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Temperature-dependent behavior of PVA/Drug composites during melt extrusion

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Abstract
This study highlights the growing collaboration between materials, engineering, and pharmaceutical research, enhancing drug efficacy and reducing side effects by optimizing polymer carriers for stability and compatibility. Polyvinyl alcohol (PVA), Rhumix, glycerol, and citric acid were used as a carrier, drug, plasticizer, and stabilizer to create polymer-drug composites at varying temperatures. A twin-screw extruder was used to mix, melt, and extrude 60% PVA, 30% Rhumix, 9.9% glycerol, and 0.1% citric acid at (160, 170, and 180)°C with a screw speed of 50 rpm. DSC, FTIR, and optical/digital microscopy techniques characterized the composites. Results showed smooth extrusion of the PVA/drug composites, with the addition of plasticizers resulting in lower T_g and T_m. The extruded compounds exhibited varying colours and surface properties. The bonding values remained stable, indicating no significant interaction. DSC curves revealed two T_g values, indicating compatibility and immiscibility. Microscope images demonstrated improved drug dispersion at 160°C. Notably, the selected components, particularly PVA and glycerol, are widely recognised for their biocompatibility and low toxicity, as confirmed by previous studies, which support the potential suitability of these compounds for biomedical applications.

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1. Introduction

Many techniques are utilized for drug delivery, including nanoparticles and nanocarriers (Wakaskar, 2017), hydrogel-based drug delivery systems (Li & Mooney, 2016), biodegradable implants (Benoit et al., 2020; Wagner et al., 2020; and Sinha & Trehan, 2003), microfluidic systems (Li et al., 2019; and Al-Jarwany et al., 2024), microneedles (Donnelly et al., 2010), stimuli-responsive drug delivery (Rao et al., 2018), targeted drug delivery (Tekade et al., 2017), liposome-based delivery systems (Patra et al., 2018), gene therapy vectors (Marshell et al., 2011), 3D-printed drug delivery systems (Goole & Amighi, 2016), electrospun nanofibers (Xue et al., 2014; and Sinha-Ray et al., 2015), and exosome-mediated drug delivery (El Andaloussi et al., 2013).

In this technique, a biopolymer is used at different temperatures to load the drug through a melt extrusion process (Saturwar et al., 2002). This ensures efficient dispersion and stability of the drug within the polymer matrix, allowing for solvent-free incorporation and delivery. The melt extrusion process is commonly employed in the pharmaceutical industry for preparing drug-loaded polymer matrices. The technique involves heating a polymer to its melting point and then incorporating the active pharmaceutical ingredient (API) into the molten polymer. This allows for the drug to be evenly dispersed within the polymer matrix, which is essential for controlled drug release and bioavailability (Breitenbach, 2002). The key benefit of this technique is its ability to produce uniform, stable, and reproducible formulations that can be tailored for various drug delivery systems, such as solid dispersions or controlled-release tablets. The success of melt extrusion mainly depends on a number of parameters, such as the temperature, screw speed, and polymer composition. Extrusion temperature is pivotal as it influences the viscosity of the polymer, the control ability of uniformly dispersing the drug. Screw speed as well plays a role in determining the shear stress applied during the extrusion process, which impacts the drug's dissolution and distribution. (Parvathaneni et al., 2022; and Liechty et al., 2010; Sabr et al., 2024). Additionally, factors such as residence time, temperature profiles across

