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Improving the Pharmaceutical Potential of Lycopene Using Hot-Melt Extrusion

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Abstract

Background: Lycopene is a powerful antioxidant, classified as a carotenoid. Numerous studies confirm its beneficial effects in both the prevention and treatment of various diseases. However, its therapeutic application is significantly limited due to its poor water solubility and low bioavailability from natural sources. Developing a formulation with improved therapeutic characteristics could enhance the effectiveness of lycopene, making it more suitable for medical and nutritional use. The objective of this work was to apply hot-melt extrusion to produce extrudates containing an acetone-based lycopene extract combined with selected polymers, aiming to enhance its dissolution properties. **Methods:** Lycopene-rich extracts were prepared using ultrasound-assisted extraction with acetone. The obtained extract was processed via hot-melt extrusion together with PVP VA64 and Soluplus. The resulting extrudates were characterized using attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR) and X-ray diffraction (XRD). Dissolution behavior was assessed using a paddle apparatus, and collected samples were quantified by HPLC. Antioxidant capacity was determined via DPPH radical-scavenging analysis. **Results:** The polymers PVP VA64 and Soluplus improve lycopene's dissolution in acidic environments while showing its antioxidant potential. **Conclusions:** The formulation combining lycopene obtained through hot-melt extrusion with PVP VA64 and Soluplus polymers will enable its wider and more effective application.

Keywords: lycopene; antioxidant; hot-melt extrusion; drug delivery system; polymers

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1. Introduction

Lycopene, classified among carotenoids, naturally imparts red and orange pigments to a variety of fruits and vegetables. Tomatoes are the richest source, but it is likewise present in watermelon, pink grapefruit, guava, apricots, papaya, and pumpkin [1,2]. In terms of dietary intake, tomatoes and products derived from them represent the primary sources of lycopene [3]. These sources account for over 85% of the lycopene consumed in the human diet [4]. Additionally, they are considered the most economical source of this carotenoid [5].

Lycopene exhibits potent antioxidant properties [3,6–8]. It is capable of quenching singlet oxygen with approximately twice the efficiency of β-carotene and around ten times

greater effectiveness than α-tocopherol [9]. Additionally, lycopene can neutralize reactive species such as hydrogen peroxide, nitrogen dioxide, hydroxyl radicals, singlet oxygen, and other reactive oxygen species (ROS) [10,11]. Its mechanisms of action against ROS include electron transfer, radical binding, and allylic hydrogen abstraction [10]. The interactions between lycopene and free radicals are diverse and complex [10,12].

One of the ways lycopene enhances antioxidant defense is by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. It initiates the transcription of antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), thereby increasing their intracellular levels. Through this pathway, lycopene indirectly strengthens the endogenous antioxidant system by upregulating the production of protective enzymes [13,14]. Additionally, lycopene contributes to the regeneration of non-enzymatic antioxidants, such as vitamins C and E, further supporting cellular antioxidant defenses [6,15]. Its antioxidant activity enables lycopene to protect critical cellular components, including DNA and membrane lipids, from oxidative damage [16].

The strong antioxidant capacity of lycopene is primarily attributed to its molecular structure, particularly its system of conjugated double bonds. The influence of its cyclic or acyclic terminal groups appears to be less significant [6]. However, the acyclic structure of lycopene does influence its solubility characteristics [17]. It is insoluble in water [18]. Among its various isomeric forms, 5-cis lycopene exhibits the highest antioxidant potential, followed in order by the 9-cis, 7-cis, 13-cis, 11-cis, and all-trans forms [19].

Lycopene exhibits a wide range of biological effects. Numerous studies have demonstrated its protective and therapeutic roles in various health conditions [3,20,21]. Increasing evidence suggests that it may contribute to the prevention and management of cardiovascular diseases, cancer, metabolic diseases, neurological conditions, liver disorders, and other [3,6,20].

Currently, lycopene is applied in the pharmaceutical, food, and cosmetic sectors owing to its health-promoting properties [2]. Nevertheless, its molecular structure, rich in unsaturated bonds, makes it highly unstable and susceptible to degradation under environmental factors such as oxygen, heat, light, acidic conditions, and metal ions [2,22,23]. This instability, combined with its water insolubility, contributes to its low bioavailability [9]. As a result, the full antioxidant potential of lycopene remains underutilized, significantly limiting its practical applications [2,9]. Therefore, the development of stable formulations with improved therapeutic properties is essential to enhance the efficacy and broader use of lycopene.

One of the many methods offering a hopeful route to obtaining formulations with such properties is hot-melt extrusion (HME). This method is considered one of the most promising techniques for enhancing the solubility of poorly water-soluble active pharmaceutical ingredients, primarily due to its ability to induce amorphization. Transitioning a compound from a crystalline to an amorphous form significantly enhances its solubility and dissolution rate, as the ordered structure is disrupted, increasing molecular mobility and surface area [24–26]. This improvement is largely attributed to the higher free energy of the amorphous form compared to the crystalline lattice, which facilitates a faster dissolution rate [27]. Among various approaches available for producing amorphous systems, HME stands out due to its numerous advantages. It is a solvent-free, continuous process that is relatively cost-effective and easily scalable to industrial production levels [28,29]. From a manufacturing perspective, HME involves the use of rotating screws to convey and mix polymeric materials at temperatures exceeding their glass transition point, allowing for molecular-level dispersion of active substances into thermoplastic carriers such as polymers or binders. This results in a homogenous, amorphous product with improved physical uniformity and enhanced dissolution profiles [30,31].

In recent years, hot-melt extrusion has gained increasing attention not only in pharmaceutical but also in nutraceutical applications due to its capacity to improve the solubility, stability, and bioavailability of poorly soluble active compounds, including carotenoids. The choice of carrier polymers plays a critical role in the success of HME formulations [32,33]. PVP VA64 (polyvinylpyrrolidone–vinyl acetate copolymer) and Soluplus (polyethylene–glycol–polyvinyl caprolactam–polyvinyl acetate-grafted copolymer) are among the most widely studied polymers for amorphous solid dispersions. PVP VA64, due to its hydrophilic nature and good plasticizing properties, facilitates the dispersion of hydrophobic compounds and improves their wettability [34]. Soluplus not only enhances drug solubility and dissolution rate but also stabilizes the amorphous form through molecular interactions such as hydrogen bonding. Additionally, it can function as a surfactant, thereby improving the dispersion of lipophilic compounds in aqueous environments [27,31,35].

