



Thermal, spectroscopic, and dielectric investigation of hydrogen-bonded lapatinib–PVP amorphous solid dispersions with enhanced *in vitro* cytotoxicity

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ABSTRACT

Lapatinib (LAP), a dual EGFR/HER2 tyrosine kinase inhibitor used in HER2-positive breast cancer, exhibits poor aqueous solubility that limits its oral bioavailability. Although amorphous solid dispersions (ASDs) can improve LAP solubility, the molecular mechanisms and drug-induced molecular mobility remain insufficiently understood. This study aimed to elucidate the molecular mobility and relaxation dynamics of LAP-based ASDs using broadband dielectric spectroscopy (BDS), with particular emphasis on drug–polymer interactions. LAP–polyvinylpyrrolidone (PVP) ASDs with drug-to-polymer ratios of 10:90 (ASD1), 20:80 (ASD2), 30:70 (ASD3), and 40:60 (ASD4) were prepared by solvent evaporation and characterized using TGA, DSC, BDS, FTIR, XRD, and DFT. Drug solubility, dissolution, and cytotoxicity were additionally evaluated. TGA demonstrated enhanced thermal stability of LAP in the polymer matrix, with T_{onset} increasing from 488 K for crystalline LAP to approximately 655 K for ASD1 and 536 K for ASD2–ASD4. DSC and BDS revealed concentration-dependent plasticization by LAP, with T_g decreasing from 406 K for PVP to 398, 384, and 371 K for ASD1, ASD2, and ASD3, respectively. BDS identified a single cooperative α -relaxation in the ASDs, supporting molecular miscibility, while changes in fragility and β - and γ -relaxation activation energies demonstrated concentration-dependent modulation of molecular mobility. XRD confirmed complete amorphization in ASD1, ASD2, and ASD3, whereas residual crystallinity was observed in ASD4. FTIR and DFT supported hydrogen bonding as a key stabilizing interaction. The ASDs markedly improved LAP solubility and dissolution compared with crystalline LAP, with ASD2 showing the highest dissolution, reaching approximately 90% release at pH 7. Importantly, ASD2 enhanced LAP cytotoxicity against MCF-7 cells, reducing the IC_{50} by more than fourfold.

1. Introduction

Lapatinib (LAP) is an oral small-molecule tyrosine kinase inhibitor that targets both the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2), making it a potent dual inhibitor. It has been approved for the treatment of HER2-positive metastatic breast cancer, particularly in patients who have progressed

on prior trastuzumab-based therapies. [1] As illustrated in Fig. 1, LAP inhibits downstream oncogenic signaling by blocking EGFR and HER2 dimerization and activation, thereby preventing activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway, which is central to cancer cell proliferation and survival. [3]

Combination therapies, such as LAP with trastuzumab, aim to more

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comprehensively block HER2 signaling. Despite its proven clinical efficacy, LAP is administered orally at relatively high daily doses (up to 1250 mg once daily in humans); however, it has extremely poor aqueous solubility, which poses a major challenge for oral delivery. The solubility of LAP at neutral pH (≈ 6.8 – 7.4) is reported to be only ~ 7 $\mu\text{g/mL}$ in water and approximately 1 $\mu\text{g/mL}$ in 0.1 N HCl, [4] placing it in the Biopharmaceutics Classification System (BCS) Class II, [5] where dissolution is the rate-limiting step for absorption. *In vitro* micro-dissolution pH-shift studies show that lapatinib behaves as a weakly basic, pH-dependent drug, exhibiting $\sim 15\%$ release at pH 1.2 that drops to $\sim 2\%$ at pH 6.5, with solubility increasing from 0.0127 mg/mL in fasted-state simulated gastric fluid to 0.0291 mg/mL in fasted-state simulated intestinal fluid (pH 6.5) due to biorelevant salt effects.[6] However, the sharp reduction in solubility at intestinal pH severely limits gastrointestinal dissolution, resulting in low and variable oral bioavailability, reported to be approximately 20–30% ($\approx 22\%$ on average). This poor biopharmaceutical profile strongly necessitates formulation strategies to enhance solubility, dissolution, and systemic exposure.[7–14]

Quench cooling is a preferred method for generating amorphous forms of active pharmaceutical ingredients (APIs), particularly during early-stage formulation development.[6,15–17] It involves rapidly cooling the molten drug to prevent molecular rearrangement and crystallization, thereby trapping the compound in a high-energy, disordered amorphous state. However, despite its simplicity and solvent-free nature, quench cooling often leads to physically unstable systems that are susceptible to recrystallization upon storage. Such limitations have been reported for several model drugs, [18–20] including dipyrindamole, [21] and ibrutinib.[21] In our previous study, we employed melt quenching to prepare amorphous LAP and investigated its molecular dynamics across a wide frequency range and a broad temperature range, from the deep glassy state to the melt. The glass-forming ability of LAP was assessed using the calculated fragility index ($m = 59.1$) in conjunction with its glass transition temperature ($T_g = 317$ K). Comparison with a range of reported APIs indicates that LAP falls into GFA II (moderate glass-forming ability), indicating reasonable amorphization upon cooling but a moderate risk of recrystallization during storage, necessitating stabilization strategies such as polymer-based amorphous solid dispersions (ASDs).[22]

Using appropriate polymers is crucial to maintain the functional advantages of the amorphous form over time. Hydrophilic polymers enhance wettability and facilitate rapid supersaturation of drug

solutions upon contact with aqueous media, thereby promoting greater drug absorption. Previous studies have demonstrated that solid dispersion approaches using hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) can significantly enhance the dissolution and oral absorption of poorly water-soluble drugs, including nilvadipine and tacrolimus, depending on formulation strategy and excipient selection. [23,24] For felodipine, HPMC and HPMCAS were shown to sustain supersaturation and delay recrystallization, thereby improving dissolution and bioavailability.[25]

Lapatinib ditosylate has also been formulated as solid dispersions using solvent rotary evaporation (SRE) and hot-melt extrusion (HME) techniques. Among the polymer systems evaluated, a combination of polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) with poloxamer 188 at a 3:1 wt. ratio showed the greatest enhancement in solubility and dissolution performance.[26] Bitay et al. reported fabricating LAP-loaded polyvinylpyrrolidone (PVP) fiber mats using the centrifugal spinning technique, enabling the formation of an amorphous drug–polymer system with rapid dissolution behavior.[12] De Araujo et al. investigated molecular interactions between LAP and hydroxypropyl methylcellulose phthalate (HPMCP) or hydroxypropyl methylcellulose (HPMC-E3) using high-energy X-ray diffraction (XRD) and pair distribution function analysis. Their study revealed that LAP was uniformly dispersed within the HPMCP matrix due to interactions between the polymer's phthalate carboxyl groups and LAP's amine groups. In contrast, formulations containing HPMC-E3 exhibited potent drug–drug interactions, indicating poorer dispersion. [11] Similarly, Song et al. showed that in spray-dried ASDs of LAP, hydroxypropyl methylcellulose acetate succinate (HPMCAS) interacted with LAP predominantly through hydrogen bonding, while HPMCP was more likely to be involved in acid–base interactions. These findings were supported by T_g measurements and ^{15}N nuclear magnetic resonance (NMR) spectroscopy data. [27]

Although LAP ASDs have been previously prepared using techniques such as spray drying, hot-melt extrusion, and solvent evaporation, these studies mainly focused on thermal and spectroscopic characterization. The novelty of the present work lies in using broadband dielectric spectroscopy (BDS) to directly probe molecular mobility and relaxation dynamics in LAP-based ASDs, establishing a clear relationship between drug–polymer interactions and molecular dynamics. Building on our earlier identification of LAP as a moderate glass former, this study provides mechanistic insight into amorphous stabilization beyond conventional T_g and XRD-based analyses, offering guidance for the rational

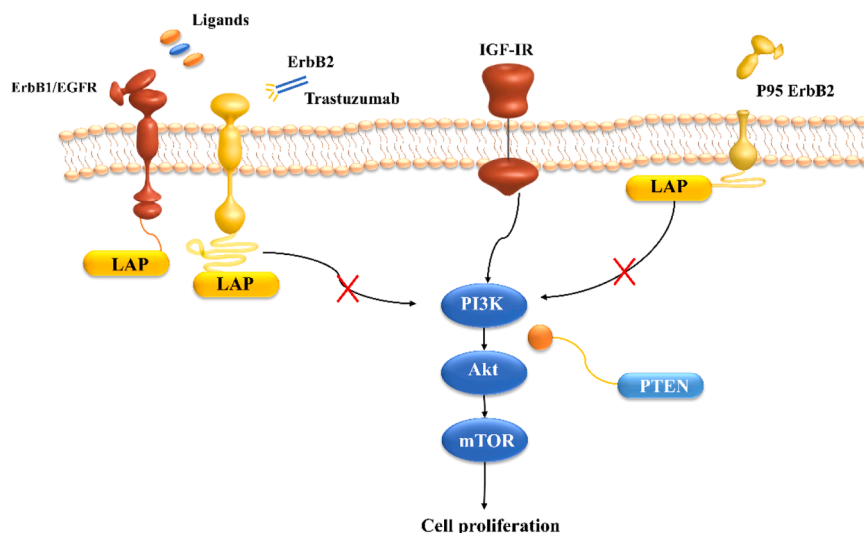


Fig. 1. Mechanism of action of LAP via ERB signaling pathways. LAP blocks the activation of ERB2 signaling pathways by inhibiting the intracellular tyrosine kinase of ERB1 and ERB2. It may circumvent trastuzumab resistance associated with IGF-1R signaling upregulation. LAP also binds to the p95 truncated variant of ERB2 and inhibits cell proliferation in trastuzumab-resistant cell lines expressing p95 ERB2. [2].

design of stable ASDs at an optimal concentration.

The objective of this study is to significantly enhance the solubility of the poorly water-soluble anticancer drug LAP by formulating ASDs using the solvent evaporation technique and to elucidate drug–polymer interactions at the molecular level using BDS to investigate molecular mobility and relaxation dynamics, thereby providing mechanistic insight into LAP-based ASDs.

The performance of ASDs depends heavily on the nature and strength of interactions between the drug molecule and the polymer matrix. This study reports the interactions between LAP (Fig. 2.a) and PVP (Fig. 2.b) (molecular weight (*MW*) 10,000 g/mol). A combination of thermal, spectroscopic, dielectric, and computational techniques—including thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray diffractometry (XRD), Fourier Transform infrared spectroscopy (FTIR), broadband dielectric spectroscopy (BDS), in conjunction with DFT—was employed to gain a comprehensive understanding of the structural, thermal, and dynamic properties of the formulations. Additionally, the enhancement of LAP's efficacy achieved through amorphization at the optimum polymer concentration was biologically assessed using the WST-8[2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H-tetrazolium] assay on the breast cancer cell line MCF-7, providing insight into the therapeutic benefits of the optimized ASD formulations.

2. Materials and methods

2.1. Materials

Crystalline LAP (purity > 98%, CAS 231277-92-2) was procured from Sigma-Aldrich (St. Louis, MO, USA). Polyvinylpyrrolidone (PVP K15) (MW 10,000 g/mol) was also supplied by Sigma-Aldrich (St. Louis, MO, USA).

The other reagents and materials were all obtained from Gibco, Thermo Fisher Scientific (USA). Sterile distilled water was prepared using a Milli-Q® purification system or equivalent ultrapure water system. The WST-8 cell proliferation reagent was purchased as part of the Cell Counting Kit-8 (CKK-8) from Dojindo Laboratories (Japan). All test solutions were filtered through 0.22 µm sterile syringe filters (Millex®, Merck Millipore, or equivalent). Phosphate-buffered saline (PBS), pH 7.4, was used as a washing buffer and was sourced from Gibco.

2.2. Preparation of binary system

ASDs of LAP and PVP were prepared by the solvent evaporation method with varying drug-to-polymer weight ratios: ASD1 (10:90), ASD2 (20:80), ASD3 (30:70), and ASD4 (40:60). The required amounts of LAP and PVP were dissolved in separate 50 mL volumes of methanol and stirred individually at 1800 rpm and 333 K for 2 hrs to ensure complete dissolution. Then, the solutions were mixed and stirred at

353 K at the same rpm for another 3 hrs to ensure homogeneous mixing. The solvent was then removed by drying the mixture in a hot air oven at 353 K till it became a hard, yellowish, transparent solid. The resulting solid dispersions (with 98% yield) were collected and stored in a desiccator over silica gel at 298 K.[30–32] FTIR spectroscopy were employed to confirm the absence of residual solvent in the prepared ASDs. The absence of characteristic methanol-related FTIR bands confirmed that the prepared ASDs were essentially free from solvent.

