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Zero-order release of poorly water-soluble drug from polymeric films made via aqueous slurry casting

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Abstract

In spite of significant recent interest in polymeric films containing poorly water-soluble drugs, dissolution mechanism of thicker films has not been investigated. Consequently, release mechanisms of poorly water-soluble drugs from thicker hydroxypropyl methylcellulose (HPMC) films are investigated, including assessing thickness above which they exhibit zero-order drug release. Micronized, surface modified particles of griseofulvin, a model drug of BSC class II, were incorporated into aqueous slurry-cast films of different thicknesses (100, 500, 1000, 1500 and 2000 μm). Films 1000 μm and thicker were formed by either stacking two or more layers of ~ 500 μm , or forming a monolithic thick film. Compared to monolithic thick films, stacked films required simpler manufacturing process (easier casting, short drying time) and resulted in better critical quality attributes (appearance, uniformity of thickness and drug per unit area). Both the film forming approaches exhibited similar release profiles and followed the semi-empirical power law. As thickness increased from 100 μm to 2000 μm , the release mechanism changed from Fickian diffusion to zero-order release for films ≥ 1000 μm . The diffusional power law exponent, n , achieved value of 1, confirming zero-order release, whereas the percentage drug release varied linearly with sample surface area, and sample thickness due to fixed sample diameter. Thus, multi-layer hydrophilic polymer aqueous slurry-cast thick films containing poorly water-soluble drug particles provide a convenient dosage form capable of zero-order drug release with release time modulated through number of layers.

Graphical abstract

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Keywords

thick films; multiple-layer films; sustained release; poorly water-soluble drug; zero order release; hydrophilic film matrix

1. Introduction

Thin polymeric films offer a promising platform for oral delivery due to several distinct advantages over more traditional solid dosage forms, including larger available surface area, improved acceptance and compliance among pediatric, geriatric, and dysphagic patients, and the potential for bypassing the first-pass metabolism via buccal delivery (Borges et al., 2015; Krull et al., 2015a). Recent research on films have demonstrated that films formed using hydrophilic water-soluble polymers offer a versatile dosage form for incorporating various particles engineering techniques for poorly water-soluble drugs while achieving fast drug release (Beck et al., 2013; Bhakay et al., 2016; Krull et al., 2017; Krull et al., 2016b; Krull et al., 2015b; Sievens-Figueroa et al., 2012a; Zhang et al., 2018). The particle engineering techniques include wet stirred media milling, high pressure homogenization, liquid antisolvent precipitation, as well as simultaneous surface modification and micronization to reduce drug particle size. Collectively, these papers established thin films as a robust platform to embed relatively high drug loading (40 wt %) of poorly water-soluble drug nano or micro particles to achieve immediate drug release, excellent drug content distribution and uniformity, none or reduced need for surfactants for full retention of very large surface area of drug particles, and excellent mechanical properties. While those papers demonstrate remarkable capabilities for developing immediate release of poorly water-soluble drugs from thin films, they did not examine the potential for using thicker films for sustained or controlled release applications, while retaining the use of hydrophilic film forming polymers, that affords ease of manufacturing (Kim et al., 2009; Maderuelo et al., 2011).

More recently, thicker films made using multiple-layers of individual films have been developed for increasing drug loading or achieving specific properties such as desired drug release profiles or mucoadhesion (Preis et al., 2014; Visser et al., 2017). There are other examples of bi-laminated or multi-layer films comprising at least one layer consisting of hydrophobic polymer resulting in longer sustained-release, although several studies claimed that hydrophobic polymer mainly promoted drug release through diffusion after an initial burst release (Perugini et al., 2003; Remuñán-López et al., 1998; Sun et al., 2016). Most

such films contained relatively low drug weight percentage, and were not designed for oral applications. Thus, none of the previous investigations involve thicker films for sustained release containing poorly water-soluble drugs made with water-soluble matrix forming polymers, which have inherent advantages such as being simpler to formulate, inexpensive and easy to produce, and having good in-vitro-in-vivo correlations (Maderuelo et al., 2011). Consequently, this paper examines capabilities of thicker films (500 μm) formed with water-soluble polymers, for potential use in sustained release dosage forms, along with the investigation of the effect of film thickness on the release mechanism of poorly water-soluble drugs. Although that is the main purpose of this paper, from perspective of applicability for oral delivery, this platform is amenable to forming disk-like tablets that can be ingested orally, having certain advantages over traditional tablets. In addition, this approach could be further developed towards delivering different APIs in different layers. Perhaps a more immediate application of such thick films may be in buccal delivery systems (Meher et al., 2013; Ramineni et al., 2014; Remuñán-López et al., 1998)

