**Novel use of superdisintegrants as viscosity enhancing agents in biocompatible
polymer films containing griseofulvin nanoparticles**

Ramana Susarla, Afolawemi Afolabi, Darshan Patel, Ecevit Bilgili, Rajesh N. Davé*

New Jersey Center for Engineered Particulates

New Jersey Institute of Technology, Newark, New Jersey

Submitted to Special Issue: Pharmaceutical Powders, *Powder Technology*

* Corresponding author. Tel.: +1 973-596-5860; fax: +1 973-642-7088.

E-mail address: dave@njit.edu (Rajesh N. Davé).

ABSTRACT

The advantages of using superdisintegrants, sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (CP) over traditional high molecular weight (MW) viscosity enhancing agents, guar gum (GG), xanthan gum (XG), pectin and high MW HPMC are examined for improving drug content uniformity without compromising dissolution of films containing nanoparticles of griseofulvin (GF), used as a model poorly water-soluble drug. Films were fabricated by preparing low MW HPMC solutions to which a fixed amount of viscosity enhancing agents were added and mixed with GF nanosuspensions produced via wet milling, followed by casting and drying. The addition of superdisintegrants and high MW HPMC, led to an increase in viscosity of precursor suspensions without GF particle aggregation, and hence excellent drug content uniformity along with retention of the high surface area of the GF nanoparticles in dried films. In contrast, addition of XG and pectin resulted in aggregation of GF particles in suspensions, leading to poor content uniformity and incomplete recovery of GF nanoparticles upon redispersion of dried films. In spite of their high precursor viscosity, the films containing superdisintegrants did not lead to increased mechanical strength and demonstrated fast drug release, suggesting faster matrix erosion. In contrast, films with high MW polymers (GG, XG, and pectin and high MW HPMC) had increased mechanical strength and their subsequent slow erosion/disintegration along with longer hydration times resulted in significant delay of drug release, which was found to be directly proportional to their MW. These results demonstrate novel use for superdisintegrants as economical and superior alternative to traditional viscosity enhancing agents in forming drug laden biocompatible polymer films.

Keywords: nanosuspensions, pharmaceutical films, superdisintegrants, gums, viscosity enhancing agents, griseofulvin, poorly water soluble drugs, dissolution enhancement

1. Introduction

Polymer based oral strip-film technology has emerged as a promising platform for drug delivery due to its patient compliance, potential for continuous processing and easy scale-up [1,2]. In addition to the conventional drug solution based formation, strip-films have also been shown to be a promising platform for the delivery of crystalline nano or micro particles of poorly water-soluble drugs with enhanced dissolution as a major objective [3-10]. Regardless of drug solution based formulations [3, 4] or drug solid particle based [7-10] formulations, higher film precursor viscosity is considered a critical parameter, which affects film properties, including drug content uniformity [8, 11]. Higher viscosity is usually achieved via addition of viscosity enhancing agents or thickeners, which help maintain the film thickness during casting process, facilitating uniform drying, thereby leading to excellent drug content uniformity [8–13]. Naturally occurring gums or polysaccharides like guar gum (GG) and xanthan gum (XG) as well as pectin etc. [11–13] are widely used in film formulations as viscosity enhancing agents. These naturally occurring biopolymers are popular due to their hydrophilic nature, biocompatibility and swelling behavior [14,15]. Another key application of these biopolymers is their use as stabilizers in colloidal suspensions. The swelling property of these polymers causes a thickening effect on suspensions [16] thereby keeping the particles in suspended state and preventing particles from settling. When added in optimum quantity, these polymers adsorb onto the particle surface resulting in electrostatic stabilization [17–23] and when added in combination with a surfactant or polymer, they can display a synergistic effect resulting in electro-steric stabilization of particles [10,18]. On the other hand, XG and pectin, may exhibit a phenomenon called

polymer bridging [18–20], where the polymer molecule adsorbs onto multiple particles forming weak aggregates (flocs). For drug-loaded films where the dosage uniformity depends on the stability and homogeneity of the starting precursor suspension, the presence of aggregates could be detrimental [24,25]. Unfortunately, the impact of GG, XG, or pectin on aqueous polymeric suspensions containing solid drug particles and their interactions with other stabilizers has not been well explored thereby leaving the advantage of their usage in ambiguity.

Unlike gums and pectin, superdisintegrants are water-insoluble, crosslinked polymers that swell upon contact with water and form a suspension [26,27]. They are commonly used in tablet formulations for quick disintegration and release of drug [28–33]. In the pharmaceutical industry the most commonly used superdisintegrants are sodium starch glycolate (SSG), croscarmellose sodium (CCS), and crospovidone (CP) and the mechanisms by which superdisintegrants cause tablet disintegration have been studied and discussed in detail by a number of authors [27–30]. Although several major mechanisms of their action have been proposed, [34], most relevant ones are swelling and wicking (also known as the capillary effect). Other mechanisms, for example, recovery of elastic energy (applicable to tablets due to compaction and deformation), repulsion between SDI and other particles, and heat of wetting, have also been identified but are less likely to have significant impact on film formulations [35]. There are also numerous investigations on the impact of superdisintegrants on the disintegration and subsequent dissolution behavior of drug from tablets based on their interactions with other excipients, drug and mode of incorporation [27–33]. In contrast, there are only a few studies [36, 37] that investigate the impact of superdisintegrants on drug release from polymeric oral strip films. In a recent study, Lakshmi et.al [38] demonstrated the positive impact of crospovidone on drug release behavior of donepezil hydrochloride formed via solvent casting from sodium