different zones of the extruder, and internal pressure significantly influence the thermal exposure, mixing behavior, and risk of degradation during processing (Maniruzzaman et al., 2012; and Patil et al., 2016). Both physical and chemical properties of the polymer and drug determine the quality of drug dispersion in the final product. This comprises solubility, molecular weight, and melting points. A crucial challenge in the melt extrusion is to attain a homogeneous drug dispersion without drug crystallization or aggregation. This can negatively influence bioavailability and stability. Numerous strategies have been explored to improve the drug solubility and prevent aggregation, such as the use of surfactants or co-polymers. Additionally, the drug's physo/chemical properties must be compatible with the selected polymer. Also, the processing conditions must be closely controlled to avoid degradation or loss of therapeutic activity (Shah & Repka, 2013; Smith & Kinch, 2011; and Patil et al., 2016). Researchers are continually improving the melt extrusion process to ensure maximum drug dispersion (Sakr et al., 2019). This involves adjusting factors such as polymer type, drug loading levels, and extrusion conditions (Kinikar & Kuchekar, 2022; Ghorab & Gaber, 2017; Li et al., 2016; and He & Feng, 2016). The melt extrusion process is widely used to develop solid dispersions and controlled-release drug formulations, especially for poorly water-soluble drugs (Okwuosa & Harrison, 2018). These formulations could refine drug solubility and dissolution rate, boosting the bioavailability (Okwuosa and Harrison, 2018; Patel and Rathi, 2015; Williams et al., 2013). Melt extrusion can notably enhance the solubility and bioavailability of poorly water-soluble drugs, as its most significant benefit. In the case of poorly soluble compounds, melt extrusion is used to produce amorphous solid dispersions by mixing the drug with polymers (Begum and Reddy, 2020; Patel and Patel, 2014; Khosravi et al., 2021; Patil et al., 2016; Corrie et al., 2019).

The versatility of melt extrusion is also notable: it can be used with a wide range of drugs and polymers, including hydrophilic, hydrophobic, and thermally sensitive compounds, making it suitable for diverse therapeutic applications (Repka et al., 2007; Patil et al., 2016; and Stanković et al., 2015).

The ratios of 60% PVA, 30% drug Rhumix, 9.9% glycerol and 0.1% citric acid were premixed and then filled into the extruder at (160, 170 and 180)°C and 50 rpm. Three composite sheet samples were produced. Differential scanning calorimetry DSC and Fourier transform infrared spectroscopy FTIR techniques were used to investigate the thermal behavior and chemical interactions of the composite materials. The morphology of the composite material was tested using an optical microscope.

2. Aims

This study aims to investigate the thermal, structural and morphological behavior of PVA/Rhumix pharmaceutical composites produced by hot melt extrusion at three different temperatures (160, 170, and 180)°C. The objective is to determine the effect of temperature on drug dispersion, material compatibility, and release properties.

3. Experimental

3.1. Materials

The components used in this study, polyvinyl alcohol PVA, glycerol, citric acid, and Rhumix, which is a mixture of ibuprofen and paracetamol in a 2:1 ratio, were selected based on their recognized safety profiles and widespread use in pharmaceutical and biomedical applications. PVA is a non-toxic, biocompatible polymer widely used in drug delivery systems and approved by regulatory bodies for medical use (Hassan and Peppas, 2000). Glycerol and citric acid are approved excipients and generally recognised as safe GRAS, typically used as a laxative and stabiliser, respectively, with low toxicity at concentrations appropriate for the formulation (Rowe et al., 2006). These properties support the suitability of the compound for potential pharmaceutical applications.

Table 1. Specifications of the materials used.

Properties	Citric Acid	Glycerol	Ibuprofen	Paracetamol
Molecular formula	$C_6H_8O_7$	$C_3H_8O_3$	$C_{13}H_{18}O_2$	$C_8H_9NO_2$
Molecular weight (g/mol)	192.13	92.09	206.28	151.16
Melting point (°C)	153	18	75-78	168-172
Solubility in water	Very soluble	Miscible	Very low (~ 0.02 mg/mL)	Moderate (~14 mg/mL)
Color	White	Colorless	White	White
Shape	Powder	Liquid	Crystalline powder	Crystalline powder

Table 2. Material composition of S1, S2, and S3 samples at different processing temperatures.