2.3. Quantum computational calculations

The molecular structure of LAP was obtained from the PubChem database [33,34] and subjected to conformational analysis using the Schrödinger Maestro software,[35,36] generating ten low-energy conformers. Geometry optimization of the conformers was subsequently performed using DFT at the B3LYP/6–311 G(d,p) level of theory with Gaussian.[37] To confirm that the optimized structures correspond to true global minima, vibrational frequency calculations were carried out and verified to have no imaginary frequencies. The computational analysis of the LAP molecule has been previously reported in our published work.[38] In parallel, a monomeric unit of PVP was optimized at DFT at the B3LYP/6–311 G (d, p). Then, the optimized unit was replicated to construct a PVP tetramer, with the polymer chain terminated by hydrogen atoms to simplify the computational model. The resulting trimer was further geometry-optimized, and harmonic vibrational frequency calculations were performed at the DFT/PBEPBE/6–311 G(d,p) level of theory. The detailed procedure for constructing and optimizing the PVP oligomer models has been reported in our published work [39] and is therefore not repeated here.

In the present work, in the final LAP-PVP complex, the optimized PVP trimer was positioned in proximity to the LAP molecule based on their electrostatic potential (ESP) maps, with electropositive regions of one molecule oriented toward electronegative regions of the other to favor possible intermolecular interactions. The resulting LAP-PVP complex was subsequently geometry-optimized using DFT at the B3LYP/6-311 G(d,p) level of theory. Harmonic vibrational frequency calculations were performed for the optimized complex, and the absence of imaginary frequencies confirmed that the optimized structure corresponds to a true energy minimum.

2.4. Fourier transform infrared spectroscopy

FTIR spectroscopy was used to analyze molecular interactions between LAP and PVP in the prepared ASDs. Spectra were recorded for pure LAP, pure PVP, and four ASD formulations—ASD1, ASD2, ASD3, and ASD4—using a JASCO FT/IR-4200ST or a JASCO FT/IR-4X spectrometer. The samples were prepared as KBr pellets and scanned over the wavenumber range of 4000–500 cm^{-1} . Each spectrum was obtained by averaging 16 scans with a spectral resolution of 4.0 cm^{-1} .

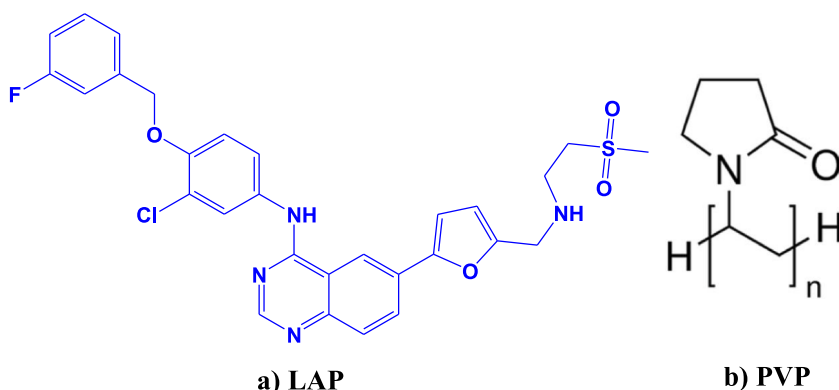


Fig. 2. a) Chemical structure of LAP molecule [28], b) PVP polymer unit [29].

2.5. X-ray diffraction

Powder X-ray diffraction (PXRD) measurements of LAP–PVP and ASDs were carried out at room temperature using a Rigaku XtaLAB PRO P200 diffractometer equipped with a two-dimensional detector. The samples were packed in tubular polyimide capillaries (inner diameter 1.00 mm, K-NEX Corporation), chosen to minimize background scattering and provide a stable environment for data collection. A CuK α radiation source ($\lambda = 1.5418 \text{ \AA}$) was used, providing high-intensity, monochromatic X-rays suitable for accurate structural characterization. X-ray diffraction data were collected over a 2θ range of $10\text{--}80^\circ$ with ϕ scanning from 0 to 300° at a rate of 1° s^{-1} and a total acquisition time of 300 s. Diffraction patterns were processed and analyzed with CrysAlisPro software.[40]

2.6. Thermal gravimetric analysis

The thermal stability of the pure LAP, and four ASD formulations—ASD1, ASD2, ASD3, and ASD4 was investigated using thermal gravimetric analysis (TGA) using Seiko Instruments Inc. - EXSTAR6000 TG/DTA from 300 K to 750 K at 10 K/min to indicate mass loss and thermal degradation on heating.

2.7. Differential scanning calorimetry

The thermal behavior of pure LAP, pure PVP, and the ASDs—ASD1, ASD2, ASD3, and ASD4—was analyzed using a PerkinElmer DSC 4000 system. The instrument was calibrated for temperature and enthalpy using an indium standard. Approximately 3 mg of each sample was accurately weighed into standard aluminum pans and hermetically sealed. The LAP was first quench-cooled from 500 K to 273 K at 30 K/min, followed by a heating from 273 K to 500 K at 10 K/min under a nitrogen atmosphere. The ASD sample thermograms were recorded during the first heating from 273 to 500 K at 10 K/min. Prior to each sample, it was preheated in the open DSC cell to 373 K and held for 30 min under a nitrogen purge to remove absorbed moisture, as identified by the low-temperature mass loss in the TGA traces, and then cooled to 273 K. The thermograms reported were recorded on the subsequent weighing and heating scan, so that the reported T_g values correspond to dehydrated samples. The T_g was determined from the midpoint of the heat capacity step in the thermograms.

2.8. Broadband dielectric studies

The dielectric measurements of LAP were already reported in our previous paper.[38] In this paper the prepared ASDs were measured at ambient pressure in a wide frequency range (10^{-2} Hz to 10^7 Hz) from 273 to 473 K using a Novo control broadband dielectric spectrometer in which the sample was sandwiched between two gold-plated copper electrodes of diameter 10 mm with Teflon spacers of thickness 0.1 mm. Temperature control was achieved using a Novocontrol Quatro Cryosystem with a dry nitrogen purge, ensuring temperature stability better than ± 0.1 K.

Before the dielectric measurements, the samples mounted between the electrodes were preheated in situ to 373 K and held for 15 min under the dry nitrogen purge of the Quatro Cryosystem to eliminate absorbed water. The dielectric spectra reported were then collected on cooling/heating over the range 273–473 K, ensuring that the relaxation processes analyzed are those of the dehydrated ASDs and are not influenced by water-induced plasticization

2.9. Solubility study

Apparent solubility studies were conducted to assess the improvement in LAP apparent solubility achieved through incorporation into the developed ASDs. A calibration curve was initially prepared using LAP in

dimethyl sulfoxide (DMSO), with a 1 mg/mL LAP stock solution used to prepare the required calibration standards. The absorbance of the standards was measured at 330 nm, and the resulting linear calibration relationship was used to quantitatively determine LAP concentration. For the solubility experiments, crystalline LAP and the prepared ASD formulations were dispersed in the respective aqueous media at 1 mg/mL and allowed to equilibrate. The experiments were performed at different pH conditions (pH 4, 5, and 7) to evaluate the influence of pH on LAP apparent solubility. After equilibration, the suspensions were filtered through a $0.4 \mu\text{m}$ hydrophilic membrane to remove undissolved drug and particulate material. The absorbance of the resulting filtrates (comprising molecularly dissolved LAP and may contain submicron colloidal or polymer-associated species that pass through the $0.4 \mu\text{m}$ filter) was measured at 298 K and 330 nm, and the apparent solubility of LAP was calculated from the established DMSO-based calibration curve. The DMSO solution was considered the 100% reference for comparison of the relative solubility of crystalline LAP and the ASD formulations. [1]

2.10. In-vitro dissolution study

The *in-vitro* release of lapatinib from the prepared ASD formulations was evaluated in distilled water with pH 7. Briefly, 10 mg of the lapatinib–PVP sample was dispersed in 10 mL of the release medium in a 15 mL conical tube. The dispersion was continuously inverted and mixed at 37°C under light-shielded conditions.[41] Equilibrium solubility measurements were performed at 37°C with three independent replicates ($n = 3$) for each formulation.

At predetermined time intervals, 0.5 mL aliquots were withdrawn from the dispersion and centrifuged at 15,000 rpm for 10 min to separate undissolved particles. Subsequently, 0.4 mL of the supernatant was carefully collected and mixed with 0.4 mL of ethanol to ensure complete dissolution of the released drug. The absorbance of the resulting solution was measured at 330 nm using a UV–visible spectrophotometer (UV-2600, Shimadzu, Kyoto, Japan). (Centrifugation (15,000 rpm, 10 min) removes undissolved particles but may not eliminate nanosized colloids; therefore, reported drug concentrations represent apparent concentrations comprising dissolved and submicron colloidal lapatinib.)

Quantification of lapatinib was performed using a calibration curve prepared by dissolving known concentrations of lapatinib in 50% (v/v) ethanol–water solution and measuring the absorbance under identical conditions. The apparent drug concentration in the samples was calculated from the calibration curve.

2.11. Biological activity- antiproliferative assay

The cytotoxicity assay was performed to evaluate the effect of increasing LAP concentrations on cellular viability and to determine the concentration-dependent biological activity of LAP and the prepared LAP–PVP ASDs. The selected concentration range also considered LAP's intrinsic aqueous-solubility limitation, as a poorly water-soluble drug with incomplete and variable absorption. Thus, the cytotoxicity study was designed to assess whether increasing the administered LAP dose resulted in a corresponding increase in biological activity under the experimental conditions.

2.11.1. Cell line and culture conditions

The human breast adenocarcinoma cell line MCF-7 (cat. JCRB0134, lot. 12192018) was procured from JCRB Cell Bank (Osaka, Japan) and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1% penicillin–streptomycin solution, and 1% non-essential amino acids. Cells were cultured at 37°C in a humidified atmosphere with 5% CO_2 .

2.11.2. Sample Preparation for cell culture

Pure LAP and LAP-loaded ASDs (ASD1 and ASD2) were directly dissolved in sterile distilled water without the use of organic solvents to

simulate physiological conditions and assess the enhancement of LAP apparent solubility by the ASD system. Working solutions were freshly prepared by dispersing an amount of each formulation equivalent to 20, 40, 60, 80, and 100 μM of LAP in distilled water under mild sonication for 10 min to ensure uniform dispersion. These aqueous solutions were subsequently filtered through a 0.22 μm sterile syringe filter and diluted with culture medium immediately before cell treatment. Control wells received medium only.

2.11.3. Cell seeding and treatment

MCF-7 cells were seeded into 24-well plates at a density of 50,000 cells per well in 500 μL of complete growth medium and incubated at 37 $^{\circ}\text{C}$ in a humidified 5% CO_2 atmosphere for 24 h to allow cell adherence. Following incubation, the medium was carefully replaced with 500 μL of fresh medium containing LAP and ASD formulations at final drug concentrations of 20, 40, 60, 80, and 100 μM of LAP, prepared in distilled water. Control wells received only fresh complete medium without any treatment. All treatments were performed in triplicate.

2.11.4. WST-8 assay procedure

After 24 h of treatment, 50 μL of WST-8 reagent (Cell Counting Kit-8, Dojindo Laboratories, Kumamoto, JAPAN) was added to each well containing 500 μL of culture medium. The plates were then incubated for an additional 2 h at 37 $^{\circ}\text{C}$ in a humidified CO_2 incubator. The formation of the orange-colored formazan dye, which correlates with viable cell metabolic activity, was quantified by measuring absorbance at 450 nm using a microplate reader.

2.11.5. Data Analysis

Percentage of inhibition was calculated as a percentage relative to the untreated control using the formula:

$$\% \text{ of inhibition} = \frac{(A_{\text{control}} - A_{\text{sample}})}{A_{\text{control}}} \times 100$$

where A_{sample} is the absorbance of treated wells, A_{control} is that of control wells without any drugs.

