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RESEARCH ARTICLE

Comparative Evaluation of Kollidon®VA64, SoluPlus®, and Aquasolve™ Hpmcas H-L Polymers: Impacts on Oral Spray Dried Powders

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SUMMARY

Ritonavir (RTV) is an anti-HIV protease inhibitor and antiretroviral medication to treat HIV /AIDS and especially COVID-19 infection. But it has low aqueous solubility which limits its oral bioavailability. Over the last decade, spray drying has become one of the most widely accepted solubility enhancement strategies in the pharmaceutical industry and academia. The spray drying process is a low-cost, solvent-based, scalable, continuous, and consistent technique to prepare an amorphous solid dispersion (ASD) of a hydrophobic drug in a single step. Even though the spray drying process has many advantages, it is a complicated system regarding process and formulation parameters. The formulation parameters such as the composition of feed (drug, polymeric carrier, and solvent) greatly impact the physicochemical properties of the spray-dried amorphous powder. Polymer selection is very crucial to developing a physiochemically stable and highly soluble ASD. However, there is a notable lack of comprehensive studies focusing on the impact of polymer type on spray dried powders. So, the objectives of this study were to perform a comparative evaluation of the impacts of Kollidon®VA64, SoluPlus®, and AquaSolve™ HPMCAS H-L polymers on spray-dried dispersion powders (SDP) of ritonavir. Powder characterization, DSC analysis, stability, solubility, and dissolution studies were performed. Short-term chemical stability studies supported that the RTV-ASD powders were stable for three months. The solubility of the coarse RTV crystalline powder was significantly increased through the ASD powders with various polymers, compared to the physical mixtures. Dissolution studies showed that the rank order was SoluPlus®>Kollidon®VA64>AquaSolve™ HPMCAS H-L SDPs for both inlet temperatures.

Key Words: *Ritonavir, soluplus®, kollidon®va64, aquasolve™ hpmcas l:h, amorphous solid dispersion*

Kollidon®VA64, SoluPlus® ve Aquasolve™ Hpmcas H-L Polimerlerinin Karşılaştırmalı Değerlendirmesi: Oral Püskürtülerek Kurutulmuş Tozlar Üzerindeki Etkileri

ÖZ

Ritonavir (RTV), HIV/AIDS ve özellikle Covid-19 enfeksiyonunu tedavi etmek için kullanılan bir anti-HIV proteaz inhibitörü ve antiretroviral ilaçtır. Ancak düşük suda çözünürlüğü oral biyoyararlanımını sınırlar. Son on yılda, püskürterek kurutma ilaç endüstrisi ve akademide en yaygın kabul gören çözünürlük artırma stratejilerinden biri haline gelmiştir. Püskürterek kurutma işlemi, tek bir adımda hidrofobik bir ilacın amorf katı dispersiyonunu (ASD) hazırlamak için düşük maliyetli, çözücü bazlı, ölçeklenebilir, sürekli ve tutarlı bir tekniktir. Püskürterek kurutma işleminin birçok avantajı olmasına rağmen, işlem ve formülasyon parametreleri açısından karmaşık bir sistemdir. Beslemenin bileşimi (ilaç, polimerik taşıyıcı ve çözücü) gibi formülasyon parametreleri, püskürtülerek kurutulmuş amorf tozun fizikokimyasal özelliklerini büyük ölçüde etkiler. Polimer seçimi, fizikokimyasal olarak stabil ve yüksek oranda çözünür bir ASD geliştirmek için çok önemlidir. Ancak püskürtülerek kurutulmuş tozlar üzerinde polimer tipinin etkisine odaklanan kapsamlı çalışmaların eksikliği dikkat çekicidir. Bu çalışmanın amaçları, Kollidon®VA64, SoluPlus® ve AquaSolve™ HPMCAS H-L polimerlerinin ritonavirin püskürtülerek kurutulmuş dispersiyon(SDP) tozları üzerindeki etkilerinin karşılaştırmalı değerlendirmesini yapmaktır. Toz karakterizasyonu, DSC analizi, stabilite, çözünürlük ve çözünme hızı çalışmaları yapılmıştır. Kısa süreli kimyasal stabilite çalışmaları, RTV-ASD tozlarının üç ay boyunca stabil olduğunu desteklemiştir. Kaba RTV kristal tozunun çözünürlüğü, fiziksel karışımlarla karşılaştırıldığında, çeşitli polimerlere sahip ASD tozları vasıtasıyla önemli ölçüde artmıştır. Çözünme hızı çalışmaları, her iki giriş sıcaklığı için sıralamanın SoluPlus®>Kollidon®VA64>AquaSolve™ HPMCAS H-L SDP şeklinde olduğunu göstermiştir.

Anahtar Kelimeler: *Ritonavir, soluplus®, kollidon®va64, aquasolve™ hpmcas l:h, amorf katı dispersion.*

