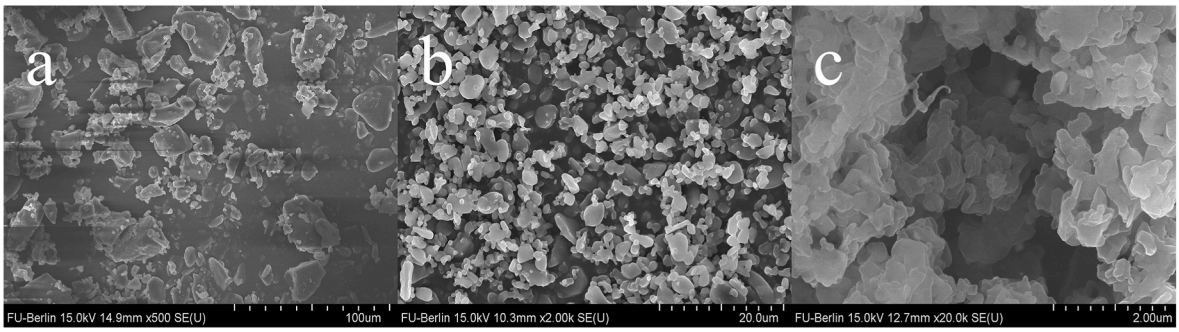


Fig. 6. SEM pictures of (a)original, (b) micronized and (c) nanosized sucrose.

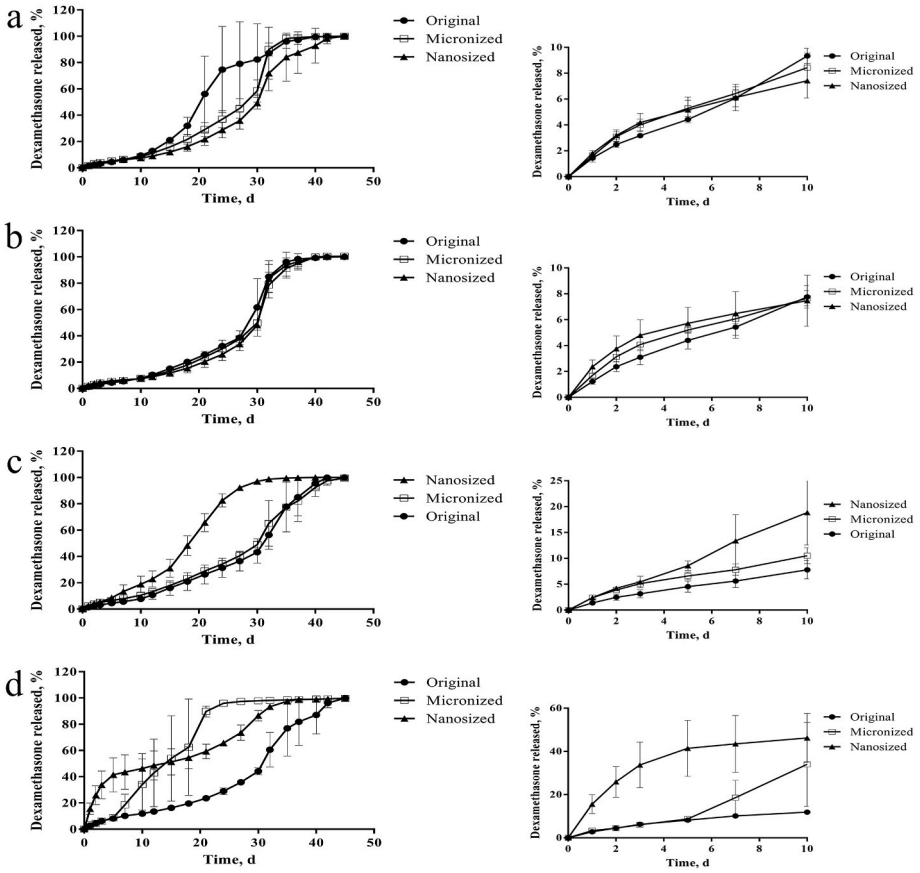


Fig. 7. *In vitro* drug release from dexamethasone PLGA films containing (a) 5 %, (b) 10 %, (c) 30 % and (d) 60 % sucrose of different particle sizes. Magnifications of the first 10 days are shown on the right.