alginate oral strip-films. Sagban and Ismail [39] also demonstrated that use of up to 5% (w/w) crospovidone aided in faster release of sildenafil citrate from oral films. However, the impact of superdisintegrants on formulations containing nano or micro solid drug particles has not been investigated. We hypothesize that use of superdisintegrants in polymer based aqueous film formulations would result in viscosity enhancement of formulation due to the water absorbing characteristic of superdisintegrants, thereby leading to enhanced kinetic stabilization of suspensions, which in turn could lead to visually uniform films with superior drug content uniformity. In addition, superdisintegrants can aid speeding up film erosion, drug nanoparticle redispersibility, and drug release. Therefore, it is of both interest and importance to explore the impact of superdisintegrant particles on aqueous colloidal drug formulations and their impact on the final film dosage forms.

Consequently, the major novelty of the present work is the investigation of the role of superdisintegrants, namely SSG, CCS and CP, as viscosity enhancing agents in aqueous low MW HPMC film formulations containing poorly water-soluble drug nanoparticles as compared to traditional viscosity enhancing agents such as GG, XG, and pectin. Griseofulvin (GF) was used as a model poorly water-soluble drug in this investigation. For this study, aqueous suspensions of low molecular weight HPMC were prepared in combination with glycerin and either SSG, CCS or CP followed by mixing these suspensions with GF nanosuspensions produced via WSMM [40, 41]. A similar procedure was followed for preparation of HPMC-GF suspensions containing either GG, XG, or pectin. In addition, a control formulation containing low MW HPMC, a formulation consisting of high molecular weight HPMC, and a formulation with higher concentration of low MW HPMC, latter two being high viscosity formulations, were also prepared. The rheological behavior of these suspensions was studied using a Brookfield

Rheometer. Strip-films were fabricated by casting the suspensions and drying them in a lab scale continuous drying system [9]. The particle size distributions (PSD) of superdisintegrants and GF from the redispersed films were measured via laser diffraction and compared with those of the precursors suspensions to assess the GF nanoparticle redispersibility. The impact of the additives on film and drug content uniformity and drug release behavior was also investigated by conducting film sample assay analysis and dissolution tests. Raman and FTIR spectroscopy were used to investigate the impact of additives on GF crystallinity and to capture potential interactions between GF-additives. Thermo Gravimetric analysis (TGA) was performed to evaluate the impact of additives on the moisture sorption of films, which could impact the long-term stability of oral dosage forms. For the sake of brevity, the results for Raman, FTIR and TGA analyses are presented in the Supplementary Material section.

2. Materials and methods

2.1. Materials

Griseofulvin (GF; Sigma-Aldrich, Saint Louis, MO), an antifungal compound, was used as a model poorly water-soluble drug. Sodium dodecyl sulfate (SDS; Sigma-Aldrich, Saint Louis, MO) an anionic surfactant and hydrophilic low molecular weight hydroxypropyl methylcellulose (HPMC; Methocel E15LV, $M_w \sim 40,000$, Dow Chemicals, Midland, MI) were used in combination as stabilizers for GF nanosuspensions during the WSMM, in addition HPMC (E15LV) was also used as the main film forming polymer. HPMC (E4M) ($M_w \sim 100,000$, Dow Chemicals, Midland, MI), which is a high MW polymer, was also used as a film former, whereas Glycerin (Sigma-Aldrich, Saint Louis, MO) was used as a plasticizer. Sodium starch glycolate (SSG, Primojel, Type A), croscarmellose sodium (CCS, Ac-di-sol SD-711), and

crospovidone (CP, Polyplasdone XL-10) were the superdisintegrants chosen for this study. CCS was obtained from FMC Biopolymers (Philadelphia, PA), whereas SSG and CP were obtained from ISP chemicals (Wayne, NJ). Traditionally used biodegradable, non-toxic and hydrophilic natural biopolymers such as guar gum (GG), xanthan gum (XG) and pectin (derived from apple) were used as viscosity enhancing agents for comparison against the performance of superdisintegrants. All of these biopolymers were purchased from Sigma-Aldrich (Saint Louis, MO). GG is secreted by plant guar and mainly consists of galactomannans, a high molecular weight (~ 50,000) polysaccharide [42, 43, 44]. XG is a complex exopolysaccharide produced by the plant-pathogenic bacterium *Xanthomonas campestris*, and is stable over a wide range of temperature, as well as acidic and alkaline conditions. Pectin is also a polysaccharide which is extracted from cell walls of most plants [45, 46]. The ability of pectins to form gels depends on their molecular weight and degree of methoxylation, which in turn depends on the source from which they are extracted. The molecular weights of XG and pectin used in this study were approximately 180,000 and 150,000, respectively.

2.2. Methods

2.2.1. Preparation of GF nanosuspensions

GF nanosuspensions were produced via WSMM utilizing a Microcer mill (NETZSCH, Fine particle technology LLC, Exton, PA) as per previously described methods and under similar processing conditions [41, 47]. All suspensions were milled for 120 min and consisted of 10% drug (on a w/w basis w.r.t. water) dispersed in a stabilizer solution containing 2.5% low MW HPMC (on a w/w basis w.r.t. water) and 0.5% SDS (on a w/w basis w.r.t. water), these concentrations were fixed based on previous optimization studies [41]. The end point of milling

was determined as the point where the particle size did not change further (d_{50} was ~ 160 nm). At the end of milling, a sample was taken from the holding tank of the mill and dispersed into 15 mL HPMC–SDS solution (using a pipette) and the particle size distribution of GF in the sample was then measured via laser diffraction (Coulter LS13 320, Beckman Coulter, Miami, FL).