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INTRODUCTION

The spray drying method has attracted high attention in pharmaceutical drug development to overcome the solubility and dissolution challenges of oral dosage forms with low aqueous soluble drugs. Almost 40% of the top 200 oral-marketed drug products in the USA have low solubility. Moreover, 90% of new chemicals and 75% of compounds in the development pipeline of the pharmaceutical industry have low aqueous solubility (Arif Muhammed, Mohammed, Visht, & Omar Yassen, 2024; Siriwannakij, Heimbach, & Serajuddin, 2021). Amorphous solid dispersions (ASD) are solid dispersions in which the active ingredient is dispersed within an excipient matrix in a substantially amorphous form. The amorphous structure of the drug is essential for increasing its solubility and dissolution, because no energy is required to break the drug's crystal lattice. Spray drying is one method to prepare an ASD and is based on the transformation of a drug-carrier combination in a fluid state (e.g. solution, suspension, or emulsion) into dried powders, by atomizing the drug-carrier in heated air (Corrigan, 1985). Spray drying has advantages due to being energy intensive, continuous ,and commercially scalable drying process in single operation with no handling (Bhujbal et al., 2021; Mujumdar, 2006; Ogawa et al., 2018; Singh & Van den Mooter, 2016). In addition to solubility and dissolution enhancement, it provides uniform and controllable particle size. Spray drying is employed for more than half of all commercially available amorphous solid dispersion products (Jermain, Brough, & Williams III, 2018; Pandi, Bulusu, Kommineni, Khan, & Singh, 2020). Even though spray drying has advantages, the role of formulation and process parameters on the quality and reproducibility of the drug product is incompletely understood. Process parameters include inlet temperature, drying gas properties, spray gas flow, feed rate, and airflow rate. Additionally, formulation parameters include the composition of the feed such as solvent type, solid content, carrier type ,and ratio. For example, the composition of the feed affects the surface tension and viscosity (Paudel, Worku, Meeus, Guns, & Van den Mooter, 2013). Polymer type and ratio are especially important due to an active substance is expected to have higher solubility in the polymeric carrier through the possibility of stronger favorable intermolecular interactions (Paudel, Van Humbeeck, & Van den Mooter, 2010). Even though the selection of the polymeric carrier is crucial to potentially developing a physicochemically stable and highly soluble formulation of a poorly soluble drug, there is a notable lack of comprehensive studies focusing on the impact of the polymer type on spray-dried powders. In this study, the aim was to bridge this gap by investigating the impacts of polymers on the physicochemical properties, stability, solubility, and dissolution profiles of spray-dried powders (SDP). Ritonavir (RTV) was selected as a model drug, as it is an orally active anti-HIV protease inhibitor and antiretroviral medication to treat HIV/AIDS and especially COVID-19 infection. It is a poorly soluble drug, with its low solubility limiting oral absorption and oral bioavailability. To overcome this problem, the preparation of spray-dried powders of RTV was considered. Previously, with a focus on the systematic approach of polymer selection for ASD formulation via film casting, Kollidon®VA64, SoluPlus® and AquaSolve™ HPMCAS H-L combination (1:1 w/w) were selected as appropriate polymers for the spray dryer process of RTV (Oktay & Polli, 2024). Therefore, these polymers were used as carriers in spray-dried powders here, and the comparative evaluation of these polymers was performed in this study. SoluPlus® is an amphiphilic polymer due to possessing hydrophilic and lipophilic groups, and it can function as a solubility enhancer via the formation of colloidal micelles in solution (Alshahrani et al., 2015). SoluPlus® is a graft copolymer of polyvinyl caprolactam-polyvinyl acetate (lipophilic) and polyethylene glycol 6000 (hydrophilic) (Linn et al., 2012). Moreover, SoluPlus® has low hygroscopicity

which aids the stability of ASDs. Kollidon®VA64 is also a copolymer composed of a chain structure of two monomers, namely N-vinylpyrrolidone and vinyl acetate (Bühler, 2008). Hypromellose acetate succinate (HPMCAS) is a cellulosic polymer, and grades of HPMCAS differ in chemical substitution of acetyl and succinoyl functional groups (Honick et al., 2019). HPMCAS has a high glass transition temperature which can prevent recrystallization and increase the stability by delayed kinetics of spray-dried powders (Al-Obaidi & Buckton, 2009). Here, the impacts of these polymers on the SDP particle size, powder densities, flowabilities, moisture content %, yield %, drug content %, stability, RTV solubility, and RTV dissolution profiles from spray-dried powders were evaluated.

MATERIAL AND METHOD

Materials

Ritonavir (ChemShuttle; Blue Current Inc.; Hayward, California), polyvinylpyrrolidone-vinyl acetate (Kollidon®VA64)(BASF SE; Ludwigshafen Germany), Polyvinyl caprolactam-polyvinyl acetate + polyethylene glycol graft copolymer (SoluPlus®) (BASF SE; Ludwigshafen Germany), 1:1 ratio (w/w) combination of hypromellose acetate succinate (AquaSolve™ HPMCAS) H and L grades (Ashland Inc; Covington, KY) were used to prepare the spray dried powders. Solvents were in analytical grade and obtained from Fischer Scientific (Fischer Scientific; Hampton, NH) and Sigma Aldrich (Sigma-Aldrich; St. Louis, MO).

Formulation of powders by spray drying

Buchi B-290 (BUCHI Corporation; New Castle, Delaware) in closed-loop mode was used for the preparation of ritonavir (RTV) spray-dried powders (SDP). Solutions were prepared with 10% of solid content (RTV and polymer). Polymer types were determined as Kollidon®VA64, SoluPlus®, AquaSolve™ HPMCAS H-L (1:1 w/w ratio) (Oktay & Polli, 2024). Polymer: RTV at composition 80:20 w/w was prepared by homogeneously dissolving in organic solvent (2:1 of dichloromethane: methanol). These solutions were pumped into the atomizer at a rate of 6 g/min, via a pump setting of 20%. The inlet temperatures were 70°C and 140°C. The atomizing N_2 gas settings were adjusted to 60 mm height at the maximum aspirator rate (100%). The produced SDPs were dried for an additional 12 hr at 40°C and stored in a desiccating cabinet (relative humidity < 5%).

Physicochemical powder characterization

Measurement of particle size

Particle size of SDPs was measured using a Master Sizer-2000 (Malvern Panalytical; Malvern, UK). Dispersive air pressure was set to 1 bar with a 50% vibrational feeding rate. The measurement time was set to 12 s, and refractive index was 1.33. The results were given the mean and standard error mean (mean±SEM) of three measurements.

Thermal analysis

Differential Scanning Calorimetry (DSC) measurements were conducted to evaluate the effect of the different polymers and two levels of the inlet temperature on the internal structure of the prepared RTV SDPs. Analysis was performed by enclosing 5-10 mg inside Tzero pans with Discovery DSC 2500 (TA Instruments; New Castle, DE) under the nitrogen flow (50 mL/min). The heat (to 200°C at 10°C/min)/cool (to 30°C at 10°C/min)/reheat (to 200°C at 10°C/min) method was applied. The glass transition temperatures (T_g) of polymers and SDPs were determined from the reheating cycle via TRIOS software (TA Instruments; New Castle, DE). A comparison of the T_g values of prepared SDPs with the value expected by the ideal mixing of two substances was carried out. Expected T_g values were calculated via Equation 1:

$$1 / T_g = W_1/T_{g1} + W_2/T_{g2} \quad \text{Eq. 1}$$

Where the W_1 and W_2 are the fractions of weight, and T_{g1} and T_{g2} are the T_g values of the RTV and the polymer, respectively. The T_g of amorphous RTV was given in the literature as 52.43°C (Wagner et al., 2012).

