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ORIGINAL ARTICLE / ÖZGÜN MAKALE

ASSESSMENT OF BIORELEVANT MEDIA TO ANTICIPATE FOOD EFFECT OF ORAL RITONAVIR AMORPHOUS SOLID DISPERSIONS

ORAL RİTONAVİR AMORF KATI DİSPERSİYONLARININ YİYECEK ETKİSİNİ TAHMİN ETMEK İÇİN BİYOUYUMLU ORTAMLARIN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: *The objective was to evaluate the polymers effects on solubility, solubilization capacity and dissolution of films in biorelevant media, thus, to understand the main mechanism underlaying RTN's negative food effect.*
Material and Method: *Amorphous films were prepared with various polymers via solvent-casting method, then solubility, solubilization capacity and dissolution studies were performed in biorelevant media (FeSSIF-V2 and FaSSIF-V2) and maleic acid buffers (pH 5.8 and 6.5).*
Result and Discussion: *Polymer rank-order to increase RTN solubility in FeSSIF-V2 was SoluPlus>EudragitS100>PVPVA=PEG6000>HPMCAS-L. For FaSSIF-V2, only EudragitS100, SoluPlus and PVP-VA increased RTN solubility. Solubilization capacity studies showed that RTN release was higher for 20% drug loaded films than for 40% for all polymers except for HPMCAS H in FeSSIF-V2, and for HPMCAS-H and HPMCAS-L:H in FaSSIF-V2. In FeSSIF-V2, dissolution studies showed that RTN films from HPMCAS-L and PVP-VA provided higher RTN release compared to other polymers in early time points. $AUC_{(0\text{-}120\ min)}$ in FaSSIF-V2 media was 9.0-fold, 8.3-fold, 5.9-fold, and 5.0-fold higher for SoluPlus, HPMCAS-L, PVPVA and HPMCAS-L:H, respectively, compared to crystalline RTN. Although, RTN's negative food effect, which was not replicated here in vitro, may be due to more complex interactions between drug, polymer, and food in vivo than simulated here using FeSSIF-V2 and FaSSIF-V2.*
Keywords: *Biorelevant media, film, food effect, ritonavir*

ÖZ

Amaç: *Polimerlerin, biyouyumlu ortamlarda filmlerin çözünürlüğü, çözünme kapasitesi ve çözünmesi üzerindeki etkilerinin değerlendirilmesi ve böylece yiyeceklerin RTN üzerindeki olumsuz etkisinin altında yatan temel mekanizmanın anlaşılması amaçlanmıştır.*
Gereç ve Yöntem: *Çeşitli polimerlerle çözücü-dökme yöntemi ile amorf filmler hazırlanmıştır, daha sonra biyouyumlu ortamlarda (FeSSIF-V2 ve FaSSIF-V2) ve maleik asit tamponlarında (pH 5.8 ve 6.5) çözünürlük, çözünme kapasitesi ve çözünme hızı çalışmaları gerçekleştirilmiştir.*
Sonuç ve Tartışma: *FeSSIF-V2'de RTN çözünürlüğünü artırmak için polimer sıralaması SoluPlus>Eudragit S100>PVPVA=PEG6000>HPMCAS-L'dir. FaSSIF-V2 için sadece Eudragit S100, SoluPlus ve PVPVA RTN çözünürlüğünü artırmıştır. Çözünürlük kapasitesi çalışmaları, RTN salınımının FeSSIF-V2'de HPMCAS-H hariç ve FaSSIF-V2'de HPMCAS-H ve HPMCAS-L:H hariç*

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tüm polimerler için %20 ilaç yüklemeye sahip filmlerde %40'tan daha yüksek olduğunu göstermiştir. FeSSIF-V2'de çözünme çalışmaları, HPMCAS-L ve PVPVA'dan elde edilen RTN filmlerinin erken zaman noktalarında diğer polimerlere kıyasla daha yüksek RTN salınımı sağladığını göstermiştir. FaSSIF-V2 ortamındaki $AUC_{(0\text{-}120\,dk)}$ sırasıyla SoluPlus, HPMCAS-L, PVPVA ve HPMCAS-L:H için kristal RTN ile karşılaştırıldığında 9.0 kat, 8.3 kat, 5.9 kat ve 5.0 kat daha yüksek bulunmuştur. Bununla birlikte, bu çalışmada in vitro olarak görülmeyen RTN'nin negatif yiyecek etkisi, burada FeSSIF-V2 ve FaSSIF-V2 kullanılarak simüle edilenden daha karmaşık ilaç, polimer ve yiyecek etkileşimlerinden kaynaklanıyor olabilir.

Anahtar Kelimeler: *Biouyumlu ortam, film, ritonavir, yiyecek etkisi*

INTRODUCTION

Ritonavir (RTN) is an anti-HIV protease inhibitor and antiretroviral medication to treat human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS) and especially Covid-19 infection. Norvir is the RTN marketed brand product in the form of tablets (100 mg strength), powder (100 mg strength) and solution (80 mg/ml). Norvir tablets and powder are amorphous solid dispersions (ASD) of RTN prepared via hot melt extrusion (HME) of RTN and the polymer polyvinylpyrrolidone/vinyl acetate (PVPVA) in the treatment of AIDS and HIV. Polymer-enabled drug supersaturation is generally a significant contributor to ASD-enhanced oral drug absorption [1,2]. The tablet and powder formulations are bioequivalent in the fasting state [3,4]. In several other tablet products, such as Paxlovid, RTN functions to boost other drugs via the inhibition of cytochrome P450 3A. All oral solid dosage forms of RTN employ PVPVA in ASD fabrication [5].

RTN is a high lipophilic, Biopharmaceutics Classification System (BCS) Class II drug [6]. Its solubility decreases with pH due to RTN being weakly basic. Its low solubility limits its intestinal absorption and oral bioavailability. After a single oral dose of RTV to healthy volunteers (600 mg), plasma half-life ($t_{1/2}$) is 3–5 h, and maximum plasma concentration (C_{max}) is 11.2 μg/ml. The fraction of dose absorbed from a 600 mg dose was estimated to be in the range of 60 to 80% [7,8].