The aim of this research was to use hot-melt extrusion to formulate extrudates containing lycopene extract with PVP VA64 and Soluplus polymers, to improve its dissolution in water.

2. Materials and Methods

2.1. Materials

The study utilized tomato powder provided by MIGOgroup, which comprised at least 99% tomato powder and a minimum of 1% anti-caking agent (SiO_2). PVP/VA64 (a copolymer of vinylpyrrolidone and vinyl acetate) was supplied by Sigma-Aldrich, Wacker Chemie AG (Burghausen, Germany). Soluplus (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) and DPPH (2,2-diphenyl-1-picrylhydrazyl) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Demineralized water was produced using a Direct-Q 3 UV purification system (Merck Millipore, Molsheim, France; model Exil SA 67120). Acetone, methanol, and L(+)-ascorbic acid were purchased from POCH (Gliwice, Poland).

2.2. Methods

2.2.1. Preparation of Extrudates

Ultrasound-Assisted Acetone Extraction

Ultrasound-assisted extraction was carried out to obtain the tomato powder extract. Tomato powder (10.0 g) was placed in a conical flask, followed by the addition of 50.0 mL of acetone. The flask was sealed and placed in an ultrasonic bath. Extraction was performed at 40 °C for 20 min. The extract obtained was filtered through a filter. The resulting extract, using a vacuum evaporator, was evaporated from the solvent to dryness and placed in an Eppendorf-type tube.

Preparation of Extrudates with Polymers Soluplus and PVP/VA64

Extrudates with lycopene-containing extract contents of 10%, 20%, 30% and 40% were prepared (Figure 1). In total, 0.18 g, 0.36 g, 0.54 g, 0.72 g of extract and 1.62 g, 1.44 g, 1.26 g, 1.08 g of polymer (Soluplus or PVP/VA64), respectively, were weighed so that each starting mixture for extrusion had a mass of 1.8 g. For each extract content, two parallel series were prepared using either Soluplus or PVP/VA64 as the polymer. The mixture was ground in a mortar. The individual mixtures were then introduced into the extruder funnel. The extrusion process was carried out at 135 °C at a speed of 90 rpm. The hot-melt extrusion process was conducted using a HAAKE MiniCTW micro-conical twin screw extruder (Thermo Scientific, Karlsruhe, Germany). The resulting extrudates were pulverized using a laboratory grinder. The powder was transferred to Eppendorf-type tubes.

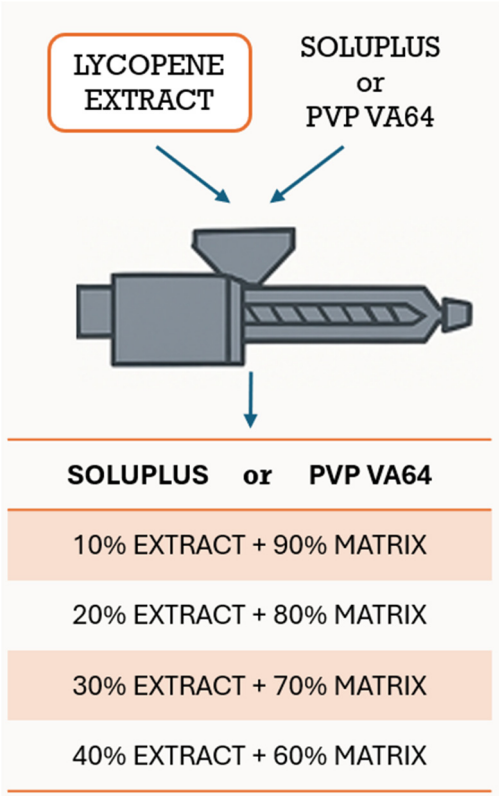


Figure 1. Graphical representation of the production of extrudates from lycopene extract and polymer matrices using the HME method.

2.2.2. Extrudate Identity Testing

X-Ray Powder Diffraction (XRPD)

Extrudates, polymers and extract diffraction patterns were acquired using X-ray diffraction (XRD, Bruker D2 Phaser diffractometer, Bruker, Karlsruhe, Germany) equipment with the copper anode (Cu-Kα-1.54060 Å, 30 kV and 10 mA). The measurement parameters: step size of 0.02° 2Θ and a counting rate of 2 s·step−1; the angular range was 5° to 40° 2Θ. The obtained data were analyzed using Origin 2021b software (OriginLab Corporation, Northampton, MA, USA).

ATR-FTIR Spectroscopy

ATR-FTIR spectra in the mid-infrared region (400–4000 cm^{-1}) were acquired using an IRTracer-100 spectrophotometer equipped with a diamond ATR accessory (QATR; Shimadzu, Kyoto, Japan). Spectra were recorded at a resolution of 4 cm^{-1}, with 100 scans averaged over the selected wavenumber range for each sample. All measurements were performed using LabSolution IR software (version 1.86 SP2; Shimadzu, Kyoto, Japan).

DSC Analysis

The DSC measurements were performed using a DSC 214 Polyma differential scanning calorimeter (Netzsch, Selb, Germany). A sealed aluminum pan with a lid served as the reference, while approximately 10–13 mg of powdered sample was placed in sealed aluminum pans with a small hole in the lid. The samples were analyzed under a single heating cycle from −50 to 210 °C at a heating rate of 10 °C·min^{-1}. A nitrogen purge gas was maintained at a flow rate of 250 mL·min^{-1} throughout the measurements. The obtained DSC data were processed using Proteus software version 8.0 (Netzsch, Selb, Germany), and the thermograms were plotted using Origin 2021b (OriginLab Corporation, Northampton, MA, USA).

2.2.3. In Vitro Dissolution Test

HPLC Method

The identity confirmation and lycopene content determination were conducted using a high-performance liquid chromatography (HPLC) method developed by Olives Barba et al. [36]. The method has been validated [7].

The chromatographic separation was performed using a Dionex Ultimate 3000 apparatus (Dionex, Sunnyvale, CA, USA). The separation was carried out on an lBondapack C18 column (300 mm × 2 mm) with a mobile phase consisting of methanol and acetonitrile in a 90:10 (v/v) ratio, with the addition of 0.9 µM triethylamine. The resulting solution was filtered through a 0.45 µm pore size membrane filter and degassed using ultrasound. The flow rate was maintained at 0.9 mL/min, and the injection volume was set to 10.0 µL. Detection was achieved using a UV detector (Dionex, Sunnyvale, CA, USA) at a wavelength of 475 nm. The total measurement time was 10 min, and the column temperature was maintained at 30 °C throughout the process.