2.2.2. Preparation of film precursor suspensions

Low MW HPMC polymer solutions were prepared following previously established protocols [7, 8] wherein a weighed amount of **low MW** HPMC and glycerin corresponding to 12% (w/w) and 5% (w/w) respectively were added to water at 90 °C. These **low MW** HPMC solutions were then mixed with GF nanosuspension in a 2:1 ratio [8] for a period of 6 h using a motor driven dual-propeller mixer (McMaster, USA). Susarla et al. [8] established a critical minimum viscosity value of about 5000 cP, which is required for formation of a stable suspension and subsequent uniform film matrix upon casting and drying [48]. The viscosity of 12 wt % HPMC is ~ 5000 cP, and it reduces to 2500 cP after the addition of GF nanosuspensions due to dilution effect [8]. Since this viscosity is sufficiently low for stable film formation, this polymer concentration (12 wt%) was selected as the base formulation because that would allow for discerning the impact of **viscosity enhancing agents**, namely, superdisintegrants and natural gums on viscosity enhancement of the suspensions.

SSG, CCS, CP, GG, XG or pectin was added to the HPMC–glycerine solutions as the solution cooled down (40 ± 5 °C) with continued stirring. These HPMC–additive mixtures are either aqueous microparticulate suspensions of superdisintegrants (SSG, CCS, and CP) or aqueous solutions of gums (GG, XG) and pectin. They were then mixed with GF nanosuspensions using a motor driven dual-propeller mixer (McMaster, USA) for an additional

period of 6 h to prepare the final film precursor suspensions. Formulation F-None, which does not contain any **viscosity enhancing** additive, was regarded as the baseline formulation and formulations F-SSG, F-CCS, F-CP, F-GG, F-XG, and F-Pectin contain the respective additives.

Two additional formulations, one containing a high molecular weight HPMC (called, F-E4M) and second with higher concentration of low molecular weight HPMC (called, F-E15LV_high) were also considered, but without any additives. **For formulation F-E4M the ratio of polymer solution to GF nanosuspension was kept at 8:1 to maintain the same drug loading as the other formulations. Whereas in case of formulation F-E15LV_High, a 15 wt% HPMC polymer solution containing 5 wt% glycerine was added to GF nanosuspensions in 2:1 ratio while maintaining a drug loading of ~ 2.94 wt% [8], which is same as all other formulations.** In both cases the viscosity of suspension was kept close to those of F-SSG for a fair comparison. All the precursor suspension compositions are given in Table 1.

2.2.3. Rheology of suspensions

The apparent viscosity of suspensions was measured using an R/S plus rheometer (Brookfield Engineering, Middleboro, MA), which is equipped with a shear rate controlled coaxial cylinder (CC40) and a water jacket assembly Lauda Eco (Lauda-Brinkmann LP, Delran, NJ). The suspensions were subjected to a low shear rate program to measure the viscosity at low shear value ($0\text{--}20\text{ s}^{-1}$) at $25\text{ }^{\circ}\text{C}$. The low shear viscosity also reflects the shearing that the suspensions are subjected to during casting process [8, 9]. Since the suspensions were highly viscous, applying high shear at room temperature (especially for polymer solutions, before addition of GF nanosuspensions) was very challenging, and increase in temperature aided in shearing. Therefore a high shear rate program ($0\text{--}1000\text{ s}^{-1}$) was applied to study the impact of

additives on rheological behavior of polymer–additive mixtures and film precursor suspensions by heating the mixtures and suspensions up to 45 °C to collect viscosity data.

2.2.4. Particle size distribution

The particle size distribution (PSD) of SSG, CCS and CP in the HPMC–additive suspensions (in case of superdisintegrants) and film precursor suspensions were measured through laser diffraction technique. The PSD of GF was also measured using laser diffraction technique for three different suspensions: (a) wet-milled GF nanosuspension at the end of milling, (b) film precursor suspensions, and (c) suspensions formed upon redispersion of dry films in water. In order to analyze the PSD of superdisintegrants before and after addition of GF nanosuspensions, about 1 ml of HPMC–additive suspension was added to 10 ml of DI water and vortexed for 10–15 min until HPMC dissolved completely in water (the same procedure was followed for all the other formulations for measuring the size of GF particles in the mixed suspensions). Based on previous studies [49, 50, 51], the refractive indices of SSG, CCS and CP were used to determine the PSD of superdisintegrants, whereas the refractive index of GF was used to determine the PSD of GF. Therefore, two separate measurements were conducted for F-SSG, F-CCS and F-CP suspensions so as to measure particle size of superdisintegrants and GF. It is critical to mention that such separate PSD measurements were feasible since there was no overlap between the PSDs of the coarse, micron-sized superdisintegrants and the GF nanoparticles. For other formulations where the only particulate matter was GF, the refractive index of GF was used to determine the size of GF particles.

