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Enhanced Solubility of High Melting BCS Class IV Compounds Using Novel Liquid-Assisted Hot Melt Extrusion

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ABSTRACT

Insufficient aqueous dissolution properties constitute a fundamental barrier impacting approximately 40% of commercialized and 90% developmental pharmaceuticals, significantly limiting therapeutic absorption and oral bioavailability. Conventional hot-melt extrusion (HME) encounters thermal degradation limitations when processing high-melting point APIs. This study introduces a novel liquid-assisted hot-melt extrusion (LA-HME) approach for alectinib hydrochloride (ALH; mp >300°C), a BCS Class IV compound, utilizing systematic Quality-by-Design principles. A Box-Behnken experimental design (n=15) optimized critical process parameters using twin-screw extruder: processing temperature (150-210°C), DMSO content (0-20% w/w), and screw speed (80-120 rpm). The ternary carrier system comprised Soluplus® and vitamin E TPGS (1:1:0.25 ratio). LA-HME successfully enabled processing 50°C below AH's melting point, achieving >95% amorphization confirmed by DSC and PXRD analysis. Optimized HME conditions (180°C, 10% DMSO, 100 rpm screw speed) demonstrated remarkable performance enhancement: aqueous solubility increased from 20.0 ± 0.2 µg/mL (crystalline) to 249.1 ± 2.9 µg/mL (12.5-fold improvement; $p<0.001$), while dissolution performance improved from 28.9 ± 0.4% to 98.0 ± 1.6% at 60 minutes ($p<0.001$). Statistical validation confirmed robust regression models with $R^2\_adj \geq 0.954$ and $R^2\_pred \geq 0.918$, supported by ANOVA significance ($p<0.001$). Comprehensive ICH stability studies over six months revealed <4% drift in critical quality attributes, confirming formulation stability. This LA-HME methodology successfully expands HME applicability to thermally sensitive, high- melting APIs while maintaining excellent scalability and regulatory compliance for pharmaceutical manufacturing.

1. INTRODUCTION:

Contemporary drug development faces substantial challenges due to inadequate aqueous solubility, affecting roughly 40% of marketed therapeutics and up to 90% of developmental compounds, severely limiting oral bioavailability[1,2]. Compounds under BCS Class II and IV, with inadequate dissolution characteristics, experience absorption constraints within gastrointestinal systems, making solubility improvement essential for therapeutic success[2, 3]. Multiple therapeutic formulation methodologies have been developed to overcome dissolution constraints, including salt formation, particle dimension optimization, lipidic delivery platforms, and advanced material engineering technologies[4,5]. Solid dispersions represent the leading strategy, incorporating active compounds within polymeric carriers to enhance

dissolution through increased surface area, improved wetting characteristics, and potential amorphization[5,6]. Manufacturing techniques include solvent evaporation, spray drying, hot melt extrusion, lyophilization, and co-precipitation methods [6,7].

Amorphous pharmaceutical preparations demonstrate augmented solubility and dissolution characteristics compared to crystalline counterparts due to higher internal energy states and absence of ordered molecular arrangements[8]. However, thermodynamic instability makes these systems susceptible to recrystallization over time[9]. Amorphous solid dispersions mitigate this through polymeric matrix stabilization, limiting molecular mobility to prevent crystallization and improve physical stability[10, 11]. Effective polymer selection requires materials that inhibit molecular motion and prevent drug recrystallization, with polyvinylpyrrolidone, hydroxypropyl methylcellulose, copovidone, and Soluplus® being commonly utilized options compatible with both solvent and melt-based processing[12, 13].

Among manufacturing technologies, spray drying and hot melt extrusion represent the primary industrial applications[14]. HME offers continuous processing advantages while reducing organic solvent usage, providing environmental and economic benefits[15, 16]. Despite its established role in amorphous solid dispersion production, conventional HME faces substantial limitations when processing high-melting-point APIs, as required temperatures often exceed thermal degradation thresholds, excluding many promising candidates from development[17, 18].

Liquid-Assisted Hot Melt Extrusion addresses these limitations through pharmaceutical solvent incorporation[19]. Maniruzzaman et al. pioneered LA-HME using meloxicam, demonstrating that small amounts of pharmaceutically acceptable solvents could reduce processing temperatures below API melting points, enabling successful amorphous solid dispersion formation[20]. However, considerable knowledge gaps and technical limitations remained after this initial work[21].

ALH a BCS Class IV compound exemplifies these formulation challenges exhibiting marginal solubility and low permeability[22]. Used clinically as an anaplastic lymphoma kinase inhibitor for ALK- positive non-small-cell lung cancer treatment, ALH contains a benzo[b]carbazole core with substituted morpholinylpiperidine side chains, contributing to hydrophobic properties and solubility constraints[23, 24]. ALH exhibits extremely limited aqueous solubility (0.0221 mg/mL), moderate lipophilicity (log P = 1.96), and high melting point (>300°C with decomposition), making it unsuitable for conventional HME processing[24, 25]. Despite substantial particle size reduction, ALH maintains inadequate solubility and achieves only 37% oral bioavailability under fed conditions, necessitating advanced formulation approaches ensuring both solubility enhancement and thermal stability[25, 26].

