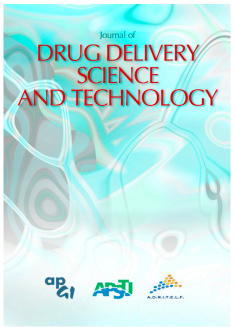

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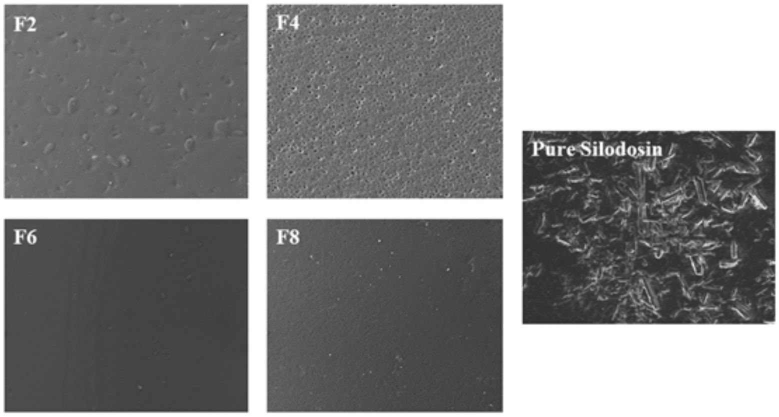
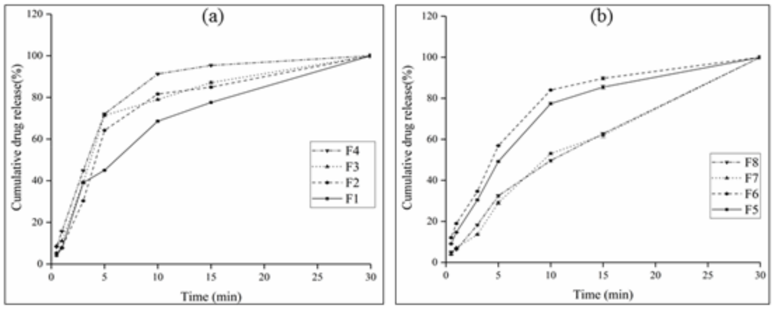
Silodosin
HPMC
HPMC-AS
TPGS


F2
F4
F6
F8
Pure Silodosin



Silodosin oral films: Development, physico-mechanical properties and *in vitro* dissolution studies in simulated saliva

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Abstract

Sublingual film dosage forms for drugs used for fast symptomatic treatment have promise because they allow a rapid onset of action. The aim of this study was to prepare films of silodosin intended for sublingual administration for the symptomatic treatment of benign prostatic hyperplasia in men. Hydroxypropyl methylcellulose (HPMC) or hydroxypropyl methylcellulose acetate succinate (HPMC-AS) were used as film-forming polymers. The effects of the polymers and the surfactant tocopherol polyethylene glycol succinate (TPGS) on the physico-mechanical properties and dissolution behavior of the films in simulated saliva were investigated. The eight silodosin oral films developed (F1–F8) contained 8 mg silodosin per 6 cm^2 film and HPMC or HPMC-AS in drug:polymer ratios of 1:5 or 1:3, while four also contained TPGS (0.5 % w/w). The films were characterized using DSC, TGA, SEM, and PXRD and the mechanical properties were investigated by measuring tensile strength, elongation at break and Young's modulus. The mechanical properties of the films were dependent on the ratio of polymer used. The *in vitro* dissolution and drug release studies indicated that HPMC-AS films disintegrated more quickly than HPMC films. Silodosin was shown to be dispersed within the polymers. Despite silodosin being submicronized in the HPMC films, the dissolution and drug release rate (time for 80% release) from HPMC films was significantly faster than from HPMC-AS films. TPGS increased the drug release rate to a greater extent with HPMC than with HPMC-AS. The degree of saturation of formulation F4 was >1, which shows potential for improving oral absorption of silodosin.

Keywords:

Silodosin, sublingual oral films, HPMC, HPMC-AS, TPGS, simulated saliva

1. Introduction

Conventional oral dosage forms, such as tablets or capsules, have challenges related to dissolution, absorption and poor bioavailability for some drugs and can also be associated with problems related to patient compliance [1, 2, 3]. Alternative drug delivery systems such as oromucosal formulations can be used to overcome these drawbacks [4]. Oromucosal formulations such as oral films have recently been receiving attention from the pharmaceutical industry because of their unique advantages [5, 6]. For instance, oral films are easy to administer, do not require chewing or intake of water, and disintegrate and dissolve rapidly to release the drug when placed in the oral cavity [7, 8]. This has the potential to improve patient compliance, mainly for pediatric and geriatric patients but also for others with mental disorders, dysphagia or emesis [9, 5]. Drugs formulated as oral films intended for sublingual administration will be directly and rapidly absorbed into the systemic circulation without passing through the gastrointestinal tract (GIT), thereby bypassing first-pass metabolism in the liver [10, 11]. The relatively extensive vascularity and high permeability of the sublingual mucosa and membranes can facilitate rapid absorption of the formulated drug and instant bioavailability [12, 13, 14, 5].