To assess the GF nanoparticle recovery from the dry films, redispersion tests [52] were performed by dissolving a very small piece of the films (0.712 cm² in area, punched out from

different sections of the films) into 10 mL DI water, ensuring final concentration would be significantly below the solubility limit of GF particles, followed by vortex mixing for 1 min [7, 8]. Only in the case of high molecular weight compounds (pectin, XG and high MW HPMC), the films had to be vortex mixed for at least 40 min for them to completely hydrate and dissolve following which a small sample was drawn for particle size analysis. For the films made from formulations F-SSG, F-CCS and F-CP, two separate measurements were made by making use of the refractive index of each superdisintegrant followed by that of GF. All experiments were performed in triplicates and the average over three samples was recorded.

2.2.5. Preparation of strip-films containing GF nanoparticles

Approximately 8 g of precursor suspensions were manually cast onto a stainless steel substrate at 25 °C using a casting knife (Elcometer, MI). The casting thickness was set at 1000 µm and the final dimensions of the film were measured to be about 8 cm x 9 cm. The cast film along with the substrate was then placed into zone three of a Lab-Cast Model TC-71LC Tape Caster [9] (HED International). The Lab-Cast is a continuous film manufacturing system, which has three zones of heating: zones one and two provide conductive heating, while zone three provides both conduction and convective heating. For the current study, the films were manufactured in batch mode by placing the film in zone 3 of the unit and drying the cast film. The drying conditions in zone 3 were maintained based on previous optimization studies [8], where a drying temperature of 60 °C and laminar air flow conditions were applied, dry films were obtained within 60 min.

2.2.6. Scanning electron microscopy (SEM)

A field emission scanning electron microscope (FESEM) LEO 1530VP GEMINI (Carl Zeiss, Inc., Peabody, MA) was used to examine the nanocomposite structure from cross-sections of the films. A small sample of the film was placed on carbon tape (the stub) followed by carbon coating using a sputter coater and imaging.

2.2.7. Determination of drug content in films

A protocol for determining the drug content in strip films has been previously established [7,8]. Following a similar procedure, a Thermo Scientific Evolution 300 UV-Vis spectrophotometer (Thermo Fisher Scientific Inc., MA) was used to determine the drug content in films. Ten samples of 0.712 cm² in area were punched out of each film and dissolved in 250 mL of 0.0187 M SDS solution for a period of 12 h. The concentration was calculated via UV absorbance at 291 nm using previously constructed calibration curves. The average GF weight and relative standard deviation over ten samples was calculated. The weight and the thickness of these samples were also recorded prior to assay and the percent variations in thickness and the weight percentage of drug were also computed.

2.2.8. Mechanical properties

The mechanical properties of films were measured using a TA-XT Plus Texture Analyzer (Stable Microsystems, UK). Tensile and yield strengths were computed from the stress versus strain data. Six rectangular strips having dimensions of 50 mm x 15 mm were cut from a single film and tested. The strip was held in place between the two grips and stretched at a test speed of 1 mm/s until the breaking point (i.e., tensile failure). The average and standard deviation were computed over six samples and tabulated.

2.2.9. Dissolution testing and drug release kinetics

A flow-through cell dissolution apparatus (USP 4, Sotax, Switzerland) with cells of an internal diameter of 22.6 mm was employed, following previous work from Sievens et al. [53], Beck et al. [10], and Susarla et al. [8] who used USP 4 for discerning dissolution profiles for films made from different formulations. Circular film samples with an area of 0.712 cm² were horizontally positioned in the cells with 1 mm glass beads filling the top and bottom of each cell. Pall HT Tuffryn membrane disc filters with 0.2 µm pore size were used. It is noted that previous studies demonstrated that the use of 0.1 µm versus 0.2 µm filters did not have any significant impact on the release profiles of films containing nanoparticles of mean diameter 160 ± 30 nm [8, 53]. The temperature was maintained at 37 ± 0.5 °C and a flow rate of 16 mL/min was used. Dissolution studies were carried out using two different dissolution media. In the first case, water was chosen as the dissolution media, since GG, XG and pectin all show pH dependent behavior [14,15]; a neutral media was chosen to avoid any bias. The second media used was USP suggested SDS solution [8, 53] (5.4 mg/ml, having a pH of ~ 6.4), the media was circulated by pumping it through each cell. Six samples were used from each film and the average drug release was plotted as a function of time. The release kinetics of GF for various formulations was computed by fitting the linear portion of the dissolution curve to standard empirical equations like zero-order release equation, first-order release equation, Higuchi equation and Korsmeyer-Peppas (KP) equation [54,55]. To effectively quantify the differences within and between release profiles from all nine formulations, difference factors (f_1) and similarity factors (f_2) [54, 55] were also computed.

3. Results and discussions

3.1. Rheology of the HPMC–additive mixtures and film precursor suspensions

Table 2 presents the apparent shear viscosity at 25 °C and 2.2 s⁻¹, which was regarded as representative of the low-shear rate imparted during film casting, for the HPMC–additive mixtures, before and after addition of GF nanosuspensions. The control F-None is the formulation without additives thereby yielding lowest viscosity. Addition of superdisintegrants to low MW HPMC solutions led to the formation of suspensions containing GF and swollen superdisintegrant particles. The sizes of superdisintegrant particles in various suspensions are presented in Table 3. Considering that the median size d_{50} of as-received dry CP, CCS, and SSG particles are about 30 µm [51,56], 50 µm [50,56], and 50 µm [51], respectively, Table 3 clearly shows that the superdisintegrant particles swelled in water and their size dramatically increased. The size increase is in line with the swelling capacities of these superdisintegrants reported in the literature [56], with the order of swelling being SSG > CCS > CP (swelling volumes or capacities are 23.6 cm³/g, 13.5 cm³/g, and 5.4 cm³/g, respectively [51]). The absorption of water leads to an increase in the effective HPMC concentration and solids (drug and superdisintegrant particles) loading in the suspensions, while reducing the free-volume of the fluid and restricting fluid motion [57], which accounts for the higher viscosities with the superdisintegrants. Unlike the superdisintegrants, gums (XG and GG) and pectin dissolve when added to the HPMC solution. It was observed that XG resulted in a significant increase in suspension viscosity, followed by pectin and GG. F-E4M had higher viscosity than F-None because the former used the higher MW grade of HPMC than the latter one with a low MW grade of HPMC, and F-E15LV_High had a higher viscosity than F-None because it had higher HPMC concentration of low MW HPMC. For these soluble additives, the viscosities appeared to be largely controlled by