In general, BCS Class II drugs with incomplete drug absorption in the fasted state can be expected to exhibit a positive food effect [9]. Indeed, RTN oral pharmacokinetics is affected by meal content [3]. However, interestingly, for both RTN powder and tablets, which are both amorphous formulations, there is about a 20% reduction in AUC and a 23−40% reduction in C_{max} in humans under the fed state as compared to the fasting state [10,11]. A slight difference in T_{max} is consistent with delayed gastric emptying following a meal [3]. While RTN drug substance in vitro solubility in the fed state is higher than the fasted state, its oral bioavailability is lower in fed state. This perhaps surprising negative food effect of Norvir tablets in humans has been attributed to the higher luminal fluid viscosity (and hence lower drug diffusivity) in the fed state, as well lower drug free fraction and hence lower gut wall permeation rate [12]. Alternatively, we hypothesize that the negative food effect is due to food reducing the PVPVA's ability to maintain RTN supersaturation in fed state compared to fasted state, but that other polymers are less prone to this effect.

The objective was to assess the impact of the fed state on RTN supersaturation from RTN ASD. Fed and fasted states were simulated in vitro using the biorelevant media Fed State Simulated Intestinal Fluid-Version 2 (FeSSIF-V2) and Fasted State Simulated Intestinal Fluid-Version 2 (FaSSIF-V2) [13]. RTN ASDs were fabricated as films, using a range of different polymers, including PVPVA as a control. In vitro dissolution of films and other tests were conducted in FeSSIF-V2 and FaSSIF-V2, in order to measure food effect on ASD supersaturation effect. This evaluation of multiple competing polymers was designed to identify a polymer that, unlike PVPVA, would not exhibit a negative food effect.

MATERIAL AND METHOD

Materials

RTN was obtained from ChemShuttle (Blue Current Inc., Hayward,CA). SoluPlus® and Kollidon®VA 64 (PVPVA) were provided by BASF (Ludwigshafen Germany). PEG-6000 (Polyethylene glycol-6000) was provided by Affymetrix (Cleveland, OH USA). HPMCAS L and

HPMCAS H (Hypromellose acetate succinate L and H grades) were provided by Ashland (Covington, KY USA). Eudragit S100 (Methyl methacrylate copolymer) was provided by Evonik (Piscataway, NJ USA). Methanol and dichloromethane (analytical grade) were purchased from Fischer Scientific (Fischer Scientific; Hampton, NH USA) and Sigma Aldrich (Sigma-Aldrich; St. Louis, MO USA).

Preparation of RTN-Containing Films

RTN films were prepared using seven different polymer systems (PEG-6000, PVPVA, SoluPlus, Eudragit S100, HPMCAS H, HPMCAS L and 1:1 combination (i.e. equal weight) of HPMCAS L: HPMCAS H). Polymers and RTN (to target 20% or 40% drug load) were solved in mixture of dichloromethane and methanol (2:1 w/w). Total solids content (i.e sum of RTN and polymer) of solutions was 10% w/w (i.e. 0.5 g RTN and polymer in 5 g solution), which aided films to have the same thickness. The solution (5 g) was poured into an aluminum dish (57 mm diameter). Solvent was evaporated at 25±2°C for 45 min. Film on dish was then placed into a desiccating cabinet (RH<5%) for 24 h. After 24 h, the dried films were triturated and milled into flakes [14]. Same solvent casting method was also applied on RTN, without polymer. Only the required amount of RTN (according to 20% or 40% drug load of films) were solved in the organic solvent without polymer. Then the effects of the polymers were evaluated compared to the no polymer. RTN was still in crystalline form after application of solvent casting.

Preparation of Biorelevant Media

The compositions of the biorelevant media are given in Table 1. FaSSIF-V2 and FeSSIF-V2 were prepared per vendor instructions [15]. To prepare 1.5 l of FeSSIF-V2 (pH 5.8), 4.905 g of NaOH pellets, 9.585 g of maleic acid and 11.00 g of NaCl were weighed as buffer components. Then, approximately 1.35 l of distilled water was added to the buffer components. After dissolving, the solution was adjusted to pH 5.8 with 1 M NaOH solution, and water was added to make up volume (1.5 l). Then, the 14.64 g of FeSSIF-V2 powder from Biorelevant.com was weighted and dissolved in the buffer component solution.

Table 1. FeSSIF-V2 and FaSSIF-V2 compositions

Component	FaSSIF-V2 Concentration (or attribute)	FeSSIF-V2 Concentration (or attribute)
Sodium taurocholate	3 mM	10 mM
Lecithin	0.2 mM	2 mM
Glyceryl monooleate	-	5 mM
Sodium oleate	-	0.8 mM
Maleic acid (MA)	19 mM	55.02 mM
NaOH	34 mM	81.65 mM
NaCl	69 mM	125.5 mM
HCl /NaOH conc. qs ad	pH 6.5	pH 5.8

To prepare the 0.25 l of FaSSIF-V2 (pH 6.5), 0.348 gr of NaOH pellets, 0.555 g of MA and 1.002 g of NaCl were weighted as buffer components. 0.225 l of distilled water was added and stirred until dissolved. pH was adjusted to 6.5, and then the volume was made up to 0.250 l with distilled water. This buffer solution was poured onto the weighted FaSSIF-V2 powder and stirred until dissolved. All media were stored at 4°C to equilibrate before using [16].

Solubility Studies

RTN solubility was measured in maleic acid buffer (pH 5.8), maleic acid buffer (pH 6.5), FaSSIF-V2 (pH 6.5), and FeSSIF-V2 (pH 5.8), each with and without 2 mg/ml of film polymer (i.e. each PEG-6000, PVPVA, SoluPlus, Eudragit S100, HPMCAS H, HPMCAS L and HPMCAS L: HPMCAS H). An excess amount of RTN (0.5mg/ml) was added to 50 mM maleic acid buffer (pH 5.8 or pH 6.5), FeSSIF-V2 (pH 5.8) and FaSSIF-V2 (pH 6.5), without and with 2 mg/ml polymer. Samples were equilibrated at

37°C for 72 hours in an orbitally shaken water bath. pH was checked after 72 h. After centrifugation, samples were filtered using a 0.22 µm membrane filter, and the amount of RTN was analyzed by HPLC.