Oral films can be prepared by various methods, including solvent casting, hot-melt extrusion, electrospinning, freeze drying and ink-jet printing [15, 16, 17, 18]. The solvent-casting method is appropriate and feasible for manufacturing on an industrial scale. Usually, oral films contain polymers, plasticizers, drug, surfactants and taste-masking agents (sweeteners and flavors) as required. The film-forming ability and water solubility are the main considerations for selecting the polymer. The polymer to plasticizer ratio is also crucial, as this affects the physico-mechanical stability of the final product, and consideration of this attribute is thus required in the design and development process for oral film formulations. Garsuch and Breitkreutz have reported that the cellulose-derived polymer hydroxypropyl methylcellulose (HPMC) forms films well and has better mechanical properties than other tested excipients [19]. In another study, Visser et al. reported the optimal physico-mechanical properties of films prepared with combined HPMC and polyol plasticizers [20]. Oral films can be considered as solid dispersions and the systematic determination of the drug's solubility in the film-forming excipients (polymers/surfactants) using the appropriate techniques is an important development step.

Cellulose-based polymers such as HPMC and hydroxypropyl methylcellulose acetate succinate (HPMC-AS) help to stabilize the physical structure of the drug, preventing it from recrystallizing, and increasing its supersaturation during dissolution [21]. It could thus be interesting to evaluate the potential of these polymers in the preparation of oral films intended for sublingual drug absorption. The oral cavity has a smaller surface area and less dissolution medium (i.e. saliva) than the GIT and the polymers could provide a vital boost to the dissolution and subsequent absorption of drugs administered as a film [22]. Furthermore, the film-forming properties and potential of HPMC and HPMC-AS in film drug delivery have been extensively investigated.

Surfactants are also an important excipient in the preparation of drug-carrying films, particularly for poorly water-soluble drugs. It is well known that surfactants can facilitate wettability and enhance the dissolution rate of poorly water-soluble drugs. For example, Vuddanda et al. have reported that the addition of surfactant enhanced the dissolution of tadalafil nanocrystal-loaded oral films [23].

Benign prostatic hyperplasia (BPH) is an enlargement of the prostate gland caused by the proliferation of prostatic stromal cells. It's an important cause of lower urinary tract symptoms in men such as frequency, urgency, nocturia, and hesitancy. BPH is a common problem among men after the age of 40 years [24, 25]. Silodosin is a selective α_{1A} adrenoceptor blocker that is a safe, effective treatment for the relief of both voiding and storage symptoms in patients with BPH [26]. Silodosin is a white to pale yellowish-white powder. The partition coefficient [LogP (octanol/water)] of silodosin is 2.87, with dissociation constants pKa1 of 8.53 and pKa2 of 4.03. According to the US Food and Drug Administration (FDA) label, silodosin is very slightly soluble in water. The oral bioavailability of silodosin administered as an oral capsule is nearly 32% and the onset of action (maximum urine flow rate) after the first dose occurs in 2-6 hours [27]. Silodosin undergoes extensive metabolism involving glucuronidation in the liver [27, 28].

Because of these issues, an oral film formulation, intended for sublingual administration, could be promising for silodosin. This would facilitate rapid absorption, provide a faster onset of action, and have potential for faster relief of symptoms than an oral capsule. In addition, patient compliance could be improved, as some patients find films easier to take than capsules. Also, the sublingual film formulation of silodosin avoids first-pass metabolism in the liver and thus has potential to improve systemic bioavailability. Films can also provide a supersaturated concentration of the drug in the saliva, which can improve the oral mucosal absorption of poorly soluble drugs. To our knowledge this is the first study of the preparation of a sublingual film dosage form for silodosin.

The main aim of this study was to prepare oral film formulations of silodosin intended for sublingual administration. The effects of added polymer and surfactant on the physico-mechanical and dissolution properties of the films were investigated. The dissolution and supersaturation properties of the films were investigated in small volumes of simulated saliva to realistically mimic the oral cavity. HPMC and HPMC-AS were investigated as film-forming polymer excipients in drug:polymer ratios of 1:3 w/w and 1:5 w/w and tocopherol polyethylene glycol 1000 succinate (vitamin E; TPGS) was included as a surfactant. The silodosin dose in each film was 8 mg (the daily recommended dose of silodosin according to the FDA) and the films were 6 cm^2 (2 cm × 3 cm) in area.

2. Materials and methods

2.1. Materials

Silodosin was obtained from Ultra Medica (Damascus, Syria). Hydroxypropyl methylcellulose 6cp (Pharmacoat 606) and Hydroxypropyl methylcellulose acetate succinate 3cp (Hypromellose Acetate Succinate NF) grade AS-HF were obtained from Shin-Etsu (Tokyo, Japan). D-α-tocopherol polyethylene glycol 1000 succinate (vitamin E; TPGS) NF grade was received as a gift sample from BASF Chemicals (Ludwigshafen, Germany). Glycerol and acesulfame potassium were purchased from VWR chemicals (Stockholm, Sweden). The water used in all experiments was ultrapure, freshly collected from a Millipore water system (Milli Q, Sweden). The other materials were purchased locally and used as purchased.

2.2. Methods

2.2.1. Drug-polymer miscibility

Silodosin and the polymers (HPMC or HPMC-AS) were mixed in three ratios (1:1, 1:3 and 1:5 w/w) to a total weight of 400 mg. The solid dispersions were prepared by the film-casting method. The drug and polymers were dissolved in ethanol:water (1:1 v/v) to a volume of 5 mL. This solution was cast onto a fluoropolymer-coated polyester sheet (Scotchpak® release liner 1022, 3 MInc., USA) and dried at 70˚C in an oven for 1 hour. The dried samples were then analyzed using differential scanning calorimetry (DSC; TA Instruments Q 1000, USA) to investigate the miscibility of the drug and the polymer.