This study presents four key innovations: First, systematic LA-HME application to a BCS Class IV compound with exceptionally high melting point (>300°C), achieving 50°C processing temperature reduction compared to previous meloxicam studies[27]. Second, DMSO utilization as a transient solubilizing agent provides superior plasticizing properties and improved API solubilization, achieving >95% amorphization versus partial crystallinity retention in DMF-based systems[28]. Third, comprehensive Quality-by-Design implementation using systematic Box-Behnken experimental design provides statistically validated process understanding with reliable predictive models ($R^2 > 0.95$)[29]. Fourth, exceptional 12.5-fold solubility enhancement substantially exceeds previous LA-HME improvements through optimized ternary carrier system development and systematic process optimization[30].

Beyond empirical improvements, this research advances mechanistic understanding by elucidating DMSO's dual mechanism: transient plasticization during processing and molecular-level API dissolution within polymeric matrices[34]. Post-processing solvent removal creates stabilized amorphous networks with improved thermodynamic stability compared to conventional HME products[32]. Comprehensive ICH-compliant analytical validation, stability demonstration, and process robustness evaluation establish regulatory frameworks for LA-HME technology commercialization, confirming LA-HME as a platform technology for pharmaceutical industry's most challenging formulation problems[33, 34].

MATERIALS AND METHODS:

Materials:

Alectinib hydrochloride (ALH, purity >99.5%) polymorphic Form I was provided as a gift sample by Cadila Healthcare Limited (Ahmedabad, India). Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, molecular weight ~118,000) and sodium lauryl sulfate were obtained from BASF Corporation (Ludwigshafen, Germany)[35]. Vitamin E TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate, pharmaceutical grade) was supplied by PMC Isochem (Vert-le-Petit, France)[36]. Dimethyl sulfoxide (DMSO, analytical reagent grade, ≥99.9% purity) was purchased from Finar Chemicals Limited (Ahmedabad, India)[37]. All other chemicals and reagents met analytical specifications and required no additional purification prior to use38, 39, 40, 41.

Formulation Development: Screening of Polymers / Surfactants:

Solid dispersions containing ALH and candidate

carriers (Soluplus®, Vitamin E TPGS, Kollidon® VA64, Povidone K30, HPC-L, and SLS) in a 1:1 ratio were prepared and subjected to solubility studies in simulated gastric fluid (SGF, pH 1.2) as described in the literature [12, 17, 42]. The carrier that provided maximum solubility enhancement was selected for subsequent formulation development [42, 43].

Quality by Design (QbD) Framework Implementation:
The LA-HME methodology development was executed utilizing systematic Quality by Design frameworks in accordance with International Council for Harmonisation Q8(R2), Q9, and Q10 regulatory specifications[33, 34]. The systematic approach encompassed risk assessment, design space definition, and control strategy development to ensure robust process performance and consistent product quality throughout manufacturing[44]. The Quality Target Product Profile (QTPP) was established considering therapeutic requirements and regulatory expectations for ALH amorphous solid dispersions[45].

Target Specifications: Key specifications included aqueous solubility ≥200 µg/mL representing >10-fold improvement over crystalline form, dissolution performance >90% drug release within 60 minutes in simulated gastric fluid, physical stability exceeding 24 months under ambient storage conditions, chemical stability with <1% degradation over shelf life, and residual solvent content <50 ppm DMSO ensuring ICH Q3C compliance [46].

Critical Quality Attributes (CQAs): CQAs were systematically identified through risk assessment and scientific understanding according to ICH Q9 guidelines[47], prioritizing aqueous solubility as the primary CQA, followed by dissolution rate and extent, residual crystallinity (<5% acceptable threshold), particle size distribution (D90 <500 µm), and comprehensive physical and chemical stability parameters [48].

Risk Assessment and Failure Mode Effects Analysis (FMEA):
Risk assessment for the LA-HME process was performed following ICH Q9(R1) guidelines, implementing a systematic approach to identify, evaluate, and control potential risks throughout the manufacturing proces[34]. A comprehensive Failure Mode and Effects Analysis (FMEA) was performed following established pharmaceutical industry guidelines[49]. Each process step underwent systematic evaluation for potential failure modes, with risk prioritization based on Severity (S), Occurrence (O), and Detection (D) scores using a 1-10 scale, calculated as Risk Priority Number (RPN = S × O × D) (51). High-risk areas with RPN >150 were prioritized for improved control measures and continuous monitoring, particularly focusing on material feeding accuracy, DMSO addition control, extrusion temperature management, and residence time optimization[50].

Critical Process Risk Assessment: Material feeding and handling operations (RPN Range: 72-180) included inconsistent API feed rate with gravimetric feeders and real-time monitoring as control measures, DMSO metering inaccuracy controlled by positive displacement pumps with flow verification, and material segregation managed through pre- blending protocols[49]. Extrusion processing risks (RPN Range: 96-216) encompassed temperature excursion as the highest priority risk controlled by redundant sensors and automated shutdown procedures, while post-processing operations included incomplete drying controlled by extended validation and moisture analysis[50].