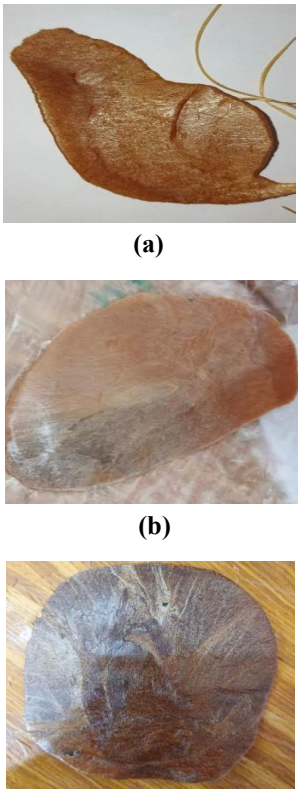
Materials	Ratio (%)	Weight (g)	Notes
PVA	60%	54	Base polymer
Glycerol	9.9%	8.91	Plasticizer
Citric acid	0.1%	0.09	Crosslinker
Rhumix	30 %	27	Drug mixture (Ibuprofen + Paracetamol)
- Ibuprofen	-	18	2:1 ratio (R)
- Paracetamol	-	9	2:1 ratio R, Ibuprofen:Paracetamol

Polyvinyl alcohol PVA was purchased from Mese company with the following characteristics: average molecular weight: 67,000, degree of hydrolysis: 88%, viscosity: 8 mPa·s (in 4% aqueous solution), physical form: pure, solid, white, odorless, degree of polymerization: 1,400. Citric acid and glycerol were acquired from Al-Manar Iraqi Chemicals Company, while Rumex was obtained from a public pharmacy. Rumex is a 2:1 fixed-dose mixture of ibuprofen and paracetamol, commonly used to relieve pain and fever. Ibuprofen, a nonsteroidal anti-

inflammatory drug NSAID, is partially soluble in water at a concentration of 0.02 mg/ml and has an MP temperature of 75–78°C. Paracetamol is more soluble at a concentration of 14 mg/ml and has an MP of 168–172°C. Their combination is widely applied in pharmaceuticals for pain relief and fever reduction, and the data summarized in Tables 1 and 2 support reproducibility and interpretation of the composite materials' thermal and solubility behavior (Rowe et al., 2006; and Hassan & Peppas, 2000). They were mixed in the specific proportions and weights; specific details are shown in Table 2.

3.2. Samples preparation

The materials were mixed according to the ratios in Table 2. The extrusion process was carried out at different processing temperatures (160, 170, and 180)°C and a speed of 50 rpm to produce the composites S1, S2, and S3, respectively. The three samples are shown in Figure 1.



(a)

(b)

(c)

Fig. 1. The composites samples of (a) S1 at 160°C, (b) S2 at 170°C, (c) S3 at 180°C

3.3. Characterization Techniques

3.3.1 Hot-Melt Extrusion

Hot-melt extrusion (HME) twin screw from EAST SUN Chinese brand DONGHUI, model SLJ30A, it is used to mix, melt and extrude the composites at a certain temperatures and speed according to (ISO9001), with a co-rotation, partially intermeshing screw.

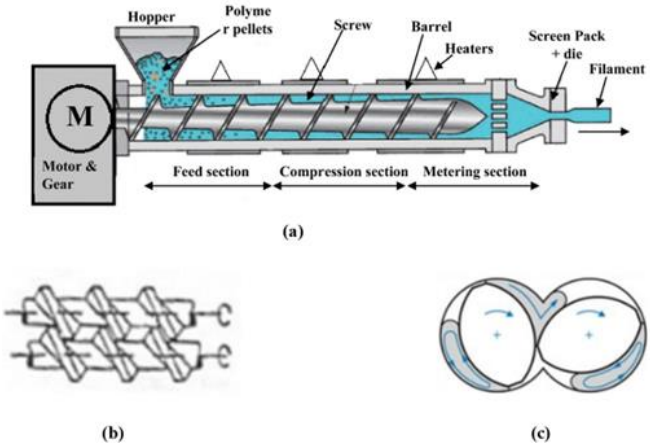


Fig. 2. (a) The extruder parts, (b) Partially intermeshing screw, (c) Co-rotation (Mishra et al., 2022; Osswald and Hernández-Ortiz, 2013)