Sustained release dosage forms prepared with various technologies have gained widespread importance in recent years with the aim to adapt the release rate to a particular therapeutic target (Fukuda et al., 2006; Khaled et al., 2014). A well-designed sustained release system would not have the burst effect that is typically associated with the conventional formulations (Colombo et al., 1992). There are several important factors that impact performance of sustained release dosage forms, such as the matrix that may be hydrophilic, hydrophobic, or combination, dosage geometry, drug solubility in water, and the form of drug in the final dosage including the drug particle size (Ford et al., 1987; Maderuelo et al., 2011; Siepmann et al., 2000). Majority of research has focused on the first two factors, i.e., the nature of the matrix, including the effect of excipient particle size, and dosage geometry. Hydrophilic matrices are most prevalent due to the advantages mentioned above, and are capable of providing near zero-order release based on the molecular weight (MW), formulation and geometry (Kim and Fassihi, 1997; Siepmann et al., 2000), with hydroxypropyl methylcellulose (HPMC) being the one most widely employed (Maderuelo et al., 2011). The primary mechanism of drug release from hydrophilic matrices involves polymer swelling on contact with the aqueous medium and forming a gel layer and the drug releasing by dissolution, diffusion and/or erosion; hence facilitating zero order release (Colombo, 1993; Ishikawa et al., 2000; Siepmann and Peppas, 2001; Tiwari and Rajabi-Siahboomi, 2008). In contrast, although hydrophobic matrices may provide longer drug release times, they do not involve polymer swelling and gel layer formation (Kim et al., 2009; Perugini et al., 2003). In terms of geometry, the drug release is mainly one-dimensional for thin films with aspect ratios (diameter to thickness) > 50 , whereas, for the aspect ratio between 0.2 and 50, it is three-dimensional (Ritger and Peppas, 1987a). Another model accounted for the initial delay or lag time in drug release and showed that for dosage aspect ratios leading to three-dimensional release, there is a linear relationship between percentage drug release rate and dosage surface area (Ford et al., 1991). The latter work also showed that poorly water-soluble drugs are more likely to achieve near zero-order release. Notable examples of tablet formed using HPMC include, Geomatrix[®], which was initially designed to achieve time-dependent control release system by coating different modulating barriers to the active core (Conte et al., 1993). Dome Matrix[®] offers another programmable

technology that allows for snapping or clicking two or more elementary release modules for time and space controlled delivery (Colombo et al., 2009).

Considering that most of the recent work in thin films employing slurry casting of poorly water-soluble drugs utilizes HPMC as a film forming polymer and that the film format allows for easily varying the aspect ratios in a very wide range, it may be worthwhile exploring this format to examine drug release mechanism from thicker films. As an example, recent work examined films with the thickness ranging from 26.2 μm to 123.2 μm (Krull et al., 2016a), representing aspect ratios from about 363 to 77 (sample diameter of 0.95 cm), with pullulan used as the film matrix. With thicker films and slightly larger sample size, it would be rather easy to vary the aspect ratio from above 100 down to about 6, and examine the impact of aspect ratio and the surface area on drug release rate. Various advantages of the film format and predominant use of HPMC as the film former suggest further investigation towards the development of sustained release dosage forms, in particular for poorly water-soluble drugs in thicker films formed via slurry casting. Consequently, this paper examines issues involved with forming thick films containing poorly water-soluble drugs and examining the drug release as a function of thickness and surface area.

Overall objective of this work is to obtain an insight into the release mechanism of griseofulvin, a model poorly water-soluble drug, from water-soluble polymeric films of different thicknesses (100-2000 μm), as well as to explore the possibility of modulating drug release based on thick films (thickness > 500 μm). In order to retain continuity with previous work, the same grade of HPMC was used, and for the sake of simplicity, drug particle size in micro range instead of nano-range was employed (Zhang et al., 2018). To form thick films, two approaches were pursued, namely, multiple layered films, also called stacked films, that has been recently used by different groups as well as casting a single thick film in a mold, called monolithic thick film. Resulting films were examined for their properties such as the drug content uniformity, moisture content, and drug release profiles. Finally, the main hypothesis is that thick films containing poorly water-soluble drug particles formed using hydrophilic polymer as the film matrix and formed via slurry casting may provide zero-order drug release profiles allowing for modulating release time by film thickness.

2. Materials and methods

2.1 Materials

Griseofulvin (GF; Letco Medical, Decatur, AL, USA) was selected as a model BCS class II drug. Pharmaceutical grade amorphous hydrophilic silica (M5P, Cabot Corporation, MA, USA) with a primary particle size of 16 nm was used as the coating material for milled coated GF (MC-GF) particles. Low molecular weight hydroxypropyl methylcellulose (HPMC; Methocel E15 Premium LV, Mw~ 40,000, The Dow Chemical Company, Midland, MI, USA) and glycerin (Sigma-Aldrich, Saint Louis, MO, USA) were used as the film former and the film plasticizer, respectively. Sodium dodecyl sulfate (SDS) (Sigma-Aldrich, Saint Louis, MO, USA) was used as the surfactant in the dissolution media. All other materials were used as-received.