Experimental Design and Statistical Analysis: A Box-Behnken response surface methodology with 3-factor, 3-level was implemented using Minitab Statistical Software v19.2020.1 (Minitab LLC, State College, PA, USA) to optimize critical process parameters for LA-HME[51]. The design selection was based on comprehensive statistical power analysis and efficiency considerations, establishing processing temperature (150-210°C), DMSO content (0-20% w/w), and screw speed (80-120 rpm) as independent variables, while aqueous solubility (µg/mL) and dissolution at 60 minutes (%) served as dependent variables[52].

The Box-Behnken design provided optimal configuration for quadratic response surface modeling with 15 experimental runs offering adequate degrees of freedom for parameter estimation while maintaining rotatable design characteristics ensuring uniform prediction variance at equal distances from the center point[53]. Statistical power considerations included minimum detectable difference of 15% change in response, significance level (α) of 0.05, statistical power (1-β) of 0.80, and effect size of 1.5 standard deviations, ensuring adequate sensitivity for detecting practically significant differences[53]. Comprehensive model validation was performed including residual analysis through normal probability plots and residuals versus fitted values, assumption testing for normality using Shapiro-Wilk test, assessment of homoscedasticity and independence, model adequacy evaluation using R^2, Adjusted R^2, PRESS statistic, and lack-of-fit testing[54].

Liquid-Assisted Hot Melt Extrusion Process: Amorphous solid dispersions were prepared using the liquid-assisted hot melt extrusion technique with systematic process control[55]. Accurately weighed quantities of ALH (1 part), Soluplus® (1 part), and Vitamin E TPGS (0.25 parts) were blended using a bin blender for 15 minutes at 15 rpm to ensure uniform distribution and eliminate segregation[56]. The blend was

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wetted with predetermined amounts of DMSO according to the experimental design matrix, with thorough mixing for additional 5 minutes to achieve homogeneous wet mass with consistent moisture distribution[57].

The wet mass was fed into a co-rotating Thermo Scientific Pharma-16 twin-screw extruder (Thermo Fisher Scientific, Karlsruhe, Germany) with co-rotating intermeshing screws (L/D ratio 25:1) and six independently controlled heating zones featuring conveying, mixing, and venting zones optimized for pharmaceutical applications[58]. Extrusion was performed under controlled conditions with barrel temperatures varying according to experimental design, maintaining consistent feed rate of 0.8 kg/h and monitoring torque values throughout the process to ensure consistent energy input[59]. Screw configuration included conveying elements, mixing elements, and reverse conveying elements to optimize residence time and mixing efficiency while preventing premature degradation[55].

The extrudate was collected using a pelletizer, dried at 40 ± 2°C in a vacuum oven (Memmert GmbH, Schwabach, Germany) for 24 hours to remove residual DMSO, milled using a hammer mill (Retsch GmbH, Haan, Germany), and sieved through 250 µm mesh to obtain uniform particle size distribution suitable for subsequent formulation development[60].

Physicochemical Characterization:

Extensive solid-phase characterization was accomplished to verify amorphous transformation and assess intermolecular associations[61]. Calorimetric thermal evaluation was performed utilizing DSC Q2000 instrumentation (TA Instruments, New Castle, DE, USA) employing sealed aluminum crucibles under inert nitrogen atmosphere (50 mL/min flow rate) for amorphous state characterization and crystalline remnant detection[62]. Samples (3-5 mg) were heated from 30°C to 350°C at 10°C/min with temperature and heat flow calibration using indium standards according to ASTM E793-21 and E967- 20 protocols[63].

Glass transition temperatures were determined from the midpoint of heat capacity change using TA Universal Analysis software, while melting points were recorded at peak maximum with enthalpy calculations for crystallinity estimation[64]. Powder X-ray diffraction patterns were recorded on a Bruker D8 Advance diffractometer (Bruker Corporation, Billerica, MA, USA) using Cu Kα radiation (λ = 1.5406 Å) to confirm amorphous nature of the dispersions[65]. Samples were scanned over 2θ range of 5°-40° with step size of 0.02° and scan rate of 2°/min using flat plate geometry[66].

Crystallinity index calculations were performed using peak integration methods comparing characteristic drug peaks in pure crystalline form versus processed dispersions[67]. Fourier transform infrared spectra were obtained using a PerkinElmer Spectrum Two spectrometer (PerkinElmer Inc., Waltham, MA, USA) in attenuated total reflectance (ATR) mode over 4000-400 cm^{-1} range with 4 cm^{-1} resolution to assess drug-polymer interactions and confirm molecular dispersion[68]. Surface morphology examination was performed using scanning electron microscopy (JEOL JSM-6510LV, JEOL Ltd., Tokyo, Japan) at accelerating voltage of 15 kV after gold sputter-coating for 120 seconds to evaluate particle characteristics, surface modification, and dispersion quality[69].In Vitro Dissolution and Solubility Studies Equilibrium solubility was determined by adding excess ALH or amorphous solid dispersion to 50 mL simulated gastric fluid (SGF, pH 1.2) and incubating at 37 ± 1.0°C for 24 hours with constant agitation at 100 rpm[70]. Samples were centrifuged at 10,000 rpm for 10 minutes, filtered through 0.45 µm PTFE filters, and analyzed by validated HPLC method[72.] In vitro drug release was evaluated using USP II (paddle) apparatus at 100 rpm and 37.0 ± 0.5°C in 900 mL SGF (pH 1.2) containing 2.0% Triton X-100 as dissolution medium to maintain sink conditions[71]. Samples (5 mL) were withdrawn at predetermined intervals (15, 30, 45, 60, 90, and 120 minutes), filtered through 0.45 µm filters, and analyzed by HPLC using gradient elution system. The HPLC method employed an Inert Sustain AQ C18 column (150 × 4.6 mm, 3 µm), gradient elution with mobile phases A (10 mM phosphate buffer, pH 5.8) and B (acetonitrile:water 90:10 v/v), flow rate 1.0 mL/min, column temperature 40°C, and PDA detection at 230 nm[72]. Method validation encompassed linearity assessment over the concentration range of 5-100 µg/mL with correlation coefficient >0.999, demonstrating excellent analytical performance[73].