Measurements of spray-dried powder densities

Bulk and tapped densities of all RTV-SDPs were determined. The bulk density of powders was calculated by filling 1.5 g of powder into a measuring cylinder and measuring the volume of powder (V_B). The tapped density was determined by placing the measuring cylinder in a Stampf volumeter JEL STAV 2003 jolting volumeter (J. Engelsmann AG; Ludwigshafen, Germany) and by tapping 250, 500, 900, 1250 ,and 1500 times. The final volume (V_T) was recorded at certain tapped times and no further volume reduction was observed. The V_{1500} was the tapped volume (V_T) due to the difference between V_{500} and V_{1500} being less than 2 mL (United States Pharmacopeia).

Estimation of powder flowability

The compressibility index (CI) and Hausner ratio (HR) are used to predict the flowability of powders. CI and HR were calculated from Equation 2 and 3, respectively:

$$\text{Compressibility Index} = 100*((V_B - V_T)/V_B) \quad \text{Eq. 2}$$

$$\text{Hausner Ratio} = V_B / V_T \quad \text{Eq. 3}$$

Where V_B and V_T are the volume of powder prior to and after tapping. Flowability was evaluated according to the USP standard (Patel, Patel, & Shah, 2023; Pharmacopeia).

Analysis of moisture content

Loss on drying of 500 mg of SDP was measured using a Mettler-Toledo HB43 Moisture Analyzer (Mettler-Toledo; Columbus, OH). The measurements were replicated three times for each sample.

Calculation of production yield

The % production yield from spray drying was calculated from:

$$\% \text{ yield} = (M_s/M_t)x100 \quad \text{Eq. 4}$$

where M_t is the total solid mass in the solution and M_s is the mass of obtained spray-dried powder (Pongsamart, Limwikrant, Ruktanonchai, Charoenthai, & Puttipipatkhachorn, 2022).

Short-term stability studies

After fabrication via spray drying, drug contents of the SDPs were measured on initial day, 1st, 7th, 14th, 30th days and three months of storage at 25°C ± 2°C with 60±5% relative humidity (RH) and 40±2°C with 75±5% RH. The SDPs were dissolved in methanol and then filtered using 0.22 µm membrane filter prior to HPLC analysis of drug. Percent drug content considered initial theoretical amount of RTV (i.e. 20% drug load).

Determination of saturation solubility of SDP powders of RTV with different polymers

Saturation solubility of the RTV SDPs (i.e. prepared with Kollidon®VA64, SoluPlus®, and AquaSolve™ HPMCAS H-L) was evaluated in maleic acid buffer (50 mM) with 60 mM of polyoxyethylene 10 lauryl ether (M-PE). This media is the USP compendial dissolution media. Solubility studies were also performed with coarse RTV powder (i.e. crystalline drug powder), and a physical mixture of RTV (RTV-PM) with Kollidon®VA64, SoluPlus®, and AquaSolve™ HPMCAS H-L polymers (20:80% of RTV: polymer). Results were compared to RTV-SDP solubilities. An excessive amount of solid (containing an equal amount of RTV) was added to the M-PE. Samples were stirred at 500 rpm and 37°C for 24 h. Samples were filtered through a 0.22 µm membrane filter (VWR International GmbH; Darmstadt, Germany). Then, RTV in filtrate was quantified by HPLC analysis.

Dissolution of spray-dried powders

Dissolution testing was performed on the SDPs which are prepared with Kollidon®VA64, SoluPlus®, and AquaSolve™ HPMCAS H-L polymers, at inlet temperatures of 70°C and 140°C. USP II apparatus (SR8PLUS, Hanson Research; Chatsworth CA) and 900 mL of M-PE medium (50 mM maleic acid buffer including 60 mM polyoxyethylene 10 lauryl ether) were used. pH was 5.8. The temperature was 37°C, and the paddle rotation speed was 100 rpm. At pre-determined time points (i.e. 0, 5, 10, 20, 30, 45, 60, 90,

120, 180, 240, and 360 min), 2 mL of the samples were taken and replaced with 2 mL of fresh M-PE medium. Samples were filtered through a 0.45 mm Millipore filter and quantified using HPLC.

High-performance liquid chromatography analysis (HPLC)

The concentration of RTV was determined using an HPLC method (Karakucuk, Celebi, & Teksin, 2016; Karakucuk, Teksin, Eroglu, & Celebi, 2019). Sample analysis was conducted with a Waters 2489 HPLC system (Waters Corporation; Milford, MA) equipped with a UV-vis detector. An isocratic mobile phase comprising 47% acetonitrile and 53% 0.05 M phosphoric acid was employed, with an injection volume of 25.0 µL and a flow rate of 1 mL/min. Separation was achieved using a 4.6 × 150 mm Zorbax C18 column with a 5-µm particle size. The UV-vis detector was set to a wavelength of 240 nm. RTV exhibited a retention time of 9–10 minutes, and the total run time was 13 minutes. A calibration curve with RTV concentrations of 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.195, and 0.098 µg/mL was generated in triplicate for each analysis, yielding an r^2 value of 0.9999. For solubility studies, calibration curves were established for the M-PE medium. Standard solutions were prepared by diluting a stock solution of RTV in methanol (1 mg/mL) at a 1:9 ratio with the M-PE medium. These standard solutions were further diluted with the mobile phase to obtain final concentrations of 0.78, 1.56, 3.125, 6.25, 12.5, 25, and 50 µg/mL.

Statistical analysis

The collected data was analyzed using SPSS database Version 16 (Systat Software Inc.; San Jose, CA USA). Analysis of variance ANOVA test at the 95% confidence level, followed by Tukey's post hoc testing was used to compare multiple groups. To compare two groups, t-test was used. Results are given as mean ± SEM (n = 3).

RESULTS AND DISCUSSION

RTV-SDPs with Kollidon®VA64, SoluPlus®, and AquaSolve™ HPMCAS H-L polymers at both 70°C and 140°C inlet temperatures were successfully prepared and characterized (i.e. stability, RTV solubility and RTV dissolution characterized).

Characterization of spray-dried powders

The powder properties were characterized, elucidating the effects of the polymer types and inlet temperatures on particle size (PS), internal structure (amorphous/crystalline), yield %, bulk density, tapped density, HR, CI, drug content %, and moisture %.