2.2 Preparation of milled coated GF particles

Two-step dry milling of coated powders were prepared following previous works and utilized pre-mixing using Laboratory Resonant Acoustic Mixer (LabRAM, Resodyn Acoustic Mixers, Inc., Butte, MT, USA) followed by continuous milling in a fluid energy milling (FEM; qualification model, Sturtevant Inc., Hanover, MA, USA) (Davé et al., 2011; Han et al., 2011). For pre-mixing in LabRAM, as-received GF powder (97 g) and M5P silica (3 g) were added to a plastic cylindrical jar, that was shaken at a frequency of 61 Hz with an acceleration of 70 G for 5 min to ensure that the M5P silica was well distributed among as-received GF particles. Simultaneous micronization and surface modification of GF particles was carried out using the FEM. Powder feeding rate was controlled by a volumetric feeder (Model 102M, Schenck Accurate, WI, USA) at 1 g/min. A constant feeding pressure (FP) of 65 psi and constant grinding pressure (GP) of 60 psi were maintained. The milled and coated GF particles were referred as MC-GF.

2.3 Preparation of microparticle-laden films

The slurry casting method of film containing nano/micro drug particles has been established previously and follows five steps (Davé et al., 2014; Sievens-Figueroa et al., 2012a): 1. preparation of film forming aqueous polymer solution that includes plasticizer, 2. mixing with drug powders to prepare film precursor suspension (polymer, plasticizer and drug), 3. defoaming the precursor solution, 4. casting of films and 5. film drying. All of these steps are also relevant for thicker films and special considerations are discussed below as pertinent.

2.3.1 Preparation of polymer solution and film precursor—Polymer solution was prepared by adding corresponding amounts of glycerin (5% wt) and HPMC-E15LV (18% wt) in the 78 ml deionized water at 30–40 °C and 80–90 °C, respectively. Sufficient amount of time was allowed for the polymer to dissolve completely without any clumps, and the polymer solution was cooled down to room temperature while being stirred continuously. The polymer solution was then mixed with MC-GF particles in a planetary mixer, called the Thinky mixer (ARE-310, THINKY, CA, USA) for 10 min at 2100 rpm, followed by 3 min of deaeration at 2200rpm, to form a homogeneous film precursor. To further ensure that no bubbles were present after deaeration, the precursor suspension was left 8–12 h at room temperature before casting.

2.3.2 Fabrications of stacked film and monolithic thick film—A schematic overview of the fabrications of stacked film and monolithic thick film is shown in Fig. 1. Two approaches were investigated.

Preparation of stacked film (Fig. 1, Method 1): The film precursor was cast on a plastic substrate (Scotchpak™ 9744, 3M, MN, USA) using a doctor blade (3700, Elcometer, MI, USA) at a casting thickness of 1.6–1.7 mm leading to a 500–550 µm dry film. The drying was performed in the tape casting equipment (TC-71LC, HED International, NJ, USA) capable of providing simultaneous conductive and convective drying. The dry film was trimmed into dimensions 8 cm × 15 cm pieces. Two, three and four layers of these films were then pasted together using 2% HPMC solution as glue, resulting in about 1000 µm

(Stack-A), 1500 μm (Stack-B), and 2000 μm (Stack-C) stacked films respectively. Prepared films were stored at ambient temperature until further analyses. The Method 1 of preparing multi-layer films is comparable to the most successful of four approaches presented by Preis et al., which was pasting a second film onto the base film (Preis et al., 2014).

Preparation of a monolithic thick film (Fig. 1, Method 2): The film precursor was dispensed into different height molds (3–6 mm) on the plastic substrate (Scotchpak™ 9744, 3M, MN, USA) using a cookie press injector (Kuhn Rikon, Switzerland). The wet film was dried in a convection oven (Stabil Therm, Blue M, IL, USA) at 50 °C for 6–10 h depending on casting film thickness. The 3 mm, 4.5 mm, and 6 mm molds resulted in about 1000 μm (Mono-A), 1500 μm (Mono-B), and 2000 μm (Mono-C) monolithic thick films respectively.

2.4 Characterization methods

2.4.1 Digital optical microscopy—Digital optical microscope (Axio Lab.A1, Carl Zeiss, Germany) was used to evaluate the cross-section of stacked films. Two-layer (Stack-A), three-layer (Stack-B), and four-layer (Stack-C) stacked films that were successfully prepared by the method described above were imaged at 5 $\times$ magnification. In the test, the samples were punched out from stacked films and then lightly smoothed using a sand paper, making the cross section flat enough to be focused.

2.4.2 Determination of drug content and uniformity in stacked films and monolithic thick films—The film assay of prepared films was performed as per previously reported method (Susarla et al., 2013). Ten circular samples of $\sim 1.26\text{ cm}^2$ were punched out and dissolved in 500 ml of 5.4 mg/ml SDS solution with continuous stirring for a minimum of 3 h. A Thermo Scientific Evolution 300 UV-vi spectrophotometer (Thermo Fisher Scientific Inc., MA, USA) was used to measure the UV absorbance of each sample using the appropriate wavelength of maximum absorbance for each drug (291 nm for GF), and the concentration was calculated using the established calibration curve. The thickness of each sample was measured using a digital micrometer (Mitutoyo Corporation, Japan) with an accuracy of 0.001 mm (1 μm) to obtain a reliable estimate of the film thickness. The average and standard relative derivation (RSD) values of film thickness, drug dose per unit area (mg/cm^2), and weight percentage of drug in the film (wt% GF) of ten samples were recorded.