2.11.6. Statistical analysis

Experiments were performed in triplicate, and results were expressed as mean $\pm$ SD. One-way ANOVA followed by Tukey's post-hoc test was used to determine statistical significance between groups ($p < 0.05$ considered significant).

3. Results and discussion

3.1. Thermal properties

TGA is used to evaluate the thermal stability and degradation behavior of materials by recording weight loss as a function of temperature. Fig. 3 shows TGA curves for crystalline LAP and its various prepared ASDs at different drug: polymer ratios (100:0, 10:90, 20:80, 30:70, and 40:60). Initially, all samples exhibit an early-stage mass loss of approximately 10%, which is attributed to the removal of absorbed moisture. This dehydration event occurs at ~ 424 K for pure LAP, ~ 428 K for the ASD 10:90 formulation, ~ 422 K for the ASD 20:80 and 30:70 formulations, and ~ 415 K for the ASD 40:60 formulation. A comparable initial weight loss associated with bound and free water has also been observed for PVP, consistent with our recent report,[39] which confirms the polymer's hygroscopic nature and its contribution to the low-temperature mass-loss behavior in the ASD systems. LAP exhibited a sharp, single-step weight loss beginning around 488 K, with an abrupt drop to 0% on the TGA curve, indicating complete degradation and poor thermal stability. In contrast, all ASD formulations (ratios 10:90–40:60) displayed a two-stage thermal degradation pattern: an initial gradual weight loss up to approximately 500–530 K, attributed to

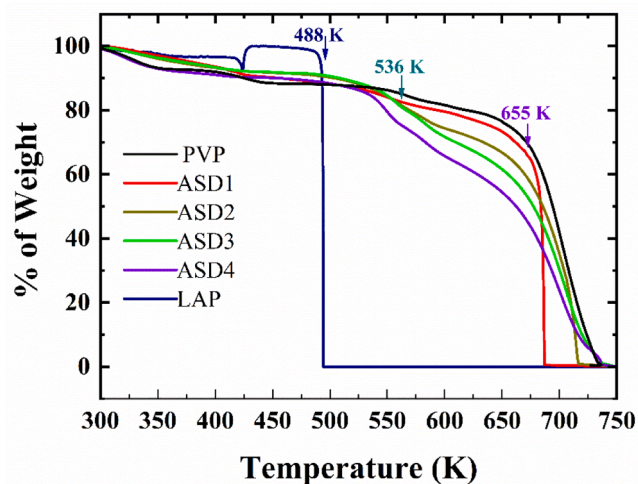


Fig. 3. The TGA curves of LAP (100:0), and its ASDs with PVP at various drug-to-polymer ratios (ASD1-10:90, ASD2-20:80, ASD3-30:70, and ASD4-40:60) and pure PVP (0:100).

the onset of polymer tail degradation, followed by a major decomposition phase corresponding to the thermal breakdown of both the polymer matrix and the drug.

Among the ASD formulations, ASD1 (red curve) exhibits the highest thermal stability, with the onset of major degradation occurring around 655 K. This enhanced stability can be attributed to the high PVP content (90%), which effectively stabilizes the drug within the polymer matrix. ASD2 shows the onset of degradation at a lower temperature, approximately 536 K, yet still demonstrates a more gradual weight-loss profile than crystalline LAP, indicating improved thermal behavior. The ASDs with higher drug loading—ASD3 and ASD4—exhibit intermediate thermal stability, falling between that of ASD2 and ASD1. Overall, the trend suggests that increasing drug content gradually shifts the degradation onset to lower temperatures, highlighting a drug-dependent destabilization effect on the polymer matrix.

The amorphization significantly enhances the thermal stability of LAP. When incorporated into PVP, the polymer acts as a stabilizing agent, likely forming hydrogen bonds with the drug molecules and delaying thermal decomposition. This stabilizing effect is particularly evident in ASD1, which exhibits the highest thermal stability among the formulations. The high PVP content (90%) creates a robust polymeric network that effectively protects against thermal degradation. However, a trade-off between drug load and stability is observed. As drug content increases from 10% to 40%, thermal stability decreases, likely because excess drug disrupts the polymer matrix and makes the system more susceptible to decomposition. Notably, ASD2, although slightly less stable than ASD1, maintains a favorable balance between drug loading and stability, rendering it a promising candidate for further formulation development.

The DSC thermograms of the prepared ASDs of LAP on heating revealed distinct T_g values, which varied systematically with composition, as depicted in Fig. 4. The ASD1 exhibited the highest T_g among the mixtures at 384 K; with increasing content of LAP, the T_g values progressively decreased to 370 K for the ASD2, 355 K for the ASD3, and 317 K for the pure LAP (100:0). In comparison, the T_g of pure PVP has been reported as 406 K.[39] This downward shift in T_g suggests a plasticizing effect of LAP, which enhances molecular flexibility and reduces the matrix's thermal rigidity. These observations highlight the tunability of glass transition behavior through compositional variation, which is crucial for optimizing thermal and mechanical properties in applications such as drug delivery.

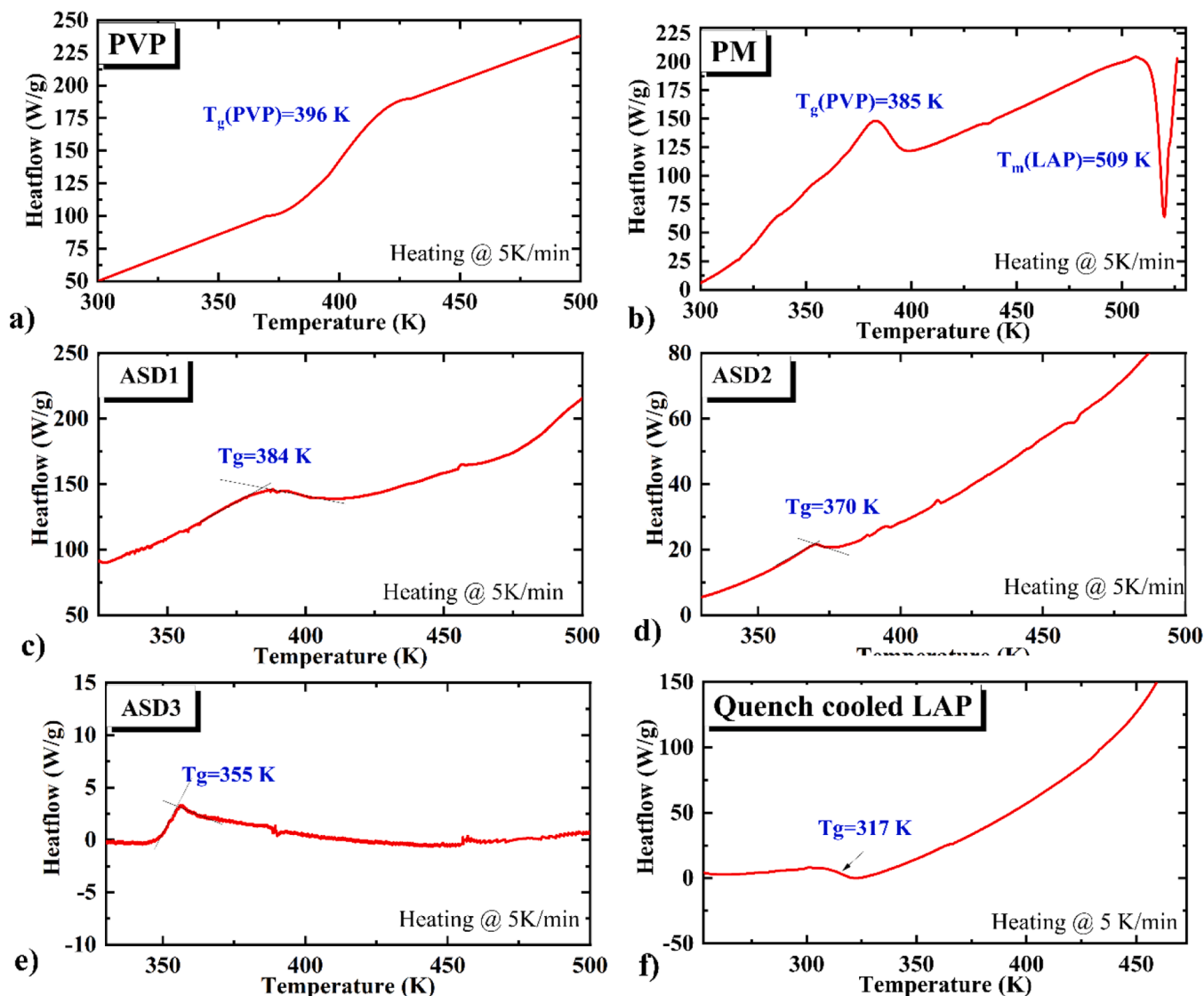


Fig. 4. DSC thermogram of a) pure PVP, b) PM, c) ASD1, d) ASD2, e) ASD3, f) quench-cooled LAP.

3.2. Molecular dynamic studies

In our previous studies, we reported the molecular dynamics of PVP [39] and LAP [38]. In this section, we present isothermal dielectric measurements conducted on ASDs formulated with varying concentrations. The representative dielectric loss spectra of all selected ASDs of LAP are shown in Fig. 5. As evident from the dielectric spectra, three relaxation processes are observed: a single primary relaxation above the T_g and two secondary relaxations, which appear as a single merged relaxation at temperatures below T_g followed by electrode polarization effect at lower frequency at higher temperatures.

ASD1 was selected first for dielectric studies to observe the transformation from the already reported PVP and to compare with the reported LAP. The dielectric loss spectra were depicted in Fig. 6.a, in which the α relaxation process was masked by electrode polarization. Hence, to get a better insight, the same data were plotted in the modulus formalism. Modulus is the inverse of complex permittivity, in which the hidden relaxation will be clearly visible, as depicted in Fig. 6.b. Thus, ASD1 has four relaxation processes; the α -process is prominent at higher temperatures, typically seen above 403 K. This relaxation shifts to higher frequencies with increasing temperature, indicating increased molecular mobility. The clear temperature dependence suggests this is the primary relaxation representing cooperative segmental motion of

the drug and polymer chains in the binary ASD1. ASD1 reveals a well-dispersed, homogeneous system with distinct molecular relaxation processes.

The data were fitted using a series of Havriliak–Negami (HN) functions with electrode polarization effect, assuming the additive behavior of the process.

$$\varepsilon^*(\omega) = \frac{\sigma_{dc}}{i\omega\epsilon_0} + \frac{\Delta\epsilon_{EP}}{1 + (i\omega\tau_{EP})^{\alpha_{EP}}} + \frac{\Delta\epsilon_{\alpha}}{[1 + (i\omega\tau_{\alpha})^{\alpha_{\alpha}}]^{\beta_{\alpha}}} + \frac{\Delta\epsilon_{\beta}}{[1 + (i\omega\tau_{\beta})^{\alpha_{\beta}}]^{\beta_{\beta}}} + \frac{\Delta\epsilon_{\gamma}}{[1 + (i\omega\tau_{\gamma})^{\alpha_{\gamma}}]^{\beta_{\gamma}}} + \epsilon_{\infty}$$

In this expression, ω denotes the angular frequency, defined by $\omega = 2\pi f$. In addition, $\Delta\epsilon$ indicates the dielectric relaxation intensity of the process studied, while ϵ_{∞} corresponds to the high-frequency limit of the real part $\varepsilon'(\omega)$. α and β are the shape parameters describing the symmetric and asymmetric broadening of the dielectric spectrum ($0 < \alpha \leq 1$ and $0 < \beta \leq 1$). The subscripts α , β , γ and δ represent distinct relaxation processes. The conductivity effects were taken into account; as said earlier, there is a contribution of dc conductivity ($\frac{\sigma_{dc}}{\omega\epsilon_0}$) to the imaginary part of the fit function, and frequency-dependent conductivity arose from electrode polarization (EP).