In Vitro Dissolution Studies

A total of 4.5 mg of dry extract and extrudates were weighed and placed into gelatin capsules, which were then subjected to testing using a paddle apparatus ERWEKA DH 1520 (Erweka GmbH, Langen, Germany). The pharmaceutical availability studies were conducted under the following parameters: temperature of 36.8 °C, an acceptor fluid consisting of 0.1 M hydrochloric acid, a paddle rotation speed of 50 rpm, and a total test duration of 360 min.

For the extrudates, 5.0 mL aliquots were withdrawn at 5, 30, 60, 120, 180, 240, 300, and 360 min. For the extract, samples were collected at 5, 10, 15, 30, 45, 60, and 90 min. All samples were subsequently prepared for analysis using HPLC.

2.2.4. Evaluation of Antioxidant Activity

Preparation of 0.2 mM DPPH Solution

The free radical scavenging activity was evaluated using a DPPH assay as previously reported in the literature [37]. A total of 7.8 mg of DPPH was weighed and transferred into a 100.0 mL conical flask, which was then wrapped in aluminum foil. Methanol was added to reach the final volume, and the flask was sealed. The solution was shaken for 45 min and subsequently stored in a refrigerator, protected from light.

Preparation of Ascorbic Acid Solution

A total of 20.0 mg of ascorbic acid was weighed into a 5.0 mL volumetric flask wrapped in aluminum foil, and the volume was adjusted with distilled water. Standard curve solutions were prepared in aluminum foil-protected Eppendorf tubes, with concentrations of 0.15 mg/mL (prepared by mixing 3.75 µL of the stock ascorbic acid solution with 996.25 µL of distilled water), 7.5×10^{-3} mg/mL, 3.75×10^{-3} mg/mL, and 1.88×10^{-3} mg/mL, using serial 1:1 dilutions.

Preparation of Extrudate Solutions

The extrudates were weighed as follows: 100.0 mg of extrudate containing 10% lycopene extract with polymer (Soluplus or PVP/VA64), 50.0 mg of extrudate containing 20% lycopene extract with the polymer, 33.33 mg of extrudate containing 30% lycopene extract with the polymer, and 25.0 mg of extrudate containing 40% lycopene extract with the polymer. Each extrudate was dissolved in 1.0 mL of distilled water to prepare solutions with a lycopene extract concentration of 10.0 mg/mL. Complete dissolution of the samples was achieved using a shaker. From each of the eight prepared solutions, 100.0 µL was

transferred to Eppendorf tubes and diluted with distilled water to a final volume of 1.0 mL, resulting in solutions with a concentration of 0.1 mg/mL. Subsequently, 500.0 µL of each solution was further diluted 1:1 with water in separate Eppendorf tubes. This procedure was repeated five times for each solution to obtain concentrations of 100.0 µg/mL, 50.0 µg/mL, 25.0 µg/mL, 12.5 µg/mL, 6.25 µg/mL, and 3.125 µg/mL.

Procedure for the Determination of Antioxidant Activity

A 96-well plate was used for the assay, with 25.0 µL of each test sample or standard substance added to the wells, followed by 175.0 µL of a methanolic DPPH radical solution. A control sample was prepared by mixing 25.0 µL of water with 175.0 µL of the DPPH reagent, while a blank sample was prepared by combining 25.0 µL of water with 175.0 µL of methanol. Each test sample was analyzed in triplicate. The plate was tightly sealed with aluminum foil and placed on a shaker for 5 min at 25 °C. It was then incubated at room temperature for 25 min. Finally, absorbance was recorded at 517 nm using a Thermo Scientific Multiskan GO plate reader (Multiskan GO, Thermo Scientific, Waltham, MA, USA).

The antioxidant activity was then calculated according to the following equation:

$$\text{DPPH scavenging activity } (\%) \left[\frac{Ao - Ai}{Ao}\right] \times 100\%$$

where Ao is the absorbance of the control sample minus the absorbance of its background, and A_i is the absorbance of the test sample minus the absorbance of its background.

The EC_{50} value, representing the antioxidant concentration required to neutralize 50% of the DPPH radicals, was determined. This was achieved by plotting the relationship between antioxidant concentration and the DPPH radical scavenging activity.

3. Results

3.1. Preparation of Extracts and Extrudates

Ultrasonic extraction using acetone allowed for the effective extraction of lycopene-rich extract from tomato raw material. The process, carried out at 40 °C for 20 min, resulted in a dry extract with an intense color characteristic of the presence of carotenoids. The extract obtained was the starting material for further processing using carrier polymers.

In accordance with the assumptions of the study, extrudates were also obtained by hot melt extrusion, in which the lycopene extract was combined with PVP/VA64 or Soluplus polymers. The use of this technique made it possible to obtain homogeneous products, which confirmed the effectiveness of the adopted methodology. The extrudates were obtained in various extract proportions (10–40%), which ensured a varied content of the active substance in the formulation.

3.2. Extrudate Identity Testing

3.2.1. X-Ray Powder Diffraction (XRPD)

The XRPD patterns of the tomato extract, pure polymers (PVP VA64 and Soluplus), and extrudates with increasing polymer content are presented in Figure 2.

The diffractogram of the tomato extract exhibited a broad peak in the range of approx. 12.5–30.0° 2Θ. The polymer carriers (PVP VA64 and Soluplus) displayed a halo effect, characteristic of amorphous materials, which is consistent with the literature [38,39]. For all prepared extrudates, irrespective of the polymer type and concentration of extract (10–40%), the diffraction peaks retained the characteristic shape of a given polymer. This indicates that the tomato extract was fully dispersed in the polymer matrix. The change in the intensity of the first peak observed for the PVP VA64 extrudates containing 30% and 40% extract is probably related to differences in the degree of crystalline order within the samples.