To understand the effects of the leaching process on in vitro drug release and polymer degradation, wet mass changes and pH variations of the release medium were monitored. Additionally, direct observations of the films were conducted from top and side views to assess structural changes.

Incorporation of the sucrose dramatically increased the amount of water uptake by films at the initial stage. Within the first 5 days, the wet mass increased with higher sucrose content, and wet mass difference became biggest on day 5. The wet mass change was 153 %, 180 %, 199 %, and 261 % for films with 0 %, 5 %, 10 %, and 30 % sucrose, respectively (Fig. 3 a). This confirmed leaching of sucrose particles can increase the water uptake into the films. More water uptake promoted water exchange in and out PLGA matrix and then accelerated the drug diffuse to the water phase. This prevented the accumulation of acids within the film by providing these acids with an outlet. Accumulation of acids has been known to participate in the phenomenon of autocatalysis when the carboxylic acid end groups catalyze the cleavage of main-chain ester bonds. In this system, the leaching out of sucrose allowed the free monomers to leave the system. Enhanced water exchange was also demonstrated by pH change, where a lower pH with increased sucrose content indicated that more acidic degradation products were removed from the PLGA matrix and neutralized (Fig. 3 b).

After day 5, the trend in wet mass changes of PLGA films (0 %–30 % sucrose content) reversed, with films containing less sucrose exhibiting larger wet mass changes. At this stage, PLGA degraded faster with lower sucrose content, leading to an earlier swelling point. pH drops in the release buffer from days 7–15 were more pronounced with less sucrose, confirming increased PLGA degradation. This corresponded with the earlier quick release observed on days 10 and 12 for films with 0 % and 5 % sucrose, respectively. The most significant pH drops occurred on

Table 2
Burst, slow-release time and slow-release drug amount of dexamethasone PLGA films containing micronized and nanosized sucrose particles.

Formulation variations		Burst, %	Slow-release time, d	Slow-release amount, %
Sucrose	Content, %			
Micronized	5	1.60 ± 0.27	30	58.41 ± 8.44
	10	1.70 ± 0.04	30	49.86 ± 1.78
	30	2.40 ± 0.30	30	48.91 ± 4.50
	60	3.32 ± 0.12	5	8.70 ± 0.30
Nanosized	5	1.80 ± 0.22	30	49.20 ± 4.50
	10	2.36 ± 0.52	30	48.20 ± 3.84
	30	2.93 ± 0.38	–	96.71 ± 0.58
	60	15.58 ± 4.33	27	71.57 ± 4.91

days 24, 27, and 30 for films with 10 % sucrose, and after day 30 for films with 30 % sucrose This also correlated with their late quick release on day 27 and day 30 respectively.

When comparing the highest points of the wet mass change, the PLGA films with 0 % and 5 % sucrose are more significant than those with 10 % and 30 %. PLGA degraded faster by auto-catalysis at the beginning resulting in a larger volume of PLGA matrix filled with release buffer, which hindered the further degradation [36]. More sucrose resulted in a larger cavity surface, which not only slowed the PLGA degradation but also homogenized degradation. When the degradation reached the swelling point, there was not enough PLGA matrix to significantly increase its bulk volume by introducing 10 % or 30 % sucrose. When further increasing the sucrose content from 30 % to 100 %, the increased wet mass change resulted from PLGA films containing more sucrose (Fig. 4 a). The reversed wet mass change might be due to a weak PLGA structure. The degraded acids can easily be exchanged out and neutralized by introducing sufficient porosity at the beginning stage, but more porous PLGA matrixes were weak and they easily swelled bigger. The swelled matrix provided enough release buffer and further decreased PLGA degradation and erosion rate [37]. The pH changes were minor and similar with more than 60 % sucrose, confirming that the degradation was slow and uniform (Fig. 4 b).