The non-Arrhenius temperature dependence of the relaxation time of

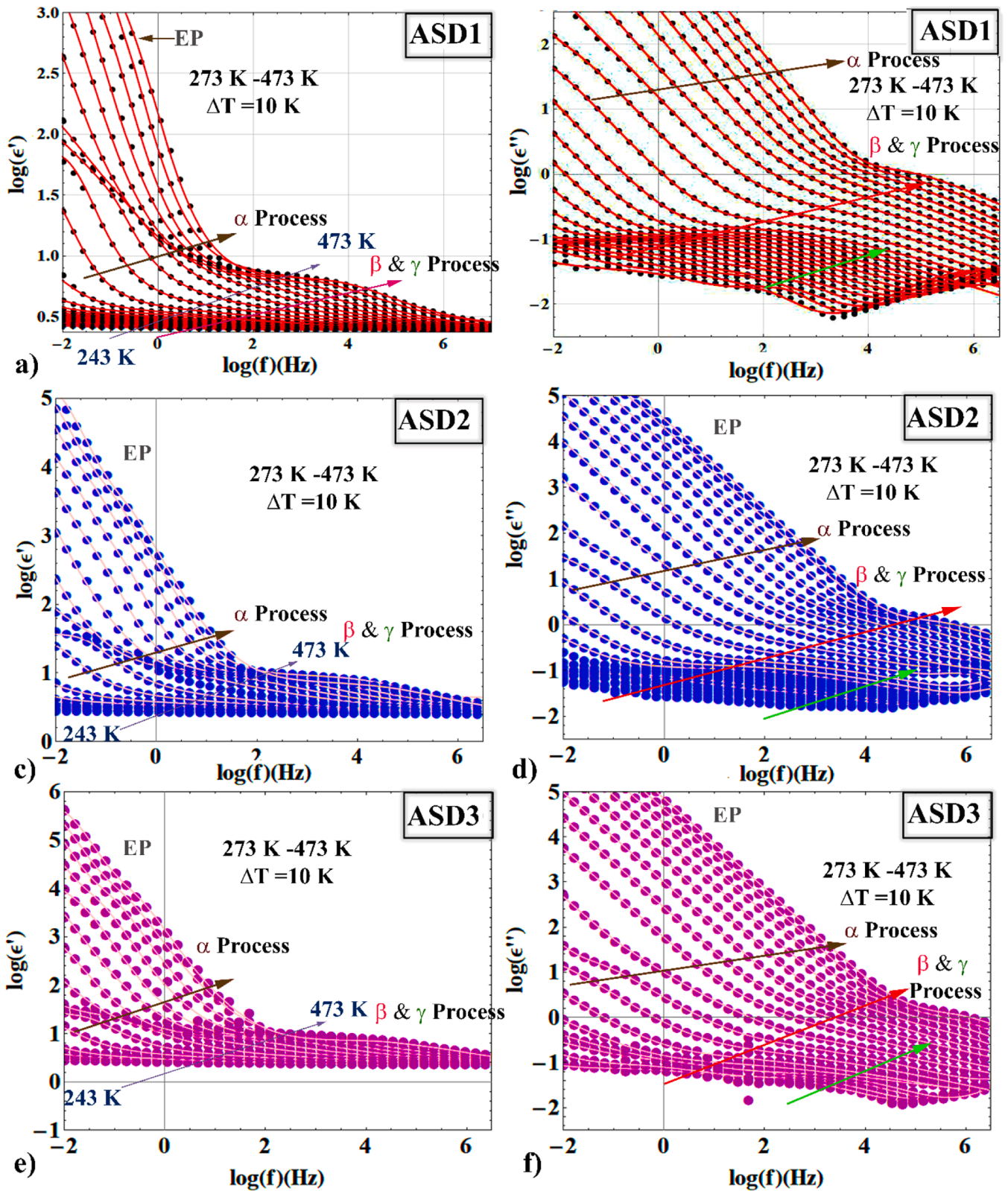


Fig. 5. The left panel shows the real part, while the right panel displays the imaginary part of the dielectric loss spectra of the ASDs. The filled colored circles represent experimental data, and the solid lines correspond to the fitted curves. Black denotes the ASD1 composition, blue represents ASD2, and magenta corresponds to ASD3.

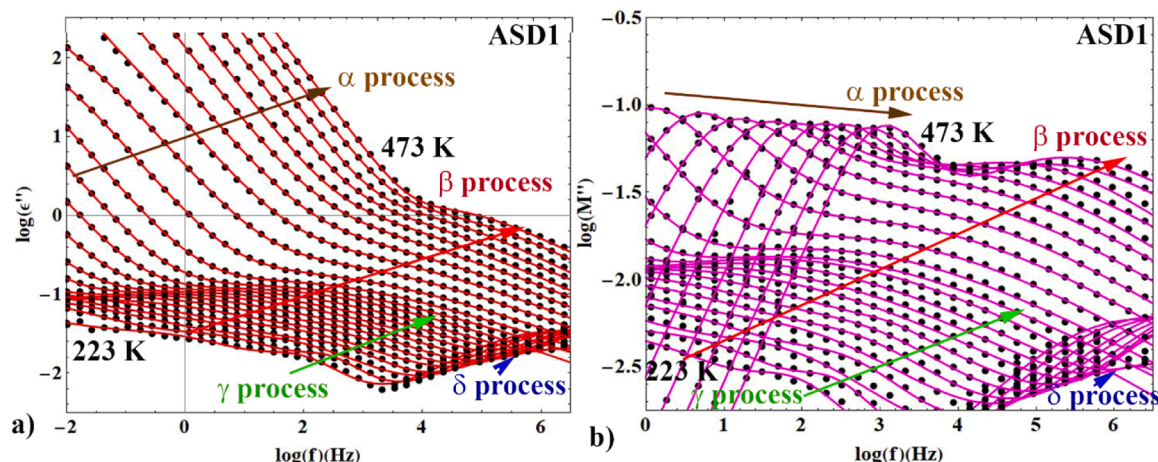


Fig. 6. Dielectric loss in permittivity and modulus window for temperatures from 223 K to 473 K.

the α -relaxation (Fig. 7.a) confirms the cooperative dynamics of the drug-polymer network and is characteristic of a single amorphous phase, which is fitted by the Vogel-Fulcher-Tammann (VFT) equation

$$\langle \tau \rangle = \tau_0 \exp \left(\frac{AT_0}{T - T_0} \right)$$

Where T_0 is the Vogel-Fulcher temperature, at which the relaxation time diverges; B is a constant; AT_0 and A are shape parameters. Compared to the pure polymer PVP, which exhibits a T_g of 402 K, when 10% LAP is

added, the molecular mobility in the amorphous solid dispersion ASD1 is increased. This slight decrease in the T_g may be due to increased freedom and less interaction between polymer chains by LAP. The fragility index is calculated using the equation

$$m = \frac{d[\log(\tau_\alpha)]}{d(T_g/T)} \bigg|_{T=T_g}$$

The fragility index of PVP is changed from 46 in pure PVP to 69.4 in ASD1. This substantial rise in fragility indicates that the incorporation of LAP disrupts the uniform polymer matrix, leading to a more sensitive system to temperature changes near the glass transition. The higher fragility suggests that the relaxation dynamics of ASD1 become more cooperative than those of the pure polymer, likely due to specific drug-polymer interactions that affect local mobility within the matrix.

For the other relaxations in ASD1, the reciprocal temperature dependences of the relaxation times of β , γ , and δ relaxations demonstrated linear behavior, likely arising local motion either arise from PVP or from LAP molecule. Hence, the relaxation times are fitted with the Arrhenius equation

$$\tau_{\beta,\gamma,\delta} = \tau_\infty \exp \left(\frac{E_a}{RT} \right)$$

The β -process represented in Fig. 7.a likely corresponds to localized motions of PVP polymer side chains.[39] The β -process in ASD1 exhibits an activation energy of 74.21 kJ/mol, indicating a notable but comparatively reduced hindrance to the local mobility of the PVP chains. This is lower than the activation energy observed for the β relaxation of pure PVP (105 kJ/mol), suggesting that incorporating 10% LAP into the matrix facilitates localized motion by disrupting the uniform polymer environment.

Conversely, the γ -process observed in the ASD1 system may originate from LAP molecular dynamics. In pure LAP, the γ -process exhibits an activation energy of 70.84 kJ/mol, which indicates restricted local motion within the drug molecule. The γ -process observed in ASD1, the other hand, has a slightly lower activation energy of 65.99 kJ/mol, suggesting it arises from localized molecular motions such as side-chain or intramolecular rotations. The proximity of the activation energies for the β - and γ -processes in pure LAP and ASD1 supports the hypothesis that these relaxation modes in the composite system are strongly influenced by the drug's intrinsic dynamics, potentially modulated by drug-polymer interactions within the amorphous matrix. The activation energy of the δ -process is 15.35 kJ/mol, which is relatively low. Due to its weak temperature dependence and limited contribution to the overall relaxation dynamics, this process may fall outside the primary focus of interest. It is likely associated with fast, localized motions such as rotation of side groups, or minor dipolar reorientations that do not

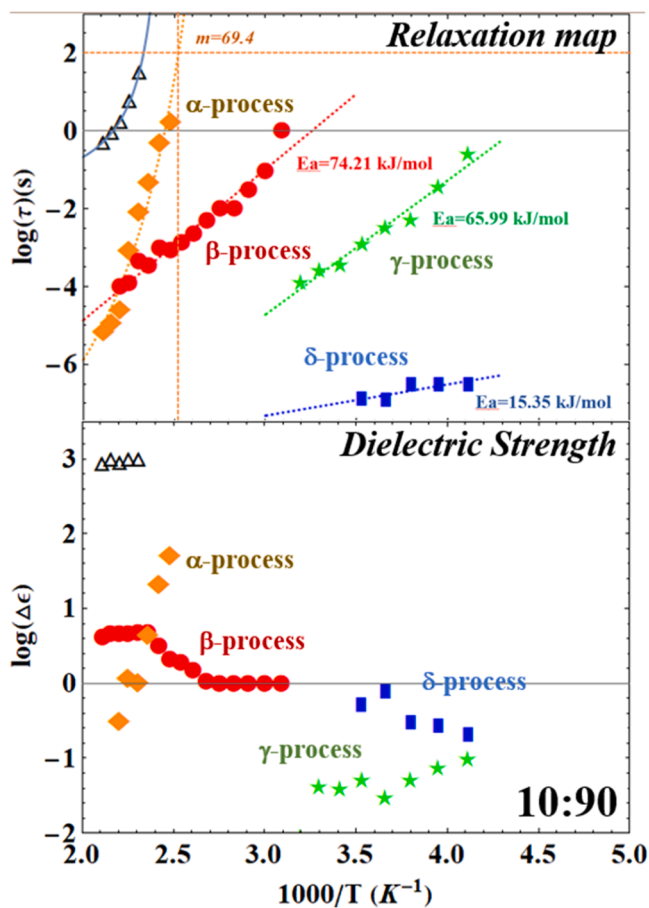


Fig. 7. Temperature dependence of (a) the relaxation time, (b) the relaxation strength of ASD1. Orange, red, green, and blue symbols indicate the α , β , γ and δ -processes, respectively.

significantly impact the macroscopic behavior of the system.

Fig. 7.b, showing the dielectric strength, provides insight into the intensity and nature of dipolar relaxation processes within the ASD1 system. The α -process exhibits a high dielectric strength at higher values of $1000/T$ (i.e., at lower temperatures), which is characteristic of structural or segmental relaxations associated with the glass transition. In contrast, the β -process maintains a relatively small strength compared to α process and has a general behaviour of a Johari- Goldstein (J-G) process. The γ - and δ -processes, on the other hand, display significantly lower dielectric strengths, which is typical of fast, localized dynamics such as intramolecular reorientations or motions of small molecular fragments. These minor processes contribute less to the overall dielectric response and may arise independently from either the drug or polymer constituents. The presence of a single α -relaxation, with a T_g that varies smoothly with composition, indicates dynamic homogeneity of the mixture on the length scale of cooperative segmental motion (a few nanometres) and thereby supports molecular-level miscibility of LAP and PVP. At the same time this observation alone does not establish the specific drug-polymer interactions, nor does it guarantee long-term physical stability; these properties are assessed by independent evidence, as discussed below.