2.2.2. Preparation of the casting gel

The casting gel consisted of HPMC or HPMC-AS (65%), glycerol and propylene glycol (7%), and sweetener (2%), with ethanol and water as vehicle, relative to the total weight of the solid base. All weights are w/w ratios. Silodosin was dissolved in ethanol (12-13%) and the remaining excipients were dissolved in water (87-88%). HPMC or HPMC-AS was gradually added to this solution under constant magnetic stirring (800 rpm) at ambient temperature (21 ± 1 ˚C) until a homogeneous gel was obtained. This casting gel was kept for 6-12 h to remove the air bubbles. Table 1 shows the overall composition of the prepared films.

2.2.3. Preparation of drug-loaded films

The casting gel (10g) was cast onto a fluoropolymer-coated polyester sheet (Scotchpak® release liner 1022, 3 MInc., USA) using an automated film applicator equipped with a coating knife (Coatmaster 510, Erichsen, Sweden). The silodosin dose of 8 mg was loaded into each 6 cm^2 film by fixing the wet film thickness at 750μm with a casting speed of 5 mm/s, estimated from the formula developed by Preis et al, [29]. The cast films were dried in a convective hot-air oven (Binder, Sweden) at 60 °C for 45-50 min. After drying, the films were carefully peeled off, sealed in plastic (polythene) zip pouches, and stored in a desiccator (23 °C/40% RH) until further characterization.

2.2.4. Dry film thickness

The thickness of the films was measured using a Vernier caliper (Cokraft®, Digital caliper, Sweden). The thickness of each film was measured at the four sides and at the middle point. The average and standard deviation were calculated.

2.2.5. Differential scanning calorimetry (DSC)

Thermograms of the drug, the drug/polymer blends and the film samples were recorded using a differential scanning calorimeter (TA Instruments Q 1000, USA) equipped with a refrigerated cooling system. Each sample (1–3 mg) was placed in a standard aluminum pan and sealed. The samples were heated at a rate of 10 °C/min from 25 to 120 °C under nitrogen purge (50 mL/min). The calorimeter was previously calibrated for temperature and heat capacities using indium and sapphire. The results were analyzed using Universal analysis software (TA instruments, USA).

2.2.6. Thermo-gravimetric analysis (TGA)

A TGA instrument (TA instruments, USA) was used for thermo-gravimetric analysis. Approximately 5–8 mg of film (small pieces) were placed in a platinum pan and heated from 25 to 150 °C at a constant heating rate (10 °C/min) under nitrogen flow (50 mL/min). The results were analyzed using Universal analysis software (TA instruments, USA).

2.2.7. Powder X-ray diffraction (PXRD)

PXRD patterns from pure crystalline silodosin and the film samples were collected using an Empyrean PXRD instrument (PANalytical, Almelo, The Netherlands) equipped with a PIXel3D detector and monochromatic Cu Kα X-Ray radiation ($\lambda = 1.54056$ Å). The voltage and current were 45 kV and 40 mA. The samples (3 × 3 cm^2 films) were placed on a silicone (zero background) plate which was fitted into the metal sample holder. The samples were scanned (diffraction angle 2θ) between 5° and 40°, increasing at a step size of 0.02. All patterns were obtained at 25 ± 1 °C. The data were processed using High Score Plus software (PANalytical, The Netherlands).

2.2.8. Mechanical properties

The dynamic mechanical strength was tested using a hybrid rheometer in DMA mode (DHR2, TA Instruments, Sweden). Briefly, samples of cast films were cut into rectangular strips of 1×5 cm^2 and 1 cm at each end was held between clamps; thus, the effective testing area was 1×3 cm^2. The upper clamp was then used to stretch the film upwards at a constant linear rate of 0.1 mm/min until the film ruptured. Stress and strain were computed by Trios® software. The tensile strength (TS) and the elongation at break (EB) were obtained from the peak stress and the maximum strain, respectively, in the stress vs strain plot. Tensile tests are commonly used to determine the robustness of film preparations. The TS is the maximum force applied to the film sample at the breaking point and the EB is the length of the film during the pulling process. In addition, Young´s modulus or the elastic modulus (EM) describes the influence of the strain and its force at this strain on the film area. The EM was obtained from the initial elastic deformation region in the stress vs strain plot [30].

$$Tensile\ strength\ (TS) = \frac{\text{Peak stress}}{\text{Cross−sectional area of the film}} \tag{1}$$

$$Elongation\ at\ break\ (EB) = \frac{\text{Increase in length at break}}{\text{Initial film length}} \times 100 \tag{2}$$

2.2.9. Scanning electron microscopy (SEM)

A Merlin scanning electron microscope (Zeiss, Oberkochen, Germany) equipped with X-Max 50 mm^2 X-ray detectors (Oxford Instruments, Abingdon, UK) was used to examine the morphology of the films. The instrument voltage was 20 kV and the current were 1 nA. The selected film samples were coated with tungsten before the examination to increase the conductivity of the electron beam.

2.2.10. HPLC analytical method

The drug content of the films was analyzed in a high-performance liquid chromatography (HPLC) system (Agilent systems Inc., USA) with an auto sampler. The sample separation was performed on an Agilent Eclipse-plus C18 column (5 μm, 250 mm × 4.6 mm) with a mobile phase of 25 mM potassium-dihydrogen phosphate buffer (pH 7.0) and acetonitrile 40:60 (v/v) at 25˚C. The flow rate was 1 mL/min. The determination wavelength was 269 nm [31].

2.2.11. Drug content

The films (1×1 cm^2) were placed in a volumetric flask containing 10 mL of water and ethanol (1:1 v/v) and kept under magnetic stirring at 100 rpm for 1 h. The obtained solution was filtered through a syringe filter (0.2 μm) and the filtrate was analyzed for drug content using HPLC.