Evaluation of the polymer impacts on particle sizes

PS of SDPs is considered a critical quality bioavailability attribute. Smaller particles increase the dissolution rate (Schmitt, Baumann, & Morgen, 2022). However, the inherently small SDP size (about 5-15 µm) can cause low flowability (Yu, Nie, & Hoag, 2024). The mean PS (d_{50}) of the neat RTV powder was 36.3±10.1 µm. The d_{50} of RTV physical mixtures with AquaSolve™ HPMCAS H-L, SoluPlus®, and Kollidon®VA64 were 196.1±11.1 µm, 124.8±33.4 µm ,and 90.0±9.9 µm, respectively. Strojewski et al. indicated that the average particle size of SoluPlus® is much larger than Kollidon®VA64 (Strojewski & Krupa, 2022). After spray drying, the SDP particle size was lower than the physical mixtures (PM). The d_{50} values of the SDPs with Kollidon®VA64 were 14.8±0.7 µm and 20.7±4.3 µm for 70°C and 140°C inlet temperatures, respectively. The d_{50} values of the SDPs with SoluPlus® were 16.1±0.05 µm and 20.7±4.3 µm for 70°C and 140°C, respectively. Similarly, Hofman et al. determined by microscopy that the particle size of SDP and PM with SoluPlus® were in the range of 2-35 µm and 10-100 µm, respectively, for 10% drug load (Hofmann, Harms, & Mäder, 2024). The d_{50} values of SDPs with AquaSolve™ HPMCAS H-L polymers were 16.2±1.0 µm and 31.4±0.7 µm for 70°C and 140°C, respectively. While spray drying decreased PS significantly, higher inlet temperature

caused a larger PS (Moshe Honick et al., 2020). The PS of SDPs and PMs prepared with PVP-VA were lower than the SDPs prepared with other polymers. These results reflect the lower particle size of the PVP-VA polymer (d_{50}=53.4 μm) (Carina Hubert, 2019) than HPMCAS-L (d_{50}= 204 μm) and HPMCAS-H (d_{50}= 245.8 μm) (Moshe Honick et al., 2020). Osei-Yeboah et al. prepared celecoxib and PVP-VA amorphous solid powders which showed particle sizes in the range of 1.9 – 3.0 μm (d_{10}); 8.6 – 14.2 μm (d_{50}); 32.8 – 40.2 μm (d_{90}) (Osei-Yeboah & Sun, 2023).

Evaluation of polymer impacts on thermal analysis

Figure 1 shows the Differential Scanning Calorimetry profiles of RTV powder, polymers ,and SDPs with 20% drug load. The amorphous nature of the SDPs was confirmed via DSC analyses. The effects of the polymers on the internal structure of the RTV SDPs were evaluated. The melting point of crystalline RTV powder was 128.21°C, and the glass transition temperature (T_g) value was 52.4 ± 1.2 °C. AquaSolve™ HPMCAS H-L, Kollidon®VA64 and SoluPlus® polymers were in the amorphous state, and their T_g values were 123.36 °C, 108.06 °C, and 66.25°C, respectively. In the literature, the T_g of SoluPlus® was 70°C, which is 30°C lower than that of Kollidon®VA64 (101°C) (Strojewski & Krupa, 2022). All SDPs were completely in the amorphous state, without any apparent phase separation and RTV crystallization, which was evident from the single T_g value (Figure 1). The T_g value was 103.83 °C and 98.61 °C for RTV-AquaSolve™ HPMCAS H-L SDPs prepared using 70°C and 140°C, respectively. These values were 89.51°C and 86.20°C for RTV-Kollidon®VA64 SDPs, and 64.94°C and 62.47°C for RTV-SoluPlus® SDPs. There was no significant difference ($\rho \leq 0.05$) in the T_g values of SDPs prepared from the two inlet temperatures. The estimated T_g values, which were 97.36, 89.14 ,and 65.42°C for AquaSolve™ HPMCAS H-L, Kollidon®VA64 and SoluPlus® were close to observed values. T_g values of SDPs were lower than the T_g value of neat polymers due to the drug-in polymer lowered T_g values. This drug disposition increases the molecular mobility of the drug in the system, increasing solubility and dissolution of RTV (Siriwannakij et al., 2021).

T_g values are also important for SDP stability. It was reported that stable SDPs can be obtained if the T_g value of SDPs is more than 50°C higher than the storage temperature (Alshahrani et al., 2015; Hancock & Zografi, 1997; Li, Konecke, Wegiel, Taylor, & Edgar, 2013). Results can be interpreted that the SDPs with AquaSolve™ HPMCAS H-L and Kollidon®VA64 polymers can be stable at room temperature (25°C). Rank order SDP stability was: AquaSolve™ HPMCAS H-L > Kollidon®VA64 > SoluPlus®, in part due to AquaSolve™ HPMCAS H-L having a higher T_g value (Al-Obaidi & Buckton, 2009).

Evaluation of polymer impacts on powder densities and flowabilities

The compressibility index (CI) and the Hausner ratio (HR) are metrics concerning the flowability of bulk solids. The HR and CI were calculated by using the bulk and tapped densities to assess the effects of inlet temperature. Table 1 lists SDP density values, CI, and HR for the three polymers at 70°C and 140°C inlet temperatures. From HR and CI, the powders were classified as either 'fair' (CI and HR in the range of 16-20% and 1.19-1.25) or 'passable' (CI and HR in the range of 21-25% and 1.26-1.34) or 'poor' (CI and HR in the range of 26-31% and 1.35-1.45) or 'very poor' (CI and HR in the range of 32-37% and 1.46-1.59), according to USP ⟨1174⟩ (United States Pharmacopeia, 2012).