3.3.2. Fourier Transform Infrared Spectroscopy (FTIR)

The Fourier transform infrared spectra of PVA with the drug were obtained using the pressed KBr pellet method using Type (IR Affinity-1) manufactured in Kyoto, Japan. The samples S1, S2, and S3 were mixed with KBr powder in a mass ratio of 1:10. The mixture was then ground together and placed on an FTIR-holder, Fig. 3. The reconstructed beam was aligned with the specimen and directed towards the detector. This device operates by using the emission, absorption, or scattering of infrared light to provide detailed structural and quantitative information on functional categories in biomolecules (Sabzi & Jazani, 2019). It is utilized extensively in biomaterials and life sciences. The infrared (IR) region is mostly used for recording spectra within the wave number range of 500–4000 cm^{-1} (Rana et al., 2022).

3.3.3. Differential Scanning Calorimetry (DSC)

The Shimadzu DSC-60 differential scanning calorimeter (-140 to 600°C) was used to analyze thermal transitions (melting, crystallization, and glass transition) in compliance with ISO 11357-3 and following characterization practices reported in Al-Mutairi et al., 2023.

4. Results and Discussion

4.1. DSC Analysis

Differential Scanning Calorimetry DSC was performed in the range of 20–230°C at a heating rate of 10°C·min^{-1} to investigate melting and decomposition behavior. The results revealed decomposition within 270–350°C, while melting of S1 occurred at 160°C, S2 at 170°C and S3 at 180°C. These three temperature settings during hot-melt extrusion were used to assess the influence of processing conditions on composite structure and melting behavior. The thermal stability of pure PVA and the composites (S1, S2, and S3) was evaluated. The DSC curves are presented in Figure 3, showing two main peaks corresponding to distinct thermal events.

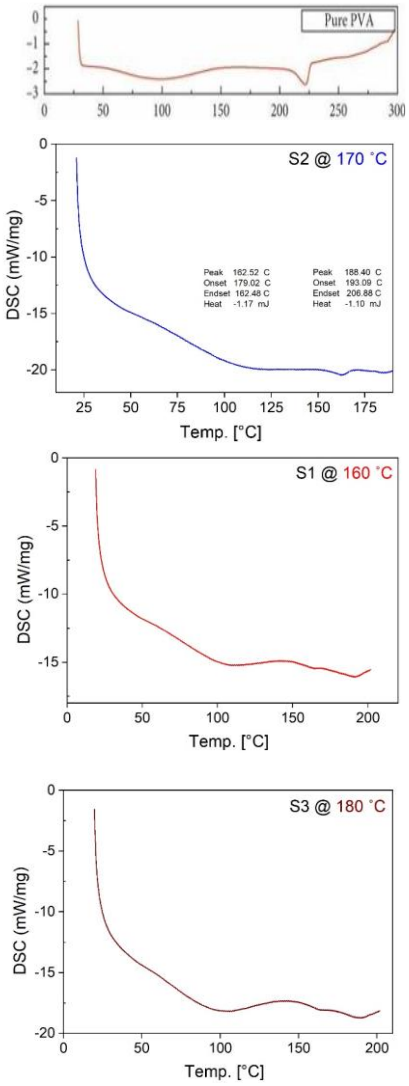


Fig. 3. Differential Scanning Calorimetry curves of Pure PVA, S1, S2, and S3 samples

The first peaks at (85, 64, 63 and 61)°C and the second peaks differ at (--, 145.9, 151.5 and 144.2)°C, which correspond to the T_g and T_m of the pure PVC and composites (S1, S2 and S3) respectively, as shown in Table 3.