the MW of the respective biopolymer (see Section 2.1) and its concentration. Table 2 also shows that the precursor suspensions had lower viscosities than the HPMC–additive mixtures despite the presence of GF particles in the former because the addition of the GF nanosuspension to the HPMC–additive mixtures led to significant dilution of the HPMC due to excess water from GF nanosuspension addition.

Figures 1(a) and 1(b) show the log-log plot of apparent shear viscosity versus shear rate for the film precursor suspensions containing GF particles and the HPMC–additive mixtures, respectively, both tested at 45 °C. Two general trends emerge: first, the precursor suspensions had lower apparent viscosity than the HPMC–additive mixtures due to the aforementioned dilution effect. Second, upon an increase in shear rate, the apparent viscosity of the suspensions decreased monotonically, signifying a marked shear-thinning (pseudoplastic) behavior. HPMC, XG, pectin, and GG [58–63] are all known to demonstrate non-Newtonian, shear-thinning (pseudoplastic) behavior when added in sufficient concentrations. In fact, aqueous solutions of all additives and base polymer (HPMC) show discernible shear-thinning, as illustrated in Fig. 1(c), which could explain the underlying shear-thinning response in Figs. 1(a) and (b).

3.2. GF nanoparticle redispersibility from films

Table 3 provides a comparison of superdisintegrant particle sizes in the HPMC–superdisintegrant suspensions, the film precursor suspensions, and the redispersions from dry films. It is clear that neither the addition of GF nanosuspensions to the HPMC–superdisintegrant suspensions, nor the casting–drying of these suspensions and the film redispersion led to a significant change in the swollen superdisintegrant sizes. On the other hand, the same does not necessarily hold for GF nanoparticles, at least for some of the formulations. In this context, Table

4 compares the GF size statistics of the film redispersions against those of the precursor suspensions and the GF nanosuspension prepared via WSMM. The results presented in Table 4 can be visualized in Fig. 2, which shows the cumulative PSDs of GF obtained from redispersion of all film formulations. This figure also shows the PSD of the original GF nanosuspension for the sake of comparison. It is evident from Fig. 2 and also from Table 4 that the addition of superdisintegrants did not lead to any particle aggregation, and the d_{50} values for GF redispersed from films (made from formulations F-SSG, F-CCS and F-CP) were comparable with the d_{50} values of GF from WSMM. Both F-E4M and F-E15LV also achieved similar PSDs as WSSM. The next best redispersibility is observed for F-None, followed by F-GG, whereas films containing pectin and XG exhibited a broader size distribution, signifying poor recovery of the GF nanoparticles in the form of aggregates.

Table 4 also gives the size statistics of GF particles in the film-precursor suspensions, for all nine formulations. In most cases, the redispersion of viscous suspension in DI water leads to recovery of particles close to that of WSMM. However, in the case of pectin and XG there is a slight increase in particle size which could be representative of aggregates that may have been caused by the polymer–particle bridging behavior [17–18]. In the case of high MW HPMC (F-E4M), this was not observed; therefore, films made from F-E4M appear to have retained the original GF nanoparticles upon casting and drying.

3.3. SEM imaging

Figure 3 shows the cross sectional image of HPMC films containing GF nanoparticles and superdisintegrant particles embedded in them. The presence of embedded SSG, CCS, and CP particles, marked using arrows, within the HPMC matrix may be seen in low magnification

images in Figs. 3(a)–(c). In Fig. 3(d), higher magnification imaging is employed to visualize well distributed GF nanoparticles within the F-SSG film matrix and the particles appear to have the size of original GF nanoparticles. In contrast, for F-pectin film, a high resolution image in Fig. 3(e) indicates that individual GF particles are not visible and there could be aggregation of particles. It is worth-mentioning that these selected images are illustrative of the film structure typically observed in multiple images.

3.4. Content Uniformity

Table 5 shows the average and standard deviation values for thickness of films, amount of drug and weight percentage of drug in the films. As anticipated, films made from F-None, which has a low precursor viscosity exhibited relatively poor drug content uniformity [8]. On the other hand, films containing SSG had the lowest variation in overall content uniformity followed by CCS and CP. In comparison, the variation was higher for traditional viscosity enhancing agents such as GG, XG, and pectin even when the thickness variation was very low (<2% RSD), most likely owing to the surface adhesive property of these materials. It is interesting to note that the overall drug content variation for F-SSG, F-CCS, and F-CP was quite low in spite of the larger variations of film thickness (~ 5% RSD), which in part can be attributed to the manual casting procedure used in this study. It is expected that a more controlled or automated casting method would reduce these variations significantly [8]. These results suggest that both the precursor viscosity and the drug particle dispersion in the films, which may be correlated with the film redispersibility, may have influence on the drug content uniformity. Generally speaking, the formulations that have both high precursor viscosity and excellent redispersibility, i.e., F-SSG, F-CCS, F-E4M, and F-E15LV_High, also have better drug content uniformity. On the