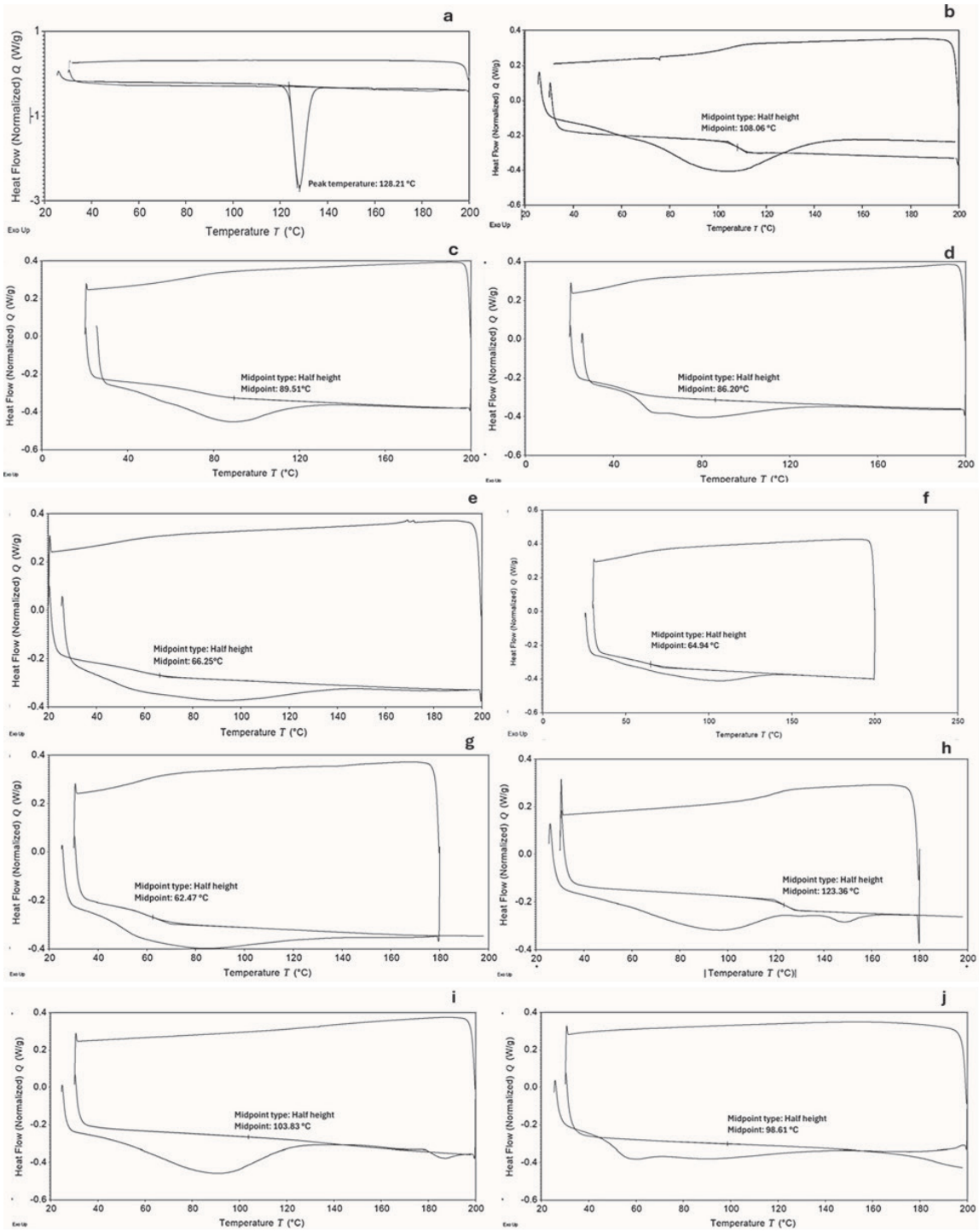

Figure 1. DSC profiles of RTV, neat polymers, and spray-dried powders of RTV and polymer. Panels are: coarse powder of RTV (a), neat Kollidon®VA64 polymer (b), RTV-SDP with Kollidon®VA64 polymer at 70°C (c) and 140°C (d), neat SoluPlus® polymer (e), RTV-SDP with SoluPlus® polymer at 70°C (f) and 140°C (g) neat AquaSolve™ HPMCAS H-L polymer (h), RTV-SDP with AquaSolve™ HPMCAS H-L polymer at 70°C (i) and 140°C (j). For all SDP, the drug load was 20% and the inlet temperature was either 70°C or 140°C.

For AquaSolve™ HPMCAS H-L polymer, the bulk density of the RTV-SDPs prepared at 140°C was 0.081±0.002 g/mL and was lower than the powder prepared at 70°C (0.252±0.005 g/mL). Similarly, the tapped density of the RTV-SDP prepared at 140°C (0.122±0.006 g/mL) was lower than the powder prepared at 70°C (0.344±0.036 g/mL). The HR were 1.364±0.116 and 1.496±0.057 for powders prepared at 70°C and 140°C, respectively. The compressibility index was 25.7±5.87% and 32.97±2.6 % for 70°C and 140°C, respectively. These values also showed that the powders with AquaSolve™ HPMCAS H-L have poor or very poor flowability.

For SoluPlus® polymer, the bulk density of the RTV-SDP prepared at 140°C (0.084±0.002 g/mL) was lower than the powder prepared at 70°C (0.290±0.002 g/mL). Similarly, the tapped density of the RTV-SDP prepared at 140°C (0.113±0.004 g/mL) was lower than the powder prepared at 70°C (0.376±0.006 g/mL). The HR were 1.294±0.019 and 1.347±0.056 for powders prepared with 70°C and 140°C inlet temperatures, respectively. The compressibility index was 22.7±1.1 % and 25.5±3.2 % for 70°C and 140°C, respectively. So, RTV SDPs with SoluPlus® polymer showed passable and poor flowability for 70°C and 140°C, respectively. This poor flowability of SDPs with SoluPlus® and AquaSolve™ HPMCAS H-L polymers stems from the inherent characteristics of low bulk densities and the cohesive nature within spray-dried powders (Yu et al., 2024).

Table 1. The bulk, tapped, and true densities, HR, and compressibility index values of SDPs prepared with various polymers at two inlet temperatures (70°C and 140°C) (mean±SEM).

Polymer	Inlet temperature	Bulk density (gr/mL)	Tapped density (gr/mL)	Hausner Ratio	Compressibility Index (%)	Flowability
AquaSolve™ HPMCAS H-L	70 °C	0.252±0.005	0.344±0.036	1.364±0.116	25.7±5.8	Poor
AquaSolve™ HPMCAS H-L	140 °C	0.081±0.002	0.122±0.006	1.496±0.057	32.9±2.6	Very poor
Kollidon®VA64	70 °C	0.4531±0.014	0.551±0.032	1.219±0.081	17.2±5.2	Fair
Kollidon®VA64	140 °C	0.176±0.003	0.231±0.009	1.315±0.031	23.9±1.8	Passable
SoluPlus®	70 °C	0.290±0.002	0.376±0.006	1.294±0.019	22.7±1.1	Passable
SoluPlus®	140 °C	0.084±0.002	0.113±0.004	1.347±0.056	25.5±3.2	Poor

For Kollidon®VA64 polymer, the flowability was better. The bulk density of the RTV-SDP prepared at 140°C (0.176±0.003 g/mL) was lower than the powder prepared at 70°C (0.4531±0.014 g/mL). Similarly, the tapped density of the RTV-SDP prepared at 140°C (0.113±0.004 g/mL) was lower than the powder prepared at 70°C (0.376±0.006 g/mL). The HR were 1.219±0.081 and 1.315±0.031 for 70°C and 140°C, respectively. The compressibility index was 17.2±5.2 % and 23.9±1.8 % for 70°C and 140°C, respectively. Even though there is no significant difference in the HR and CI values for different temperatures, 70°C inlet temperature was better than 140°C for better flowability and compressibility (Table 1). Moreover, the lowest HR and CI were observed on the RTV-SDP prepared with Kollidon®VA64, indicating better flowability than other polymers. Rank order was Kollidon®VA64 > SoluPlus® > AquaSolve™ HPMCAS H-L.