Table 3. Thermal data of Pure PVA, S1, S2, and S3 samples

Samples #	T_g1 (°C)	T_g2 (°C)	T_m (°C)
Pure PVA	85	--	180
S1	64	145.9	191
S2	63	151.5	193
S3	61	144.2	192

For sample S3 (processed at 180°C), a broad endothermic peak in the 50–100°C range corresponds to moisture evaporation and composite dehydration. The heating curve between 100–180°C shows an onset peak at 179°C, attributed to the plasticizing effect of glycerol, which produces a baseline shift rather than a sharp melting peak. A sharp endothermic peak observed at 180–230°C reflects the melting of crystalline PVA regions. The reduced peak intensity and broadening result from glycerol's plasticizing action, while citric acid further weakens the melting peak. No exothermic transition is observed below 230°C, as thermal decomposition of PVA, glycerol, and citric acid typically occurs within 250–350°C (Shi et al., 2008; Ghanbarzadeh & Almasi, 2013; Abdul Khalil et al., 2020; Tsioptsias et al., 2023).

4.2. Fourier transform infrared spectroscopy FTIR Analysis

The FTIR spectra of pure polyvinyl alcohol (PVA) and the composite samples S1, S2, and S3 (blended with citric acid and glycerol, and processed at 160, 170, and 180°C) are presented in Figure 4. The spectra highlight key functional groups and the interactions among the composite components. As summarized in Table 4, a broad band in the 3200–3500 cm^{-1} region corresponds to O–H stretching vibrations, attributed to strong hydrogen bonding (Coates, 2000; and Ren et al., 2017). This band shows slight shifts depending on the degree of crosslinking and interactions introduced by citric acid and glycerol (Stuart, 2004). Peaks around 2900 cm^{-1} are assigned to C–H stretching vibrations of aliphatic hydrocarbons present in PVA and glycerol (Mansur et al., 2004; Castro et al., 2023; and Xiao et al., 2019). Additionally, a characteristic peak at approximately 1720 cm^{-1} indicates C=O stretching vibrations of ester groups formed by the reaction between PVA and citric acid (Stuart, 2004; and Smith, 2011).

Although Fourier transform infrared analysis did not reveal any new covalent bond formation, subtle shifts in key functional groups, such as O–H, C=O, and C–H stretching vibrations, suggest the presence of non-covalent interactions based on hydrogen bonds and possibly van der Waals forces between the drug (Rhumix) and the PVA-based matrix (Stuart, 2004; Mansur et al., 2004; and Krumova et al., 2000).

The esterification peak at approximately 1720 cm^{-1}, attributed to the interaction between citric acid and PVA, remained constant across all samples, further supporting the integrity of the polymer structure during processing (Castro et al., 2023). The presence of O–H and C=O band shifts indicates that weak hydrogen bonding and van der Waals interactions are likely contributing to the stabilization of the amorphous dispersion. While no new covalent bonds were formed, these secondary interactions can explain the stability of the drug within the polymer matrix (Wegiel et al., 2013; and Repka et al., 2018). The absence of significant peak shifts or the appearance of new vibrational bands suggests that the drug is physically distributed and stabilized within the polymer matrix, rather than chemically bound (Qian et al., 2010; Maniruzzaman et al., 2012; and Pham et al., 2017). This physical encapsulation likely contributes to the observed thermal stability and controlled release behavior of the drug (Tung et al., 2010).

While current FTIR and DSC data support the thermocompatibility, further studies involving solid-state NMR, XPS, or post-extrusion HPLC analysis will be necessary to confirm the molecular stability of the drug and elucidate the detailed interaction mechanisms (Wegiel et al., 2013; and Repka et al., 2018).