PLGA films containing 0 % sucrose exhibited wrinkling by day 7, indicating the onset of significant swelling (Fig. 5). The onset of swelling was delayed with increasing sucrose content from 0 % to 30 %. Films with higher sucrose content required a longer time to become transparent, signifying slower PLGA degradation. Additionally, films containing 10 % and 30 % sucrose particles adhered to the container substrate throughout the degradation process, likely due to minimal swelling and uniform degradation. However, further increasing the sucrose content from 30 % to 200 % caused the PLGA films to wrinkle before day 5 and lose adherence to the container bottom, indicating that a more porous structure enhanced water exchange and resulted in a weaker matrix (Appendix Fig. 1). Beyond 60 % sucrose content, the morphology of the PLGA matrix remained consistent, confirming that high porosity and weak structure were established at these higher sucrose levels.

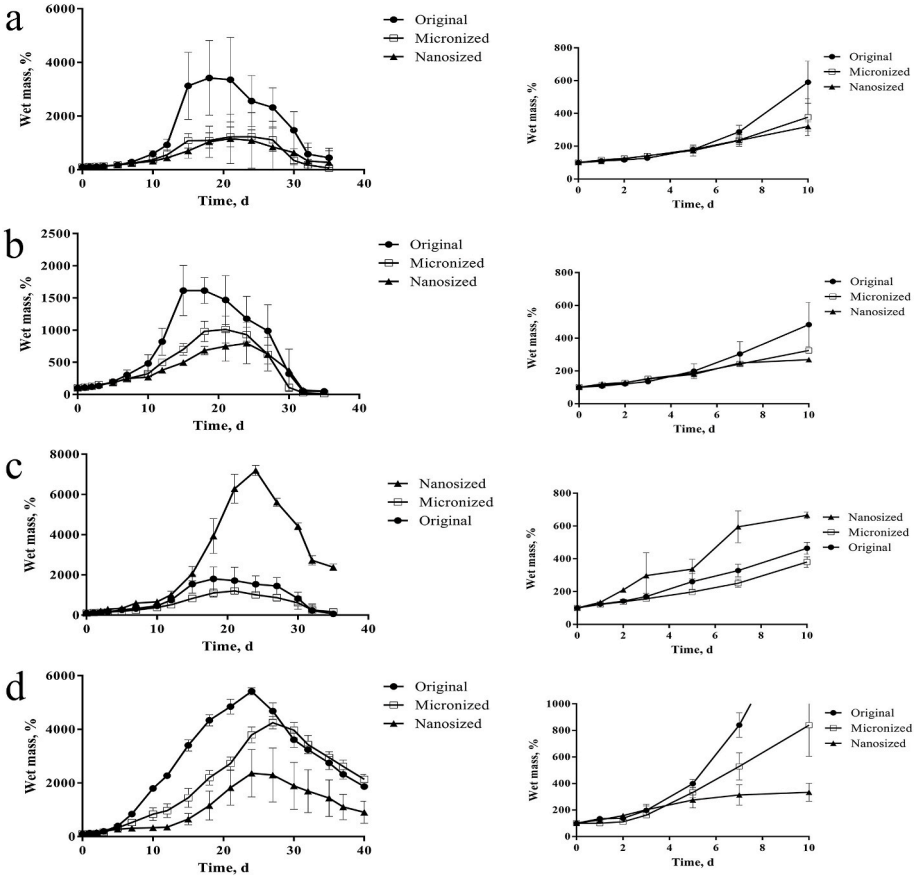


Fig. 8. Dynamic wet mass change of dexamethasone PLGA films containing (a) 5 %, (b) 10 %, (c) 30 % and (d) 60 % sucrose of different particle sizes. Magnifications of the first 10 days are shown on the right.