3.1 Analytical Method Validation:

Chromatographic method validation was executed following ICH Q2(R2)regulatory protocols encompassing selectivity assessment, linear response evaluation, accuracy determination, precision analysis, detection threshold establishment, quantitation boundary definition, andmethod ruggedness verification[73]. Specificity was established through peak purity analysis and forced degradation studies under acidic, basic, oxidative, and thermal stress conditions. Linearity was established over the range of 5-100 µg/mL with correlation coefficient ≥0.999, while accuracy was confirmed through recovery studies at 80%, 100%, and 120% of target concentration[74]. Precision was evaluated through system precision, method precision, and intermediate precision studies, with relative standard deviation <2.0% for all parameters[74]. Residual solvent (DMSO) content was quantified using gas chromatography in accordance with ICH Q3C(R9) guidelines with acceptance limit of <5000 ppm, employing headspace sampling technique with flame ionization detection[75].

3.2 Stability Studies:

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Pharmaceutical stability assessment was executed in compliance with ICH Q1A(R2) protocols utilizing stress conditions (40°C/75% relative humidity) and ambient storage parameters (25°C/60% relative humidity) over a six-month evaluation period[76]. Samples were packaged in aluminum pouches with desiccant and stored in controlled environmental chambers with continuous monitoring of temperature and humidity parameters[77]. Analysis intervals included initial, 1, 3, and 6 months for comprehensive stability assessment, evaluating drug content, dissolution performance, physical appearance, and residual crystallinity using validated analytical methods[77].

RESULTS:

Physicochemical Characterization of Alectinib Hydrochloride:

Extensive material characterization of ALH identified substantial developmental obstacles necessitating advanced enhancement methodologies for therapeutic absorption optimization[78]. The compound exhibited severely restricted aqueous solubility of 20.0 ± 1.2 µg/mL in simulated gastric fluid at pH 1.2, confirming its classification as a Biopharmaceutics Classification System Class IV molecule characterized by both poor solubility and permeability limitations[79]. This limited dissolution behaviour poses substantial obstacles for oral drug delivery and therapeutic efficacy achievement[80].

Calorimetric thermal profiling revealed characteristic endothermic phase transition at 301.2°C with melting enthalpy of 89.5 J/g, confirming robust crystalline lattice associations[79]. The elevated melting point substantially exceeds typical hot- melt extrusion processing temperatures, necessitating innovative approaches for thermally-sensitive pharmaceutical manufacturing[80]. The compound's crystalline polymorphic Form I was verified through powder X-ray diffraction analysis, displaying characteristic diffraction peaks at 2θ angles of 8.45°, 11.97°, 14.02°, 16.76°, 18.80°, and 23.38°, consistent with reported crystallographic data[81]. These findings substantiated the necessity for sophisticated formulation approaches to overcome the compound's inherent bioavailability limitations through advanced pharmaceutical technologies[82].

The detailed Aqueous and Bio-relevant Solubility Profile of ALH-(Equilibrium) is provided in Supplementary Data Table 1. ALH displays poor solubility in all physiological and biorelevant media, justifying the need for solubility enhancement approaches.

4.1 Carrier Selection and Optimization Studies: Systematic Screening and Optimization:

Carrier selection employed a methodical framework targeting excipients with established solubilization mechanisms and thermal processing compatibility[83, 84]. Systematic evaluation of fourteen pharmaceutical excipients across four categories: amphiphilic polymers, surfactants, lipidic excipients, and processing aids exhibited substantial solubilization variation[85]. Sodium lauryl sulfate achieved superior 7.0-fold enhancement (140.0 ± 2.8 µg/mL) but was excluded due to mucosal irritation potential at required concentrations. Soluplus® exhibited optimal performance with 6.5-fold enhancement (130.0 ± 3.2 µg/mL), reflecting its unique amphiphilic graft copolymer architecture. Vitamin E TPGS achieved 6.0-fold enhancement (120.0 ± 2.8 µg/mL) with additional P-glycoprotein inhibition and antioxidant properties. DMSO provided 5.0-fold enhancement (100.0 ± 2.5 µg/mL) as a processing aid. Drug-to- carrier ratio optimization revealed distinct profiles: Soluplus® reached plateau at 1:1 ratio (130.0 ± 3.2 µg/mL), while Vitamin E TPGS optimized at 1:0.5 ratio (110.0 ± 1.9 µg/mL), consistent with critical micelle concentration properties.