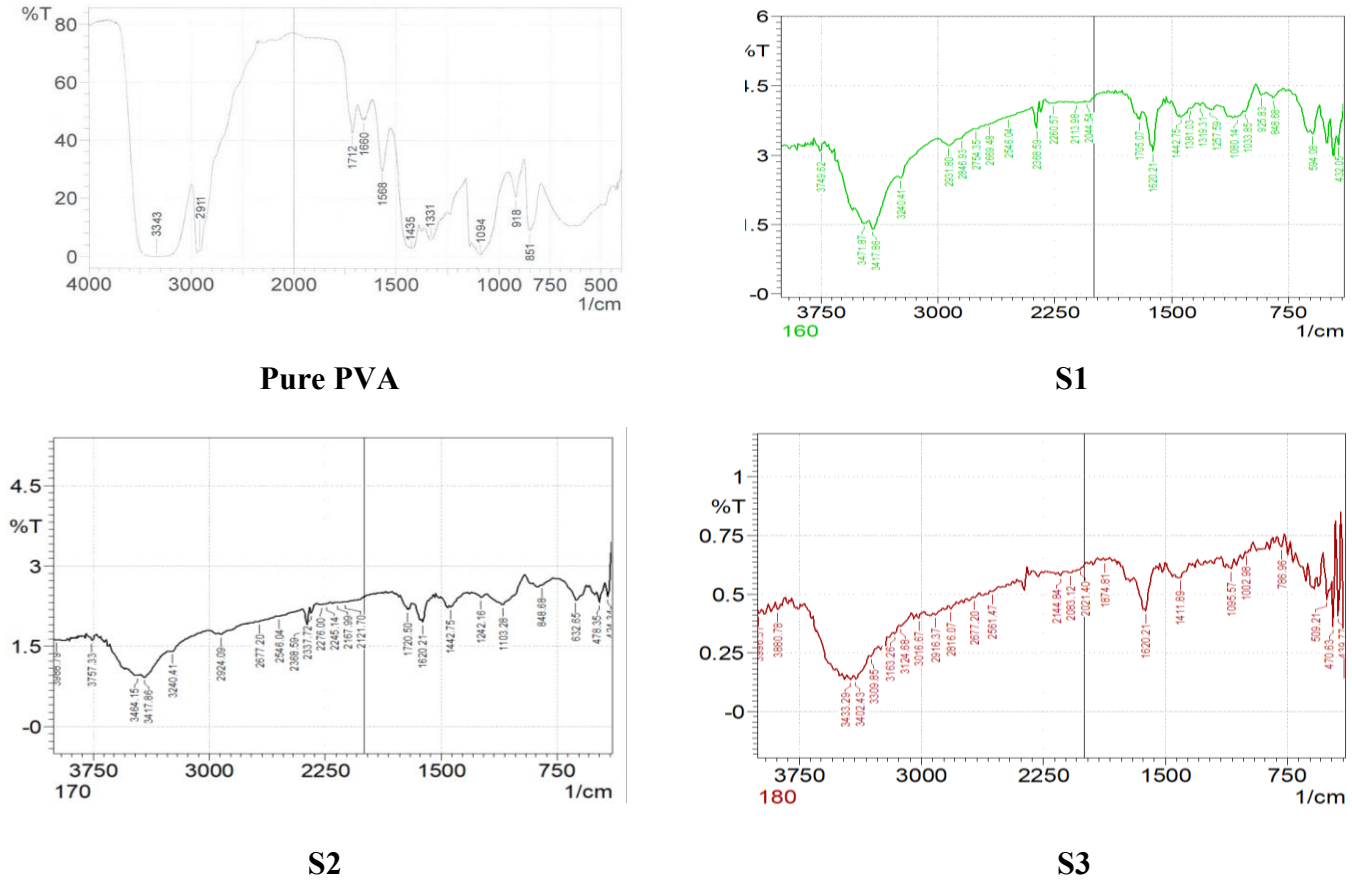


Fig. 4. FTIR diagrams analysis for PVA, S1, S2, and S3 samples

DSC results clearly show that T_g and T_m decrease with increasing extrusion temperature, indicating improved chain mobility and decreased crystallinity in the polymer matrix. These parameters indirectly influence the interaction with-in the composites and their release behavior (Zhang et al., 2010). This behavior is attributed to the plasticizing effect of glycerol, which disrupts intermolecular hydrogen bonds within PVA (Mansur et al., 2004; and Krumova et al., 2000). The broad endothermic peaks indicate moisture loss and partial dehydration during heating, consistent with thermal events in co-plasticized systems. Similar effects have been reported in starch-based blends plasticized with citric acid and glycerol (Shi et al., 2008), supporting the observed trends.