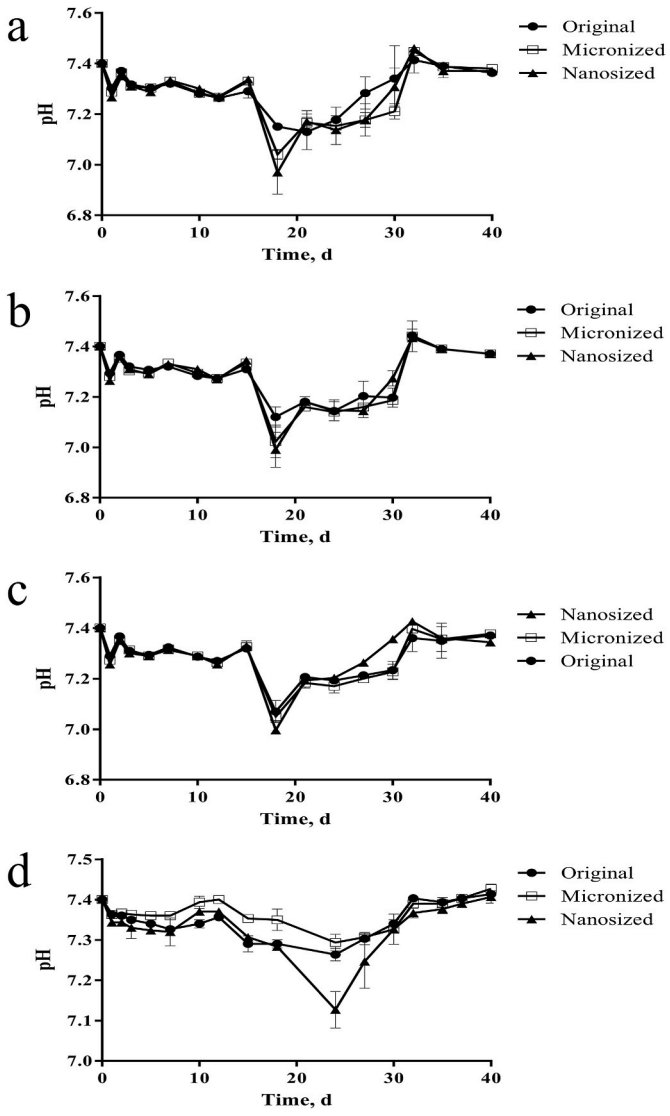


Fig. 9. Dynamic release medium pH change of dexamethasone PLGA films containing (a) 5 %, (b) 10 %, (c) 30 % and (d) 60 % sucrose of different particle sizes.

3.2. *Effect of sucrose particle size*

Sucrose particles as received have a diameter of approximately 20 μm. Air milling reduced the particle size to 2.8 μm. Further reduction in particle size proved challenging due to high static electric absorption. In previous studies, wet bead milling of sugars in pure dichloromethane successfully produced nanosized particles without the need for stabilizers [33,34]. SEM pictures confirmed the 2–3 μm micronized sucrose and 400 nm nanosized sucrose were prepared by the corresponding methods (Fig. 6), although fierce agglomeration of nanosized sucrose happened after solvent evaporation.

With the same amount of sucrose, smaller particles possess a larger overall surface area and a greater number of particles. Reducing the particle size from 20 to 2 μm can increase the surface area and particle number by 10^3 times, and further decreasing the particle size to 400 nm can increase the surface area and particle number by 50^3 times. This substantial change affects the film's properties. When incorporated into PLGA films via solvent evaporation, sucrose and dexamethasone particles become embedded in the PLGA matrix. Upon contact with water, the water penetrated the matrix and dissolved the highly water-soluble sucrose, a process that may take several days [19]. The dissolution of sucrose creates water-filled cavities where the sucrose particles were previously located. By varying the sucrose particle size, the number and size of these cavities can be significantly altered, impacting drug release and PLGA matrix degradation. Dexamethasone films containing 5 % sucrose with different particle sizes exhibited different in vitro release profiles, confirming that sucrose particle size indeed can modify the drug release characteristics. Smaller sucrose particles accelerated drug release during the first 7 days, then slowed and prolonged subsequent release (Fig. 7 a). This pattern can be explained by the fact that more dissolved sucrose particles create more cavities and a larger overall cavity surface area, allowing more dexamethasone to dissolve and diffuse out initially. Later, PLGA films with fewer cavities (from larger sucrose particles) could not adequately exchange acidic degradation products, leading to autocatalysis, which accelerated PLGA degradation and thus increased drug release.