2.4.3 Drug particles size after re-dispersion from films—Particle size distribution of surface modified micronized GF powders was measured in dry state via laser diffraction technique (Rodos/Helos system, Sympatec, NJ, USA) where the d_{10} , d_{50} , and the d_{90} size statistics are reported at 0.5 bar dispersion pressure.

The size distribution of re-dispersed drug particles from dry films was assessed by a laser diffraction particle size analyzer (Coulter LS 13320, Beckman Coulter, FL, USA). To assess the redispersibility of drug particles, a 500 μm thick film sample was obtained using a circular punch of area $\sim 0.72\text{ cm}^2$ and was mixed with 10–15 ml deionized water by a digital vortex mixer (Fisher Scientific, USA) at 1500 rpm for 20–30 min. The re-dispersion procedure follows previously reported methodology except the mixing time is higher due to the use of thicker film, and is intended to provide an indication of the extent of drug particle

agglomeration during the processing including film drying (Bhakay et al., 2013; Krull et al., 2015b).

2.4.4 Thermo-gravimetric analysis (TGA)—Thermo-gravimetric analysis (TGA) of monolithic and stacked films at 500–2000 μm was performed using a TGA/DSC1/SF STAR^e system (Mettler Toledo, Inc., OH, USA). A film sample weighing about 8–10 mg was cut from the thick film and crushed into small pieces and was placed in a ceramic crucible. The ceramic crucible loaded with film sample was heated under a nitrogen atmosphere from 25 °C to 150 °C at a constant rate of 10 °C/min, maintained at 150 °C for 15 min, heated to 250 °C at a rate of 10 °C/min, and finally cooled back to 25 °C at a rate of -10 °C/min (Krull et al., 2015b).

2.4.5 X-ray diffraction (XRD)—X-ray diffraction was performed to determine the crystallinity of pure GF, dry MC-GF particles, and MC-GF particles embedded in the film. Diffraction patterns were acquired for analysis of the amorphous/crystalline behavior of these samples using Philips X'Pert (Almelo, Netherlands), scanning a 2θ angle in the range of 5.0–50.0° (0.01° step).

2.4.6 Drug release—Dissolution profiles of monolithic thick films and stacked films (500–2000 μm) containing MC-GF were obtained using an automated flow-through cell dissolution apparatus (USP-IV; Sotax, Nordring, Switzerland) equipped with six flow-through cells ($\varnothing$ 22.6 mm) and 0.2 μm HT Tuffryn® filters (Pall Corporation, NY, USA). A ruby ball (5 mm diameter) and 3 g of glass beads of 1 mm diameter were placed at the bottom of the cone to ensure uniform flow of dissolution media entering the cell. Punched circular samples from each film with an area of $\sim 1.27\text{ cm}^2$ were horizontally positioned in the cells with 2 g of glass beads on the top. The glass beads prevented the film from floating in flowing media (Krull et al., 2015b; Sievens-Figueroa et al., 2012b). The temperature of cells was maintained at $37 \pm 0.5\text{ }^{\circ}\text{C}$ and 900 ml dissolution media (5.4 mg/ml SDS aqueous solution) was circulated at a flow rate of 16 ml/min. The dissolved percentage of drug as a function of time for a mean of six samples was calculated for each film sample.

2.4.7 Analysis of drug release—The drug release profiles were analyzed using a mathematical model capable of describing the solute release kinetics and the mechanism from polymeric hydrophilic matrices. Eq. (1) is a modified Korsmeyer-Peppas power law equation with the lag time used for identifying drug release mechanism for up to 90% of drug released (Ford et al., 1991; Rinaki et al., 2003; Ritger and Peppas, 1987a). It is noted that although the power law and power law equation with the lag time were used for identifying drug release mechanism up to 60% of release data in Ford et al., 1991; Rinaki et al., 2003 has validated that the power law can be also used for >60% of drug release.

$$\frac{M_t}{M_{\infty}} = k(t - t_{lag})^n \quad (1)$$

Here M_t/M_∞ is the fraction of drug released, k is the kinetic constant characteristic of the structure and geometry of the dosage shape, and n is the diffusional exponent for drug release indicating the release mechanism.

The difference and similarity tests were used for assessing the relevance of the differences between release curves. The dissolution profiles of stacked film and monolithic thick film at the same thickness were compared using difference and similarity factors, f_1 and f_2 using Eqs. (2) and (3) (Costa et al., 2001). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percentage of dissolution between two curves (Albertini et al., 2014).

$$f_1 = \frac{\sum_{i=1}^n |R_i - T_i|}{\sum_{i=1}^n R_i} \quad (2)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \right\} \times 100 \quad (3)$$

Here n is the number of sampling points, R_i and T_i are the percentage drug dissolved from the monolithic thick film or stacked film at each time point t . To confirm two curves are similar, f_1 values close to 0 and f_2 values close to 100 could verify the similarity of two dissolution curves according to FDA guideline. Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure the equivalence of two dissolution curves indicating an average difference of no more than 10% at the sample time point (Food and Drug Administration, 1997). For the f_1 and f_2 calculations, sampling points corresponding to 50%, 75% and 90% of drug released were considered.