The existence of two distinct T_g values suggests partial immiscibility or phase separation. Specifying that although the polymer and drug are physically dispersed, their overall miscibility is limited, consistent with earlier reports (Qian et al., 2010; and Maniruzzaman et al., 2012). These changes in thermal properties confirm the effective interaction between plasticizers and the polymer matrix under varying thermal conditions. A deeper study may be considered in future studies.

Table 4. FTIR data of pure PVA and PVA/Drug composite samples extruded at different temperatures.

Functional Group	Pure PVA	(S1) At 160°C	(S2) At 170°C	(S3) At 180°C	Possible Interpretation
O–H, Stretching	3453	3417.51	3173.57	3380.78	Strong hydrogen bonding (PVA-related)
C–H, Stretching	2911	2933.78, 2855.42	2916.75, 2849.32	2916.87, 2850.16	Aliphatic hydrocarbons (PVA backbone)
C=O Stretching	1722–1660	1729.87	1622.18	1623.21	Carbonyl group (esters, acids, ketones)
C–O–C, Stretching	1094	1095.87	1095.67	1093.12	Ether groups in polymer
Aromatic Ring Mode, bending and stretching	750	786.98	786.12	786.98	Drug-polymer interactions
Skeletal Vibration	450	470.21	470.98	470.21	Low-frequency polymer vibrations

The C–O stretching region, typically found between 1000–1300 cm^{-1}, shows significant changes due to interactions between the hydroxyl groups of PVA and the added plasticizers (Kizil et al., 2002; and Thermo Fisher Scientific, 2017). These changes confirm the formation of hydrogen bonding and partial crosslinking between the compounds. The fingerprint region, particularly peaks at 600–900 cm^{-1}, can be attributed to the bending and stretching modes of glycerol and PVA frameworks, which further confirm the compatibility of the blend (PerkinElmer, 2020). Table 4 provides summaries of FTIR data, including the wavenumber, observed bonds, and types of vibrations.

The solubility of a composite depends on the equilibrium between hydrophobic groups due to C–H bonds and hydrophilic groups, such as hydroxyl (O–H) and carbonyl (C=O), which can form hydrogen bonds with water. Plasticisers, low molecular weight molecules that intercalate between polymer chains, lead to breaking hydrogen bonding, reducing intermolecular forces, and further increasing chain mobility. This boosts flexibility, modifies the glass transition temperature, improves water vapor and gas permeability, and smooths processing (Teixeira et al., 2021). Also, hydroxyl groups (O–H) in PVA and plasticisers, along with ester groups that formed from citric acid–PVA reactions, promote of increasingly water-affine property. This increases solubility in water and other polar solvents (Liu et al., 2023; and Lee et al., 2015)

Interactions between functional groups, including (C–H) bonds and polar groups such as (O–H) and (C=O), play a unique role in the thermal and chemical stability of a compound (Sari et al., 2017; and Krumova et al. 2000).

4.3 Density Evaluation

As shown in Table 5, PVA density changes with temperature, likely due to structural changes or water loss. High temperatures can increase porosity, alter crystallinity, or cause partial thermal degradation. Because diffusion is affected by both porosity and density, PVA exhibits a higher density of 1.2418 g/cm³ at 160°C, making it more cohesive and less porous, which slows drug diffusion.

Table 5. Density of PVA/drug composites extruded at different temperatures.

Samples Temperature	Density g/cm³
160°C	1.2418
170°C	1.2868
180°C	1.2089

At 170°C, the density increases slightly to 1.2868 g/cm³, possibly due to structural re-arrangement or water loss, and slightly affects drug release. At 180°C, the density decreases to 1.2089 g/cm³, indicating increased porosity or degradation, allowing for faster drug release.