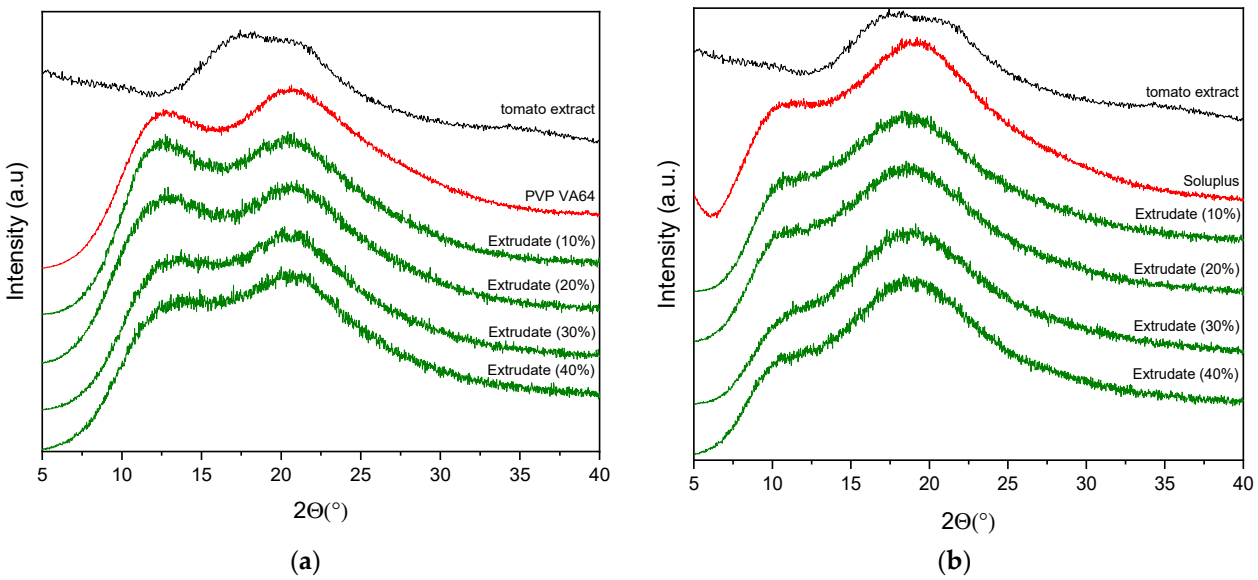


Figure 2. XRPD analysis: (**a**) samples with PVP VA64; (**b**) samples with Soluplus.

3.2.2. FT-IR Spectroscopy

FT-IR spectra of extract, polymers and extrudates with increasing polymer content are presented in Figure 3.

In the spectral range of 400–1800 cm^{-1}, no significant differences were observed between the extrudates, the physical mixtures, and the individual components, indicating the absence of new interactions or the formation of covalent bonds during the HME process. The only differences were observed in the range of 2600–4000 cm^{-1}. The tomato extract displayed a strong, broad absorption centered at ~3312 cm^{-1}, attributable to water in the extract [40]. PVP VA64 showed the C–H stretching vibration in the range of 2800–3100 cm^{-1} [38], while Soluplus exhibited distinct C–H stretching bands at ~2876 and ~2940 cm^{-1} [39]. In the extrudates, the intensity of the ~3312 cm^{-1} band decreased and its position shifted relative to the neat extract. These results suggest that in extrudates is a lower water content-plausibly due to partial dehydration during extrusion at 135 °C-and with changes in the hydrogen-bonding environment upon dispersion of the extract within the polymer matrices. Specifically, attenuation and/or shifting of the O–H band indicates reduced bulk water and altered hydroxyl interactions (e.g., with carbonyl and ether groups in PVP VA64 or Soluplus), rather than the formation of new covalent bonds. Across all spectra, the polymer C–H stretching regions remained characteristic (PVP VA64: broad 2800–3100 cm^{-1}; Soluplus: ~2876 and ~2940 cm^{-1}), and no new bands emerged. FT-IR analysis support physical incorporation of the extract into the carriers with dehydration and modified hydrogen bonding, without evidence of chemical degradation or new bond formation during extrusion.

3.2.3. DSC Analysis

The DSC thermograms (Figure 4) show the thermal behavior of the tomato extract, Soluplus or PVP VA64, and their extrudates containing different proportions of the tomato extract (10–40%). The tomato extract exhibits two main endothermic peaks at approximately 86.3 °C and 149.1 °C, which can be attributed to the evaporation of residual moisture and the melting of certain extract components, respectively. The PVP VA64 polymer shows two endothermic peaks at approximately 90.5 °C and 145.0 °C, whereas Soluplus shows two endothermic peaks at about 67.7 °C and 98.9 °C. In the extrudates, the thermal profile changes depending on the tomato extract content. Endothermic peaks in PVPVA64 extrudates are characteristic of PVPVA64, whereas in Soluplus extrudates, they are characteristic

of Soluplus. This indicates that the tomato extract is fully dispersed in the polymer matrix. Notably, as the proportion of extract increases, the intensity of these peaks decreases and shifts slightly toward lower temperatures, indicating possible molecular interactions or miscibility between the extract and polymer. The disappearance of the distinct melting peaks observed in the pure extract at 149.1 °C suggests that the extract components are amorphized or molecularly dispersed within the polymer matrix after hot-melt extrusion. This behavior confirms the formation of a solid dispersion system, which may enhance the physical stability and solubility of the extract compounds.