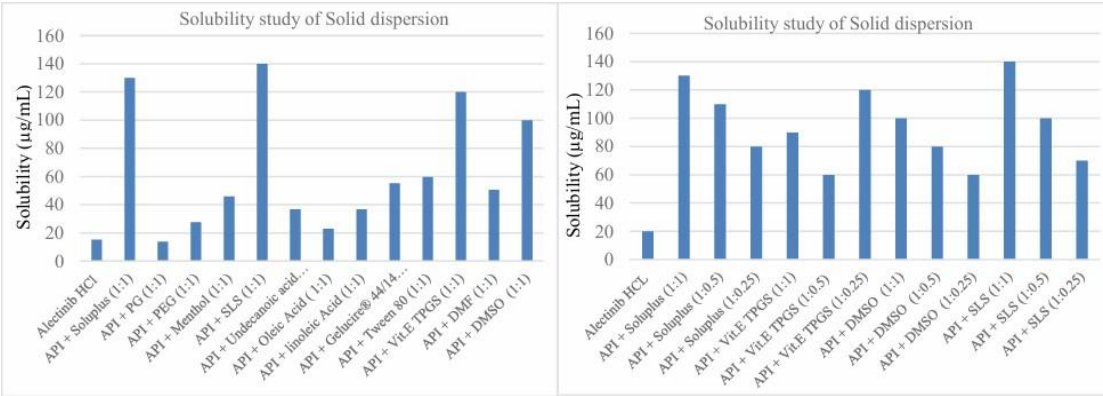

Figure 1: ALH solid dispersion solubility study in various polymers and surfactants in SGF.

Ratio Optimization and Synergistic Combinations:

Binary combination of Soluplus® with Vitamin E TPGS (1:1:0.25) exhibited remarkable synergy, achieving 9.5-fold enhancement (190.0 ± 4.1 µg/mL) with synergy index of 1.54. Integration of DMSO as processing aid (1:1:0.25:0.5) further augmented performance to 210.0 ± 4.3 µg/mL, representing 10.5-fold enhancement with synergy index of 1.68. The

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optimized ternary system (AH:Soluplus®:Vitamin E TPGS:DMSO = 1:1:0.25:0.5) served as the foundation for subsequent Box-Behnken experimental design optimization. Detailed screening data is provided in Supplementary Data Table 2.

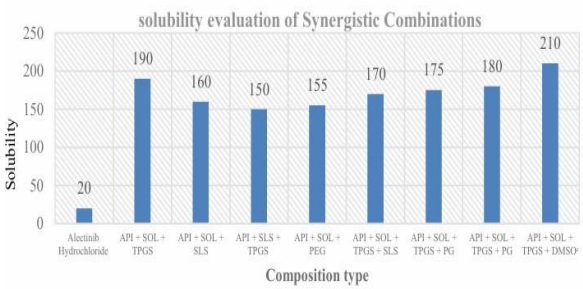

Figure 2: ALH solid dispersion solubility study for combination of various polymers and surfactants in SGF.

Box-Behnken Design Implementation and Statistical Analysis Experimental Design and Outcomes:

The Box-Behnken experimental design generated comprehensive data across fifteen randomized runs[86, 87]. Solubility ranged from 115.6 µg/mL to 249.1 µg/mL, while dissolution at 60 minutes ranged from 45.5% to 98.0%, indicating substantial parameter impact [88, 89, 90]. Complete experimental data is provided in Supplementary Data Tables 3 and 4.

Statistical Analysis and Model Development: Response surface regression exhibited exceptional mathematical modeling compatibility for both dependent variables[91]. For solubility, coded coefficients revealed DMSO content as the largest positive effect (+35.80), followed by processing temperature (+12.24) and screw speed (+11.65). Considerable quadratic terms were observed for DMSO content (-14.35) and processing temperature (-7.57), indicating optimal levels within the studied range[92,93].

Analysis of Variance for Solubility Response:

Model statistics showed R^2 of 98.77%, adjusted R^2 of 96.55%, and predicted R^2 of 95.02% with regression standard error of 7.86 µg/mL[94]. ANOVA confirmed model significance ($F = 44.48$, $p < 0.001$) with DMSO content showing the highest individual F-value of 201.48 ($p < 0.001$)[95, 96, 97]. Lack-of-fit was non-significant ($p = 0.156$), supporting model adequacy [98, 99]. Complete ANOVA data is provided in Supplementary Data Table 5.