3.3. Concentration dependence

Fig. 8 depicts the concentration dependence of relaxation times as a function of inverse temperature. As shown, the α -relaxation shifts to lower temperatures as drug concentration increases, indicating a shorter relaxation time at a given temperature with increasing drug content. The drug incorporation hindered PVP's stability and mobility, leading to a lower T_g . The T_g of pure PVP was observed at 406 K, indicating its inherently high molecular mobility threshold due to strong intermolecular interactions and polymer chain entanglement. Upon incorporating 10 wt% LAP into the polymer matrix, the T_g of ASD1 decreased to 398 K, suggesting the initial onset of a plasticizing effect by the drug

molecules. As the drug content increased further, the T_g of ASD2 (20 wt. % LAP) dropped significantly to 384 K, and with 30 wt. % LAP (ASD3), the T_g reduced further to 371 K. Although the T_g of pure amorphous LAP is significantly lower at 313 K, the T_g of the dispersions remains notably higher than that of the pure drug across all concentrations, suggesting miscibility between the drug and polymer even at higher loadings. The gradual decrease in T_g with increasing drug content can be attributed to plasticization by the LAP molecule. Introducing LAP molecules interferes with native hydrogen bonding and van der Waals interactions among PVP chains and may reduce the rigidity of the polymer matrix by increasing free volume.

The β -process (red circles in the plot) in Fig. 8 reflects a secondary relaxation process typically associated with localized motions within the PVP matrix, since the β -process of the ASDs extrapolates in position and activation energy from the β -relaxation measured for pure PVP.[39] These localized motions occur independently of the cooperative segmental motions observed in the primary α -process. Upon loading LAP into the PVP matrix, a slight shift of the β -process toward a shorter relaxation time is observed. This shift suggests that the local mobility of PVP segments is enhanced. This behavior arises because introducing LAP molecules disrupts some hydrogen bonding or weak van der Waals interactions among PVP chains, reducing local friction or constraints within the polymer matrix. As a result, the segments involved in the β -relaxation can reorient more rapidly, thereby increasing the relaxation frequency. This interpretation is quantitatively supported by the comparative slope and activation energy (E_a) values derived from Arrhenius plots of the β -process as tabulated in Table 1. As LAP was loaded to 10%, the reduced slope of β relaxation indicates a lower E_a (105 kJ/mol to 69.48 kJ/mol), suggesting that LAP addition lowers the energy barrier, enhancing local flexibility and speeding up relaxation. However, with further increases in LAP, the slope and E_a values increase significantly (E_a - 94 kJ/mol for 20% LAP and 110.48 kJ/mol for 30% LAP), emphasizing stronger constraints. This variability reflects the dual role of LAP: it can either act as a plasticizer (lowering E_a by disrupting

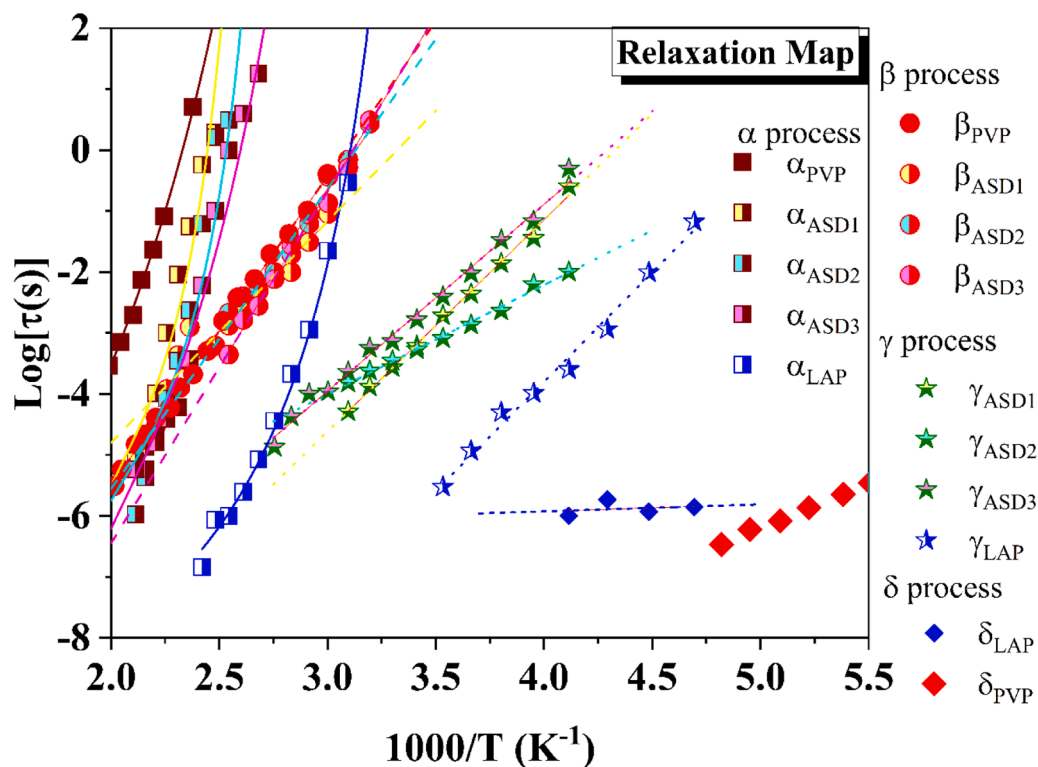


Fig. 8. Relaxation map of pure PVP, LAP, along with formulated ASDs. The squares depict α process, circles depict β process, the stars depict γ process, and the diamonds depict δ process.

Table 1

The fitting parameters of α β γ and δ process together with T_g and m of pure PVP, LAP, along with formulated ASDs.

Sample	α Process			T_g	m	β Process			γ Process		
	$\log(\tau_0)$	A	T_0 (K)			$\log(\tau_\infty)$	slope	E_a (kJ/mol)	$\log(\tau_\infty)$	slope	E_a (kJ/mol)
PVP				406	46	-15.60	5.07	105			
ASD1	-11.0	6.1	329	398	69	-12.05	3.63	69	-15.02	3.47	66
ASD2	-14.0	14.6	272	384	56	-15.37	4.91	94	-9.37	1.79	34
ASD3	-16.4	16.4	219	372	72	-17.98	5.77	110.	-13.14	3.06	59
LAP	-11.7	7.0	225	313	74				-18.14	3.58	69

local order) or as a structural constraint (raising E_a due to specific interactions or physical confinement), depending on the drug-polymer ratio, dispersion quality, and molecular interactions.

At the same time, for the secondary relaxation associated with the LAP molecule (γ -process), a notable reduction in the relaxation frequencies of nearly two decades is observed in ASD1 (10% of LAP in 90% PVP matrix) in comparison with pure LAP.[38] This implies that LAP experiences restricted localized mobility, likely due to encapsulation or tight embedding within the polymer matrix. As the polymer content decreases, the E_a increases, suggesting that at low polymer concentrations LAP molecules are less constrained, possibly due to insufficient polymeric encapsulation, which allows greater local freedom and faster secondary relaxation. At 20:80, the E_a for LAP's local motion drops to its lowest (34.28 kJ/mol), indicating enhanced molecular mobility. This can help improve dissolution and bioavailability, which is often desired in ASD systems.

As seen in Fig. 9, both BDS and DSC data are presented, showing a consistent decrease in T_g with increasing drug concentration. To analyze this behavior, several predictive models were applied as follows

Gordon–Taylor Equation

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2}$$

where w_1 , w_2 : weight fractions of PVP and LAP, respectively, T_{g1} , T_{g2} : glass transition temperatures of pure PVP and LAP, respectively, and k : fitting parameter that accounts for the relative contributions of each

component. This equation (purple dashed line in Fig. 9) captures the general downward trend but slightly underpredicts T_g at intermediate drug concentrations.

While Fox equation

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}}$$

The Fox equation (blue dashed line) assumes ideal miscibility and no specific interactions. It tends to underpredict T_g at all drug concentrations, highlighting the limitations of ideal mixing assumptions in systems with significant drug–polymer interactions.

And Kwei equation is

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} + q w_1 w_2$$

This model includes both the Gordon–Taylor term and an additional interaction term $q w_1 w_2$, where q accounts for specific interactions like hydrogen bonding.

Different values of q were tested:

- $q = 1$ (red dotted line) provides a better fit than Fox or Gordon–Taylor, capturing intermediate data points more accurately.
- $q = 2$ (cyan dashed line) improves the fit further, suggesting moderate interaction strength.

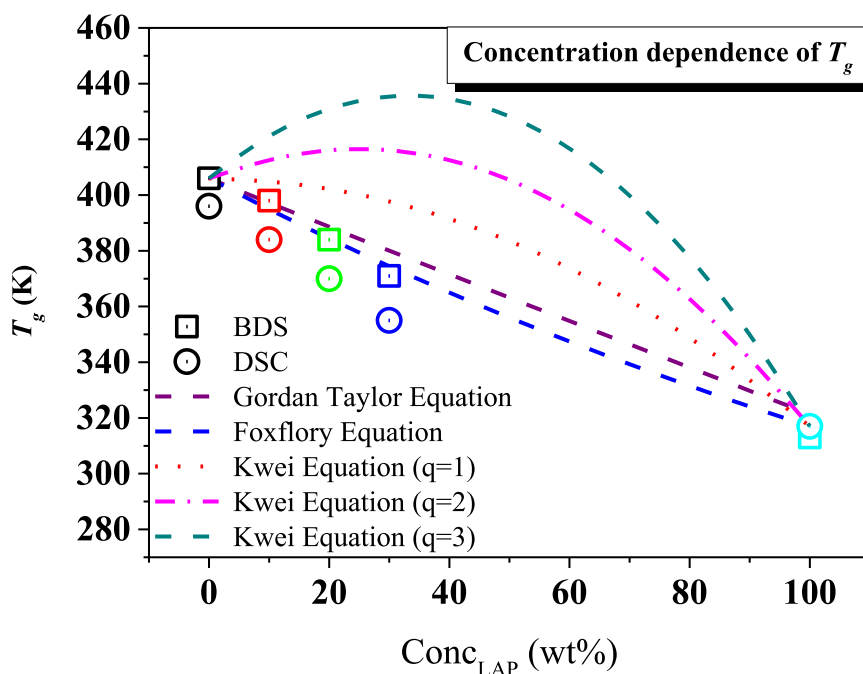


Fig. 9. Concentration dependence of T_g of prepared ASDs of LAP in PVP matrix determined by BDS and DSC experiments. The experimental data are fitted using the Gordon–Taylor equation (purple dashed line), Fox equation (blue dashed line), and Kwei equation with interaction parameters $q = 1, 2$, and 3 (red, magenta, and green dashed lines, respectively).

- $q = 3$ (magenta dashed line) gives the best overall agreement with both BDS and DSC data, indicating strong specific interactions, likely due to disruption of PVP's hydrogen bonding network by LAP.

Among the three fits, the blue dashed line (representing the Fox equation) best fits the experimental data, indicating a simple additive rule based on the weight fractions and individual T_g values of the components and suggesting ideal miscibility without strong drug-polymer interactions. The observed reduction in T_g is mainly due to plasticization through physical dilution, not specific interactions. These results emphasize that LAP is molecularly dispersed in PVP across the tested concentrations.

The concentration dependence of the LAP-PVP amorphous solid dispersions (ASDs) was further evaluated using the Fox and Gordon-Taylor equations to assess deviations from ideal mixing, and the results are tabulated in Table 2. For the DSC measurements, the experimental values of the ASDs were consistently lower than the corresponding Fox predictions, with deviations of -2.4 , -7.2 , and -13.5 K for ASD1, ASD2, and ASD3, respectively. The Fox model yielded an of 0.9364 and an RMSE of 6.91 K. In comparison, the Gordon-Taylor model, with a fitted value of 2.13, provided a substantially improved fit (RMSE = 2.13 K), indicating appreciable composition-dependent non-ideal mixing behavior in the DSC measurements.

For the BDS measurements, the experimental values showed much smaller deviations from the Fox predictions, namely $+3.7$, $+0.8$, and -1.8 K for ASD1, ASD2, and ASD3, respectively. The Fox model provided an excellent fit with an of 0.9968 and an RMSE of 1.87 K. The Gordon-Taylor model, with a fitted value of 1.2772, showed only a marginal improvement, yielding an of 0.9968 and an RMSE of 1.86 K. Overall, these results demonstrate that the LAP-PVP system exhibits composition-dependent deviations from ideal glass-transition behavior, which are more pronounced in the DSC measurements than in the BDS measurements. Although the deviations alone cannot be considered definitive evidence of specific LAP-PVP interactions, their combination with the FTIR and molecular-level simulation results provides complementary evidence for altered molecular mobility and intermolecular interactions within the amorphous solid dispersions.