2.2.12. Disintegration time

Samples (1×1 cm^2) were placed in a Petri dish containing 2 mL of water and shaken at 60 rpm using an orbital shaker water bath at 37 ± 1 °C. The disintegration time of the films was evaluated using a modified Petri dish method [19]. The time to disintegration or disruption was measured with a stopwatch.

2.2.13. Solubility studies

The solubility of silodosin was determined in simulated saliva containing pre-dissolved HPMC or HPMC-AS with or without TPGS in concentrations similar to those used in the film formulations. The simulated saliva was prepared using compositions mentioned by Hobbs and

David [32]. An excess of drug was added to conical flasks containing 10 mL of saliva and the other polymer-surfactant excipients. The flasks were tightly closed and placed in a shaker water bath at 37°C. After 48 h, the separated aliquots were filtered through a 0.45 μm filter, diluted appropriately and analyzed using HPLC. Each experiment was performed in triplicate ($n = 3$) and the results were reported as means ± standard deviation (SD).

2.2.14. *In vitro* dissolution in simulated saliva

Non-sink dissolution studies were carried out in simulated saliva at pH 6.8. The films (F1-F8; 2 × 3 cm) were carefully dropped into 10 mL dissolution medium under continuous orbital shaking (60 rpm) at 37˚C. Experimental conditions such as volume of the dissolution medium, shaking speed and temperature were chosen according to literatures [33, 34, 35, 36, 37]. Samples of the medium were then withdrawn at different times, filtered through syringe filters (0.45 μm) and analyzed by HPLC.

The degree of supersaturation (DS) was calculated from the drug concentrations at different times during dissolution of the films (F1-F8) and the drug concentrations at equilibrium. DS calculations for the formulated drug were based on equation 3:

$$\mathrm{DSt} = \frac{\mathrm{Ct}}{\mathrm{Ceq}} \tag{3}$$

Where: C_t is the drug concentration at time t and C_{eq} is the equilibrium solubility of the drug in the test medium. The obtained values of DS for F1-F8 were plotted versus time.

2.2.15. Statistical analysis

One-way ANOVA and Tukey's post hoc multiple comparisons were used to determine statistically significant differences ($p < 0.05$). All results were expressed as averages plus standard deviation (n=3). Mechanical properties were investigated using $n = 5$.

3. Results and Discussion

3.1. Thermal and solid-state properties

DSC thermograms of pure and amorphous silodosin showed a sharp endothermic event at ~106 ˚C for pure silodosin, confirming its crystalline state. This is in line with results from a previous report by Singh and Mirmehrabi [38]. The endothermic peak was absent in case of amorphous silodosin confirming an amorphous state. To choose the best drug: polymer ratio in the miscible system for forming films, different polymer ratios were investigated (Fig. 1). The melting peak of the crystalline silodosin (~106 ˚C) was absent in the thermograms of all the silodosin: polymer systems under investigation, indicating that all the systems were miscible and formed solid dispersions (Fig. 1). These results confirmed the formation of miscible dispersions with the studied ratios. Thus, the silodosin: polymer ratios 1:3 and 1:5 were chosen for film formulations with either HPMC or HPMC-AS, with or without the surfactant (TPGS) (Table 1). The polymer content was necessary for casting the films and preventing drug recrystallization during storage.

The thermal properties of pure silodosin and the formulated films were assessed as shown in Fig. 2. The melting peak of the crystalline form was absent from the DSC thermograms of all the prepared films (F1-F8), which was interpreted as molecular dispersion of the drug in the polymer (Fig. 2). ElMeshad and El Hagrasy have also reported the formation of a uniform dispersion with complete molecular miscibility of different film components in films prepared with HPMC [39]. A similar finding of solid dispersions of amorphous nifedipine in HPMC-AS was reported by Curatolo et al. [21]. A glass transition temperature (T_g) of 92.9 ˚C for

HPMC-based films and 79.28 ˚C for HPMC-AS-based films was observed (data not shown). The T_g values for the films were higher than the temperature in the buccal cavity and also the environmental temperature, which is important for keeping the product stable during storage (from the perspective of the product logistics from manufacturing to consumption) [40, 19].

TGA was performed to determine the moisture content in the prepared films, as shown in Fig. 3. Weight loss was between 0.9 and 1.6 % for the films prepared with the HPMC polymer (F1-F4) and between 1.6 and 1.9 % for the films prepared with the HPMC-AS polymer. These results suggest that the film formulations retained some moisture, possibly because of the inherent water sorption properties of both polymers, as suggested by the moisture content in pure HPMC and HPMC-AS (data not shown). A moisture content of about 2% is essential for flexibility of the films and this was found not to affect the physical stability of the solid dispersions, as confirmed by DSC and PXRD analysis (Fig.s 2 and 4). However, it was observed that the films prepared with HPMC-AS, but not the HPMC films, were tacky. The tacky nature of the films prepared with HPMC-AS could be attributed to the significantly higher moisture content, as observed from thermogravimetric analysis.

The solid state of pure silodosin and the film formulations were analyzed using PXRD (Fig. 4). The PXRD pattern of pure silodosin showed sharp, characteristic peaks at 2θ angles of approximately 10, 11 and 20, illustrating the crystalline nature of the starting material. This is in agreement with the PXRD patterns reported by Singh and Mirmehrabi [38]. These characteristic peaks disappeared, and a hollow shape was observed in the PXRD patterns for all the HPMC-AS film formulations (F6-F8), which confirms the formation of a solid dispersion with the drug uniformly dispersed in the polymer. However, in the case of HPMC films (F1-F4), very low intensity diffraction peaks were observed, which suggests that the drug may not have been fully dispersed or may have existed as submicron particles in the polymer matrix.