Specifically, on the first day, the burst release was 1.22 % with 20 μm sucrose, increasing to 1.60 % and 1.80 % with 2 μm and 400 nm sucrose, respectively (Table 2). The onset of the quick release phase was delayed from day 12 with 20 μm sucrose to day 30 with 2 μm and 400 nm sucrose. The time to release more than 80 % of the drug extended from 27 days (20 μm sucrose) to 32 days (2 μm sucrose) and 35 days (400 nm sucrose) (Fig. 7a).

Although the initial 5-day wet mass changes were not easily distinguishable, the pH changes of the release buffer were more pronounced for smaller sucrose particles, indicating that more acidic degradation products were released through the additional cavities (Fig. 8a and 9a). This pH change indirectly explained the increased drug release during this period for smaller sucrose particles due to the increased diffusion surface area. After 7 days, the wet mass increased more for films with larger sucrose particles, correlating with the swelling of the PLGA matrix and rapid drug release [38,39]. Similar to films with less than 30 % original sucrose, films with larger sucrose particles degraded faster due to initial autocatalysis, resulting in a larger volume of the PLGA matrix being filled with water, which hindered further degradation. In contrast, small sucrose particles created a larger overall cavity surface, slowing and homogenizing PLGA degradation. At the degradation swelling point, there was not enough PLGA matrix to significantly increase the volume in films containing 5 % micronized and nanosized sucrose.

PLGA films containing 5 % original sucrose exhibited more pronounced morphology changes, with an earlier onset of swelling compared to micronized and nanosized sucrose (Fig. 10). Smaller sucrose particles required a longer time to achieve a transparent matrix, indicating slower PLGA degradation. These morphological changes were consistent with the drug release profiles described earlier.

Decreasing the sucrose particle size at 10 % sucrose content also resulted in increased initial drug release and slower release in the subsequent stages (Fig. 7b). Increasing the sucrose content from 5 % to 10 % amplified the differences in drug release among different sucrose sizes during the initial stage, but these differences diminished in the following period. This is attributed to the additional sucrose content further increasing the overall cavity surface area difference, leading to larger disparities in early release. However, increasing the sucrose content from 5 % to 10 % also provided PLGA films containing 20 μm sucrose with sufficient cavity surface for acid exchange, significantly extending PLGA degradation. It can be concluded that there exists a critical threshold of overall cavity surface area, beyond which PLGA films exhibit rapid swelling starting around day 30, indicating a similar PLGA degradation process.

Further increasing the sucrose content to 30 %, decreasing sucrose particle size increased the drug release at the beginning stage (Fig. 7 c). The burst of PLGA films containing 30 % nanosized sucrose is 2.9 %, while 2.4 % and 1.4 % bursts for 30 % micronized and original respectively. In the first 7 days, 30 % nanosized sucrose accelerated the drug release to 20 %, which was significantly higher than containing the same amount of micronized and original sucrose (drug releases were less than 10 %). 30 % nanosized sucrose had a larger number of particles in