3.4. FTIR analysis

The FTIR spectra of pure LAP, pure PVP K15, and their ASDs at various weight ratios are presented in Fig. 10. The FTIR spectrum of LAP revealed several characteristic vibrational bands corresponding to its functional groups. The peaks observed in the lower wavenumber region at 676, 801, and 844 cm^{-1} can be attributed to out-of-plane C-H bending modes of substituted aromatic rings, indicative of the drug's multiple aromatic systems. A distinct band at 926 cm^{-1} is assigned to C-H bending vibrations or ring deformation modes of the furan ring. The absorption near 961 cm^{-1} likely arises from N-H wagging or C-H

wagging vibrations. A prominent peak at 1020 cm^{-1} corresponds to the C-F stretching vibration, confirming the presence of fluorinated aromatic moieties in the molecule. The bands at 1059 and 1133 cm^{-1} are assigned to C-O-C and the sulfone ($-\text{SO}_2-$) stretching vibrations, respectively, consistent with the presence of ether linkages and amine functionalities. The peak at 1285 cm^{-1} also supports C-N stretching in aromatic amines or C-O stretching of aryl ethers. In the higher frequency region, the band at 1386 cm^{-1} is attributed to CH_3 symmetric bending or C-N deformation, while the strong absorption at 1496 cm^{-1} is due to aromatic C=C stretching or ring breathing modes.

At the same time, the FTIR spectrum of PVP K15 exhibited several characteristic peaks corresponding to its functional groups and polymer backbone. In the low wavenumber region, the bands at 575 and 653 cm^{-1} are attributed to skeletal deformations involving the C-C-N framework and ring deformation modes of the pyrrolidone ring. The absorption at 735 cm^{-1} is associated with CH_2 rocking and out-of-plane bending vibrations. A distinct peak at 852 cm^{-1} corresponds to CH_2 wagging and N-C=O bending within the lactam structure. The band at 1285 cm^{-1} indicates C-N stretching and CH_2 twisting, characteristic of amide-type linkages. The prominent peak at 1465 cm^{-1} arises from CH_2 scissoring and CH_3 bending vibrations. A strong absorption at 1652 cm^{-1} is assigned to the C=O stretching vibration of the lactam ring, which is a defining feature of PVP. Finally, the band at 2956 cm^{-1} corresponds to the asymmetric C-H stretching of CH_2 and CH_3 groups along the polymer chain.

In the ASD spectra, all major peaks of both LAP and PVP were retained, confirming the presence of both components without chemical degradation. However, intensity varied across the series depending on the relative concentration of LAP in the formulation. With increasing PVP content, the intensity of LAP's characteristic peaks decreased, while PVP-associated bands became more prominent. Notably, a broadening and shift in the region around 3300–3500 cm^{-1} was observed, especially in the ASD spectra containing both drug and polymer (e.g., 10:90, 20:80, 30:70). This broadening is indicative of hydrogen bonding interactions between the carbonyl groups of PVP and functional groups (e.g., NH or aromatic systems) of LAP. Such interactions suggest molecular-level miscibility and possible stabilization of the amorphous form. Furthermore, the C=O stretching peak of PVP at 1652 cm^{-1} appears to undergo slight shifting or broadening in the ASD spectra, which supports the presence of specific drug-polymer interactions. These interactions are critical for inhibiting recrystallization of the amorphous dispersion.

The PM provides an important control for distinguishing simple spectral superposition from drug-polymer interactions. In the PM spectrum, the characteristic vibrational bands of both LAP and PVP K15 were retained, with no pronounced alteration in the hydrogen-bond-sensitive region compared with the pure PVP. This indicates that simple physical mixing does not produce substantial molecular-level interaction between LAP and PVP. The enlarged hydrogen-bonding region shown in Fig. 10.b further highlights these differences. Compared

Table 2

Experimental values of pure LAP, PVP, and ASDs obtained by DSC and BDS, together with the corresponding theoretical values predicted by the Fox and Gordon-Taylor equations and the deviations between experimental and theoretical values. The fitted Gordon-Taylor values, coefficients of determination, and root-mean-square errors (RMSE) are also presented.

Sample	DSC(T_g) (K)					BDS (T_g) (K) versus Fox				
	Experimental	Theoretical Fox (T_g) (K)	Exp – Fox (K)	Gordon-Taylor (K)	Exp – GT (K)	Experimental	Theoretical Fox (T_g) (K)	Exp – Fox (K)	Gordon-Taylor (K)	Exp – GT (K)
LAP	396	396.0	0.0	396	0	406	406.0	0.0	406	0
ASD1	384	386.4	−2.4	380.87	+3.13	398	394.3	+3.7	394.44	+3.56
ASD2	370	377.2	−7.2	368.53	+1.47	384	383.2	+0.8	383.49	+0.51
ASD3	355	368.5	−13.5	358.28	−3.28	371	372.8	−1.8	373.10	−2.10
PVP	317	317.0	0.0	317	0	313	313.0	0.0	313	0
Fitted k value				2.13					1.2772	
R ²		0.9364		0.9939			0.9968		0.9968	
RMSE		6.91		2.13			1.87		1.86	

Table 3

Characteristic peaks of pure LAP (100:0), pure PVP (0:100), PM, and their ASDs at different weight ratios.

Wave Number cm^{-1}	Wave Number cm^{-1}	Wave number cm^{-1}	Wave number cm^{-1}	Wave Number cm^{-1}	Wave number cm^{-1}	Wave number cm^{-1}	Vibrational Assignments
LAP	(10:90) ASD1	(20:80) ASD2	(30:70) ASD3	(40:60) ASD4	PM	(0:100) PVP	
575	575	575	575	575	575	575	C–C–N deformation or ring deformation (pyrrolidone ring skeletal vibration)
653	653	653	653	653	653	653	C–C skeletal bending or out-of-plane ring deformation
676	676	676	676	676	676	676	Out-of-plane C–H bending (aromatic ring, possibly disubstituted ring)
735	735	735	735	735	735	735	C–H rocking (CH_2) or out-of-plane bending of ring hydrogens
801	801	801	801	801	801	801	Aromatic C–H out-of-plane bending (meta-substituted benzene)
844	844	844	844	844	844	844	C–H out-of-plane bending (aromatic, possibly para-substituted)
852	852	852	852	852	926	852	CH_2 wagging or N–C=O bending (lactam ring)
926	926	926	926	926	961	926	C–H bending vibrations or ring deformation modes associated with furan ring
961	961	961	961	961	961	961	C–H wagging (alkyl or aryl), or N–H wag (secondary amine)
1020	1020	1020	1020	1020	1020	1020	C–F stretching (from fluorinated aromatic ring in Lapatinib)
1059	1059	1059	1059	1059	1059	1059	C–O–C stretching (ether group), or aromatic C–H in-plane bending
1133	1133	1133	1133	1133	1131	1131	C–N stretching or the sulfone ($-\text{SO}_2-$) stretching vibration
1285	1285	1285	1285	1285	1285	1285	C–N stretching (aromatic amine)
1386	1386	1386	1386	1386	1386	1386	Aromatic C=C stretching or ring breathing (highly conjugated system)
1496	1496	1496	1496	1496	1496	1496	CH_3 symmetric bending or C–N deformation
1465	1465	1465	1465	1465	1465	1465	CH_2 bending (scissoring) and CH_3 asymmetric bending
1652	1652	1652	1652	1652	1652	1652	C=O stretching (lactam ring carbonyl) — strong and characteristic for PVP
2956	2956	2956	2956	2956	2956	2956	C–H stretching (asymmetric stretch of CH_2 and CH_3 groups)
3300–3500	3300–3500	3300–3500	3300–3500	3300–3500			Intermolecular hydrogen bonding

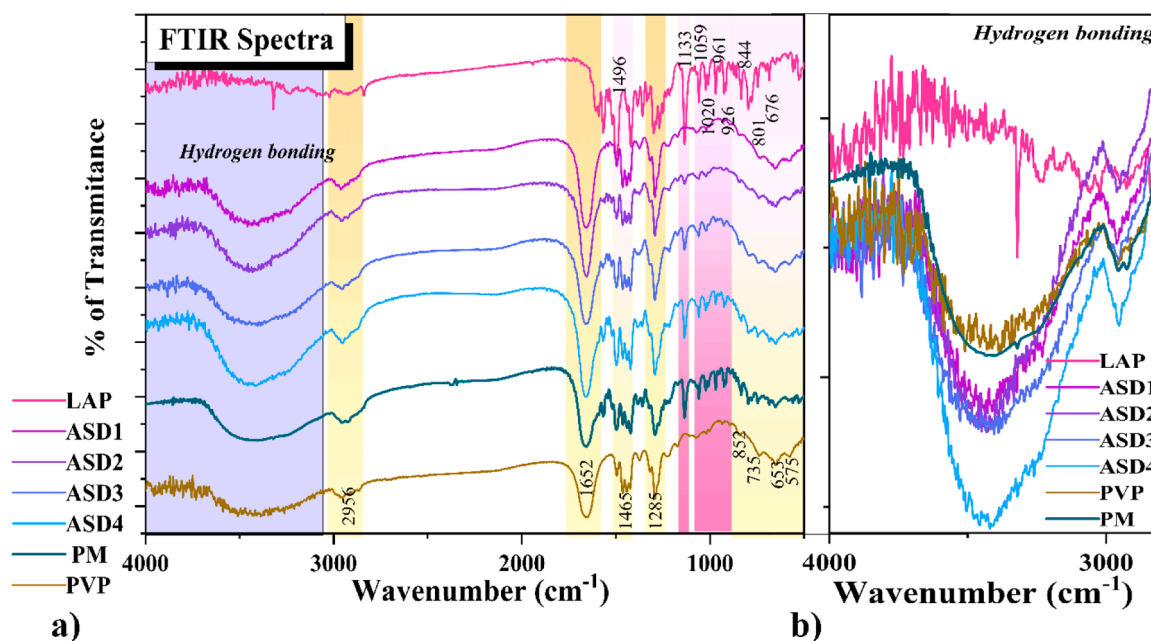


Fig. 10. FTIR spectra of pure LAP, pure PVP, PM, and their ASDs at various weight ratios. The pink-shaded regions highlight the primary vibrational modes of LAP, while the yellow-shaded regions indicate the characteristic peaks of PVP. B) Strengthening and broadening in the 3300–3500 cm^{-1} range suggest hydrogen bonding interactions between LAP and PVP in comparison to pure PVP and PM.

with PM and pure PVP, the ASDs showed changes in band shape, broadening, and intensity that increased with LAP concentration. Pure PVP and the physical mixture (PM) exhibited a relatively weak hydrogen-bonding profile, which may be attributed to the hydrophilic nature of PVP. In contrast, the hydrogen-bonding profile of the ASDs increased progressively with increasing concentration of the hydrophobic drug, LAP. This pronounced increase strongly suggests the formation of specific intermolecular hydrogen-bonding interactions between LAP and PVP, indicating enhanced drug–polymer association within the amorphous matrix. The carbonyl group of PVP, which acts as a strong hydrogen-bond acceptor, can interact with hydrogen-donor functionalities of LAP, particularly its NH-containing groups.

These spectroscopic observations of intermolecular hydrogen

bonding are strongly supported by DFT calculations, as visualized in Fig. 11.a. The optimized molecular structure clearly shows the formation of intermolecular hydrogen bonds (green dotted lines) between the functional groups of LAP and PVP, with bond lengths with bond lengths of 1.81 Å for 8O–54 H, 2.21 Å for 8O–41 H, and 2.19 Å for 8O–42H, respectively. The theoretical model highlights interaction sites involving LAP CH_3 group near to NH group and the PVP C=O group. The combined experimental and computational FTIR results are depicted in Fig. 11.b, in which the characteristic peaks of ASD3 and the theoretical model are in good agreement. In both spectra, hydrogen-bonding interactions are visible, which may be holding the drug and PVP in an amorphous phase, inhibiting recrystallization of the ASD system.