3.2. Film Morphology

As shown in Fig. 5, the surface morphology of the pure silodosin and representative film formulations were characterized using SEM. The SEM micrographs of the pure silodosin show particles with irregular morphology. The HPMC-based films (F2 and F4), but not the HPMC-AS-based films (F6 and F8), had submicron silodosin particles and tiny pores (Fig 5). This observation was in agreement with the PXRD results. The submicron particles of silodosin may have formed at the point of supersaturation in HPMC during preparation of the casting gel. Alonzo et al. reported the formation of submicron particles in HPMC-based amorphous solid dispersions that were related to the degree of supersaturation [41]. This also suggests that more uniform dispersion was obtained in HPMC-AS as a result of the higher solubility of silodosin in HPMC-AS than in HPMC [42, 43].

3.3. Mechanical properties

The mechanical and tensile properties of the thin films were measured under ambient conditions. The EM, TS and EB of the silodosin films are shown in Table 2. TS was greater in HPMC-based films than in HPMC-AS-based films, while the EB was longer in HPMC-AS-based films. Decreasing the content of the polymers reduced the TS of the films. TS and EM values decreased by 53% and 54%, respectively, in HPMC samples with a drug:polymer ratio of 1:3 compared with a ratio of 1:5. The effect of less polymer was even more profound with HPMC-AS; TS and EM decreased by 73% and 86%, respectively. The EB was also affected by decreasing the proportion of polymer, increasing in HPMC- and HPMC-AS-based films with a drug:polymer ratio of 1:3 by 24% and 67%, respectively, compared with a ratio of 1:5.

Interestingly, the addition of TPGS had no significant effect on the EM or TS, whereas a mixed result was seen for the EB. When TPGS was added to the formulations containing the higher proportion of polymer (drug:polymer ratio 1:5), the EB was increased for HMPC films and decreased for HMPC-AS films; however, there was no change in EB when TPGS was added to the films containing the lower proportion of polymer (ratio 1:3). Further studies are needed to determine the cause of this difference.

The ability to sustain TS is important for packaging and handling the thin films. The obtained TS values for our HPMC films are similar to those in the literature [20]. Our TS values are also comparable to those of the commercial products examined by Pries et al. [44] with respect to maximum force, displacement and elongation, particularly in comparison with PediaLax and Triaminic® Cold & Cough products. Thus, it can be inferred that our formulated batches would be suitable for commercialization. In fact, the elongation properties of the HPMC-AS films considerably exceeded those of the commercial products; hence films made to this formulation would possess superior toughness. Tensile properties are a function of the molecular structure. HPMC-AS has fewer polar substituents, which are known to improve elongation, but also to decrease TS [45]. In contrast, while TS was higher with HPMC, the films were not as tough, i.e. they were hard and brittle [46].

3.4. Film thickness, drug content uniformity

The average thickness of the HPMC-based films (F1-F4) ranged from 106.7±0.0 to 116.7±0.0 mm while that of the HPMC-AS-based films (F6-F8) ranged from 86.7±0.0 to 106.7±0.0 mm. Despite the constant monitoring of processing parameters for all film formulations, there were differences in the thicknesses of the two types of film. These differences were attributed to variations in the density of the casting gels for the two polymers as a result of their intrinsic polymer properties. Differences in film thickness between films with the same polymer-based formulations may have resulted from the different solid contents and drug:polymer ratios among the formulations. Evaluation of the drug content in the films showed values ranging from 96 ± 28 to 117±28.9 %, as shown in Table 1. These results indicated uniform distribution of drug in the films, within the acceptable limits for standard oral solid dosage forms, according to the USP [47, 48].

3.5. Disintegration time:

The disintegration times are shown in Table 2. The fastest disintegration was observed with the HPMC-AS-based film F5 (drug: polymer ratio 1:5) which disintegrated in 15.3±1.2 sec. Disintegration was slower for the film based on the HPMC polymer with the same drug:polymer ratio (35.3±0.6 sec). This effect may have been related to the properties of the polymer, i.e. wettability and surface tension. Thus, HPMC-AS films disintegrated more quickly than HPMC films [49]. Addition of the surfactant (TPGS) to the film formulation had an additive effect on the disintegration time (Table 2). These results were in agreement to those of Vuddanda et al, who found an additive effect of the surfactant TPGS on speed of disintegration, and films containing polymer/surfactant disintegrated faster than HPMC alone [23]. Surface tension, wettability, porosity and intra- and inter-molecular interactions between polymer composed materials can affect both disintegration and dissolution [49]. TPGS based films showed a better disintegration because of reduced surface tension and enhanced wettability.

3.6. *In vitro* dissolution in simulated saliva

The solubility of pure silodosin in simulated saliva was 0.46 mg/mL. The solubility of silodosin in simulated saliva with additional dissolved HPMC (with and without TPGS) ranged from 0.48 to 0.51 mg/mL at equilibrium after 48 hours, and with additional dissolved HPMC-AS (with and without TPGS) ranged from 0.94 to 1.1 mg/mL. The dissolution results for the films formulated using HPMC and HPMC-AS are shown in Fig.s 6a and 6b, respectively. In the HPMC-based films, 80% of the drug was released in 10 minutes from F2 (with a drug:polymer ratio of 1:3), while dissolution was poorer for F1 (1:5 drug:polymer ratio), with 80% release after 25 minutes. This may be because the increase in polymer concentration led to the formation of a gel-like state which decreased water uptake and retarded drug release, as reported by Singh and Harmanpreet [50]. Alhayali et al. have previously reported that, in some cases of solid drug dispersions, the drug concentrations do not change with different drug:polymer ratios [51]. Addition of TPGS also improved the drug release noticeably. Thus, films containing TPGS dissolved faster than TPGS-free films. Other workers have mentioned this effect of the surfactant TPGS in terms of its ability to improve the solubility, dissolution rate and bioavailability of some drugs formulated as oral films [52, 23].