Solubilization Capacity of Films

Prepared films with 20% (w/w) drug load (i.e. 20:80 ratio of drug:polymer; 12.5 mg which contained 2.5 mg of RTN) and films with 40% (w/w) drug load (i.e. 40:60 ratio drug:polymer; 12.5 mg which contained 5 mg of RTN) were incubated at 37°C for 1 h in 5 ml of FaSSIF-V2 or FeSSIF-V2. Sample was filtered via 0.22 µm membrane filter. The RTN solubilization capacity of the films, which differed in polymer component, was determined using HPLC.

Film Dissolution into Biorelevant Media

Films were subjected to USP II dissolution testing, with sample replacement. USP II apparatus (SR8PLUS, Hanson Research; Chatsworth CA) was used. USP II dissolution testing on each film formulation (n=3) used 900 ml of FeSSIF-V2 (pH 5.8) and FaSSIF-V2 (pH 6.5) at 37°C at 100 rpm for 6 h. Two ml samples were taken at the determined time points (0, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240 and 360 min) and then filtered through a 0.45 mm membrane filter. Two ml of fresh dissolution media was added to the dissolution vessel to keep dissolution volume constant. USP II dissolution testing yielded RTN mass dissolved profile. Drug was quantified using HPLC method and the dissolution profiles were compared via comparing area under the dissolution curve (AUC) values.

Quantification of Ritonavir by HPLC

RTN concentration was determined via Waters 2489 HPLC system (Waters Corporation; Milford, MA USA). An isocratic mobile phase consisting of 53% phosphoric acid and 47% acetonitrile solution and a 4.6 × 150 mm Zorbax C18 5-µm HPLC column were used [17]. The injection volume and flow rate were 25.0 µl and 1 ml/min, respectively. The UV-vis detector was set to 240 nm [17,18]. The retention time of RTN was 9-10 min, with a 13 min run time. A calibration curve containing a range of 0.098-50 µg/ml RTN was run in triplicate with each analysis (r^2 = 0.9999). For solubility and solubilization capacity studies, the calibration curves were obtained for each media, which were maleic acid buffer (pH 5.8 and 6.5), FaSSIF-V2, and FeSSIF-V2, separately. The standard samples were obtained from the stock solution of RTN in methanol (1 mg/ml) by diluating 1:9 ratio with the solubility media. The standard solutions obtained for each media were diluted with mobile phase to prepare the 0.098-50 µg/ml concentrations.

Statistical Analysis

Data was analyzed using SPSS database Version 16 (Systat Software Inc., San Jose, CA USA). The statistical analysis of variance (ANOVA) was carried out at the 95% confidence level (n = 3). A comparison variance analysis ANOVA test followed by Tukey's post hoc testing was used to compare multiple groups. The t-test was used to compare two groups. Results were given as mean ± standard error of mean (SEM) (n = 3).

RESULT AND DISCUSSION

Evaluation of RTN Solubility

An increase in RTN solubility in both the fed and fasted states may be a way to mitigate the negative food effect of Norvir tablets and powder, which as RTN ASDs using PVPVA. To improve RTN solubility, the effect of different polymers (HPMCAS L, HPMCAS H, HPMCAS L:H, SoluPlus, PVPVA, PEG-6000 and Eudragit S100) was evaluated in FeSSIF-V2 (pH 5.8), and FaSSIF-V2 (pH 6.5). Moreover, to see the effect of the surfactant in FeSSIF-V2 (sodium taurocholate, lecithin and glyceryl monooleate, sodium oleate) and FaSSIF-V2 (sodium taurocholate, lecithin), biorelevant solubilities were compared to solubilities in each pH 5.8 and pH 6.5 buffers (Table 2 and Table 3).

Table 2 lists solubility results in buffer (pH 6.5) and FaSSIF-V2. RTN solubility was 2.99 µM (2.16±0.23 µg/ml) in maleic acid buffer (pH 6.5). Xu et al. found a similar solubility of about 2 µg/ml at pH 6.8 [10]. Table 3 lists the solubility results in buffer (pH 5.8) and FeSSIF-V2. RTN solubility in

the maleic acid buffer (pH 5.8) was 3.24 μM (2.34±0.02 μg/ml). RTN's lower solubility at higher pH reflects RTN being a weakly basic drug with pKa values of 1.8 and 2.6 [19-21]. RTN has a high aqueous solubility at pH < 1 and an extremely low solubility at pH 4−7 [10].

Table 2. RTN solubility in 50 mM maleic acid buffer (pH 6.5) and FaSSIF-V2 with and without polymer. When polymer present, polymer concentration was 2 mg/ml. pH = 6.5 in all media. Mean ± SE from n=3

Media (pH 6.5)	Solubility (μM)	Fold-enhancement compared to no polymer
Maleic acid buffer (MA) (no polymer)	2.99±0.33	-
MA (pH 6.5) + HPMCAS L	2.92±0.18	0.989±0.078
MA (pH 6.5) + HPMCAS H	1.34±0.33	0.481±0.173
MA (pH 6.5) + HPMCAS L:H (1:1)	1.08±0.05	0.365±0.030
MA (pH 6.5) + Soluplus	8.89±2.63	3.13±0.96
MA (pH 6.5) + PVPVA	2.96±0.11	1.00±0.074
MA (pH 6.5) + PEG-6000	2.75±0.13	0.931±0.064
MA (pH 6.5) + Eudragit S100	12.3±0.5	3.59±0.98
FaSSIF-V2 (no polymer)	4.25±0.24	-
FaSSIF-V2 + HPMCAS L	3.96±0.27	0.93±0.12
FaSSIF-V2 + HPMCAS H	1.35±0.05	0.315±0.030
FaSSIF-V2 + HPMCAS L:H (1:1)	1.20±0.13	0.284±0.049
FaSSIF-V2 + Soluplus	11.0±0.3	2.56±0.79
FaSSIF-V2 + PVPVA	4.40±0.19	1.03±0.11
FaSSIF-V2 + PEG-6000	4.17±0.25	0.98±0.12
FaSSIF-V2 + Eudragit S100	15.3±0.5	3.56±0.14

In FeSSIF-V2 and FaSSIF-V2, RTN solubility increased about 5-fold and 1.5-fold, respectively, compared to the buffer media. Solubility was higher in the fed state (15.8 μM; 11.37±0.42 μg/ml) than the fasted state (4.25 μM; 3.06±0.18 μg/ml), similar to literature [22,23]. Xu et al. found RTN solubility was 7.4±1.1 μg/ml in FaSSIF-V2 and 18.5±1.9 μg/ml in FeSSIF-V2 [10]. Kokott et al. reported RTN solubility in FaSSIF was 5.4±0.6 μg/ml [23].