3. Results and discussion

3.1 Fabrication of stacked films and monolithic thick films

For the preparation of monolithic thick films, there are several difficulties in the preparation of microparticle-laden films as compared to standard thin films of about 100 microns or less. Film precursor preparation requires balancing the solid content and wet film thickness necessary to achieve final dry film thickness. On one hand, low solid content and hence higher water amounts help in mixing and casting but lead to cracks or ripples in the drying process. On the other hand, high solid content leads to mixing difficulties due to its high viscosity, which further increases after adding dry drug powder, and also leads to casting issues. To help reduce severity due to such issues, the polymer solution formulation for all cases was selected to be 18% HPMC-E15 LV and 5% Glycerin, which afforded loading of up to 50% micronized drug powders in dried films. However, about 20% drug loading was used to continue the study. Another manufacturing issue about the monolithic thick films was the need to cast directly into a square mold (Fig. 1, method 2) using a cookie press injector instead of conventional casting such as using a doctor blade. As a side note, such an

approach may be amenable in automated dispensing of film precursor, where individual tray may become part of the final packaging. Due to the large initial wet film thickness of 3–6 mm, drying had to be done in a convection oven at 50 °C for very long time ranging from 6 h to 10 h.

In contrast, manufacturing individual layers used for preparing two or more layers of films was found to be easier, supporting use of this approach by other groups. Using the same formulation, which consisted of approximately the same polymer, plasticizer and drug combination (18% HPMC-E15 LV, 5% Glycerin, 17–20% GF), individual layers were formed. That led to about the same composition for the stacked films as was the case for monolithic thick films. Drying time of a typical single layer film, having wet thickness of 1.6–1.7 mm, was 2 h in the tape casting equipment, employing conduction and convection heating at 50 °C. Stacked films were prepared by layering several dried films (500–550 μm), glued together as described before. Preparing a single thin layer may be easily done in a continuous casting-drying with cycle time of about 2 hours and may allow for subsequent processing to form multi-layer films. Regardless, the purpose of this work is to examine both the approaches to provide a relative assessment.

To understand the structure of stacked films, the film cross-section was examined using an optical digital microscope. As shown in Fig. 2 (a)–(c), the layers appear to be well-attached in a homogeneous manner for 2, 3, and 4 layer stacked films. Thick films exhibited fairly homogenous structure without visible bubbles or irregularities. Surprisingly, the interfaces between the layers were barely visible, and layers appeared even. Moreover, the stacked films were firmly glued, and the configuration was maintained without individual layers separating until the end of drug release in an in vitro dissolution testing.

3.2 Content uniformity of stacked films and monolithic thick films

As in any pharmaceutical dosage form, consistency in dosing is critical, and films are no exception (Krull et al., 2017). Recent works show that thin films containing uniformly dispersed poorly water-soluble drug nanoparticles and microparticles have very low relative standard deviation (RSD) of drug content uniformity (CU) (Krull et al., 2015b; Zhang et al., 2018). In the current work, since the film thickness increases, the RSD should improve, except that the drug particle size in current work is much higher than in previous work (Krull et al., 2015b). In addition, the aforementioned casting and drying difficulties for thick films may pose challenges in ascertaining the thickness uniformity, which directly affects drug dosage per unit area (Nair et al., 2013), and hence the accuracy of drug dose. Consequently, CU tests were performed on stacked films (1000–2000 μm) as well as corresponding monolithic thick films (500–2000 μm). The results are presented in Table 1, which includes average and standard relative derivation (RSD) of film thickness, drug dose per unit area and weight percentage of drug in the film. It should be noted that the sample size used here (1.26 cm^2) is smaller than the conventional film dosage (4–6 cm^2), or other dosage forms such as patches, and was selected for the purpose of better discernment of the differences between various cases. First, it is observed from Table 1 that monolithic thick film and stacked film have similar thickness values, suggesting that layered approach can be conveniently used to prepare thicker films of desired thickness. Next, the expected trend in

dose per unit area as a function of thickness is evident; increasing film thickness from 1052 μm to 1982 μm for monolithic thick films, dose per unit area increased from 25.0 mg/cm^2 to 42.2 mg/cm^2 . Likewise, for stacked films, it increased from 24.0 mg/cm^2 to 43.2 mg/cm^2 as film thickness increased from 1068 μm to 1983 μm . Moreover, drug weight percentage of stacked films and monolithic thick films remained similar, in the range 17–20.5%.