In HPMC-AS-based films, about 80% of the drug was released in around 10 minutes (F5 and F6), with no significant differences in dissolution rate between the two ratios (1:3 and 1:5). Addition of the surfactant TPGS to the HPMC-AS-based films negatively affected the dissolution rate for both ratios. Therefore, this study has demonstrated that HPMC works well as a film-forming polymer when combined with TPGS. In a case study by Garsuch and Verena [19], HPMC was the most suitable film-forming material of the excipients tested, providing faster dissolution and easier-to-handle films. Interestingly, the submicron particles appear not to have affected the faster drug release from HPMC films. Further, it was observed that the dissolution behavior of HPMC-AS (TPGS-free) films was similar to that of HPMC films containing amorphous solid dispersions (Fig. 6).

The dissolution studies were conducted in simulated saliva (pH 6.8) under non-sink conditions, mimicking the conditions of the oral cavity. These studies suggested that both polymers are capable of increasing and prolonging the supersaturation of the drug and helping to prevent the tendency of the drug to precipitate and recrystallize during dissolution. This could be attributed to the existence of the drug in the amorphous state and molecularly dispersed in the polymer matrix. This was also evident from the thermal, solid-state and morphological results.

It has been reported that cellulose-derived polymers such as HPMC, HPMC-AS and hypromellose phthalate (HPMCP) are superior for preparing solid, amorphous dispersions, particularly with poorly water-soluble drugs, compared to other polymers. The bulky structure of the polymer network and worse solubility properties (compared to highly water-soluble polymers) facilitate the reduction of drug mobility in the polymer matrix and prevent the drug from recrystallizing as normally induced by supersaturation during dissolution [53]. This consequently improves the product's physical stability and *in vitro* drug release performance. In general, our dissolution results revealed that HPMC and HPMC-AS would be useful for preparing films intended for oral cavity absorption, which is more complex than GIT absorption.

The DS values for silodosin formulated as an oral film are presented in Fig. 7. The highest DS was obtained for HPMC-based formulations at early time points. F4, in particular, had a DS value of > 1 (supersaturated) before 5 minutes, which was earlier than the other films formulated using the HPMC polymer (F1-F3), as shown in Fig. 7. In the dissolution results, 80% of the drug was released from film formulation F4 during the first 10 minutes (Fig. 6). This effect could be attributed to the synergistic effect of the surfactant (TPGS) and the polymer (HPMC), resulting in improved solubility and maintained supersaturation [54, 55, 56]. Therefore, film formulation F4 appears to have potential for the development of a silodosin film formulation with improved performance and improved oral sublingual absorption as a result of the high degree of supersaturation solubility [57, 58].

4. Conclusions

Oral films of silodosin intended for the sublingual administration route were prepared successfully for the first time. DSC studies confirmed the existence of silodosin in an amorphous form in films formulated with HPMC or HPMC-AS. SEM and PXRD studies revealed the presence of submicron particles of the drug in HPMC-based films, while the drug remained fully amorphous in HPMC-AS films. The mechanical properties of HPMC films were better than those of HPMC-AS films with respect to stability during patient handling and packing. The dissolution behavior of HPMC was similar to that of HPMC-AS when the surfactant TPGS was added (0.5 % w/w) to the HPMC film formulation. TPGS at the tested concentration had no effect on the dissolution of the drug in HPMC-AS-based formulations. Silodosin formulation F4 had a DS >1, which could be promising for improving its oral absorption. Further studies are required to evaluate the dissolution of the film in human saliva, and to investigate the permeability of the oral cavity to the drug and the drug absorption characteristics. Film palatability and crystallization during storage (stability) also require investigation.

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Table1. Silodosin oral films. Summary of the drug:polymer ratios for the eight developed films, and the mean thickness, speed of disintegration and drug content ± SD **(n ≥ 3).**

Formulation code	**Drug:polymer ratio**	**Thickness** (mm)**	**Disintegration time (seconds)**	**Drug content (mg)**
F1	1:5 (Silodosin:HPMC)	**106.7±0.0**	**35.3±0.6**	**96±28**
F2	1:3 (Silodosin:HPMC)	**110±0.0**	**61.0±0.0**	**97 ±5.8**
F3*	1:5 (Silodosin:HPMC)	**116.7±0.0**	**65.7±0.6**	**96±1.1**
F4*	1:3 (Silodosin:HPMC)	**113±0.0**	**62.7±1.5**	**104 ±26.1**
F5	1:5 (Silodosin:HPMC-AS)	**106.7±0.0**	**15.3±1.2**	**98 ±6.5**
F6	1:3 (Silodosin:HPMC-AS)	**86.7±0.0**	**33.7±2.5**	**113±18.4**
F7*	1:5 (Silodosin:HPMC-AS)	**90±0.0**	**33.0±1.0**	**117±28.9**
F8*	1:3 (Silodosin:HPMC-AS)	**86.7±0.0**	**56.7±0.6**	**99±19.8**

HPMC = hydroxypropyl methylcellulose; HPMC-AS = hydroxypropyl methylcellulose acetate succinate.