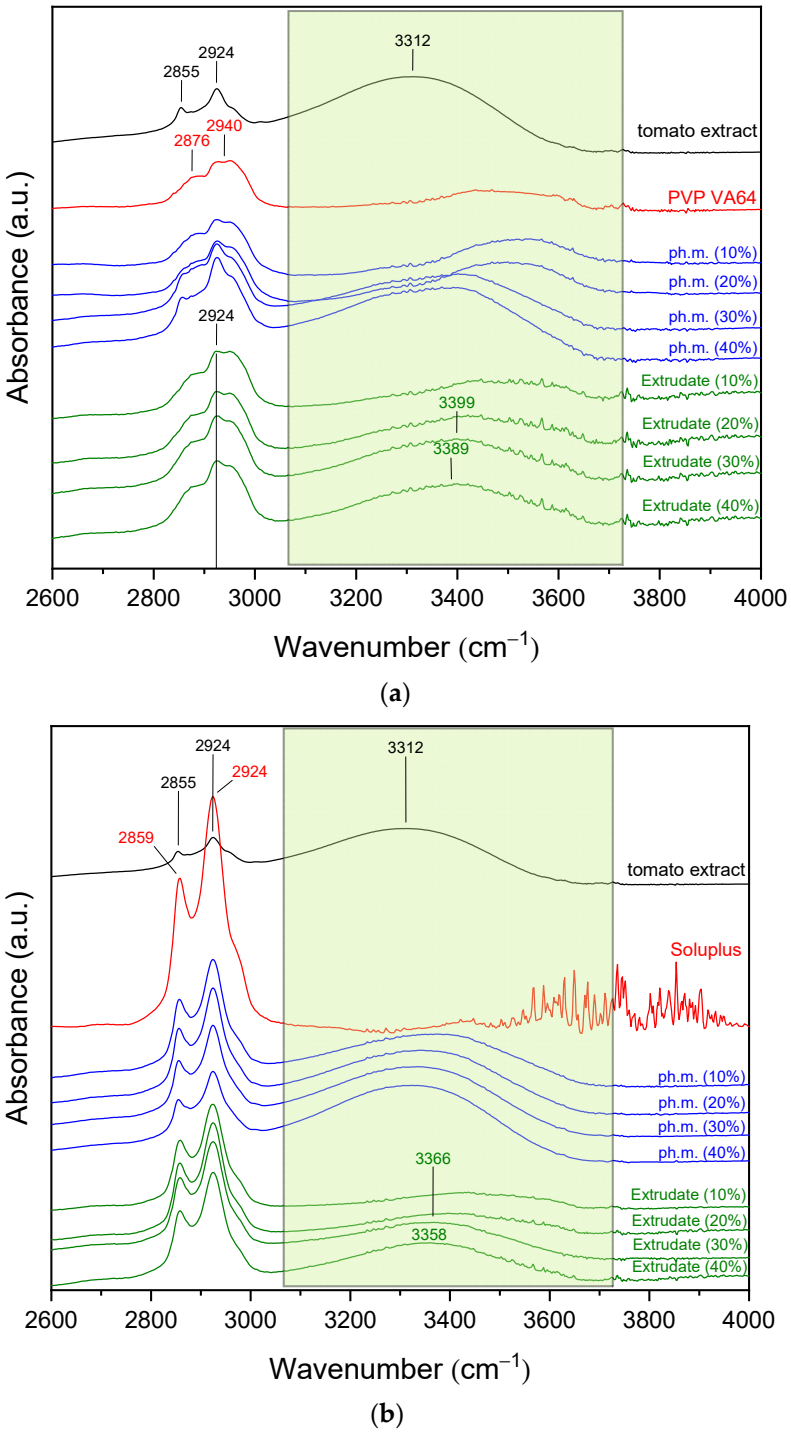


Figure 3. FT-IR analysis: (**a**) samples with PVP VA64; (**b**) samples with Soluplus.

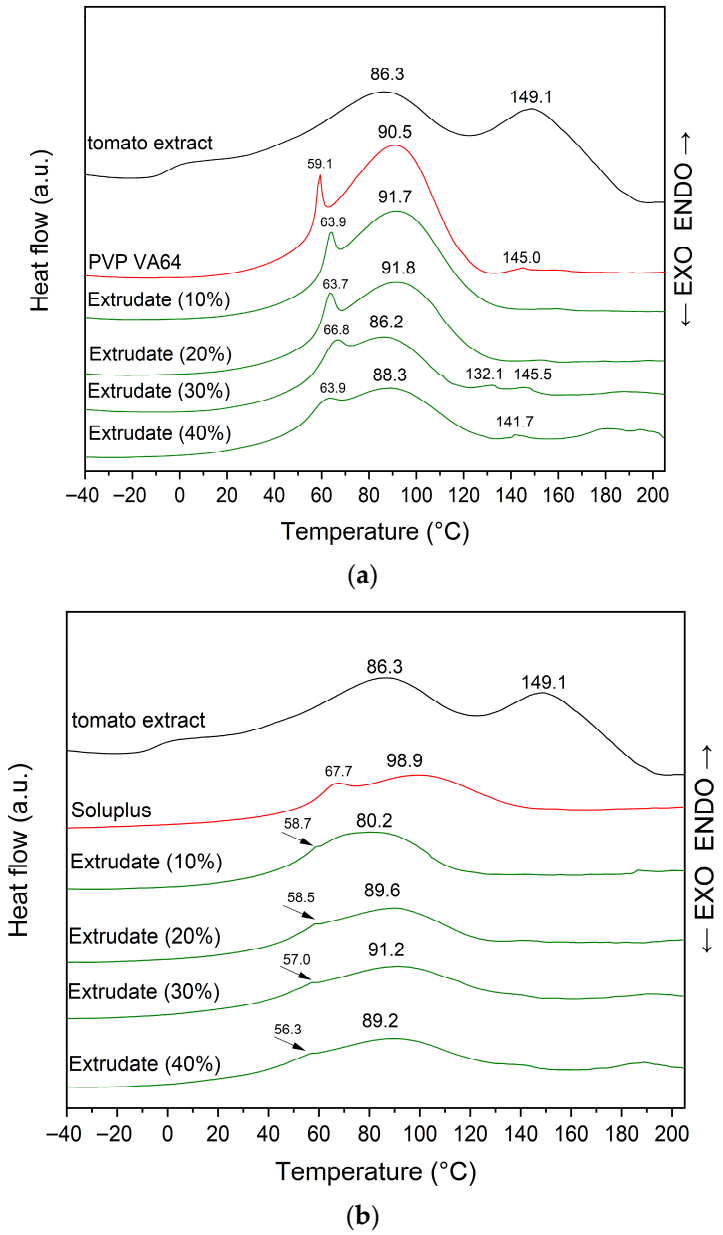


Figure 4. DSC analysis: (**a**) samples with PVP VA64; (**b**) samples with Soluplus.

3.3. In Vitro Dissolution Test

The study aimed to assess how the method of extract preparation and combinations with selected polymers influence the degradation and dissolution behavior of lycopene. After confirmation of the extrudates' identity, a series of HPLC measurements was conducted, followed by data analysis, including calculations and graphs (Figure 5). The experiment was carried out under acidic conditions simulating the gastric environment, as lycopene is known to exhibit its highest chemical stability in such conditions [10].