Most important outcome in Table 1 is the film sample RSD values. First, thickness RSD values are relatively high, which also impacts the RSD values for drug dose per unit area. Monolithic thick films have slightly higher thickness RSD values than stacked films, which was expected due to manufacturing difficulties and may be attributed to ripples on the surface and other thickness variations after drying. That leads to higher RSD values of drug dose per unit area for stacked films. Fortunately, excellent total drug weight percentage RSD values (<6%) are observed in both monolithic and stacked films. This may be attributed to the good dispersion and mixing of drug microparticles in the film precursors due to the surface modification of GF dry powder leading to reduced agglomeration as well as the higher shear rate provided by the Thinky mixer. As compared to previous work for thin films (Krull et al., 2015b; Zhang et al., 2018), the RSD results obtained for thick films are encouraging and suggest more attention should be paid in future to improve the uniformity of film thickness, which is a critical factor that can impact the drug dose per unit area. In that respect, stacked films containing well-manufactured individual thinner films may be more preferred for achieving better RSD values.

3.3 Drug particle size after milling and re-dispersion from films

Physically stable MC-GF particles were produced using hydrophilic silica as the coating material. In Fig. 3, particle sizes (d_{10} , d_{50} , and d_{90}) of AR-GF powders, MC-GF powders prior to mixing with polymer solutions, and MC-GF powder re-dispersed from thick film are reported. The particle size of AR-GF was reduced from a d_{50} of 11.46 μm down to d_{50} of 7.33 μm (MC-GF) after milling. As was discussed in previous work (Krull et al., 2017; Krull et al., 2015b; Sievens-Figueroa et al., 2012a), retaining particle size of poorly water-soluble drug throughout the film formation process including drying and upon re-dispersion into water is critical to maintaining the enhanced dissolution of the drug. In particular, the ability to recover GF nanoparticles from films made from a high concentration of HPMC-E15LV solution (19% wt) has been evaluated by Krull et al. (Krull et al., 2017). Accordingly, all films were subjected to re-dispersion tests as per previous protocols (Krull et al., 2017; Krull et al., 2015b; Sievens-Figueroa et al., 2012a) in deionized water, and the resulting particle sizes were compared with that of the original MC-GF dry powders. Notwithstanding some agglomeration observed in the d_{90} size, the d_{10} and d_{50} of MC-GF dry powder (2.73 μm and 7.33 μm , respectively) were mostly retained (2.34 μm and 7.84 μm , respectively) after the re-dispersion from thick films, demonstrating MC-GF particles are stable and well-dispersed within the film. It is noted that the extent of agglomeration as indicated by the d_{90} size may appear large, i.e., d_{90} of ~25 microns after redispersion as compared to ~15 microns before adding to film precursor. However, as compared to previous papers this extent of enlargement in d_{90} is considered very low. For example, (Krull et al., 2017) showed their particle sizes d_{90} increased from about 200 nm before inclusion in the film precursor to about 1 μm , 10 μm , and 100 μm after re-dispersed from different molecular weight HPMC

polymer strip films. The extent of agglomeration upon re-dispersion in the present work may be attributed to the use of high HPMC-E15LV concentration. The impact of this on *in vitro* dissolution, if any, is presented in a later section.

3.4 Thermo-gravimetric analysis (TGA)

Since the film thickness in all cases is much larger than 200 μm , the drying may not be as efficient and complete as in thinner films, hence the moisture content may be high, leading to quality issues. High moisture content can lead to tacky films and facilitate the growth of microorganisms (Visser et al., 2015). Consequently, TGA analysis was performed and the moisture content was calculated accounting for free or molecularly bound water content in films. As shown in Fig. 4, films exhibited a weight loss between 1.2% to 1.8% for monolithic films, and between 1.2% to 2.2% for stacked films at up to 100°C. These results are comparable to those reported in thin films and suggest that the drying process is effective in keeping the moisture content under 3% even for thick films (>500 μm) (Krull et al., 2017). Low moisture content is also expected to result in a relatively flexible film with increased long-term stability (Dixit and Puthli, 2009; Krull et al., 2016b).

3.5 Drug crystallinity

XRD analysis was performed to study the crystal structure of drug particles as well as the drug incorporated in film. Fig. 5 shows the XRD patterns of pure GF, dry powder MC-GF, placebo film and film with MC-GF. Pure GF and MC-GF presented sharp, high intensity peaks at the main diffraction angles (2θ) 10.0–30.0°, indicating the crystalline form of the GF. Placebo film did not show any peak due to amorphous nature of HPMC-E15LV. For the films loaded with MC-GF particles, although the peaks (see arrows) were subdued due to the presence of HPMC, they were distinct and are attributed to GF, confirming that HPMC-E15LV did not affect the drug crystalline structure. The results demonstrate that the MC-GF particles in the film have crystalline structure that is preserved during the milling, mixing and drying processes.

3.6 Drug release analysis of monolithic thick and stacked films

The drug release profiles of stacked films as well as monolithic thick films with four different thicknesses were evaluated to understand the impact of film thickness and film forming method on the dissolution behavior as well as the drug release mechanism.