*Four films (F3, F4, F7 and F8) also contained the surfactant tocopherol polyethylene glycol succinate.

**Standard deviation values for all investigated formulations are too small.

Table 2: Mechanical properties of silodosin films

Means ± SD (n ≥ 5)

Film (F)	**Young´s Modulus (Mpa)**	**Max. Tensile Strength (Mpa)**	**Elongation at Break (%)**
1	490±63	10.08±1.59	3.82±0.96
2	225±120	4.74±2.66	4.74±2.21
3	458±34	9.81±0.67	6.35±0.45
4	158±17	3.29±0.25	4.44±0.71
5	337±25	7.31±3.01	12.31±1.33
6	48±19	1.94±0.29	20.57±3.95
7	314±25	6.91±0.96	8.53±1.16
8	54±11	1.99±0.17	20.98±4.33

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Figure captions

Figure 1

Differential scanning calorimetry results for drug-polymer miscibility determination.

Figure 2

Differential scanning calorimetry results for the silodosin film formulations. HPMC-based films, F1-F4; and HPMC-AS-based films, F5-F8.

Figure 3

Thermogravimetric analysis results for the formulated silodosin films showing moisture content.

Figure 4

X-ray diffraction patterns for pure crystalline silodosin and the developed films (F1-F8).

Figure 5

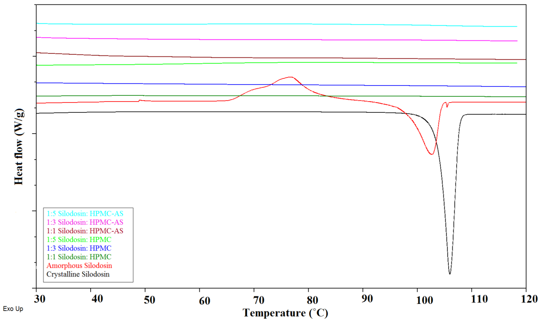
Scanning electron microscopy micrographs for the formulated films and the pure drug (silodosin). The bar represents 100 μm for F2, F4, F6, and F8, and 20 μm for pure silodosin.

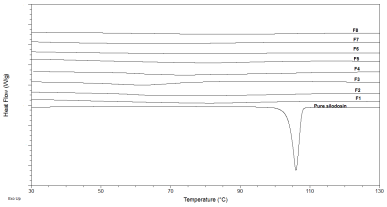
Figure 6

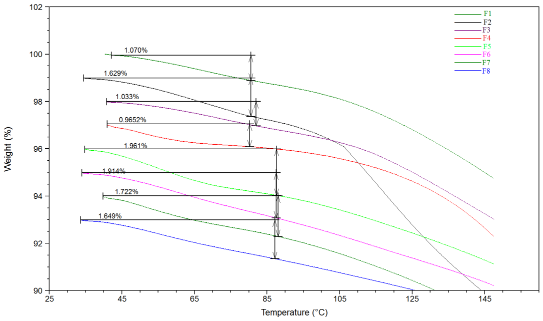
Film dissolution in simulated saliva for (a) the HPMC-based films and (b) the HPMC-AS-based films. n=3 ± SD

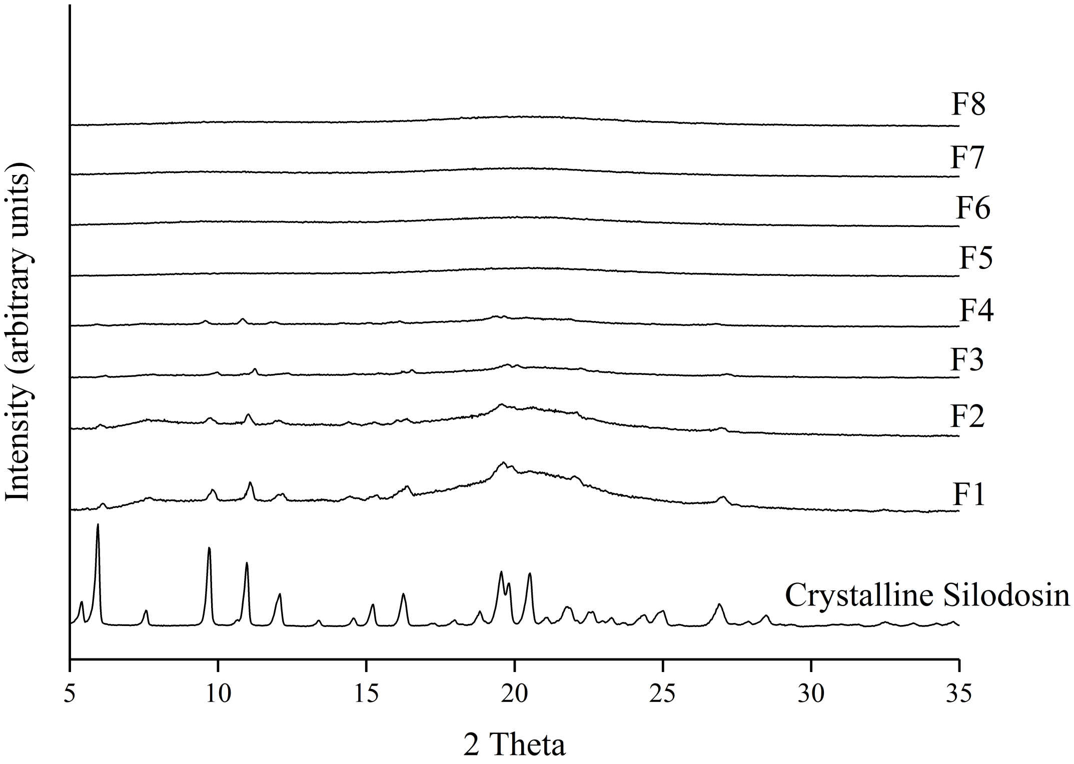
Figure 7

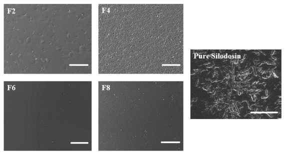
Degree of supersaturation as a result of formulating the drug silodosin in film formulations containing HPMC (F1-F4) or HPMC-AS (F5-F8). n= 3± SD