Evaluation of the polymer impacts on moisture content %

Moisture content (MC) is another factor impacting flowability, powder stability, and compressibility (Yu et al., 2024). MC, which is a measure of free water in the spray-dried powder, was determined (Table 2). For AquaSolve™ HPMCAS H-L polymer, the MC % of the powder prepared with high inlet temperature (1.217±0.067 %) was significantly lower than the low temperature (3.017±0.120 %), as expected. Similar results were observed for the Kollidon®VA64 and SoluPlus® polymers. The MC % of the SDPs with Kollidon®VA64 was 2.11±0.12 %

for high inlet temperature and 4.32±0.04 % for low inlet temperature. These values were 3.25±0.19 and 1.27±0.07% for SoluPlus® polymer. Moreover, yield % and drug content % of the RTV-SDPs are listed in Table 2. The higher moisture content was observed on SDPs containing Kollidon®VA64 than SoluPlus® and AquaSolve™ HPMCAS polymers, which reflects polymer differences in their hygroscopicity. From the moisture content of SDPs, the rank order was: Kollidon®VA64 > SoluPlus® > AquaSolve™ HPMCAS. The relatively lower moisture content of the SoluPlus® and AquaSolve™ HPMCAS polymer was due to the low hygroscopic nature of the polymers, which promotes stability during storage. In particular, the low level of succinoyl substituent in HPMCAS-H induced a strong interaction with the hydrophobic drug, reducing moisture uptake and inhibiting recrystallization (Alshahrani et al., 2015).

Evaluation of the polymer impacts yield and drug content %

Table 2 shows the influence of polymer and inlet temperature on powder yield and drug content %. While %yield of SDPs containing AquaSolve™ HPMCAS, Kollidon®VA64 and SoluPlus® were 83.51±0.46 %, 80.42±0.51 % and 81.63±0.43 % for 70°C, these values were 86.15±0.93 %, 84.54±0.60 % and 85.73±0.89 % for 140°C. Higher inlet temperature also provided higher yield. Inlet temperature effect on yield correlated with the concentration of the solution and feed rate (LeClair, Cranston, Xing, & Thompson, 2016). The rank order was AquaSolve™ HPMCAS > SoluPlus® > Kollidon®VA64, independently from temperature. The effects of the polymers on yield% reflected the hygroscopicity and viscosity of the polymers. For all polymers, the % production yield exceeded 80%, showing sufficient drying at either inlet temperature. However, the drug content of powders containing AquaSolve™ HPMCAS polymer decreased from 95.3±0.5 % to 91.8±0.5 % when the inlet temperature increased from 70°C to 140°C. These values were 94.3±0.5 % and 91.0±0.3 % for Kollidon®VA64, and 94.3±0.3 % and 91.8±0.2 % for SoluPlus®. Lower drug content reflected melted RTV at 140°C, resulting in sticking on the cyclone surface. For this reason, lower inlet temperature was concluded to be the preferred option to prepare the SDPs having high drug content (Table 2).

Table 2. The moisture content %, yield %, and drug content % of the spray-dried powders. Spray-dried powders were fabricated at either 70°C or 140°C inlet temperature.

Polymer	Temperature (°C)	Moisture (%)	Yield (%)	Drug content (%)
AquaSolve™ HPMCAS H-L	70	3.02±0.12	83.5±0.5	95.3±0.5
AquaSolve™ HPMCAS H-L	140	1.22±0.07	86.2±0.9	91.8±0.5
Kollidon®VA64	70	4.32±0.04	80.4±0.5	94.3±0.5
Kollidon®VA64	140	2.11±0.12	84.5±0.6	91.0±0.3
SoluPlus®	70	3.25±0.19	81.6±0.4	94.3±0.3
SoluPlus®	140	1.27±0.07	85.7±0.9	91.8±0.2

Evaluation of the polymer impacts on short-term chemical stability

Drug content of SDPs over three months was investigated via short-term chemical stability. RTV content (%) of powders prepared using 70°C was 95.0±0.5, 94.1±0.5 and 93.8±0.1 % respectively for AquaSolve™ HPMCAS H-L, Kollidon®VA64, and SoluPlus® after the storage at room temperature for three months. For 140°C inlet temperature, these values were 91.7±0.2, 90.8±0.1 and 91.8±0.1%, respectively (Table 3). While higher inlet temperature had lower drug content, there was no significant difference in drug content % between the initial and after 3 months.

Table 3. The drug content of the SDPs prepared with various polymers and two levels of inlet temperatures after storage at *room temperature* for three months.

Drug content (%) after storage at room temperature							
Polymer	**Inlet temperature (°C)**	**Initial**	**1st day**	**7th day**	**14th day**	**1st month**	**3rd month**
AquaSolve™ HPMCAS H-L	70°C	95.3±0.5	95.3±0.5	95.2±0.5	95.1±0.5	95.1±0.5	95.0±0.5
AquaSolve™ HPMCAS H-L	140 °C	91.8±0.5	91.8±0.5	91.8±0.5	91.7±0.5	91.7±0.1	91.7±0.2
Kollidon®VA64	70°C	94.3±0.5	94.2±0.5	94.2±0.5	94.2±0.5	94.2±0.5	94.1±0.5
Kollidon®VA64	140 °C	91.0±0.3	91.0±0.3	91.0±0.3	91.0±0.2	90.9±0.3	90.8±0.1
SoluPlus®	70 °C	94.3±0.3	94.3±0.4	94.3±0.4	94.2±0.3	93.9±0.2	93.8±0.1
SoluPlus®	140 °C	91.8±0.2	91.8±0.3	91.8±0.1	91.9±0.1	91.8±0.1	91.8±0.1

The drug content of the powders prepared with 70°C were 94.8±0.5, 93.9±0.5 and 93.7±0.2 respectively, for AquaSolve™ HPMCAS H-L, Kollidon®VA64 and SoluPlus® after the storage at 40°C for 3 months. These values were 91.5±0.1, 90.7±0.02 and 91.6±0.1 respectively for 140°C (Table 4). RTV was chemically stable for three months.