The effects of polymers, which were used to prepare the amorphous films of RTN, on RTN solubility in buffer and biorelevant media were also evaluated. In buffer (pH 6.5), only SoluPlus (3.1-fold increase) and Eudragit S100 (3.6-fold increase) increased RTN solubility. In maleic acid buffer (pH 5.8), only SoluPlus materially impacted solubility, where RTN solubility increased about 5-fold with SoluPlus. In FaSSIF-V2, Soluplus and Eudragit S100 increased RTN solubility 2.6-fold and 3.6-fold, respectively, compared to no polymer. In FeSSIF-V2, SoluPlus and Eudragit S100 increased the solubility the most (i.e. 2.1-fold, and 1.7-fold, respectively) compared to no polymer.

Polymers tended to have more complex effects on drug solubilization in biorelevant media than in buffer, particularly in FaSSIF-V2. Most polymers slightly increased RTN solubility in FeSSIF-V2, where SoluPlus, Eudragit S100, and PVPVA performed the best across both biorelevant media. However, in FeSSIF-V2 and FaSSIF-V2, HPMCAS H and HPMCAS L:H (1:1) reduced RTN solubility.

Polymer rank-order to increase RTN solubility in FeSSIF-V2 was SoluPlus> Eudragit S100> PVPVA= PEG6000 > HPMCAS L. For FaSSIF-V2, only Eudragit S100, SoluPlus and PVPVA increased RTN solubility and the order was Eudragit S100 > SoluPlus >PVPVA. Similar results were previously obtained in media containing polyoxyethylene (10) lauryl ether (POE10), where SoluPlus performed the best [14]. SoluPlus may function as a surfactant to form RTN-loaded micelles to increase drug solubility [24]. Eudragit S100 is highly soluble at higher pH [25,26], so it was more effective here in pH 6.5 than pH 5.8. Interestingly, HPMCAS H (and HPMCAS L:H combination) decreased RTN solubility, in contrast with grade L's enhancement of solubility. Compared to HPMCAS L, HPMCAS H has a higher ratio of acetyl substitution to succinoyl substitution. Hence, HMPCAS H is more lipophilic and has less of an ionizable character than HPMCAS L [14,27].

Table 3. RTN solubility in 50 mM maleic acid buffer (pH 5.8) and FeSSIF-V2 with and without polymer. When polymer present, polymer concentration was 2mg/ml. pH = 5.8 in all media. Mean ± SE from n=3.

Media (pH 5.8)	Solubility (µM)	Fold-enhancement compared to no polymer	pH and Food effect (fed / fasted)
Maleic acid buffer (MA) (no polymer)	3.24±0.02	-	1.11±0.12
MA (pH 5.8) + HPMCAS L	4.24±0.14	1.31±0.04	1.46±0.01
MA (pH 5.8) + HPMCAS H	2.96±0.10	0.914±0.032	2.49±0.56
MA (pH 5.8) + HPMCAS L:H (1:1)	3.38±0.08	1.04±0.02	3.14±0.11
MA (pH 5.8) + Soluplus	15.6±1.1	4.74±0.31	2.13±0.79
MA (pH 5.8) + PVPVA	4.46±0.19	1.37±0.05	1.51±0.02
MA (pH 5.8) + PEG-6000	4.04±0.14	1.25±0.04	1.47±0.02
MA (pH 5.8) + Eudragit S100	3.23±0.14	0.994±0.032	0.360±0.103
FeSSIF-V2 (no polymer)	15.8±0.6	-	3.70±0.40
FeSSIF-V2 + HPMCAS L	20.2±0.9	1.28±0.04	5.12±0.15
FeSSIF-V2 + HPMCAS H	12.6±0.4	0.801±0.057	9.38±0.66
FeSSIF-V2 + HPMCAS L:H (1:1)	13.6±0.8	0.861±0.033	11.5±0.80
FeSSIF-V2 + Soluplus	32.9±7.3	2.08±0.44	3.20±0.36
FeSSIF-V2 + PVPVA	23.5±0.5	1.49±0.03	5.35±0.14
FeSSIF-V2 + PEG-6000	23.3±0.3	1.48±0.04	5.62±0.32
FeSSIF-V2 + Eudragit S100	26.8±2.8	1.71±0.20	1.74±0.14

In Table 3, pH and food effect results are listed. pH and food effect compare RTN solubility in Table 3 (i.e. fed state or pH 5.8 buffer, with or without polymer) against the corresponding RTN solubility in Table 2 (i.e. fasted state or pH 6.5 buffer, with or without polymer). A lower food effect was observed with SoluPlus (3.2-fold) and Eudragit S100 (1.7-fold), in part due to these polymers having provided greatest solubility enhancement in FaSSIF-V2. The food effect was about 5-6 fold with PVPVA, PEG-6000, HPMCAS L. The highest food effect was observed with HPMCAS H and HPMCAS L:H polymer, in part due to these polymers having reduced RTN solubility in FaSSIF-V2.