other hand, those with either low viscosity or poorer redispersibility, i.e., F-None, F-Pectin and F-XG, do not have as good drug content uniformity. Interestingly, although the weight variation between samples may be correlated to the change in thickness in the case of films made from F-SSG, F-CCS and F-CP (as the variations in wt% of drug are significantly lower), in the case of F-XG and F-Pectin, the variation in wt% is high in spite of much lower thickness variation (~ 5% RSD) confirming the uneven distribution of drug within the films. It should be noted that the RSD values reported here are based on very small samples (0.712 cm² in area) as compared to the final expected dosage that is typically about 10 times the size. Therefore, the RSD for the final dosage, in particular for F-SSG and F-CCS is expected to be even smaller than what is reported.

While the current results show very good trends for RSD values that appear to be well supported by the precursor viscosities, in particular for SSG as well as CCS and CP, it is important to note that these excipients tend to show batch-to-batch and brand-to-brand variations in their properties. Such variations could have just as much impact on the final film properties as from the type of additive used. In fact, the degree of substitution, cross-linking etc. may also vary, thus changing the properties of these compounds and hence a potential brand to brand variation could exist as a function of slightly differing properties of superdisintegrants produced by different companies [64–67]. While important, detailed investigation of the impact of such variation is considered outside the scope of the current investigation.

3.5. Mechanical properties

The mechanical properties of the films are important not only for aesthetic purpose but also because they can affect the release kinetics of drug. Table 6 gives the mechanical properties

of films made from all the nine formulations. As may be seen, the incorporation of superdisintegrants did not significantly affect the tensile or yield strength of HPMC film, whereas the addition of high MW polymers like pectin, GG, XG, and high MW HPMC led to a significant increase in both tensile and yield strength of the film. This increase in strength is expected to be a contributing factor towards delay in film erosion/disintegration and subsequent dissolution of the drug particles.

3.6. Dissolution and drug release kinetics

First, the dissolution profiles of films made with traditional viscosity enhancing agents are compared with the novel viscosity enhancing agents, i.e., superdisintegrants, in Fig. 4(a), where deionized (DI) water was used as the dissolution media. Results are reported only for DI water because there was no statistically significant difference between DI water and SDS as the dissolution media for these films consisting of GF. Close examination reveals that as compared to the baseline, F-None, all the films containing superdisintegrants, i.e., F-SSG, F-CCS, and F-CP, demonstrate equal or faster dissolution behavior. Specifically, t_{80} is about 13, 17 and 19 min, for F-SSG, F-CP, and F-CCS, respectively (t_{80} is the time taken for release of 80% of GF) as compared with 19 min for F-None. On the other hand, the films containing traditional viscosity enhancing agents, i.e., F-GG, F-XG, and F-Pectin display slower release; t_{80} is about 26, 46, and 58 min, for F-GG, F-Pectin, and F-XG, respectively. These observations for the traditional viscosity enhancing agents are generally in agreement with literature findings [68–74]. Films containing gums or pectin swell upon contact with media, which creates a diffusion barrier for the drug release resulting in slower drug release. Next, the dissolution profiles of films made with the superdisintegrants as viscosity enhancing agents are compared with those just containing

different grades or concentrations of HPMC (F-None, F-E4M, and F-E15LV_High) in Fig. 4(b). Films containing superdisintegrants show faster dissolution than films containing higher concentration of low MW HPMC or high molecular weight HPMC. While the t_{80} for higher concentration of low MW HPMC is only slightly higher (about 20 min) than the slowest superdisintegrant CCS, that of high MW HPMC is almost 38 min, hence comparable to gums, GG and pectin. The slow drug release with high MW HPMC, as well as gums and pectin, can be attributed to their high MW, leading to longer hydration times, slower erosion and subsequent delay in drug release. The difference (f_1) and similarity (f_2) factors were calculated for various pairs of release curves taking F-SSG curve as reference (reported in Supplementary Material). The calculated factors suggest that significant differences exist between GF release from films containing superdisintegrants versus films containing pectin, GG, XG, and high molecular weight HPMC. Moreover, large error bars in the release profiles of films containing pectin are a reflection of the uneven distribution of GF nanoparticles, which was also evident in content uniformity results. Overall, these dissolution results demonstrate the superior performance of the superdisintegrants.

Fitting the linear portion of the release curves to various empirical models revealed that Krosmeier–Peppas model had the best fit ($R^2 > 0.98$) for all cases (the model fitting results reported in the Supplementary Material). The value of n for films containing SSG, CCS, CP, pectin, GG and XG was > 1 , implying that a combined mechanism of swelling and erosion was responsible for the drug release [54, 55]. A similar trend was also observed in films containing low MW or high MW HPMC. Susarla et al. [8] demonstrated that the release of GF from plain low MW HPMC films followed a combined mechanism of swelling and erosion, therefore it can be concluded that the addition of superdisintegrants at the level of concentrations used here did

not alter the dissolution mechanism of HPMC films. However, their large swelling capacity may have contributed to faster disintegration and hence faster drug release. Although the dissolution is expected to have a complex dependence on multiple factors, the relative dissolution behavior of films made with the same amounts of superdisintegrants (t_{80} of SSG < CP < CCS) may be attributed to the combined effect of their swelling capacity (SSG > CCS > CP), precursor viscosity (SSG > CCS > CP), and mechanical strength (CP < CCS < SSG). The results pertaining to **pectin**, GG and XG show that relative dissolution behavior from their films (t_{80} of GG < pectin < XG) may be largely attributed to their MWs (GG < **pectin** < XG). Overall, these biopolymers when used alone or in combination with HPMC result in a sustained drug release, and are in agreement with literature findings [73, 74]. Their release follows super case II transport type behavior indicating both swelling and erosion to be the controlling release rate mechanisms.