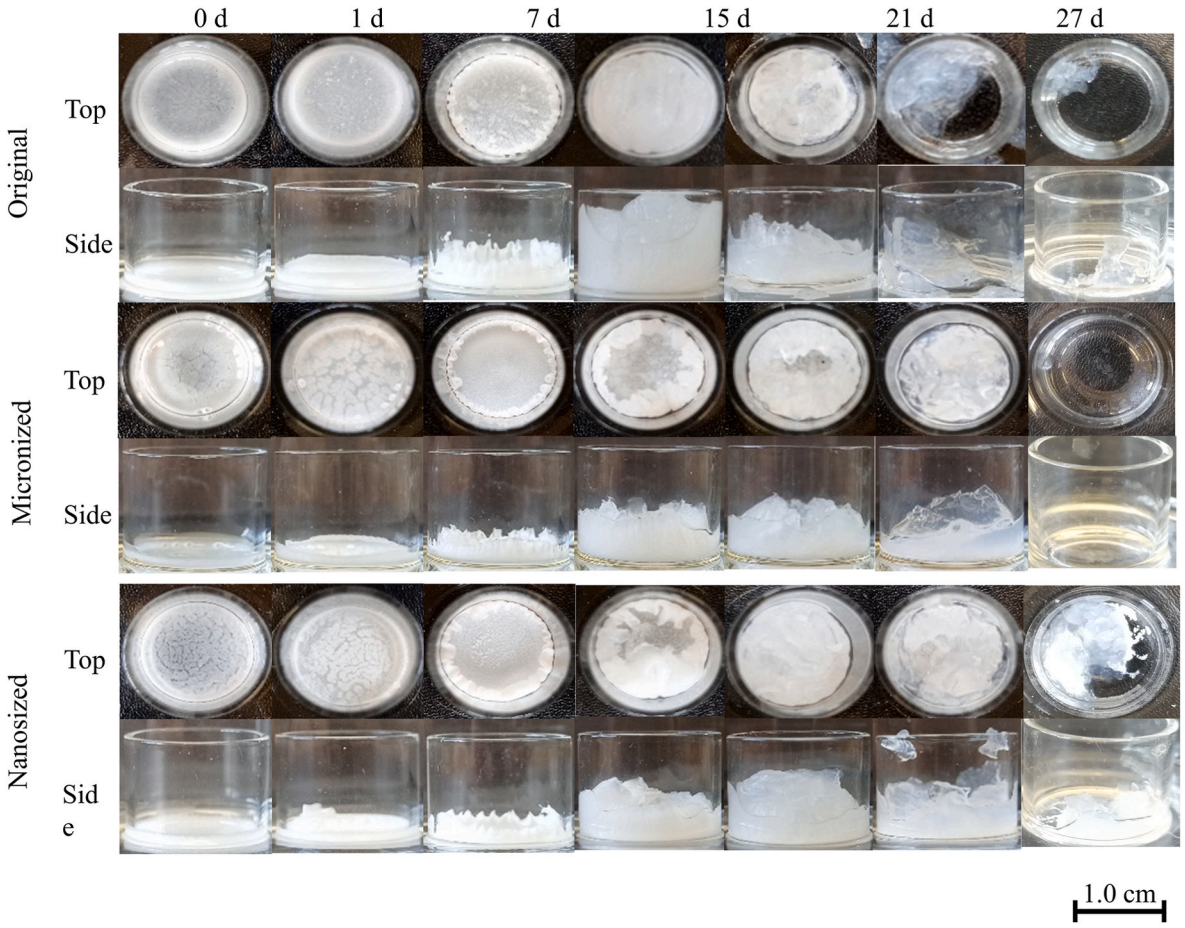


Fig. 10. The top and side views of dexamethasone PLGA films containing 5 % sucrose of different particle sizes.

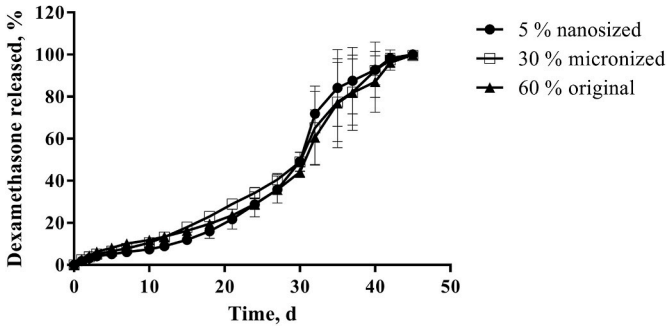


Fig. 11. *In vitro* drug release from dexamethasone PLGA films containing 5 % nanosized, 30 % micronized and 60 % original sucrose.