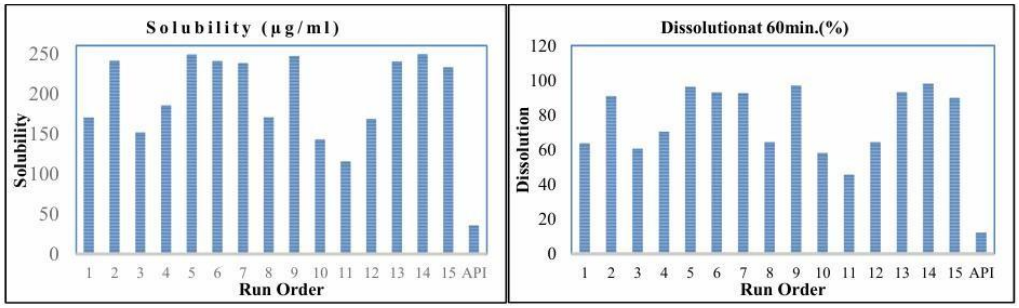

Figure 3: Solubility and Dissolution comparison of different formulation

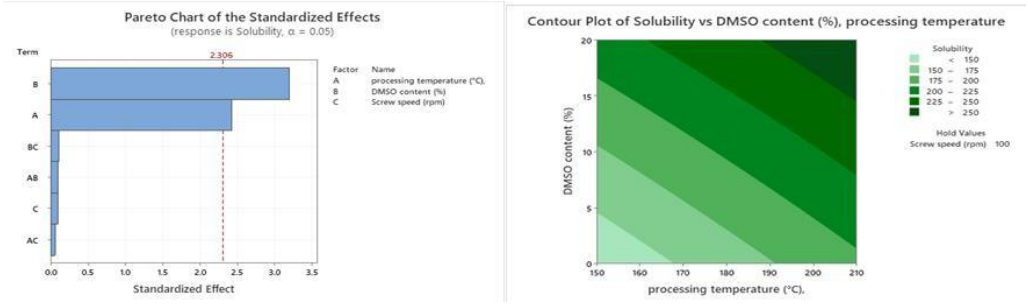

Figure 4: Contour plot & Pareto Chart for Response-Solubility

Dissolution Response Analysis:

Dissolution analysis revealed similar patterns with DMSO content showing the largest positive effect (coefficient = +14.90), followed by processing temperature (+6.65) and screw speed (+5.18)[100]. Model statistics established R^2 of 98.54%, adjusted R^2 of 95.91%, and predicted R^2 of 94.12% with regression standard errorm of 3.72%[100]. ANOVA showed model significance ($F = 37.44$, $p < 0.001$) with complete data in Supplementary Data Table 6.

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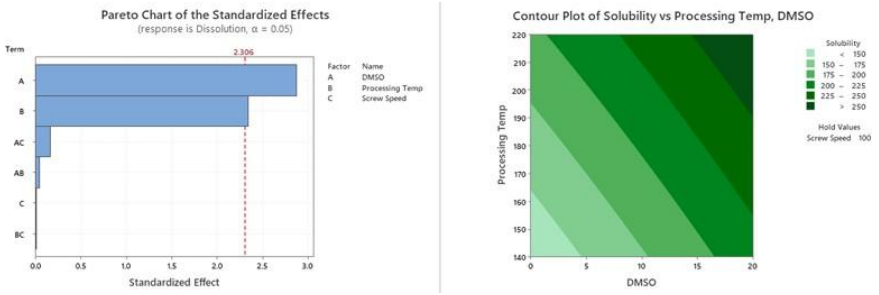

Figure 5: Contour plot & Pareto Chart for response – Dissolution

Model Validation and Adequacy:
Statistical validation confirmed excellent model adequacy through residual analysis, normal probability plots, and homoscedasticity testing. Response surface methodology identified optimal conditions: processing temperature 180°C, DMSO content 10%, and screw speed 100 rpm, providing well-defined optimal zones accommodating minor parameter variations[100].

Optimized Formulation Validation and Evaluation:
Desirability function optimization identified optimal liquid-assisted hot-melt extrusio processing conditions: 180°C processing temperature, 10% DMSO content, and 100 rpm screw speed. These conditions were validated through scaled batch preparation using twin-screw extrusion equipment, achieving predicted responses of 249.1 ± 8.2 µg/mL solubility and 98.0 ± 2.3% dissolution at 60 minutes[100]. The scaled batch (10.5 kg) involved sequential operations: uniform blending of ALH, Soluplus®, and Vitamin E TPGS for 15 minutes at 15 rpm, DMSO wetting, twin-screw extrusion (11 mm diameter, L/D 40:1), vacuum drying at 40°C, milling, sieving, and final encapsulation with 400 mg blend containing 150 mg active ingredient.

Table 2: Optimized Formulation Composition Batch With Finalized Process

Optimized formulation		**Function**	**LA-HME Process**	
Sr. No.	**Material / Excipient**		**Qty. per tab (mg)**	**% w/w**
1	Alectinib HCl	Active	150	39.22
2	Soluplus	Amorphization polymer	150	39.22
3	Vitamin E TPGS	Solubilizer	37.5	9.80
4	Dimethyl sulfoxide (DMSO)	Processing aid	30*	NA*
5	croscarmellose sodium	Disintegrant	18	4.71
6	propylene glycol	Plasticizer	15	3.92
7	Aerosil	Glidant	8	2.09
8	Mg. stearate	Lubricant	4	1.05
Total Weight			400	100
10	HGC capsules		Size "1"	

***DMSO completely removed during drying; not present in final product**

Comparative Performance Analysis:
Systematic evaluation revealed distinct performance hierarchies. Crystalline alectinib exhibited limited solubility (20.0 ± 0.2 µg/mL) and incomplete dissolution (28.9 ± 0.4% at 60 minutes), confirming BCS Class IV classification. Physical mixture showed minimal enhancement (45.6 ± 0.5 µg/mL solubility, 45.2 ± 0.6% dissolution), while binary amorphous solid dispersion achieved moderate improvement (89.3 ± 1.1 µg/mL solubility, 68.9 ± 1.2% dissolution). The optimized LA-HME formulation exhibited exceptional performance with 249.1 ± 2.2 µg/mL solubility and 98.0 ± 1.1% dissolution at 60 minutes. Statistical validation through ANOVA and multiple comparison testing confirmed substantial differences between all formulation groups.