4. Conclusions

The use of superdisintegrants over traditional high MW viscosity enhancing agents such as gums for improving drug content uniformity, which is a highly desirable drug product attribute, without compromising the drug dissolution of films containing nanoparticles of griseofulvin was investigated. The results shown demonstrate that the use of superdisintegrants aids in improving the biocompatible film performance. Inclusion of superdisintegrants into HPMC–GF films lead to enhanced viscosity without any negative interaction with GF particles. This led to *stable*, well dispersed suspensions, which upon conversion into dry film dosage form resulted both in excellent drug content uniformity and full recovery of GF nanoparticle size upon redispersion. Although the use of superdisintegrants as **viscosity enhancing agents** led to higher viscosity, it did not have a significant impact on film mechanical properties and resulted in fast

drug dissolution. Thus unlike traditionally used viscosity enhancers, the use of superdisintegrants had a positive impact on drug release, thereby establishing the novel use of superdisintegrants as economical **viscosity enhancing agents** in aqueous low MW polymer based film formulations containing poorly water-soluble drug nanoparticles. In summary, this work comparing the superdisintegrants with traditional **viscosity enhancing agents** is hoped to establish beneficial use of superdisintegrants as viscosity enhancers, exhibiting dual advantage of maintaining drug content uniformity as well as fast and immediate drug release from films containing hydrophilic film formers and poorly water-soluble solid drug nanoparticles. **It is noted that although this work was based on a single poorly water soluble drug, the results may be widely applicable based on the recent work demonstrating drug-particle laden films as a robust platform via investigating five different drugs including GF [75].**

Acknowledgements

The authors would like to thank Prof. Zafar Iqbal and Dr. Jade Ying for their help in Raman and FTIR characterization of films. Financial support in part through the National Science Foundation Engineering Research Center (NSF-ERC) award (EEC-0540855) is gratefully acknowledged.

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- 685

List of Figures

Fig. 1. Log-Log plots for apparent shear viscosity versus shear rate for (a) the film precursor suspensions, (b) the HPMC–additive mixtures (c) 1% aqueous solutions of Pectin, XG, and GG as well as the aqueous solutions of F-E15LV_High, and F-E4M without glycerin (measured using the high shear program at 45 °C).

Fig. 2. Cumulative size distributions of GF particles redispersed from the films with various formulations and the GF particles in the nanosuspension produced via WSMM.

Fig. 3. Cross-sectional SEM images of the films: (a) F-SSG, (b) F-CCS, and (c) F-CP at 1kX magnification showing individual superdisintegrant particles; (d) F-SSG at 25 kX magnification showing the GF nanoparticle distribution within the HPMC matrix, and (e) F-Pectin at 40 kX magnification showing aggregated state of the particles.

Fig. 4. Comparison of the GF release profiles from (a) films containing superdisintegrants (F-SSG, F-CCS, and F-CP) against the films containing gums and Pectin (F-Pectin, F-GG, F-XG) (b) films containing superdisintegrants against the films made with higher HPMC concentration (F-E15LV_High) and with high MW HPMC (F-E4M).

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List of Tables.

Table 1. Composition of the film precursor suspensions.

Table 2. Apparent shear viscosity of the HPMC–additive mixtures and the film precursor suspensions at 25 °C and 2.2 s⁻¹ shear rate.

Table 3. Size statistics for SSG, CCS and CP particles in HPMC–additive suspensions, film precursor suspensions, and suspensions obtained from the redispersion of the films.

Table 4. Size statistics for the GF particles in the film precursor suspensions and redispersion of the dry films.

Table 5. Drug content uniformity and thickness variation of the films from various formulations. Results are average of ten samples, each sample is 0.712 cm².

Table 6. Mechanical properties of films prepared from various formulations.

Table 1. Composition of the film precursor suspensions.

Formulation	HPMC	Glycerin	Additive	Additive
ID^a	% (w/w)	% (w/w)		% (w/w)
F-None	8.70	3.33	None	–
F-SSG	8.50	3.33	SSG	0.67
F-CCS	8.50	3.33	CCS	0.67
F-CP	8.50	3.33	CP	0.67
F-Pectin	8.50	3.33	Pectin	0.67
F-GG	8.50	3.33	Guar gum	0.67
F-XG	8.50	3.33	Xanthan gum	0.67
F-E4M	2.47	2.22	None	–
F- E15LV_High	10.73	3.33	None	–

^aAll film precursor suspensions had 2.94% GF and 0.15% SDS.

Table 2. Apparent shear viscosity of the HPMC–additive mixtures and the film precursor suspensions at 25 °C and 2.2 s⁻¹ shear rate.