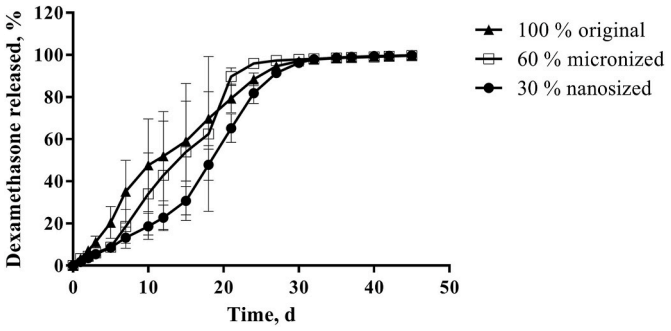


Fig. 12. *In vitro* drug release from dexamethasone PLGA films containing 30 % nanosized, 60 % micronized and 100 % original sucrose.

the matrix, which were more connective compared to bigger sucrose particles. The connected sucrose particles finally dissolved and left interconnected voids. These interconnected structures significantly increased the possibility of dexamethasone particle contact with release medium and also increased the surface area for the following drug diffusion. Upon further increasing the sucrose content to 30 %, decreasing the sucrose particle size amplified drug release during the initial stage (Fig. 7c). The burst release from PLGA films containing 30 % nanosized sucrose was 2.9 %, compared to 2.4 % and 1.4 % for films with 30 % micronized and original sucrose, respectively. Within the first 7 days, 30 % nanosized sucrose accelerated drug release to 20 %, significantly higher than films containing the same amount of micronized and original sucrose, where drug releases were less than 10 %. The higher number of interconnected particles in the matrix of 30 % nanosized sucrose facilitated the formation of interconnected voids upon dissolution, significantly increasing the likelihood of dexamethasone particle contact with the release medium and enhancing the surface area for subsequent drug diffusion.

Remarkably, 30 % nanosized sucrose resulted in quasi-linear drug release. Instead of further extending and prolonging the onset of quick release, this point was absent with 30 % nanosized sucrose, indicating proper channels formed by nanosized sucrose and uniform PLGA degradation. Over the initial 5 days, the wet mass change followed the order of 30 % nanosized >30 % micronized >30 % original, suggesting greater water infiltration into the PLGA films through increased cavities (Fig. 8c). The lower pH in the release medium with 30 % nanosized

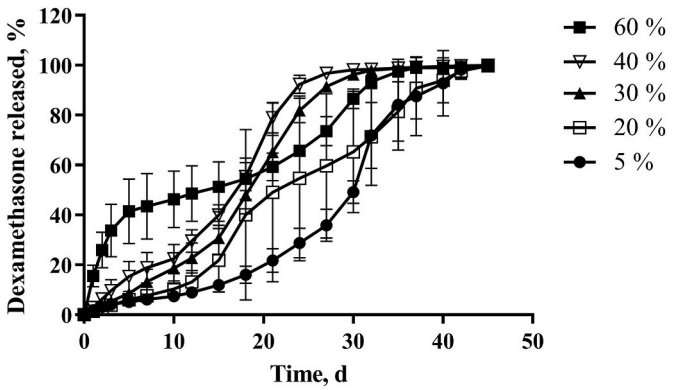


Fig. 13. *In vitro* drug release from dexamethasone PLGA films containing 5 %–60 % nanosized sucrose.

sucrose also confirmed enhanced removal of acids through more efficient water exchange during this period (Fig. 9c). Subsequently, the wet mass change followed the order of 30 % nanosized >30 % original ≈30 % micronized, indicating that 30 % nanosized sucrose expedited the swelling process. Typically, fewer cavities and less surface area result in insufficient acid exchange and PLGA autocatalytic degradation, leading to more pronounced wet mass changes. However, 30 % nanosized sucrose exhibited the opposite effect. Despite sufficient acid exchange, it induced the greatest wet mass change. This suggests that 30 % nanosized sucrose uniformly introduced water into the entire PLGA matrix, weakening its structure and facilitating homogenous porous structure formation, resulting in easier swelling that was not solely dependent on acid exchange. This highlights the emergence of another critical threshold: sufficient porosity weakens the PLGA matrix structure and triggers the early onset of swelling.