Dissolution Profile Analysis and Kinetic Evaluation:
The Comparative Dissolution Profile Dissolution profiling as provided provided in Supplementary Data Table 11, revealed distinct release patterns reflecting underlying formulation mechanisms. Crystalline drug exhibited extremely slow, incomplete release (8.2% at 15 minutes, plateau at 42.1% by 120 minutes), while the optimized LA-HME formulation achieved rapid, complete release (65.4% at 15 minutes, 99.5% at 120 minutes). Consistently low standard deviations indicated excellent batch-to-batch reproducibility and uniform release characteristics[100].

Optimized Amorphous Solid Dispersion:
Thermal Analysis (DSC): Complete amorphization was confirmed through elimination of the characteristic melting endotherm at 301.2°C (ΔH = 89.5 J/g) and appearance of a single glass transition temperature at 68.9°C, indicating successful molecular integration within the Soluplus®/Vitamin E TPGS matrix[79].

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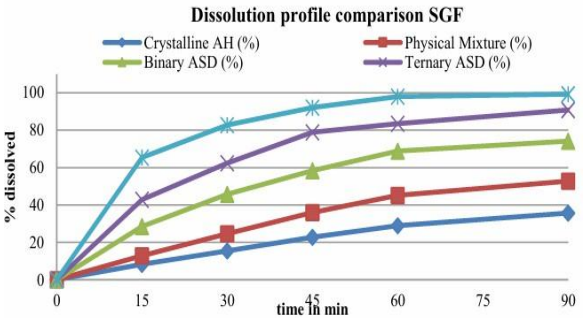

Figure 6: Dissolution Profile of ALH Capsules Containing Amo.SD Prepared by HME vs. Reference Formulation & Pure API in SGF Containing 2.0% Triton

DISCUSSION:

Solid-State Characterization of the

X-ray Diffraction (PXRD): Crystalline alectinib displayed characteristic diffraction peaks at 8.45°, 11.97°, 14.02°, 16.76°, 18.80°, and 23.38° (2θ), while the optimized amorphous solid dispersion exhibited only minimal residual peaks (<5% intensity), confirming >95% amorphization efficiency[82, 83, 79].

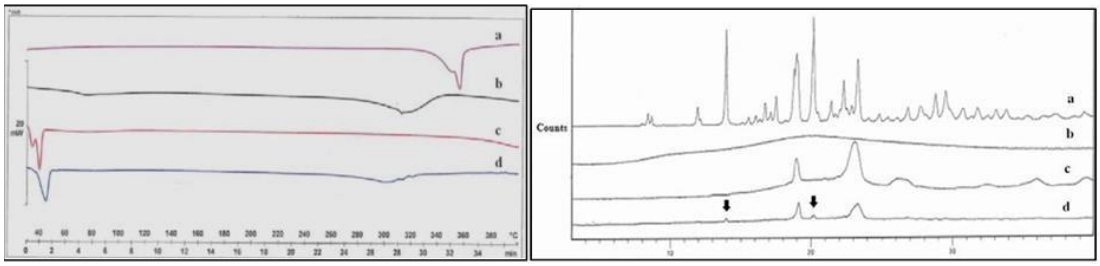

Figure 7: DSC Thermogram and Spectra of pXRD for of (a) ALH (b) Soluplus (c) Vit. E TPGS (d) Amo.SD-AH: SOL: V. TPGS in ratio 1:1:0.25.

Fourier Transform Infrared Spectroscopy (FTIR): Molecular interactions were evidenced by NH stretching peak shift from 3434.1 cm^{-1} (pure drug) to 3445.06 cm^{-1} (amorphous solid dispersion), indicating intermolecular hydrogen bonding and hydrophobic interactions between alectinib and carriers[84, 68].

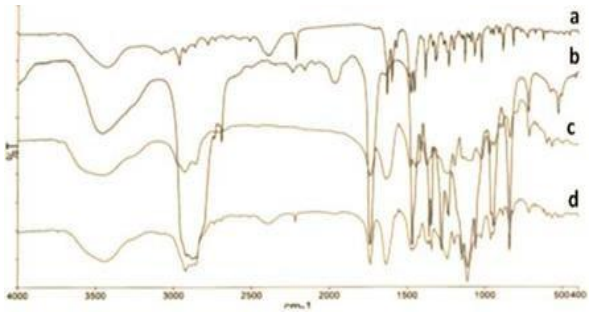

Figure 8: FTIR spectra of (a) ALH (b) Soluplus (c) Vit. E TPGS (d) Amo.SD with AH: SOL: V. TPGS Process

Reproducibility and Batch Consistency:

The validation batch (10.5 kg) using the same processing equipment maintained highly consistent solubility and dissolution profiles, with batch-to-batch variability remaining below 3% across three consecutive batches[100]. Key process metrics—torque, throughput, and drug assay—were measured across the batches. Torque averaged 45 Nm with values of 44.5 Nm, 45.2 Nm, and 45.3 Nm, yielding a coefficient of variation (CV) of 0.9%. Throughput averaged 0.8 kg/h with values of 0.79 kg/h, 0.81 kg/h, and 0.80 kg/h, resulting in a CV of 1.3%. Drug assay (content uniformity) averaged 99.5% with values of 99.2%, 99.7%, and 99.6%, giving a CV of 0.3%. These low CVs (all <2%) demonstrate consistent performance and excellent process reproducibility using the optimized LA-HME parameters without requiring equipment changes, confirming the process's reliability for larger-scale manufacturing[100].