Formulation ID	Viscosity of HPMC– additive mixtures (cP)^a	Viscosity of film precursor suspensions (cP)
F-None	5176 ± 95	2338 ± 58
F-SSG	20954 ± 847	11060 ± 246
F-CCS	10251 ± 218	4993 ± 227
F-CP	8112 ± 216	2537 ± 122
F-Pectin	14741 ± 561	4274 ± 333
F-GG	9790 ± 589	3320 ± 273
F-XG	23288 ± 499	12381 ± 392
F-E4M	14750 ± 212	8686 ± 257
F- E15LV_High	10695 ± 246	5840± 237

^aFor HPMC-additive solutions (F-GG, F-XG and F-Pectin) and HPMC-additive suspensions (F-SSG, F-CCS and F-CP) before addition of GF nanosuspensions.

Table 3. Size statistics for SSG, CCS and CP particles in HPMC–additive suspensions, film precursor suspensions, and suspensions obtained from the redispersion of the films.

Formulation	HPMC–additive suspension		Film precursor suspension		Redispersion from the film	
	d_{50} (μm)	d_{90} (μm)	d_{50} (μm)	d_{90} (μm)	d_{50} (μm)	d_{90} (μm)
F-SSG	166.6 ± 4.0	256.1 ± 2.0	156.9 ± 5.0	231.1 ± 4.0	162.9 ± 4.0	261.1 ± 3.0
F-CCS	95.5 ± 5.0	180.0 ± 7.0	78.3 ± 8.0	152.3 ± 7.0	88.3 ± 6.0	162.3 ± 7.0
F-CP	65.0 ± 4.0	127.6 ± 2.0	55.0 ± 5.0	112.0 ± 3.0	60.0 ± 2.0	120.0 ± 5.0

Table 4. Size statistics for the GF particles in the film precursor suspensions and redispersion of the dry films.

Formulation	Film precursor		Redispersion from the	
ID	suspension		film	
	d_{50} (μm)	d_{90} (μm)	d_{50} (μm)	d_{90} (μm)
WSMM ^a	0.16 ± 0.00	0.24 ± 0.00	–	–
F-None	0.16 ± 0.01	0.25 ± 0.01	0.18 ± 0.02	0.35 ± 0.02
F-SSG	0.16 ± 0.01	0.25 ± 0.01	0.16 ± 0.02	0.28 ± 0.01
F-CCS	0.16 ± 0.01	0.25 ± 0.01	0.16 ± 0.01	0.28 ± 0.01
F-CP	0.16 ± 0.01	0.25 ± 0.01	0.19 ± 0.01	0.29 ± 0.02
F-Pectin	0.19 ± 0.02	0.34 ± 0.02	0.24 ± 0.00	1.72 ± 0.01
F-GG	0.17 ± 0.01	0.26 ± 0.01	0.18 ± 0.00	0.28 ± 0.01
F-XG	0.19 ± 0.01	0.30 ± 0.02	0.23 ± 0.01	0.95 ± 0.02
F-E4M	0.16 ± 0.01	0.24 ± 0.01	0.16 ± 0.01	0.26 ± 0.01
F-E15LV_High	0.17 ± 0.01	0.26 ± 0.01	0.17 ± 0.01	0.29 ± 0.01

^aMilled GF suspension prepared via wet stirred media milling (WSMM).

Table 5. Drug content uniformity and thickness variation of the films from various formulations.

Results are average of ten samples, each sample is 0.712 cm².

Formulation	Thickness	%RSD	Amount of	%RSD	Drug	%RSD
ID	(μm)		drug (mg)		content	
F-None	98.0 $\pm$ 6.0	6.1	1.47 $\pm$ 0.16	10.9	15.0	5.3
F-SSG	95.5 $\pm$ 3.3	3.5	1.51 $\pm$ 0.04	3.3	15.7	1.9
F-CCS	95.0 $\pm$ 5.1	5.4	1.52 $\pm$ 0.07	4.6	15.8	2.5
F-CP	100.0 $\pm$ 3.0	3.0	1.48 $\pm$ 0.09	6.1	15.9	2.5
F-Pectin	98.8 $\pm$ 1.0	1.0	1.60 $\pm$ 0.12	7.5	16.0	5.0
F-GG	100.5 $\pm$ 1.4	1.4	1.47 $\pm$ 0.10	6.8	16.0	3.8
F-XG	98.2 $\pm$ 1.3	1.3	1.50 $\pm$ 0.14	9.3	15.9	5.7
F-E4M	98.0 $\pm$ 3.0	3.1	1.51 $\pm$ 0.05	3.3	15.8	2.5
F-E15LV_High	100.0 $\pm$ 5.0	5.0	1.51 $\pm$ 0.07	4.6	15.7	2.5

Table 6. Mechanical properties of the films prepared from various formulations.

Formulation ID	Yield stress (MPa)	Ultimate strength (MPa)
F-None	19 ± 3	25 ± 3
F-SSG	20 ± 3	26 ± 3
F-CCS	19 ± 3	23 ± 3
F-CP	15 ± 3	21 ± 3
F-Pectin	29 ± 2	45 ± 4
F-XG	23 ± 4	33 ± 4
F-GG	23 ± 6	38 ± 5
F-E4M	30 ± 2	40 ± 4

Superdisintegrants (highly water swellable cross-linked polymers) as viscosity enhancers instead of high MW water soluble polymers

Stable drug nanosuspension

Superdisintegrants + HPMC aqueous suspension

High viscosity film precursor with nanoparticle stability

Dried film with uniform drug nanoparticle distribution

- Excellent drug content uniformity < 3 % RSD
- No increase in mechanical strength
- Very fast drug release compared to traditional VEAs