This interpretation is consistent with DSC results, which did not show a clear decomposition peak below 230°C, suggesting that the reduced density is primarily due to structural porosity rather than full thermal degradation. However, minor baseline shifts in the DSC curve may reflect localized chain scission, which can also contribute to decreased compactness (Shi et al., 2008; and Ghanbarzadeh & Almasi, 2013).

4.4 Microscopy Analysis

The drug diffusion mechanism in the PVA matrix depends on the surface structure of the material, which can be analyzed through optical and digital examination at different temperatures, as shown in Figures 5 and 6.

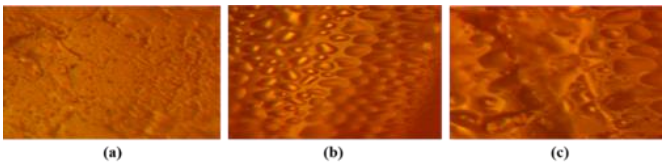


Fig. 5. Optical microscopy images of: (a) S1, (b) S2, and (c) S3

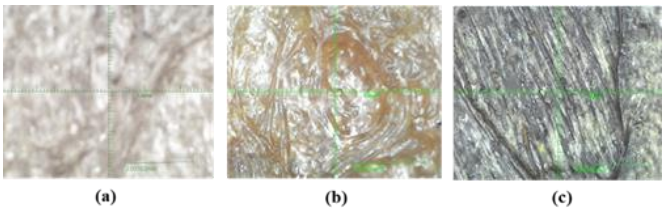


Fig. 6. The digital images with 1600x of: (a) S1, (b) S2, and (c) S3

At 160°C, the surface appears relatively homogeneous with minor cracks. There are no visible pores or large voids, indicating slow drug diffusion. The density at this temperature is 1.2418 g/cm³, which is related to the material's more compact nature, resulting in a lower drug release rate. Porosity begins to appear at 170°C with the formation of small bubbles or cavities within the material structure. Increased porosity means more channels for drug release, leading to higher diffusion rates. The density at this temperature is 1.2868 g/cm³, the highest among the three values, which may reflect rearrangement in the polymer structure or partial water evaporation, influencing the release mechanism. At 180°C, the porosity turns into further pronounced and expanded, showing greater drug diffusion. The existence of larger pores and voids suggests, the structure has become more disintegrated, facilitating drug release. The density was 1.2089 g/cm³, the lowest among the three samples, showing that the composite became less cohesive and more porous, resulting in a faster drug release rate.

These morphological observations are in good agreement with DSC findings, confirming that porosity and partial structural disintegration, rather than complete degradation, dominate the behavior of composites processed at higher temperatures.

5. Summary and Conclusions

PVA/Rhumix/glycerol/citric acid composites were extruded at (160, 170, and 180) °C and 50 rpm using a twin-screw extruder. Drug dispersion depended on mixing, temperature, polymer type, shear, and residence time. Glycerol lowered PVA's T_g and T_m, reducing melting point and energy consumption. Sample colors ranged from light to dark brown with varied surface topography. FTIR spectra confirmed consistent

bonding before and after adding drug and glycerol, indicating minimal polymer/drug interaction. Thermal analysis revealed two T_g values, suggesting partial immiscibility and limited drug/polymer miscibility. The T_g and T_m varied with extrusion temperature, affecting solubility, stability, and release behavior. DSC and density data classified the samples as S2, S1, and S3. Faster drug release correlated with lower melting temperature, density, and crystallinity. Sample S1 showed superior solubility and thermal properties, whereas S2 exhibited enhanced carboxyl and hydroxyl bonding and more uniform drug distribution. Extrusion parameters and composition indirectly influenced composite interactions and release profiles, making both S1 and S2 suitable for tailored drug delivery applications depending on release requirements.

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