Table 4. Drug contents of the SDPs prepared with various polymers and two levels of inlet temperatures after storage at 40°C for three months.

Drug content (%) after storage at 40°C							
Polymer	**Inlet temperature (°C)**	**Initial**	**1st day**	**7th day**	**14th day**	**1st month**	**3rd month**
AquaSolve™ HPMCAS H-L	70°C	95.3±0.5	95.2±0.5	95.2±0.5	95.1±0.5	94.9±0.5	94.8±0.5
AquaSolve™ HPMCAS H-L	140 °C	91.8±0.5	91.8±0.5	91.8±0.5	91.7±0.4	91.6±0.4	91.5±0.1
Kollidon®VA64	70°C	94.3±0.5	94.2±0.5	94.2±0.5	94.1±0.5	94.0±0.5	93.9±0.5
Kollidon®VA64	140 °C	91.0±0.3	91.0±0.3	91.0±0.3	90.9±0.2	90.8±0.2	90.7±0.1
SoluPlus®	70 °C	94.3±0.3	94.3±0.3	94.2±0.3	94.2±0.3	93.8±0.2	93.7±0.2
SoluPlus®	140 °C	91.8±0.2	91.8±0.2	91.9±0.1	91.7±0.1	91.7±0.1	91.6±0.1

Similar to the results here, Liu et al. indicated that the aprepitant ASD with SoluPlus® was stable for 3 months at 40°C and 60% RH by confirming that there was no recrystallization of the amorphous aprepitant (Liu et al., 2015). The high stability of carbamazepine amorphous solid dispersion was also provided via HPMCAS-H polymer. This stability reflects the low level of succinoyl groups of polymer increased the hydrophobic interaction with the drug and decreased the recrystallization (Ueda, Higashi, Yamamoto, & Moribe, 2013). Moreover, the high T_g of HPMCAS-H and its hydrophobic nature inhibited the molecular mobility of the drug within the solid dispersion, preventing crystallization growth (Alshahrani et al., 2015). Kollidon®VA64 polymer was also confirmed as stable for ASDs, in part due to the polymer having a high T_g value. In the literature, copovidone was found to effectively protect amorphous indomethacin from recrystallization during storage in a stability chamber for 3 months at various temperatures, from 5 to 50°C (Sarode, Sandhu, Shah, Malick, & Zia, 2013). Findings here demonstrated that all three polymers were suitable and promising to provide stable RTV spray -dried powders at 25°C and 40°C for 3 months.

Evaluation of the polymer impacts on saturation solubility

The effect of polymer type on RTV solubility was evaluated in the M-PE medium. Solubility studies were performed with coarse RTV powder and with SDPs from the three polymers at two inlet temperatures. Results are given in Table 5. While the saturation solubility of RTV in M-PE medium was 201.8 µg/mL, the solubility of SDPs with AquaSolve™ HPMCAS H-L were 2521.2 and 2982.3 µg/mL for 140°C and 70°C, respectively. The solubility of SDPs with SoluPlus® were 1879.3 and 2163.8 µg/mL for 140°C and 70°C, respectively. The solubility of SDPs with Kollidon®VA64 were 1645.0 and 2093.9 µg/mL for 140 °C and 70°C, respectively. While there was no significant impact of inlet temperature on solubility from SDPs, a significant improvement (10-15 fold increase) was observed with spray-dried powders compared to the RTV coarse powder. A 1.2-1.4 fold increase was observed with the physical mixture.

Table 5. Solubility of the coarse powder of RTV, physical mixtures (PMs), and spray-dried powders (SDPs)

Sample	Solubility in M-PE (µg/mL, mean ±SEM)
RTV coarse powder	201.8±2.4
RTV- AquaSolve™ HPMCAS H-L PM	258.4+4.2
RTV- AquaSolve™ HPMCAS H-L SDP – 70°C	2982.3±11.8
RTV- AquaSolve™ HPMCAS H-L SDP – 140°C	2521.2±70.1
RTV-SoluPlus® PM	273.7+20.1
RTV- SoluPlus® SDP – 70°C	2163.8±106.7
RTV- SoluPlus® SDP – 140°C	1879.3±20.0
RTV- Kollidon®VA64 PM	229.3+19.0
RTV- Kollidon®VA64 SDP – 70°C	2093.9 ±17.9
RTV- Kollidon®VA64 SDP – 140°C	1645.0±113.5

The highest solubility increase was with HPMCAS polymer. Rank order was: AquaSolve™ HPMCAS H-L > SoluPlus® > Kollidon®VA64. This result may reflect the lower hygroscopic nature of AquaSolve™ HPMCAS and SoluPlus® polymers than Kollidon®VA64, which was confirmed by moisture content analysis and inhibited recrystallization to maintain supersaturation (Alshahrani et al., 2015). Kollidon®VA64 is a copolymer composed of a chain structure of N-vinylpyrrolidone and vinyl acetate (Bühler, 2008). In contrast to Kollidon®VA64, SoluPlus® is a graft copolymer consisting of PEG 6000, polyvinyl caprolactam, and polyvinyl acetate, and is an amphiphilic polymer and serves as a surfactant (70–100 nm diameter micelles) to increase drug solubility (Oktay & Polli, 2024; Strojewski & Krupa, 2022). Even though copovidone does not have an amphiphilic structure, its ability to increase the solubility of hydrophobic drugs was confirmed by several studies (Strojewski & Krupa, 2022). Moreover, Alshahrani et al. indicated that the intensity of the hydrogen bond in the FTIR spectrum of carbamazepine is increased by adding HPMCAS-HF, which is a sign of the hydrogen bond formation with the hydroxyl group of HPMCAS-HF. The hydrogen bond formation worked synergistically with Soluplus® to enhance the solubility and stability of the formulations (Alshahrani et al., 2015; Rumondor, Stanford, & Taylor, 2009).