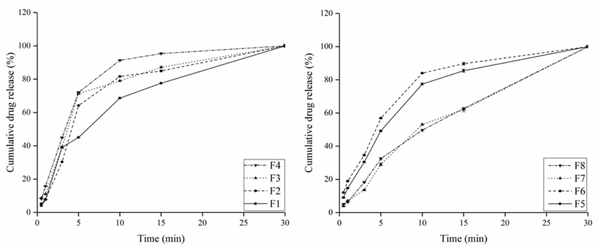

Heat flow (W/g)
1:5 Silodosin: HPMC-AS
1:3 Silodosin: HPMC-AS
1:1 Silodosin: HPMC-AS
1:5 Silodosin: HPMC
1:3 Silodosin: HPMC
1:1 Silodosin: HPMC
Amorphous Silodosin
Crystalline Silodosin
30
40
50
60
70
80
90
100
110
120
Exo Up
Temperature (˚C)

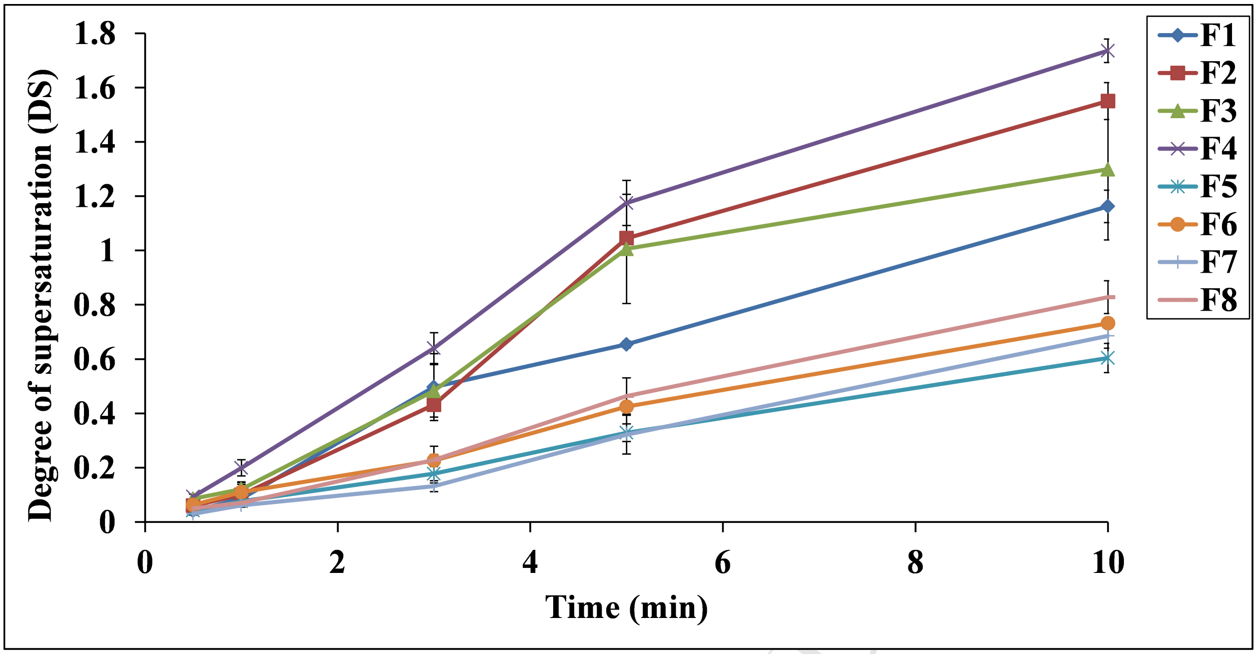

F8
F7
F6
F5
F4
F3
F2
F1
Pure silodosin
Heat Flow (W/g)
30
50
70
90
110
130
Temperature (°C)
Exo Up


102
100
98
96
94
92
90
Weight (%)
25
45
65
85
105
125
145
Temperature (°C)
F1
F2
F3
F4
F5
F6
F7
F8
1.070%
1.629%
1.033%
0.9652%
1.961%
1.914%
1.722%
1.649%


F8
F7
F6
F5
F4
F3
F2
F1
Crystalline Silodosin
Intensity (arbitrary units)
5
10
15
20
25
30
35
2 Theta


F2
F4
Pure Silodosin
F6
F8


120
100
80
60
40
20
0
Cumulative drug release (%)
0
5
10
15
20
25
30
Time (min)
F4
F3
F2
F1
120
100
80
60
40
20
0
Cumulative drug release (%)
0
5
10
15
20
25
30
Time (min)
F8
F7
F6
F5


Degree of supersaturation (DS)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Time (min)
F1
F2
F3
F4
F5
F6
F7
F8

Declaration of interest

None.