Evaluation of Solubilization Capacity

Figure 1 and 2 show the solubility capacity results of films having 20% and 40% drug loads in FeSSIF-V2 and FaSSIF-V2, respectively. The percentage RTN release from film after 1 h was assessed as the solubilization capacity of the film. In Figure 1, only about 0.6% of RTN was released in the absence of polymer (i.e. from crystalline RTN). Overall, in Figure 2, release in FeSSIF-V2 was higher for 20% drug load (panel a) than for 40% drug load (panel b) for all polymers except HPMCAS H. For 20% of drug loaded films, RTN % release was 38.4% with SoluPlus, 5.2% with HPMCAS L, 4.9% with HPMCAS L:H, 2.1% with PVPVA, 1.9% with PEG-6000, 0.6% with HPMCAS H, and 0.2% with Eudragit S100. So, there was 68-fold, 9.3-fold, 8.8-fold, 3.8-fold, and 3.4-fold increase with SoluPlus, HPMCAS L, HPMCAS L:H, PVPVA, and PEG-6000 compared to without polymer (i.e. 0.6% release). HPMCAS H and Eudragit S100 did not increase solubilization capacity (Table 4). RTN % release in FeSSIF-V2 from films with 40% drug load are shown in Figure 4 panel b. Percent release was 2.2% with SoluPlus, 1.8% with HPMCAS L, 2.0 % with HPMCAS L:H, 1.3% with PVPVA, 0.9% with PEG-6000, 1.9% with HPMCAS H, and 0.07% with Eudragit S100. So, there was 3.9-fold, 3.6-fold, 3.1-fold, 2.3-fold, 1.9-fold, and 1.6-fold increase with SoluPlus, HPMCAS L:H, HPMCAS L, PVPVA, HPMCAS H, and PEG-6000 compared to without polymer (i.e. 0.6% release). Only Eudragit S100 did not increase the solubilization capacity (Table 5).

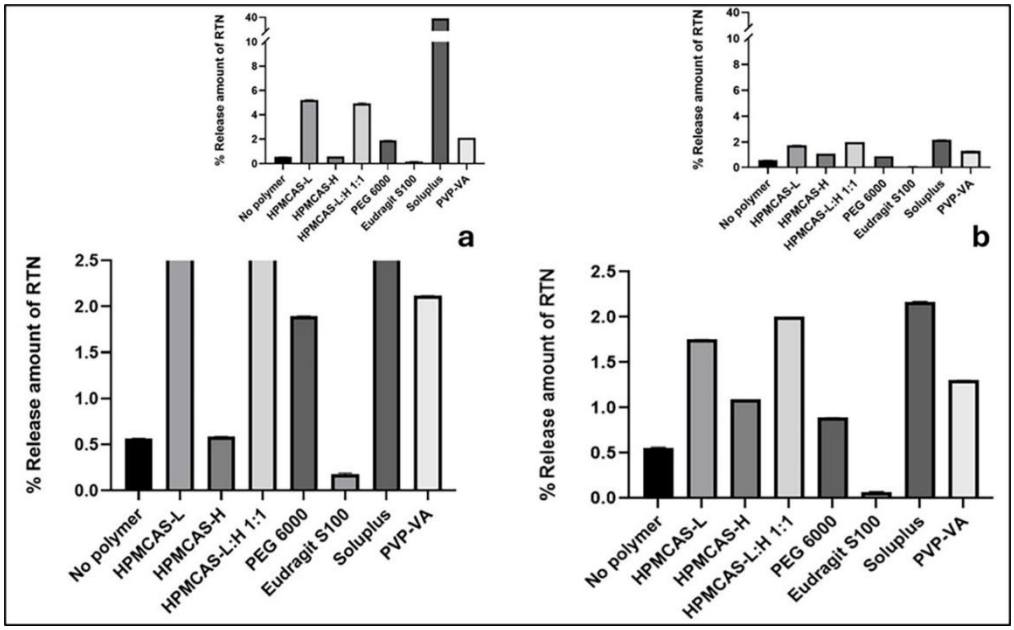

Figure 1. The solubilization capacity of the films contains 20% (a) and 40% (b) drug load of RTN films in FeSSIF-V2. Values are percent RTN dissolved after 1 h, out of 2.5 mg RTN (a) and out of 5 mg RTN (b). 12.5mg of film was tested. Each panel shows two plots with differing extents of RTN release, to facilitate comparisons across polymers and drug loads

Figure 2 plots the solubilization capacity of films in FaSSIF-V2. Only about 0.3% of RTN was released in the absence of polymer (i.e. from crystalline RTN). Like FeSSIF-V2, release was higher for 20% drug load (panel a) than for 40% drug load (panel b) for all polymers except HPMCAS H and HPMCAS L:H. For films having 20% drug load, RTN %release was 1.5% with SoluPlus, 1.0% with HPMCAS L (17.1±0.02 µg/ml), 0.4% with HPMCAS L:H, 2.3% with PVPVA (38.6±0.03 µg/ml), 1.4% with PEG-6000, 0.8% with HPMCAS H, and 0.09% with Eudragit S100.

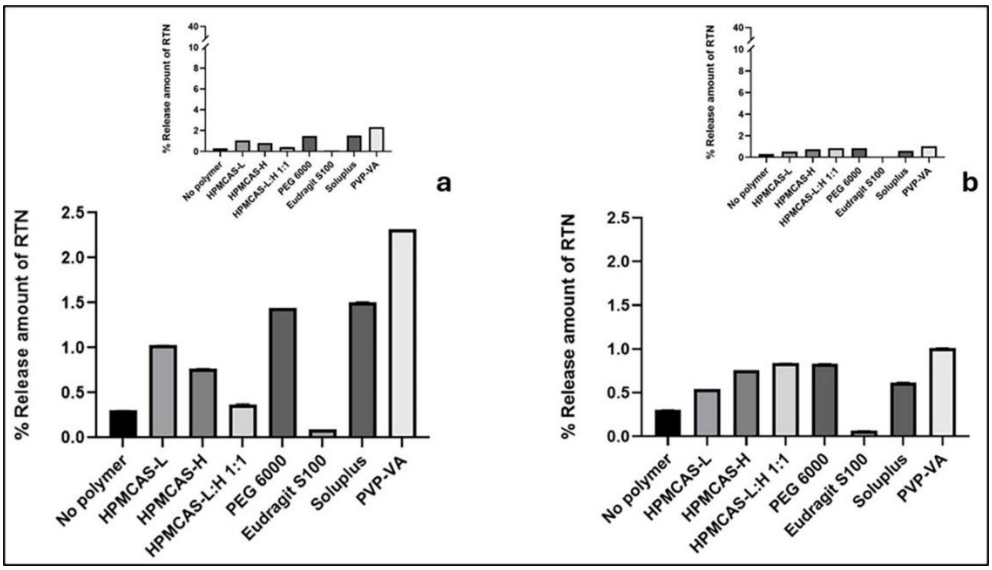

Figure 2. The solubilization capacity of films contains the 20% (a) and 40% (b) drug load of RTN films in FaSSIF-V2. Values are percent RTN dissolved after 1 h, out of 2.5 mg RTN (a) and out of 5 mg RTN (b). 12.5 mg of film was tested. Each panel shows two plots with differing extents of RTN release, to facilitate comparisons to FeSSIF-V2 in Figure 1