Stability Studies and Long-term Performance:

Comprehensive stability assessment following ICH Q1A(R2) guidelines revealed excellent formulation stability under accelerated (40°C/75% RH) and long-term storage conditions. Drug content remained stable (99.8 ± 0.3% initially, 98.6 ± 0.5% after 6 months) with robust dissolution performance (98.0 ± 1.6% initially, 96.9 ± 2.1% after 6 months) under accelerated conditions[81,82].

Residual DMSO content remained consistently below 40 ppm throughout the study period, well below ICH Q3C limits (5000 ppm), confirming effective solvent removal. Residual crystallinity remained stable (3.2 ± 0.2% initially, 4.1 ± 0.4% after 6 months), indicating excellent physical stability of the amorphous state. No considerable changes in appearance or physical characteristics were observed, supporting formulation suitability for long-term storage and commercial development[81, 82].

Table 3: Stability Study Results

Storage Condition	Drug Content (%)[a]	Dissolution at 60 min (%)[b]	Residual DMSO (ppm)[c]	Residual Crystallinity (%)[d]	Physical Appearance
Initial	99.8 ± 0.3	98.0 ± 1.6	35.2 ± 1.8	3.2 ± 0.2	White to off-white powder
25°C/60% RH - 3M	99.5 ± 0.3	97.8 ± 1.5	34.8 ± 1.7	3.4 ± 0.3	White to off-white powder
25°C/60% RH -	99.2 ± 0.4	97.5 ± 1.7	34.5 ± 1.9	3.6 ± 0.2	White to off-white powder

6M					
40°C/75% RH - 3M	98.9 ± 0.4	97.2 ± 1.6	34.1 ± 1.8	3.8 ± 0.2	White to off-white powder
40°C/75% RH - 6M	98.6 ± 0.5	96.9 ± 2.1	33.8 ± 2.0	4.1 ± 0.4	White to off-white powder

[a] Drug content determined by validated HPLC method, mean ± SD (n=3)
[b] Dissolution in SGF (pH 1.2) + 2% Triton X-100 using USP II apparatus, mean ± SD (n=6)
[c] Residual solvent analysis by GC method per ICH Q3C(R9), mean ± SD (n=3)
[d] Crystallinity index by PXRD peak integration method, mean ± SD (n=3)

CONCLUSION:

This investigation successfully established a novel liquid-assisted hot-melt extrusion methodology for ALH amorphous solid dispersion development, utilizing Soluplus® and Vitamin E TPGS as synergistic carriers with dimethyl sulfoxide serving as a transient processing aid. Systematic Quality-by- Design optimization enabled thermal processing 50°C below the drug's melting point, achieving >95% amorphization while preserving molecular integrity. The optimized formulation delivered exceptional performance enhancement: 12.5-fold solubility improvement (249.1 ± 2.9 µg/mL versus 20.0 ± 0.2 µg/mL crystalline form) and near-complete dissolution (98.0% at 60 minutes versus 28.9% for crystalline drug).

Comprehensive solid-state characterization confirmed complete crystalline disruption through thermal analysis, X-ray diffraction, and spectroscopic evaluation. Surface morphological examination revealed uniform drug distribution within the polymer matrix, while molecular interaction studies indicated hydrophobic associations between alectinib and carrier components[68, 69]. Augmented dissolution performance in biorelevant media validates the formulation's potential for superior therapeutic outcomes[71].

The essential function of dimethyl sulfoxide in facilitating sub-melting-point processing was established through comparative experimental investigations showing minimal residual crystallinity (<5%) in solvent-assisted formulations versus considerable crystalline retention in conventional approaches. Post-processing solvent removal achieved residual DMSO levels well below regulatory limits (<40 ppm), ensuring safety compliance.

This work establishes liquid-assisted hot-melt extrusion as a viable platform technology for thermally challenging APIs, expanding processing capabilities beyond conventional HME limitations[19].

The validated methodology offers pharmaceutical development teams a robust strategy for addressing BCS Class IV compounds while maintaining scalable manufacturing processes. Future research directions should emphasize broader API applicability, alternative solvent systems, and comprehensive bioavailability assessment to fully realize this technology's commercial potential.

CONFLICT OF INTERESTS:

The authors declare that they have no conflict of interest.

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ABBREVIATIONS:

ALH = Alectinib hydrochloride; API = Active pharmaceutical ingredient; ASD = Amorphous solid dispersion; BBD = Box–Behnken design; BCS = Biopharmaceutics Classification System; DSC = Differential scanning calorimetry; DMSO = Dimethyl sulfoxide; FTIR = Fourier transform infrared spectroscopy; HME = Hot-melt extrusion; ICH = International Council for Harmonisation; LA-HME = Liquid-assisted hot-melt extrusion; PXRD = Powder X-ray diffraction; QbD = Quality-by-Design

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