In Figs. 6 (a) and (b), the mean percentage cumulative release against time of 500 μm films, as well as Stack-A, Stack-B, Stack-C and Mono-A, Mono-B, Mono-C films are shown. The 500 μm film showed the fastest percentage release rate, followed by Stack-A, Stack-B, and Stack-C films (Fig. 6 (a)). The same trend was observed in the monolithic thick films (Fig. 6 (b)). More importantly, both stacked films and monolithic thick films demonstrated the sustained release of GF drug that ranged from 240 min to 500 min which is comparable to commercially available Geomatrix® with barrier layers (Conte et al., 1993) and Dome Matrix® (5% drug loading) (Casas et al., 2010) tablets formulated with high molecular weight HPMC, having release time of 400–700 min and 200–800 min, respectively. In addition, appreciable lag time was observed for all films, although difficult to visualize in Figs. 6 (a)–(b), with no drug released from film matrices for about 7 min to about 22 min

(shown for better visualization in supplementary material, Fig. S1). Such trends are similar to previously reported results for tablets, and the delayed drug release might be attributed to the polymer swelling process as well as the low diffusion rate of GF particles in the eroding layer of HPMC matrix (Ford et al., 1987). Interestingly, the lag time has an almost linear relationship with film thickness (also plotted as a function of initial dosage surface area, to be further discussed later) for the thick films (Fig. S1).

Since the relative amounts of drug released are also important (Siepmann et al., 2000), those trends are shown in Figs. 6 (c) and (d). For the purpose of better visualization of GF release from monolithic thick films and stacked films at the same thickness, the results from Figs. 6 (c) and (d) are plotted as Fig. S2 in supplementary material along with the photographs of respective film samples. The $t_{50\%}$, $t_{75\%}$, $t_{90\%}$ dissolution times from monolithic and stacked films (Fig. S2 and Figs. 6(a) and 6(b)) were compared based on the similarity and difference factors (Table 2). For the dissolution profiles to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100 (Food and Drug Administration, 1997). Generally, f_1 values up to 15 and f_2 values greater than 50 should ensure equivalence of the dissolution curves, indicating an average difference of no more than 10% at a given sample time point (Food and Drug Administration, 1997). As the dissolution time evolved, f_1 tended to be closer to 0 and f_2 stayed close enough to 100; only deviating slightly. Therefore, it can be concluded that monolithic thick films and stacked films have similar release rates.

To better understand the drug release behavior depicted in Fig. 6 (also Fig. S2), the modified Korsmeyer-Peppas power law model (Eq. (1)) was applied and the diffusional exponent n (Eq. (1)), representing the mechanism of drug release, was computed, along with an additional result for 100 μm film as an example of typical thin film from literature (Krull et al., 2015b). Fig. 7 shows that the diffusional exponent n is about 1 ($n=0.97-1.05$) for all films 1000 μm and thicker, indicating true zero-order release. As a reference, values of the exponent lower than 0.5 indicate that the drug release mechanism is Fickian diffusion; whereas for n between 0.5–1.0, it is termed anomalous transport and when n is equal to 1.0 it is case-II transport (Ritger and Peppas, 1987a, b). To summarize, the release mechanism for thin films, i.e., 100 μm film matrix ($n=0.4$), is predominantly one-dimensional and follows Fickian diffusion (Ford et al., 1987). However, as the film thickness increases making the release three-dimensional, the mechanism is that of anomalous for intermediate thickness, i.e., 500 μm film matrix ($n=0.86$), and true zero-order release for thicker films, i.e., 1000 μm and higher. As was expected, both the monolithic and stacked films matrixes exhibit similar release mechanisms, which was the swelling of HPMC matrix coupled with an important diffusive contribution for thinner films (Ritger and Peppas, 1987b). It is noted that similar, but slightly lower values for n (0.9 and 0.82) were obtained for poorly water-soluble drugs, indomethacin and diazepam, released from tablets having a near zero-order release (Ford et al., 1987). The present results for slurry cast films of poorly water-soluble drug GF exhibit n to be essentially 1, which suggests that the performance compares favorably with HPMC based tablets.

Since the aspect ratio, i.e., disk diameter divided by disk thickness for this disk type dosage shape ranges from about 6 to 25 for thickness of 500–2000 μm , the release, being predominantly three-dimensional, is expected to be linearly related with the surface area of

the dosage (Ford et al., 1987). However, because the film samples have the same diameter, the thickness becomes the controlling factor, leading to the drug release mainly influenced by the thickness. In order to examine how the kinetic constant, k , from Eq. (1) varies as a function of the characteristic indicator of the structure and geometry of the dosage shape, the results are plotted in Fig. 8 for both thickness and dosage surface area, confirming the behavior to be linearly dependent on the surface area as predicted previously (Ford et al., 1987), but may be easily represented by thickness. Complimenting results shown in supplementary, Fig. S3, for the release time for $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$ of monolithic films and stacked films exhibited a linear relationship with both dosage surface area and thickness.

The dissolution behavior presented above suggests that the multi-layer thick film system may provide a very simple approach for preparing film-based dosage forms by simply assuring that the film-thickness is above certain threshold for a given sample diameter. It is noted that apart from being a strong function of thickness, the release kinetics, and total time of release may depend on the properties of the polymer forming the matrix, including its molecular weight, further adding to the dosage design flexibility. This would be an interesting topic for future research.