There was 7.7-fold, 5.0-fold, 4.8-fold 3.4-fold, 2.5-fold, and 1.2-fold increased with PVPVA, SoluPlus, PEG-6000, HPMCAS L, HPMCAS H, and HPMCAS L:H compared to without polymer (i.e. 0.3% release) (Table 4). Only Eudragit S100 did not increase solubilization capacity. Findings here were like literature, where RTN solubilization from 20% drug loaded ASDs was about 30-35 µg/ml with PVPVA and about 10-15 µg/ml with HPMCAS L, compared to 38.6±0.03 µg/ml for PVPVA and 17.1±0.02 µg/ml for HPMCAS L here [23].

Table 4. Food effect for solubilization capacity of 20% drug load RTN films. Media were FaSSIF-V2 (pH 6.5) and FeSSIF-V2 (pH 5.8), with and without polymer. When polymer present, polymer concentration was 2 mg/ml. Mean ± SE from n=3.

Media	Solubilization capacity (%release)	Fold-enhancement compared to no polymer	pH and Food effect (fed / fasted)
FaSSIF-V2 (no polymer)	0.302±0.001	-	-
FaSSIF-V2 + HPMCAS L	1.03±0.001	3.40±0.019	-
FaSSIF-V2 + HPMCAS H	0.769±0.002	2.54±0.02	-
FaSSIF-V2 + HPMCAS L:H (1:1)	0.373±0.005	1.23±0.02	-
FaSSIF-V2 + Soluplus	1.51±0.002	4.99±0.02	-
FaSSIF-V2 + PVPVA	2.32±0.002	7.66±0.04	-
FaSSIF-V2 + PEG-6000	1.44±0.001	4.77±0.02	-
FaSSIF-V2 + Eudragit S100	0.0876±0.0004	0.290±0.003	-
FeSSIF-V2 (no polymer)	0.562±0.004	-	1.86±0.01
FeSSIF-V2 + HPMCAS L	5.21±0.03	9.26±0.10	5.07±0.03
FeSSIF-V2 + HPMCAS H	0.583±0.003	1.04±0.01	0.759±0.002
FeSSIF-V2 + HPMCAS L:H (1:1)	4.92±0.08	8.75±0.19	1.57±0.02
FeSSIF-V2 + Soluplus	38.4±0.04	68.4±0.5	25.5±0.05
FeSSIF-V2 + PVPVA	2.12±0.003	3.76±0.02	1.63±0.01
FeSSIF-V2 + PEG-6000	1.89±0.003	3.365±0.03	2.33±0.01
FeSSIF-V2 + Eudragit S100	0.180±0.008	0.321±0.016	2.06±0.08

In Figure 2 panel b, RTN %release into FaSSIF-V2 was 0.6%, 0.5%, 0.8%, 1.0%, 0.8%, 0.8% and 0.07% with SoluPlus, HPMCAS L, HPMCAS L:H, PVPVA, PEG-6000, HPMCAS H and Eudragit S100, respectively. So, there was 3.4-fold, 2.8-fold, 2.8-fold, 2.5-fold, 2-fold, and 1.8-fold increase with PVPVA, PEG-6000, HPMCAS L:H, HPMCAS H, SoluPlus, and HPMCAS L compared to without polymer (i.e. 0.3% release). Like for 20% drug load, only Eudragit S100 did not increase solubilization capacity. By considering their collective results, SoluPlus, PVPVA, HPMCAS L and HPMCAS L:H are concluded to be preferred polymers for RTN ASD with higher solubilization capacity (Table 5).

Table 5. Food effect for solubilization capacity of 40% drug load RTN films. Media were FaSSIF-V2 (pH 6.5) and FeSSIF-V2 (pH 5.8), with and without polymer. When polymer present, polymer concentration was 2 mg/ml. Mean ± SE from n=3

Media	Solubilization capacity (%release)	Fold-enhancement compared to no polymer	pH and Food effect (fed / fasted)
FaSSIF-V2	0.302±0.001	-	-
FaSSIF-V2 + HPMCAS L	0.539±0.001	1.78±0.008	-
FaSSIF-V2 + HPMCAS H	0.759±0.0004	2.51±0.01	-
FaSSIF-V2 + HPMCAS L:H (1:1)	0.836±0.001	2.77±0.008	-
FaSSIF-V2 + Soluplus	0.618±0.001	2.05±0.01	-
FaSSIF-V2 + PVPVA	1.01±0.001	3.35±0.02	-
FaSSIF-V2 + PEG-6000	0.833±0.0003	2.76±0.01	-
FaSSIF-V2 + Eudragit S100	0.0648±0.001	0.214±0.002	-

Table 5 (*continue*). Food effect for solubilization capacity of 40% drug load RTN films. Media were FaSSIF-V2 (pH 6.5) and FeSSIF-V2 (pH 5.8), with and without polymer. When polymer present, polymer concentration was 2 mg/ml. Mean ± SE from n=3

Media	Solubilization capacity (%release)	Fold-enhancement compared to no polymer	pH and Food effect (fed / fasted)
FeSSIF-V2	0.562±0.004	-	1.86±0.01
FeSSIF-V2 + HPMCAS L	1.75±0.003	3.12±0.03	3.25±0.01
FeSSIF-V2 + HPMCAS H	1.94±0.01	1.94±0.01	1.44±0.001
FeSSIF-V2 + HPMCAS L:H (1:1)	2.00±0.001	3.56±0.02	2.39±0.005
FeSSIF-V2 + Soluplus	2.17±0.01	3.85±0.01	3.50±0.02
FeSSIF-V2 + PVPVA	1.30±0.01	2.31±0.01	1.28±0.002
FeSSIF-V2 + PEG-6000	1.58±0.01	1.58±0.01	1.07±0.001
FeSSIF-V2 + Eudragit S100	0.069±0.007	0.12±0.01	1.07±0.10

As expected, 20% drug load performed better than 40% of the drug load, similar to literature [23,28,29]. Simões et al. observed that drug release from polymeric blends decreased drastically with higher drug load [29]. Kokott et al. also performed small scale dissolution setup with RTN in FaSSIF-V2 and found that 40% drug load showed lower dissolution profile than 20% drug load for PVPVA and HPMCAS [23].