Evaluation of the polymer impacts on the dissolution of spray-dried powders

The dissolution profiles of the SDPs were determined in the M-PE medium and plotted in Figure 2. Graphs 'a' and 'b' refer to dissolution profiles of SDPs prepared with low and high inlet temperatures, respectively. The rank order was SoluPlus® > Kollidon®VA64 > AquaSolve™ HPMCAS H-L for both inlet temperatures. At the end of the 360 min, SDP powder prepared using Kollidon®VA64 polymer releases 89.2% and 88.0% for 70°C and 140°C, respectively. For SoluPlus®, they were 99.3% and 93.5%. For AquaSolve™ HPMCAS H-L, they were 84.0% and 80.5% respectively.

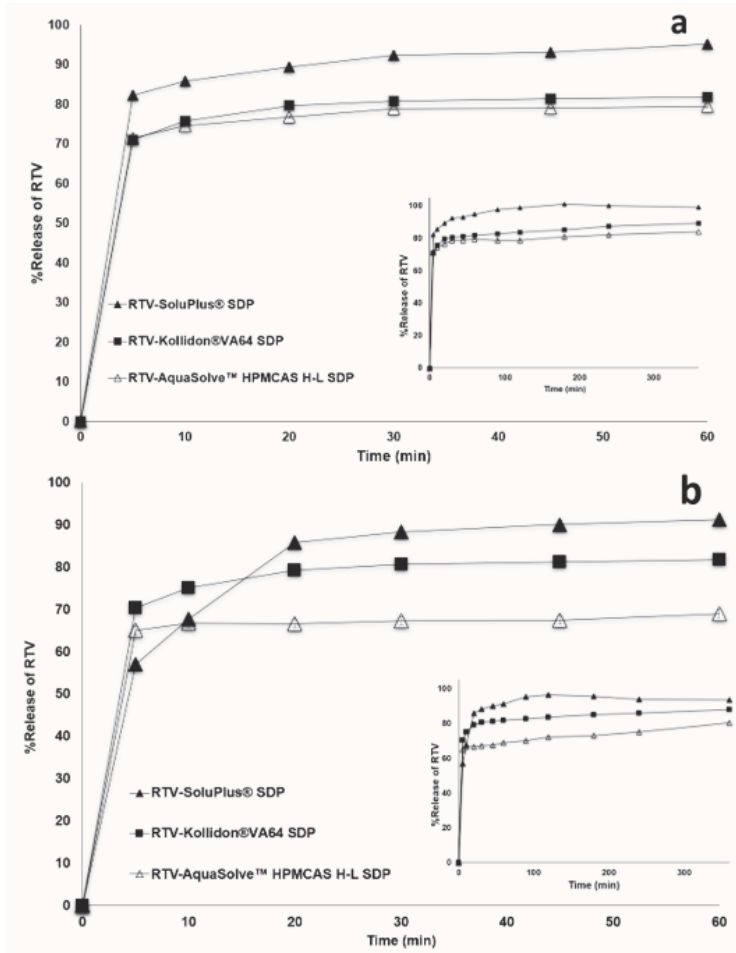

Figure 2. Dissolution profiles of SDPs prepared using AquaSolve™ HPMCAS H-L, SoluPlus® and Kollidon®VA64 polymers. Panels are: a) SDPs prepared with 70°C inlet temperature, and b) SDPs prepared with 140°C inlet temperature.

After the first 10 min, drug release was 75.7%, 85.8% and 74.6% for Kollidon®VA64, SoluPlus® and AquaSolve™ HPMCAS H-L with 70°C. They were 75.1%, 67.7%, and 66.8% for 140°C. The dissolution profiles of the SDPs from 70°C were higher than from 140°C, reflecting that 140°C is higher than the melting point of ritonavir, yielding a sticky, melted drug caused delayed dissolution profile. While there was no significant difference on dissolution profiles of SDPs containing Kollidon®VA64 and AquaSolve™ HPMCAS H-L for 70 °C, Kollidon®VA64 showed better profile than AquaSolve™ HPMCAS H-L for 140°C inlet temperature. Similar results were observed on the indomethacin ASD tablets prepared with HPMCAS and PVP polymers (Yu et al., 2024). AUC values of the dissolution profiles are given in Table 6. AUC values have been used to characterize the rate and extent of dissolution (Maghsoodi & Shahi, 2019; Ruiz & Volonté, 2014). The highest dissolution profile and AUC values were observed on the SDPs containing SoluPlus®. It can be related to the amphiphilic nature of SoluPlus®, which stabilizes the amorphous form and maintains the supersaturation leading to higher dissolution of RTV. Moreover, SoluPlus® acts as a surfactant which helps the micelle formation and increases the wettability and dispersibility of RTV in the medium (Strojewski & Krupa, 2022). Smaller particle sizes of the micelles (70-100 nm) provide a larger surface area and so it increases the dissolution rate of RTV.

Table 6. AUC values of dissolution profiles (mean±SEM, n=3).

Powder	Inlet temperature (°C)	$AUC_{0\text{-}20\ min}$ (µg.min/mL)	$AUC_{0\text{-}60\ min}$ (µg.min/mL)	$AUC_{0\text{-}120\ min}$ (µg.min/mL)
RTV- SoluPlus® SDP	**70**	1672±329	4003±789	8040±1629
RTV- SoluPlus® SDP	**140**	1531±291	3878±758	7988±1550
RTV- Kollidon®VA64 SDP	**70**	1469±298	3436±696	7028±1394
RTV- Kollidon®VA64 SDP	**140**	1465±298	3432±696	7009±1390
RTV- AquaSolve™ HPMCAS H-L SDP	**70**	1427±281	3303±677	6647±1351
RTV- AquaSolve™ HPMCAS H-L SDP	**140**	1236±243	2886±574	6022±1187

CONCLUSION

Characterization studies, along with the ability to successfully form spray-dried powders of RTV with various polymers using spray-drying method, showed that all three polymers were suitable for spray-dried amorphous powders with lower moisture content, better flowability, lower particle size, and high %yield. SDP was also stable and highly soluble. The saturation solubility of the coarse RTV was significantly increased through the ASD powders with various polymers compared to the physical mixtures. Dissolution studies showed that the rank order was SoluPlus® SDP > Kollidon®VA64 SDP > AquaSolve™ HPMCAS H-L SDP for both inlet temperatures. Short-term chemical stability studies supported that the RTV-ASD powders were stable for all polymers for three months. Results indicate the high potential of these polymers for the development of stable spray-dried amorphous powders with hydrophobic drugs such as RTV.

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AUTHOR CONTRIBUTION STATEMENT

Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization (A.N.O). Writing – review & editing, Resources, Conceptualization (J.E.P).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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