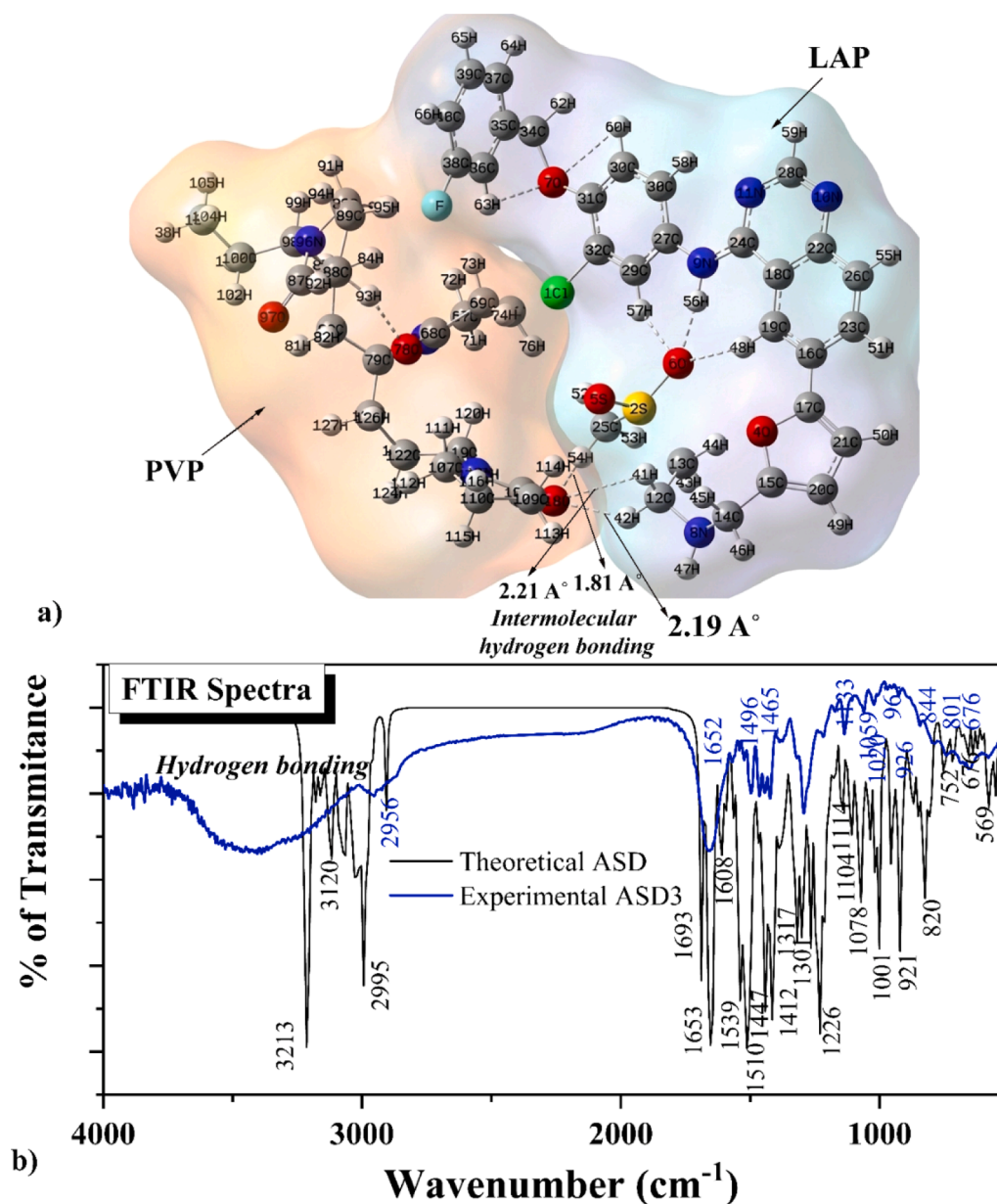


Fig. 11. DFT-optimized molecular structure illustrating the hydrogen bonding interactions between LAP and PVP (The shading is given just to distinguish LAP and PVP separately).b) Theoretical and experimental FTIR spectra of ASD.

3.5. XRD Analysis

XRD is used here to assess the crystallinity of the samples and confirm the amorphous nature of the dispersions. Fig. 12 depicts the XRD patterns of prepared ASDs with varying drug loading along with pure LAP and PVP. The pure LAP (100:0) exhibited sharp diffraction peaks at 9.5°, 11.6°, 15.5°, 17.3°, 19.0°, 20.6°, 23.3°, 25.9°, and 27.5° which are characteristic of its crystalline structure. Such patterns have been previously reported in the Patents (WO 2009/140144) describing the crystalline forms of LAP. [42] These characteristic crystalline peaks were also clearly observed in the physical mixture (PM), indicating that simple blending did not alter the crystalline structure of LAP. At the same time pure PVP displayed a broad diffuse halo with no sharp peaks, indicating its completely amorphous nature. A progressive reduction in peak intensity and sharpness of LAP is observed with increasing PVP content, indicating a loss of crystallinity and successful amorphization of LAP within the PVP matrix. ASD1 and ASD2 exhibited an amorphous halo similar to pure PVP, with the complete disappearance of LAP

crystalline peaks. However, in the ASD3 ratio, significantly suppressed diffraction peaks, with mostly broad peaks, were observed, suggesting a recrystallization tendency. At the ASD4 composition, prominent residual crystalline peaks were observed, indicating incomplete amorphization due to the relatively higher drug content. Hence, from here onwards we will neglect ASD4.

3.6. Apparent solubility enhancement

The solubility analysis demonstrated a substantial improvement in the apparent aqueous solubility of the ASD formulations compared with crystalline LAP. LAP dissolved in DMSO was used as the reference as shown in Fig. 13.a, the calibration curve exhibited excellent linearity over the investigated concentration range, with a Pearson's correlation coefficient of approximately 0.9999 and an adjusted R² of 0.99976. Crystalline LAP exhibited relatively low apparent aqueous solubility, with relative solubility values of approximately 20.6% at pH 7, 36.8% at pH 4, and 29.3% at pH 5, when compared with the DMSO reference

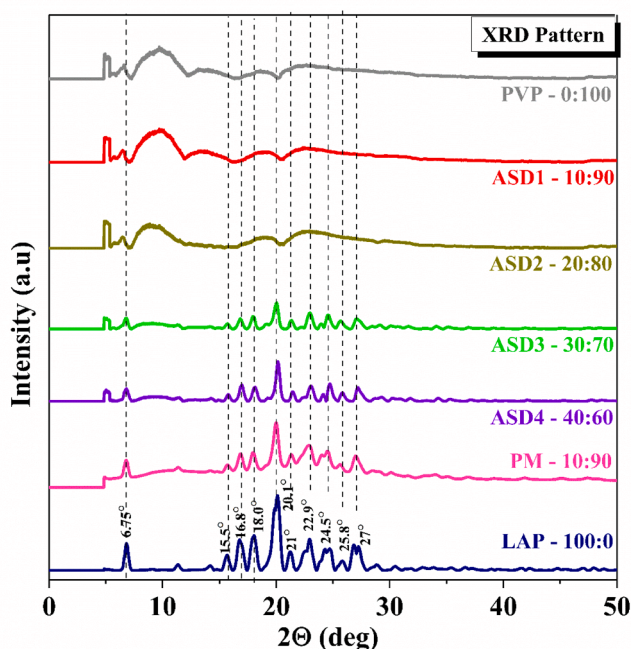


Fig. 12. XRD patterns of crystalline LAP, its prepared ASDs along with pure PVP and its PM.

(100%). Nevertheless, all ASD formulations exhibited markedly higher apparent solubility than crystalline LAP across the tested pH conditions (Fig. 13.b). Among the ASDs, ASD1 showed relative solubilities of approximately 88.9%, 88.9%, and 86.4% at pH 7, pH 4, and pH 5, respectively. ASD2 exhibited further enhancement, reaching approximately 92.6% at pH 7, 96.2% at pH 4, and 98.8% at pH 5. ASD3 demonstrated the highest overall apparent solubility, with values of approximately 96.3% at pH 7 and 98.8% at both pH 4 and pH 5. Thus, the apparent solubility enhancement followed the general order ASD3 > ASD2 > ASD1, with all formulations substantially outperforming crystalline LAP.

3.7. In vitro dissolution profile

Fig. 14.a show the calibration curve of LAP at 330 nm,

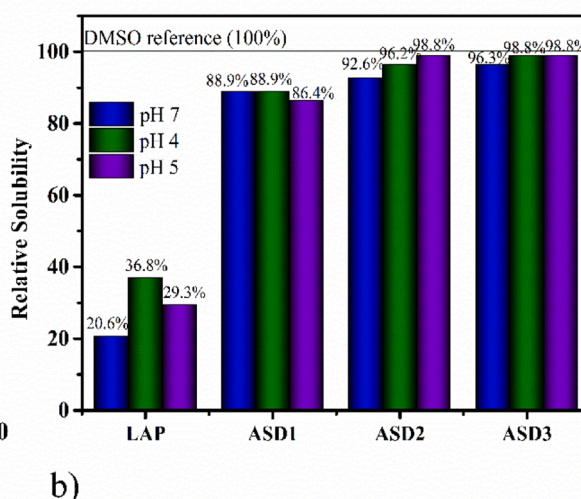
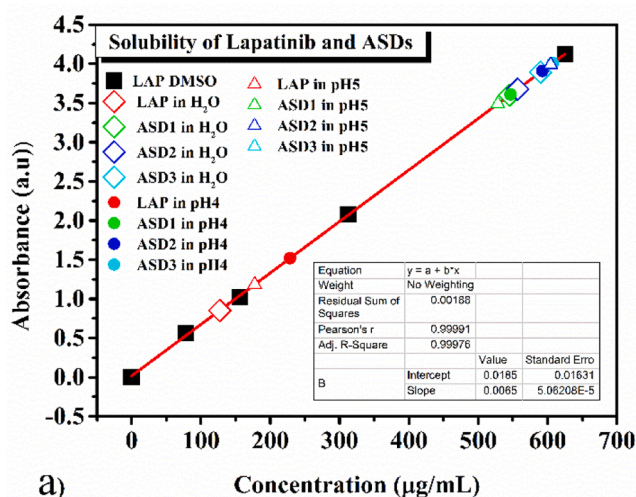


Fig. 13. Apparent solubility analysis of lapatinib (LAP) and amorphous solid dispersions (ASDs): (a) calibration curve of LAP in DMSO, used as the 100% reference for quantitative solubility determination; (b) relative solubility of crystalline LAP and ASD1–ASD3 at pH 7, pH 4, and pH 5, expressed relative to the DMSO reference.

demonstrating a linear relationship between concentration and absorbance. The regression equation obtained from the calibration plot showed a slope of 0.03 with a correlation coefficient $R^2 = 0.99$, indicating excellent linearity and confirming the reliability of the analytical method for quantification of LAP in dissolution samples.

Fig. 14.b presents the in vitro drug release profile in pH7 medium (water). The pure drug (LAP) exhibited very limited drug release, remaining below approximately 10% throughout the dissolution period due to its poor apparent aqueous solubility and crystalline nature. In contrast, all ASDs significantly enhanced the dissolution behavior of the drug. Among them, ASD2 demonstrated the highest drug release, indicating the most effective improvement in dissolution performance. ASD1 showed moderate drug release, while ASD3 exhibited comparatively lower release than ASD2, although still significantly higher than the pure drug.

The enhanced dissolution observed in the ASD formulations can be attributed to the conversion of the drug into an amorphous form, improved wettability provided by the polymer matrix, increased surface area, and reduced crystallinity. The superior performance of ASD2 suggests that its drug–polymer ratio and intermolecular interactions are more favorable for stabilizing the amorphous drug and maintaining supersaturation in the dissolution medium. In contrast, the comparatively lower release observed for ASD3 may be associated with the presence of residual crystallinity or partial recrystallization at higher drug loading, as indicated by the XRD analysis, which can reduce the dissolution advantage of the amorphous system.