The food effect for solubilization capacity is also given in Table 4 and 5. For 20% drug load (Table 4), the lowest food effect was with HPMCAS H (0.759-fold) and highest was with SoluPlus (25.5-fold). There was a 2-fold increase with PVPVA, Eudragit S100, PEG-6000, and a 5-fold increase with HPMACS L. For 40% drug load, there was essentially no food effect with PEG-6000, Eudragit S100, PVPVA and HPMCAS H. There was 3-fold, 3.5-fold and 2.4-fold increase with SoluPlus, HPMCAS L, and HPMCAS L:H, respectively.

SoluPlus and PVPVA possessed good aqueous solubility, and their films improved RTN release compared to no polymer. SoluPlus has amphiphilic chemical structure, with a large number of hydroxyl groups, resulting in it serving as a good solubilizer of poorly soluble drugs in aqueous media [30]. HPMCAS L is more hydrophilic than HPMCAS H due to its lower ratio of acetyl substitution versus succinoyl substitution. HPMCAS L's enhancement of RTN solubility and solubilization capacity reflects the polymer's hydrophilicity. Adhikari et al. indicated that the dissolution performance of HPMCAS L was higher than the M and H grade contrasts with the solution stabilization and drug-polymer molecular interactions. By means of hydrophobicity of HPMCAS H and greater hydrophobic interactions between itraconazole and HPMCAS H provided retardation of itraconazole precipitation and higher stabilization of itraconazole [2]. Interestingly, Eudragit S100 did not provide an increase in solubilization capacity, although increased RTN solubility in both biorelevant media, perhaps reflecting to the precipitation or crystallization of RTN during the formation of films with Eudragit S100 [14]. The solubilization capacity results were confirmed by solubility enhancement in FeSSIF-V2 and FaSSIF-V2 by SoluPlus, PVPVA and HPMCAS L. Also, there was no increase with HPMCAS H. So, films with 20% drug load and fabricated from SoluPlus, HPMCAS L, HPMCAS L:H and PVPVA were selected for further comparative dissolution studies, similar to prior results of film dissolution into POE10 medium [14].

Evaluation of RTN Dissolution Profiles from Films into Biorelevant Media

Figure 3 and 4 plot RTN dissolution profiles from films of SoluPlus, HPMCAS L, PVPVA and HPMCAS L:H into FeSSIF-V2 and FaSSIF-V2, respectively. In FeSSIF-V2, the highest release was from HPMCAS L film. Early release was higher for PVPVA, but RTN precipitation occurred after 20 min. Meanwhile, HPMCAS L provided the highest, sustained supersaturation in FeSSIF-V2 for 6 h. Slower onset of dissolution of RTN from HPMCAS L compared to PVPVA agrees with the literature [23]. At 360 min, rank order release from films was HPMCAS L (88.3%) > PVPVA (53.7%) > SoluPlus (36.8%) > HPMCAS L:H (23.0%), which were higher than from RTN crystalline powder. Table 6 lists

AUC values over 120 min ($AUC_{0\text{-}120\ min}$). The highest AUC value was with HPMCAS L (2810 µg.min/ml). The lowest AUC was with HPMCAS L:H polymer (385 µg.min/ml). Rank order of $AUC_{(0\text{-}120\ min)}$ in FeSSIF-V2 was HPMCAS L > PVPVA > SoluPlus > HPMCAS L:H. While there was no increase in $AUC_{(0\text{-}120\ min)}$ with HPMCAS L:H compared to crystalline RTN powder (385 µg.min/ml), there was 2.31-fold, 7.31-fold and 6.55-fold increase with SoluPlus, HPMCAS L and PVPVA, respectively.

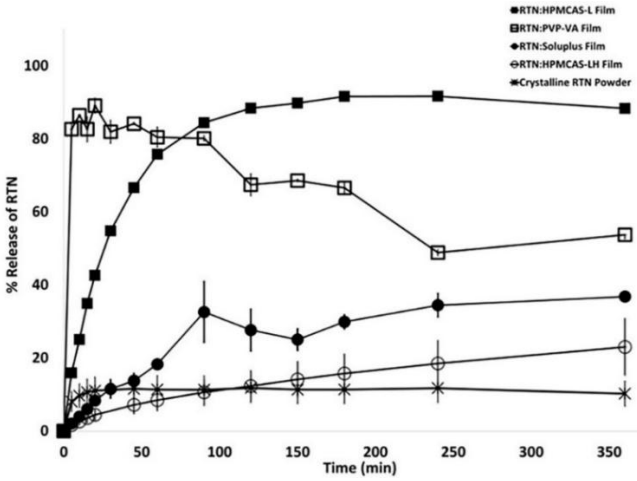

Figure 3. RTN dissolution profiles from films with 20% drug load into FeSSIF-V2. Best polymers were PVPVA, SoluPlus, HPMCAS L and HPMCAS L:H. Mean ± SE from n=3

Figure 4 plots dissolution from 20% drug loaded films containing SoluPlus, HPMCAS L, HPMCAS L:H and PVPVA in FaSSIF-V2, which has a higher pH than FeSSIF-V2. Dissolution was lower in FaSSIF-V2 (Figure 4) than into FeSSIF-V2 (Figure 3), similar to above solubility and solubilization capacity study findings where solubility and solubilization capacity were lower at higher pH condition, in agreement with literature [11]. Drug solubility is higher in low pH. This situation can be explained by the drug solubility was higher in lower pH [31]. Also, the increase in dissolution of HPMCAS L:H films in FaSSIF-V2 compared to FeSSIF-V2 can be related to the HPMCAS H polymer has higher solubility in pH 6.5 compared to the 5.8 [32].