It has been demonstrated that lycopene extracted with acetone exhibits limited permeation into an acidic environment, reaching merely 1%. However, in in vitro dissolution studies with polymers such as Soluplus and PVP VA64, improved dissolution performance was observed. Both polymers had a comparable effect on the dissolution rate and the overall dissolution profiles of lycopene. A higher polymer content in the extrudate correlated with an increased percentage of lycopene dissolved over time. Notably, higher lycopene dissolution was observed in formulations with PVP VA64, particularly at polymer concentrations of 90% and 80%. An extrudate containing 10% extract and 90% PVP VA64

increased lycopene dissolution from 1% to 34%. In comparison, an extrudate with 10% extract and 90% Soluplus achieved a dissolution rate of 31%. The calculations for the dissolution test are presented in the Tables S1–S9 in the Supplementary Materials.

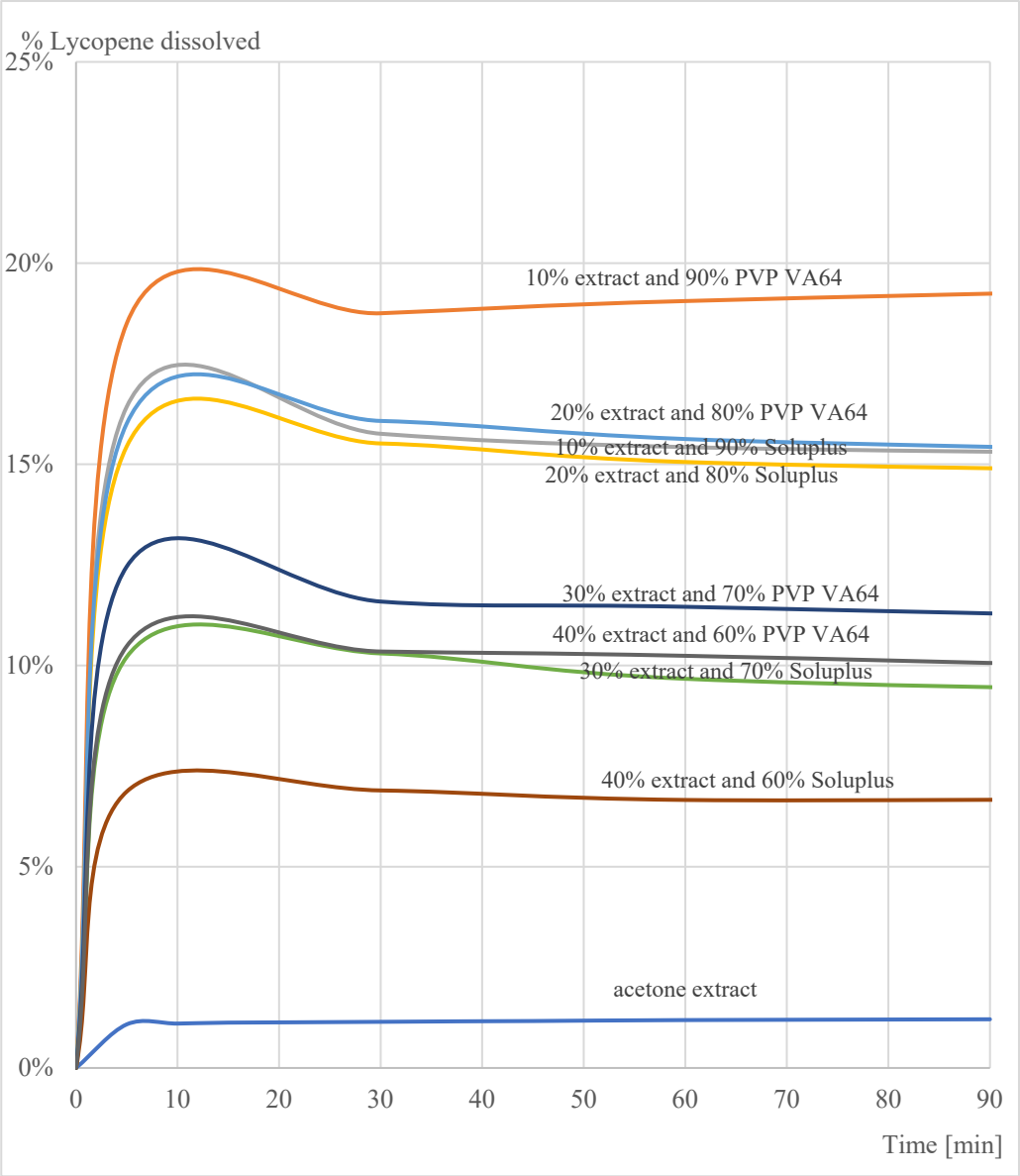


Figure 5. Percentage of lycopene released from acetone extract and extrudates per unit time.

3.4. Determination of Antioxidant Activity Using the DPPH Radical

The antioxidant activity of the resulting extrudates was assessed using the DPPH free radical method, with ascorbic acid serving as the standard. The EC_{50} parameter, representing the concentration of an antioxidant required to inhibit 50% of the free radicals, was used to analyze and compare the results. A lower EC_{50} value indicates a higher antioxidant potential of the tested compound. The results are presented in the chart (Figure 6). The calculations for the antioxidant activity are presented in the Tables S10–S18 and Figures S1–S9 in the Supplementary Materials.