3.8. Antiproliferative activity

Fig. 15 presents the cytotoxic effect of crystalline LAP and its two amorphous solid dispersions (ASDs)—ASD1 and ASD2—against MCF-7 breast cancer cells after 24 h of treatment, analyzed through microscopy and WST8 cell viability assays. In Fig. 15.a, in the crystalline LAP-treated wells, the cells appeared densely packed at low concentrations at 20 and 40 μM , with modest morphological change at 60–100 μM , consistent with its IC_{50} of 90 μM (obtained by nonlinear fitting). However, in ASD1, well-treated moderate cell death and detachment were observed with an increase in concentration. This is in line with the IC_{50} of 85 μM (obtained by nonlinear fitting), indicating similar efficacy as crystalline LAP. While prominent cell death and detachment were observed even at 20 μM , they increased markedly at higher concentrations, indicating potent cytotoxicity. These observations are strongly supported by its IC_{50} being < 20 μM . The findings clearly establish that

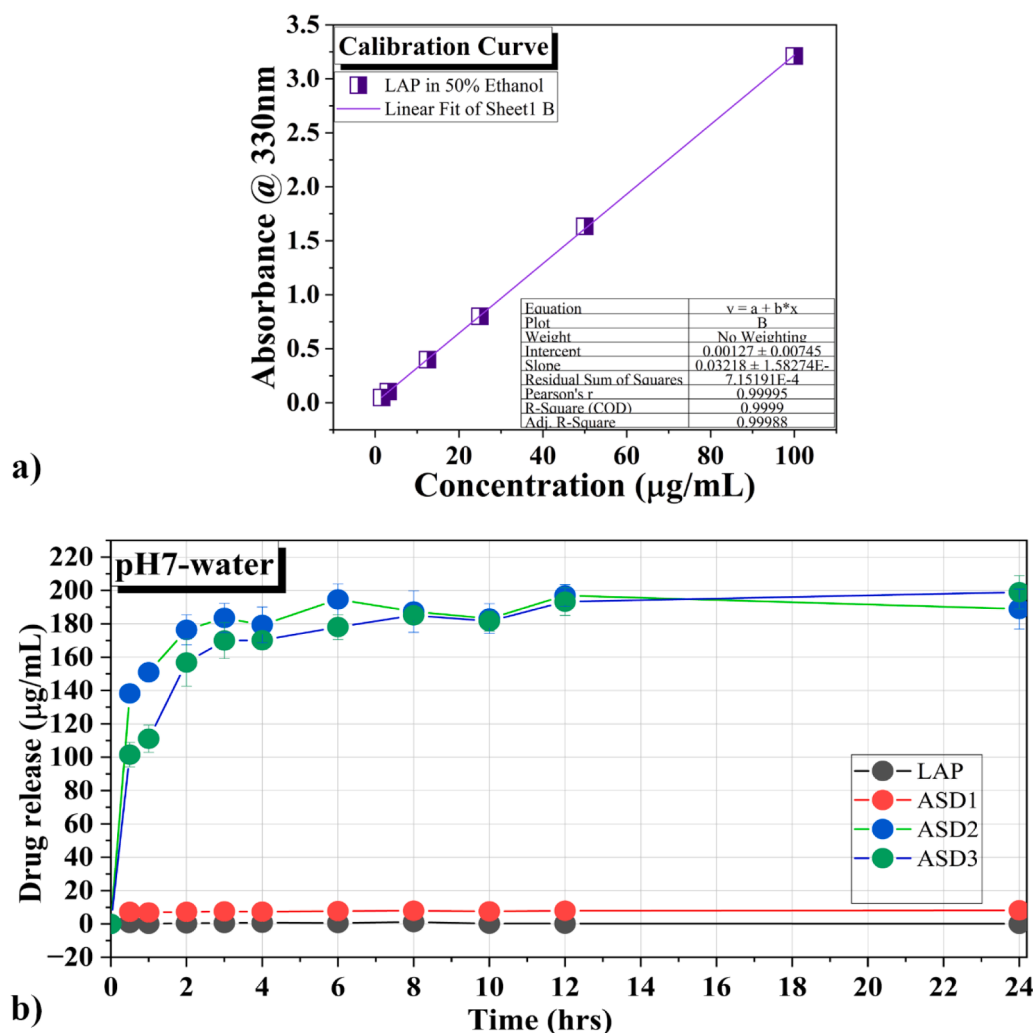


Fig. 14. a) Calibration curve of LAP at 330 nm in 50% ethanol. In vitro drug release profile of pure LAP and amorphous solid dispersions (ASD1, ASD2, and ASD3) in b) pH 7 medium (water).

amorphous solid dispersion of ASD2 significantly enhances its cytotoxic effect against MCF-7 breast cancer cells. The observed decrease in IC_{50} from 90 µM (crystalline) to < 20 µM (ASD2) underscores the potential of ASD technology to improve the therapeutic efficacy of poorly soluble chemotherapeutics like LAP.

4. Conclusion

This study successfully developed and characterized LAP-PVP amorphous solid dispersions (ASDs) using the solvent evaporation method at varying drug-to-polymer ratios: ASD1 (10:90), ASD2 (20:80), ASD3 (30:70), and ASD4 (40:60). The ASDs exhibited markedly improved apparent solubility and thermal stability compared with crystalline LAP. TGA showed enhanced thermal resistance of LAP within the polymer matrix, with the onset of degradation increasing from 488 K for pure LAP to approximately 530 K in the ASDs, while FTIR and DFT analyses confirmed drug-polymer interactions, particularly hydrogen bonding. DSC revealed a tunable T_g that decreased with increasing LAP content, indicating LAP's plasticizing effect and increased molecular mobility. The main aim of this work was to elucidate the molecular mobility and relaxation dynamics of LAP-based ASDs using BDS, with particular emphasis on drug-polymer interactions. BDS provided insights into the complex molecular dynamics of the ASDs, revealing cooperative α -relaxation, localized β -relaxation of PVP, and γ -relaxation associated with LAP, highlighting the role of composition-dependent

drug-polymer interactions in stabilizing the amorphous phase. Spectroscopic analyses confirmed that hydrogen bonding is a key factor in amorphous stabilization and in inhibiting recrystallization. XRD results further supported these findings, showing complete amorphization at lower drug loadings (10–20%) and partial recrystallization at higher LAP content. Furthermore, *in vitro* dissolution studies revealed a marked enhancement in drug release from the ASDs compared to crystalline LAP, with the release rate following the order ASD2 > ASD3 > ASD1, where ASD2 exhibited the highest dissolution in both neutral and acidic media. Although all ASDs showed improved apparent solubility and dissolution, their rankings differed. This variation underscores the fundamental distinction between thermodynamic solubility and kinetically governed dissolution behavior. Notably, the ASD containing 20% LAP showed a significant increase in *in vitro* cytotoxicity against MCF-7 cells, reducing the IC_{50} by more than fourfold compared with the crystalline drug. Overall, these findings demonstrate that PVP-based ASD formulations represent a promising strategy to address the solubility limitations of lapatinib, with potential to enhance its therapeutic performance in HER2-positive breast cancer. Although dissolution and pharmacokinetic evaluations were not included in the present study, amorphous solid dispersions are inherently formulation-driven drug delivery systems whose *in vivo* performance is strongly governed by molecular mobility, polymer-drug interactions. The comprehensive dielectric, thermal, and structural analyses presented herein provide mechanistic insights into these critical factors and establish a rational

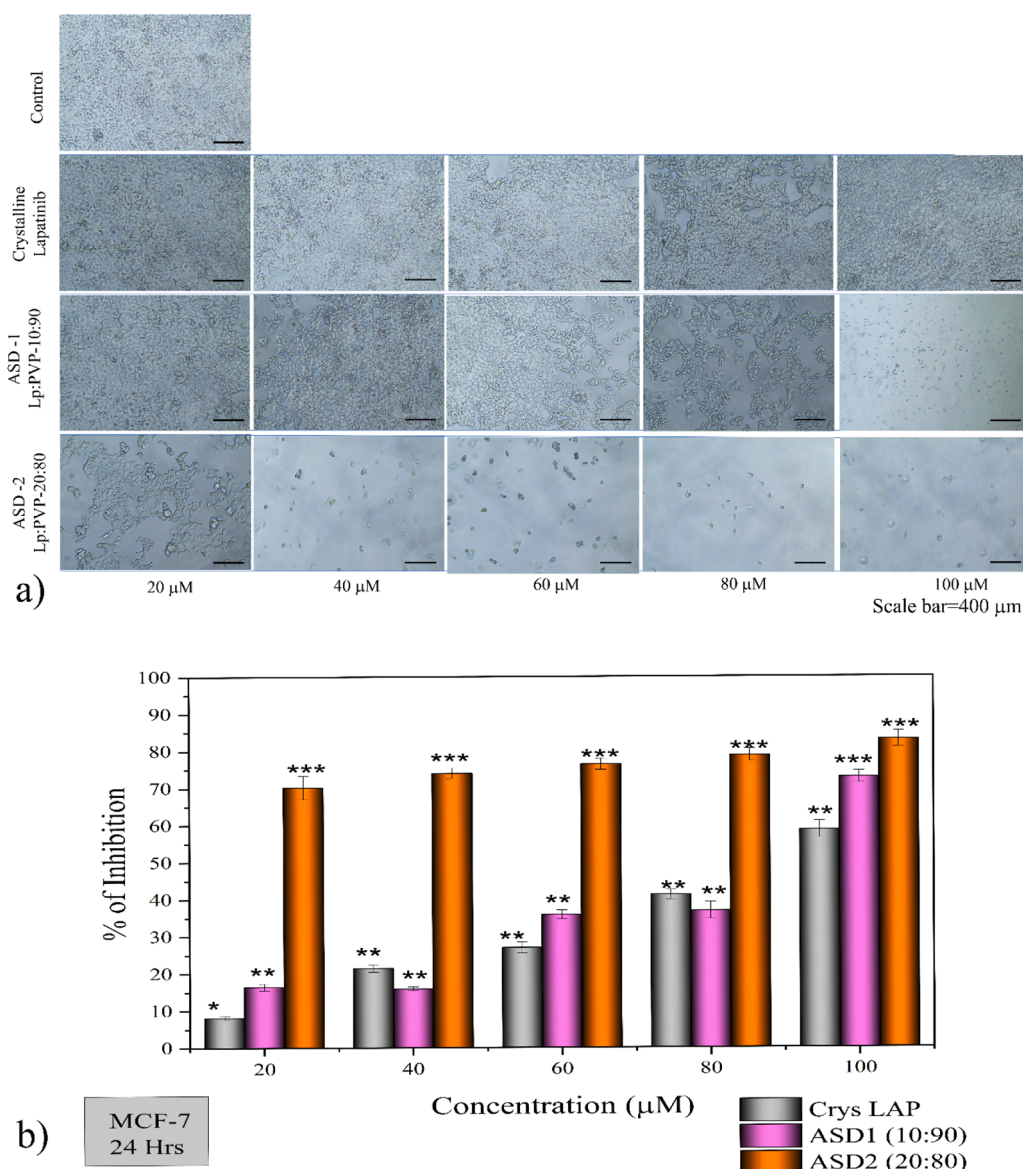


Fig. 15. (a) Representative phase-contrast microscopic images of MCF-7 breast cancer cells treated with crystalline LAP, ASD1, and ASD2 at varying concentrations (20, 40, 60, 80, and 100 μM) for 24 h. (b) Quantitative analysis of percentage inhibition in MCF-7 cells following 24-h treatment with crystalline LAP, ASD1, and ASD2. A dose-dependent increase in cytotoxicity is observed, with significantly higher inhibition for ASD2 across all tested concentrations compared to the crystalline drug and ASD1. Data are expressed as mean $\pm$ SD (n = 3). Statistical significance: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***), compared with the control group.

framework for the design, optimization, and long-term performance prediction of LAP-based ASD drug delivery systems.

CRediT authorship contribution statement

Hayato Yokose: Data curation. **Yosuke Oki:** Data curation. **K.P. Safna Hussan:** Writing – original draft, Data curation, Conceptualization. **Takeru Ito:** Validation. **Sinha Kenta:** Data curation. **Laner Chen:** Data curation. **Kahori Furuhashi:** Investigation. **Naoki Shinyashiki:** Writing – review & editing, Supervision. **Rio Kita:** Writing – review & editing. **Hiroshi Kimura:** Data curation. **Yosuke Okamura:** Formal analysis, Data curation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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