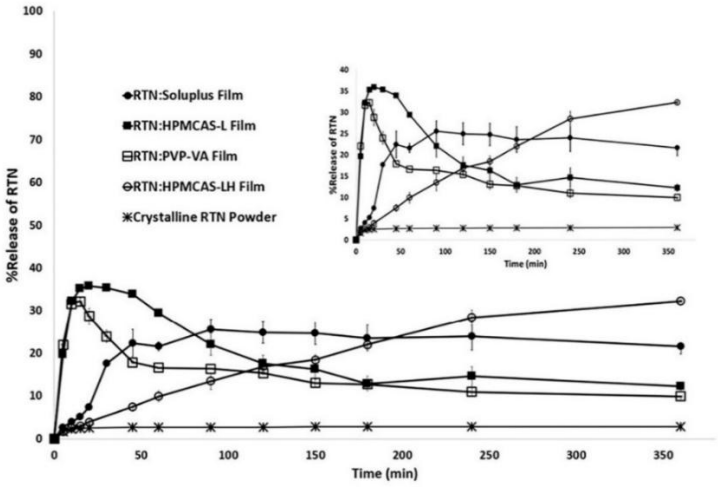

Figure 4. The dissolution profiles of the films contain the 20% drug load into FaSSIF-V2. Overall, RTN film dissolution into FaSSIF-V2 was lower than that into FeSSIF-V2. The graph shows an expanded view of the lower level of release. Mean ± SE from n=3

At 30 min, the highest RTN release was with HPMCAS L. Rank order release was HPMCAS L (35.4%) > PVPVA (24.0%) > SoluPlus (17.7%) > HPMCAS L:H (5.1%). Both HPMCAS L and PVPVA profiles showed drug precipitation, while HPMCAS L:H and SoluPlus profiles only increased with time. Hence, at 360 min, the rank order release was HPMCAS L:H >SoluPlus> HPMCAS L > PVPVA.

Table 6 lists AUC $_{(0\text{-}120\ min)}$. Overall, AUC $_{(0\text{-}120\ min)}$ in FaSSIF-V2 media was 9.0-fold, 8.3-fold, 5.9-fold, and 5.0-fold higher for SoluPlus, HPMCAS L, PVPVA and HPMCAS L:H, respectively, compared to crystalline RTN (2.9% release at 120 min). Food effect was also calculated by considering the ratio of AUC values in FeSSIF-V2 to FaSSIF-V2 and given in Table 6. While there was 3-fold enhancement for films containing HPMCAS L and PVPVA in FeSSIF-V2, there was no increase with SoluPlus and HPMCAS L:H polymers. 3-fold enhancement was also observed on the RTN crystalline powder in FeSSIF-V2. The films formulations and RTN powder showed the positive food effect, although there is about a 20% reduction in AUC under the fed state as compared to the fasting state in humans [10,11]. In the literature, there is higher in vitro dissolution of each Norvir tablet and Norvir oral powder in fed than fasted, using biorelevant dissolution media [10]. Likewise, Patel et al. also observed this same discordance with RTN in vivo negative food effect, as in vitro lipolysis profiles showed positive food effect [11]. The difference between the in vivo and in vitro may be related to the physiological parameters such as delayed gastric emptying, altered gastric pH, changes in regional distribution of bile salts, fluid volumes, viscosity, and blood flow [12,33,34].

Table 6. Dissolution profile AUC$_{(0\text{-}120\ min)}$ values of films containing SoluPlus, HPMCAS L, PVPVA, and HPMCAS L:H polymers in FeSSIF-V2 and FaSSIF-V2.

	FeSSIF-V2	**FaSSIF-V2**	**Food effect (fed / fasted)**
Film	**AUC $_{0\text{-}120}$ (µg.min/ml)**	**AUC $_{0\text{-}120}$ (µg.min/ml)**	
RTN-SoluPlus	889±442	1350±190	0.755±0.390
RTN- HPMCAS L	2810±160	1260±370	3.00±1.61
RTN- PVPVA	2520±1490	895±182	3.08±1.54
RTN- HPMCAS L:H	362±200	739±93	0.549±0.290
RTN crystalline powder	385±217	152±30	2.82±1.39

Drug release from ASD is determined in part by the dissolution of the polymeric carrier and not simply by the drug itself [29,35,36]. While solubility and solubilization capacity generally reflects dissolution results, there was some difference in the rank order of dissolution profiles, compared to rankings from solubility and solubilization capacity. These differences can be related to the dissolution test being a short-term test, while solubility reflected a longer-term assessment [37-39]. Overall, films from HPMCAS L and PVPVA provide higher RTN release compared to other polymers in early time points. Meanwhile, HPMCAS L maintained supersaturation for 6 hours in FeSSIF-V2 and provided 9-fold increase in RTN release in FaSSIF-V2, which has promised to remove the food effect of RTN oral dosing.

Conclusion

The films containing various polymer with different drug:polymer ratio was successfully prepared. To assess the effect of the various polymers, RTN solubility, solubilization capacity and dissolution profiles in biorelevant media were performed. By considering their collective favorable results of solubility and solubilization capacity studies, SoluPlus, PVPVA, HPMCAS L and HPMACS L:H preferred polymers for potential RTN films. 20% of the drug load performed better than 40% drug load in both FeSSIF-V2 and FeSSIF-V2. The highest in vitro dissolution AUC value was observed with HPMCAS L polymer in FeSSIF-V2, and it provided the highest supersaturation over 6 h. Also, RTN films containing HPMCAS L provided 9-fold increase in RTN % release in FaSSIF-V2, which can help to remove the food effect of RTN.

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AUTHOR CONTRIBUTIONS

Concept: A.N.O.; Design: A.N.O.; Control: A.N.O., J.E.P.; Sources: A.N.O., J.E.P.; Materials: A.N.O., J.E.P.; Data Collection and/or Processing: A.N.O.; Analysis and/or Interpretation: A.N.O., J.E.P.; Literature Review: A.N.O., J.E.P.; Manuscript Writing, A.N.O., J.E.P.; Critical Review: A.N.O., J.E.P.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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