For 60 % sucrose, reducing the sucrose particle size further increased bursts from 2.8 % with original sucrose to 3.3 % with micronized sucrose and 15.6 % with nanosized sucrose (Fig. 7d). Within the initial 10 days, 60 % nanosized/micronized sucrose notably accelerated drug release to over 30 %, significantly higher than with original sucrose. The inclusion of 60 % micronized sucrose particles in the matrix enhanced connectivity similar to that observed with 30 % nanosized sucrose. This interconnected structure also substantially increased the possibility of dexamethasone particles coming into contact with the release medium and increased the surface area for subsequent drug diffusion.

3.3. Continous release

Having confirmed that both sucrose content and particle size can modulate drug release and PLGA degradation, it becomes intriguing to explore the combined effects of these factors. Due to the increased number of sucrose particles and overall surface area, 5 % nanosized sucrose can achieve a similar drug release adjustment effect as 30 % micronized and 60 % original sucrose (Fig. 11). Moreover, 20–30 % nanosized sucrose can achieve continuous drug release due to the enhanced connectivity of sucrose particles. This effect is comparable to that achieved by 60 % micronized and 100 % original sucrose (Fig. 12). To minimize the porogen content in PLGA films, nanosized sucrose emerges as the optimal choice for adjusting drug release, a novel finding introduced in this study.

Upon closer examination of drug release from PLGA films containing different amounts of nanosized sucrose, increasing nanosized sucrose content enhances drug release during the initial stage (Fig. 13). The burst releases from PLGA films containing 5 % and 60 % nanosized sucrose were 1.8 % and 15.6 %, respectively. Within the initial 7 days, 40 % and 60 % nanosized sucrose elevate drug release to 20 % and 50 %, respectively, significantly higher than films containing the same content of micronized and original sucrose (less than 10 %). With more than 20 % nanosized sucrose, a higher number of particles in the matrix enhance connectivity, leading to interconnected voids and channels upon dissolution. These structures significantly increase the likelihood of dexamethasone particle contact with the release medium and augment the surface area for subsequent drug diffusion. Intriguingly, 30 % and 40 % nanosized sucrose result in quasi-linear drug release, devoid of distinct slow release and quick release phases. This is attributed to proper channels formed by nanosized sucrose and homogeneous PLGA degradation. Although films containing 20 % nanosized sucrose still exhibit slow drug release in the initial 10 days, the subsequent quick release phase vanishes, as sucrose particles leached during the initial 10 days provide sufficient cavities for drug release in the subsequent stage. Further increasing the nanosized sucrose to 60 %, a traditional triphasic release was obtained. A quick release at first 5 days from the interconnected channels, and a slow release phase caused by slow drug diffusion. Adequate water exchange via water channels significantly delays PLGA degradation, hindering drug release during this period.

4. Conclusion

Micronized and nanosized sucrose particles were prepared and effectively used as fast-dissolving porogens within dexamethasone: PLGA films. Varying the particle size and content of sucrose particles resulted in good control of PLGA degradation and drug release profiles. Notably, PLGA films containing nanosized sucrose demonstrated the highest efficacy in modulating polymer degradation and drug release. These results could be potentially applied to other PLGA drug delivery systems such as microparticles or implants.

CRediT authorship contribution statement

Chenghao Zhang: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Roland Bodmeier:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

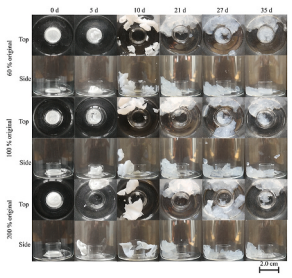
Data availability

Data will be made available on request.

Acknowledgments

The authors would like to thank China Scholarship Council for its financial support. Furthermore, we thank Ms. Catarina Bentes Mestre for the help with the study of dynamic changes in the film mass and morphology.

Appendix



Appendix Fig. 1. The top and side views of dexamethasone PLGA films incorporating 60 %, 100 % or 200 % original sucrose particles.

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