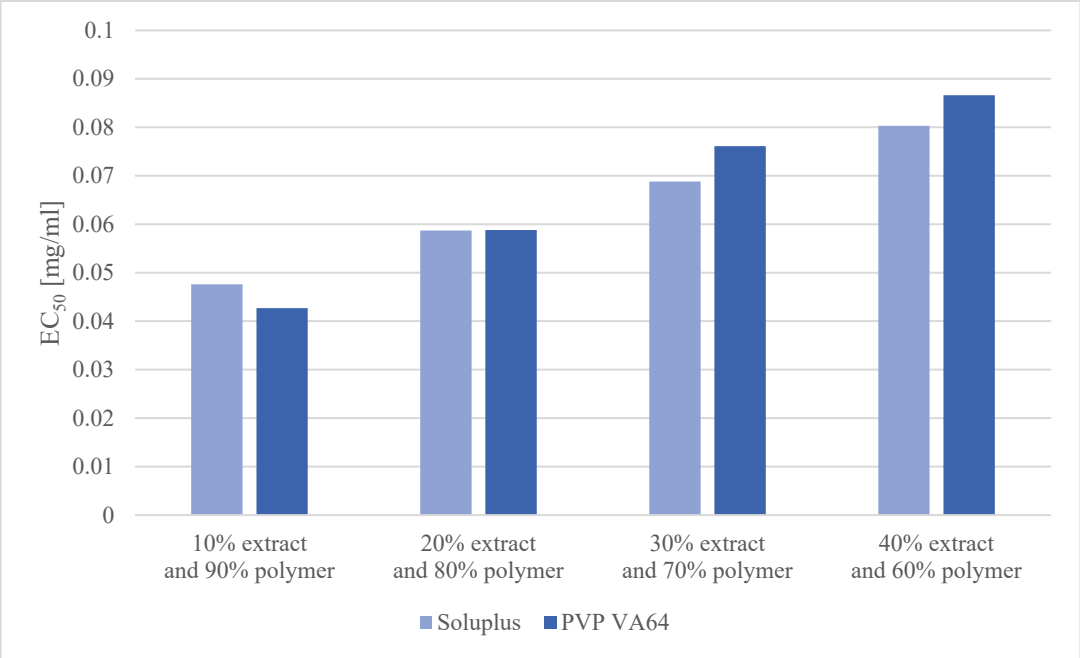


Figure 6. Comparison of the antioxidant activity of the extrudates.

The antioxidant activity of the extrudates increased with the polymer content. For samples containing 10% extract, both Soluplus and PVP VA64 combinations exhibited comparable antioxidant potential. At higher extract concentrations (30% and 40%), the extrudates with Soluplus demonstrated lower EC_{50} values, indicating stronger antioxidant activity compared to those with PVP VA64. In all cases, the antioxidant potential of the extrudates was lower than that of ascorbic acid (7.8×10^{-3} mg/mL), which served as the reference compound.

4. Discussion

The first stage of the study confirmed the feasibility of obtaining lycopene extract using ultrasound-assisted extraction. This method, widely described in the literature, is considered effective and efficient in the isolation of carotenoids, including lycopene [41].

The next achievement was the production of extrudates via hot-melt extrusion. The resulting formulations with PVP/VA64 and Soluplus demonstrated good uniformity, indicating effective dispersion of the extract within the polymer matrix. These results are in agreement with previous reports, in which HME was used to improve the solubility and bioavailability of hydrophobic compounds, including lycopene and other carotenoids [42–44]. The use of amphiphilic polymers, such as Soluplus, or vinylpyrrolidone copolymers like PVP/VA64, enables the formation of amorphous dispersion systems that significantly enhance the solubility properties of lipophilic active compounds.

However, it should be emphasized that the number of studies directly addressing lycopene formulations obtained by HME is still limited. In the available literature, researchers reported the successful use of this technique to combine lycopene with different carriers, such as PVP-K30 [43], lycopene–cyclodextrin–PEG complexes [44], and corn grit as a natural carrier [42]. These examples confirm the versatility of HME for lycopene processing.

Our XRPD, FTIR and DSC findings are consistent with literature reports demonstrating that hot-melt extrusion and solid dispersion techniques effectively stabilize lycopene in an amorphous state and promote its molecular dispersion within polymer matrices. Importantly, incorporation into PVP VA64 or Soluplus matrices maintained this amorphous character across all extrudates, indicating that extrusion enabled homogeneous molecular

dispersion of the extract components in the carriers. Similar observations were made by Mirahmadi et al. [43], who showed that both isolated whey protein and PVP-K30 stabilized lycopene in amorphous solid dispersions and markedly enhanced its dissolution rate. These findings are in line with our results.

In another study Ma et al. [44] demonstrated that lycopene–cyclodextrin–PEG ternary systems obtained by hot-melt extrusion achieved nearly a 32-fold increase in aqueous solubility compared to binary inclusions. XRPD and FTIR confirmed the amorphous state of lycopene within the ternary systems and highlighted the role of hydrogen-bonding interactions in stabilizing the formulations.

Both our study and the cited works highlight that the choice of polymer or carrier is crucial. Matrices such as PVP, Soluplus, or cyclodextrin–PEG systems not only enhance dissolution in water but also maintain lycopene in an amorphous, bioavailable state, and showing its antioxidant activity.

The poor water solubility and low oral bioavailability of lycopene present significant challenges for its effective utilization. This is largely due to its hydrophobic nature and crystalline structure, which includes a system of conjugated double bonds [45]. In this study, we observed that acetone-extracted lycopene exhibited minimal dissolution (1%) in 0.1 M HCl, which aligns with the known characteristics of lycopene.

Lycopene, a carotenoid with significant health benefits, has been the subject of various attempts to enhance its bioavailability. Approaches such as microencapsulation, liposomes, cyclodextrins, and solid dispersions have been explored in previous studies [7,22,46,47]. Hot-melt extrusion has emerged as a promising technique for improving the solubility and stability of poorly water-soluble drugs due to its speed, continuous manufacturing process, and the absence of organic solvents [28,29]. This study utilized HME to prepare lycopene-containing extrudates with Soluplus and PVP/VA64, which demonstrated improvements in solubility and bioactivity.

Compared to alternative formulation strategies like liposomal encapsulation, cyclodextrin inclusion, or nanoemulsions, which are commonly used to improve lycopene bioavailability, hot melt extrusion stands out due to its solvent-free processing, continuous manufacturing capability, and industrial scalability [44,48]. This makes HME particularly advantageous for formulating lipophilic active compounds, like lycopene, with improved functional performance.

The findings of our study underscore the potential of hot-melt extrusion to enhance the aqueous solubility, release profiles, and demonstrate antioxidant activity of lycopene. Incorporation of polymers such as Soluplus and PVP/VA64 improved the dissolution of lycopene, as seen in the increased release from the extrudates. Specifically, the inclusion of polymers increased the release of lycopene to 34% and 31% for extrudates containing 90% PVP VA64 and Soluplus, respectively, compared to just 1% release from the acetone extract alone in acidic media. This is consistent with prior research by Dehghan-Shoar et al. [49], which highlighted the role of extrusion in disrupting crystalline structures and promoting lycopene solubility.

In agreement with our results, previous research by Mirahmadi et al. [43] demonstrated that solid dispersion techniques involving polymers like polyvinylpyrrolidone (PVP-K30) can significantly improve lycopene's dissolution profile. Their study found that PVP-based systems, alongside isolated whey protein, could enhance lycopene's bioavailability via molecular interactions and stabilization in the amorphous state. These findings are consistent with our study, where polymers improved lycopene's solubility and likely interacted with the carotenoid through hydrogen bonding and hydrophobic forces.