4. Conclusions

The effect of film thickness on the release time and mechanisms was investigated by varying thickness from 100–2000 μm . For 500 μm and thicker films, the release time ranged from about 240 min to 500 min, with no initial burst-release and lag time that was linearly dependent on film thickness. Release mechanism shifted from Fickian diffusion for typical thin films of 100 μm to anomalous transport for intermediate thickness of 500 μm , which was the unit film used for constructing multi-layer films, to almost perfect zero-order release for thickness of 1000 μm and above, where the diffusional power law exponent, n , achieved value of 1, which is a significant outcome. The aspect ratio of the film samples ranged from about 25 to 6 for thickness of 500–2000 μm , leading to predominantly three-dimensional drug release, that was linearly related to the surface area. Since the sample diameter was fixed, the drug release was mainly influenced by the thickness. Stacked films required simpler manufacturing process due to ease of casting and drying, and also resulted in better critical quality attributes, such as the appearance, uniformity of thickness as well as drug content per unit area. Overall, both the monolithic thick films and stacked films were found to have low RSD values of drug loading ($\text{RSD} < 6\%$), low moisture content of dry films ($< 3\%$), and similar release rates. Overall, such multi-layer thick film system provides zero-order sustained delivery of poorly water-soluble drugs, while maintaining a constant release rate and tailoring total release time based on the number of layers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Schematic of fabrication methods for stacked films (Method-1) and monolithic thick films (Method-2).

Fig. 2.
Digital microscope images of the cross-section of stacked films: (a) 2 layered (Stack-A), (b) 3 layered (Stack-B), (c) 4 layered (Stack-C). Scale bars are 200 μm each.

Fig. 3. Particle size distribution (d_{10} , d_{50} , and d_{90}) of as-received GF (AR-GF) powder, surface modified micronized GF (MC-GF) powder and MC-GF drug particles redispersed from film.

Fig. 4. Moisture content of stacked films (Stack-A, Stack-B, Stack-C) and monolithic thick films (Mono-A, Mono-B, Mono-C) obtained through TGA analysis.

Fig. 5. XRD patterns of pure GF, MC-GF powder, placebo film and film laden with MC-GF powder. Arrows indicate standard GF peaks.

Fig. 6. Dissolution profiles of stacked films and monolithic thick films: Dissolved percentage (a) stacked films (500 μm , Stack-A, Stack-B, Stack-C) and (b) monolithic thick films (500 μm , Mono-A, Mono-B, Mono-C); Dissolved mass (c) stacked film (Stack-A, Stack-B, Stack-C) and (d) monolithic thick film (Mono-A, Mono-B, Mono-C).

Fig. 7. Diffusional exponent, n , of Eq. (1) for drug release from monolithic thick films (Mono) and stacked films (Stack), as a function of their aspect ratio. The dashed lines represent general trends.

Fig. 8. Release kinetics constant, k , of Eq. (1) as a function of (a) thickness and (b) surface area of monolithic thick films and stacked films.

Table 1**Content uniformity of stacked films and monolithic thick films**

	Thickness (µm)	RSD%	Drug dose per unit area (mg/cm ²)	RSD%	Wt% GF	RSD%
Single ~500 µm layer	542	3.6	11.5	4.1	20.5	4.3
Stack-A	1068	5.2	24.0	4.2	18.4	3.7
Stack-B	1489	8.1	33.9	6.5	19.3	3.5
Stack-C	1983	5.6	43.2	3.1	19.4	2.0
Mono-A	1052	9.3	25.0	8.1	17.0	4.1
Mono-B	1492	8.8	35.7	6.8	20.9	2.7
Mono-C	1982	5.8	42.2	2.8	20.1	3.5

Stack-A 1000 µm stacked film; Stack-B 1500 µm stacked film; Stack-C 2000 µm stacked film;

Mono-A 1000 µm monolithic thick film; Mono-B 1500 µm monolithic thick film; Mono-C 2000 µm monolithic thick film

Table 2
Similarity and difference factors for dissolution profiles of monolithic thick films and stacked films compared at the same thickness

	Sample	Fit Factor	
		f_1	f_2
$t_{50\%}$	Mono-A/Stack-A	9.8	87.2
	Mono-B/Stack-B	3.6	94.9
	Mono-C/Stack-C	5.8	94.1
$t_{75\%}$	Mono-A/Stack-A	7.8	83.3
	Mono-B/Stack-B	5.0	85.4
	Mono-C/Stack-C	5.5	88.1
$t_{90\%}$	Mono-A/Stack-A	6.7	80.2
	Mono-B/Stack-B	6.2	75.5
	Mono-C/Stack-C	4.6	84.7

Stack-A 1000 μm stacked film; Stack-B 1500 μm stacked film; Stack-C 2000 μm stacked film;

Mono-A 1000 μm monolithic thick film; Mono-B 1500 μm monolithic thick film; Mono-C 2000 μm monolithic thick film.