Additionally, the DPPH antioxidant activity assay revealed that extrudates, particularly those with higher extract content, exhibited improved radical scavenging activity.

This enhancement may be due to the improved dispersibility and accessibility of lycopene molecules in aqueous environments provided by the polymer matrices. Sharma and Gujral [50] also found that extrusion at elevated temperatures could enhance antioxidant properties, aligning with our findings.

Tonyali et al. [42] support the notion that matrix disruption via extrusion enhances lycopene bioaccessibility. In their study, tomato pulp-extruded corn products exhibited an increase in vitro lycopene bioaccessibility, especially under higher temperature extrusion conditions. The matrix softening and improved dispersion facilitated more effective lycopene release during digestion, even though some loss in lycopene content occurred during processing. Similarly, our results confirm that the structural modification of the lycopene delivery system via extrusion facilitates its release, particularly in acidic environments.

The comparative effectiveness of Soluplus and PVP/VA64 suggests that the choice of polymer significantly influences both release kinetics and biofunctionality. While PVP/VA64 showed superior performance at lower extract levels, Soluplus offered more potent antioxidant effects at higher concentrations, possibly due to differing solubilization mechanisms and hydrophilic-lipophilic balance. Moreover, the DPPH radical scavenging assays revealed that higher polymer contents led to lower EC_{50} values, indicating enhanced antioxidant potential.

Interestingly, extrudates with higher lycopene content showed reduced antioxidant efficiency, suggesting potential interactions or saturation effects that warrant further investigation. These findings suggest that the polymer selection and lycopene concentration are key factors in optimizing formulations for both dissolution and bioactivity.

Nevertheless, the present study has certain limitations, as only the DPPH method was applied; the findings provide preliminary insight into antioxidant activity. Additional assays (e.g., ABTS, FRAP, ORAC), including analysis of the raw extract, are required to fully evaluate antioxidant performance. It also does not include storage stability testing or in vivo correlation of the observed effects. Addressing these aspects will be essential to fully validate the long-term performance and biological relevance of the developed formulations.

Overall, this study supports the potential of solid dispersion and HME in improving the dissolution of lipophilic active compounds like lycopene. The results also emphasize the importance of polymer selection based on the desired functional outcomes. Future studies should focus on in vivo evaluations, stability assessments under gastrointestinal conditions, and exploring synergistic effects with other bioactive compounds.

5. Conclusions

The conducted research demonstrated that combining lycopene-containing extracts with PVP VA64 and Soluplus significantly enhances the compound's water dissolution. The observed increase in dissolution is the result of complex formation with polymers, which is a key mechanism for improving bioavailability. Lycopene extracted with acetone does not permeate into 0.1 M HCl fluid, highlighting the need for modifications to improve its release profile in acidic environments. Extrudates formulated with PVP VA64 and Soluplus were shown to markedly increase lycopene release under such conditions, with the release percentage rising proportionally to the polymer content in the extrudates.

Additionally, as a result of improved dissolution, the antioxidant activity of lycopene is also observed, which indicates the beneficial effect of formulation modifications. Antioxidant activity studies using the DPPH radical revealed that extrudates with PVP VA64 and Soluplus positively influence the antioxidant potential of lycopene. A higher polymer content in the extrudates resulted in lower EC_{50} values, indicating enhanced antioxidant activity. These findings underscore the importance of polymer-based formulations in optimizing the bioavailability and functionality of lycopene.

However, the present study did not include storage stability testing or in vivo correlation experiments, which should be considered as limitations. Future work should focus on evaluating the long-term stability of the developed extrudates and verifying their biological efficacy in relevant in vivo models.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app152212311/s1, Figure S1: Dependence of the antioxidant activity of ascorbic acid on concentration; Figure S2: Dependence of the antioxidant activity of the 10% extract and 90% Soluplus polymer extrudate on the concentration; Figure S3: Dependence of the antioxidant activity of the 20% extract and 80% Soluplus polymer extrudate on the concentration; Figure S4: Dependence of the antioxidant activity of the 30% extract and 70% Soluplus polymer extrudate on the concentration; Figure S5: Dependence of the antioxidant activity of the 40% extract and 60% Soluplus polymer extrudate on the concentration; Figure S6: Dependence of the antioxidant activity of the 10% extract and 90% PVP VA64 polymer extrudate on the concentration; Figure S7: Dependence of the antioxidant activity of the 20% extract and 80% PVP VA64 polymer extrudate on the concentration; Figure S8: Dependence of the antioxidant activity of the 30% extract and 70% PVP VA64 polymer extrudate on the concentration; Figure S9: Dependence of the antioxidant activity of the 40% extract and 60% PVP VA64 polymer extrudate on the concentration; Table S1. Lycopene release profile from acetone extract; Table S2. Lycopene release profile from extrudate containing 10% extract and 90% Soluplus; Table S3. Lycopene release profile from extrudate containing 20% extract and 80% Soluplus; Table S4. Lycopene release profile from extrudate containing 30% extract and 70% Soluplus; Table S5. Lycopene release profile from extrudate containing 40% extract and 60% Soluplus; Table S6. Lycopene release profile from extrudate containing 10% extract and 90% PVP VA64; Table S7. Lycopene release profile from extrudate containing 20% extract and 80% PVP VA64; Table S8. Lycopene release profile from extrudate containing 30% extract and 70% PVP VA64; Table S9. Lycopene release profile from extrudate containing 40% extract and 60% PVP VA64; Table S10: Results of the antioxidant activity test for ascorbic acid; Table S11: Results of the antioxidant activity test of the extrudate of 10% extract and 90% Soluplus polymer; Table S12: Results of the antioxidant activity test of the extrudate of 20% extract and 80% Soluplus polymer; Table S13: Results of the antioxidant activity test of the extrudate of 30% extract and 70% Soluplus polymer; Table S14: Results of the antioxidant activity test of the extrudate of 40% extract and 60% Soluplus polymer; Table S15: Results of the antioxidant activity test of the extrudate of 10% extract and 90% PVP VA64 polymer; Table S16: Results of the antioxidant activity test of an extrudate containing 20% extract and 80% PVP VA64 polymer; Table S17: Results of the antioxidant activity test of an extrudate containing 30% extract and 70% PVP VA64 polymer; Table S18: Results of the antioxidant activity test of the extrudate containing 40% extract and 60% PVP VA64 polymer.

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