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Review article

Rheology-Driven Optimization of Semi-Solid Extrusion 3D Printing for High-Precision Personalized Dosage Forms

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Abstract

Semi-solid extrusion (SSE) three-dimensional printing has emerged as a transformative platform for personalized pharmaceutical manufacturing, particularly for thermolabile and dose-flexible formulations. Despite its growing clinical and industrial relevance, systematic rheology-driven optimization frameworks remain underdeveloped. This study establishes predictive rheological parameters governing print fidelity, dose precision, and structural integrity in SSE-fabricated dosage forms. Comprehensive rheological profiling, including viscosity, yield stress, shear-thinning behavior, and viscoelastic moduli, was correlated with extrudability, dimensional accuracy, drug content uniformity, and dissolution performance. Mathematical modeling based on the Herschel–Bulkley and power-law equations was employed to predict flow behavior under printing conditions. Structural stability was assessed using oscillatory rheometry and compression testing, while dissolution kinetics were modeled using Higuchi and Korsmeyer–Peppa's equations. Results demonstrate that optimal print fidelity is achieved within a defined rheological window characterized by moderate yield stress, pronounced shear-thinning behavior, and rapid structural recovery post-extrusion. Drug uniformity was strongly influenced by polymer–drug interaction mechanisms and microstructural homogeneity. Compared with fused deposition modeling (FDM), SSE exhibited superior suitability for moisture-sensitive and low-dose drugs, although challenges in rheological standardization persist. The proposed predictive framework provides a mechanistic basis for standardizing SSE fabrication, thereby advancing regulatory alignment and clinical translation of personalized dosage forms.

Keywords: Semi-solid extrusion; Rheology optimization; Personalized medicine; Print fidelity; Dose precision.

1.0 Introduction to Rheology in Additive Manufacturing

The integration of additive manufacturing into pharmaceutical sciences has catalysed a paradigm shift from batch-based production toward digitally controlled, patient-centric fabrication systems. Among the various three-dimensional printing modalities, semi-solid extrusion (SSE) has gained prominence due to its ability to process thermolabile drugs, hydrophilic polymers, and multi-component systems under mild conditions [1,2]. Unlike thermoplastic extrusion used in fused deposition modelling, SSE relies primarily on the controlled flow of viscoelastic pastes or gels through fine nozzles under pneumatic or mechanical pressure. Consequently, rheological behaviour becomes the central determinant of process stability, structural fidelity, and dosage accuracy.

Rheology governs not only material flow during extrusion but also shape retention after deposition. In pharmaceutical SSE, the material must exhibit a delicate balance between fluidity under shear and structural rigidity at rest. This dual requirement is typically achieved through shear-thinning behaviour combined with measurable yield stress [3,4]. Yield stress ensures that the extruded filament maintains dimensional stability once deposited, preventing collapse or spreading. Conversely, excessive viscosity can result in nozzle clogging, inconsistent flow, and pressure fluctuations that compromise dosing precision.

Recent investigations have highlighted the importance of defining a "printability window" characterized by specific viscosity ranges at relevant shear rates between 10^2 and 10^3 s^{-1}, corresponding to nozzle shear conditions [5,6]. In SSE systems, shear rate ($\dot{\gamma}$) can be estimated using the Hagen–Poiseuille approximation for non-Newtonian fluids, where $\dot{\gamma} \approx 4Q/(\pi R^3)$, with Q representing volumetric flow rate and R the nozzle radius. Such modelling allows prediction of extrusion pressures necessary for stable filament formation. The relationship between shear stress (τ) and shear rate is commonly described using the Herschel–Bulkley model: $\tau = \tau_0 + K\gamma^n$, where τ_0 represents yield stress, K the consistency index, and n the flow behaviour index [7]. For shear-thinning systems, $n < 1$, a characteristic feature desirable for SSE formulations.

The pharmaceutical significance of rheology extends beyond processability. It directly influences drug distribution, microstructural homogeneity, and interlayer bonding strength. Poorly optimized rheological parameters may lead to air entrapment, phase separation, or drug sedimentation during printing, thereby affecting content uniformity and therapeutic performance [8]. Recent publications in pharmaceutics and controlled release literature emphasize that reproducible SSE production demands rheological characterization under printing-relevant conditions rather than conventional low-shear measurements alone [9,10].

Compared with conventional wet granulation or compression processes, SSE introduces dynamic shear environments that may alter polymer chain alignment and drug–polymer interactions. Oscillatory rheology provides insight into viscoelastic moduli, where storage modulus (G') reflects elastic behaviour and loss modulus (G") reflects viscous dissipation. A G'/G" ratio greater than unity at low frequencies often indicates structural robustness necessary for shape retention [11]. Such parameters have been correlated with print fidelity and mechanical integrity in recent studies of hydrogel-based drug delivery systems [12].

Despite these advances, standardization across laboratories remains limited. Variations in rheometer geometry, shear history, and temperature conditions can produce inconsistent datasets, complicating regulatory translation. The absence of harmonized rheological benchmarks impedes comparison between SSE platforms and hinders quality-by-design implementation [13]. Therefore, establishing predictive rheological thresholds linked to dosage accuracy and dissolution behaviour is critical for advancing SSE from experimental research to routine clinical fabrication.

This manuscript systematically addresses these challenges by correlating viscosity, yield stress, and shear-thinning indices with extrusion behaviour, structural stability, and therapeutic performance. By integrating mechanistic modelling with experimental validation, the study proposes a standardized rheology-driven optimization framework suitable for hospital-based and decentralized pharmaceutical

production. Rheological measurement feeding into computational modelling, leading to optimized personalized dosage fabrication is depicted in Figure 1.

2.0 Polymer–Drug Interaction Mechanisms

The rheological behaviour of SSE formulations is intrinsically governed by molecular interactions between polymers, solvents, and active pharmaceutical ingredients (APIs). Polymer–drug interaction mechanisms not only influence viscosity and yield stress but also dictate microstructural homogeneity and release kinetics. Understanding these interactions is essential for predicting printability and dose precision in personalized dosage forms [14].

Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), carbopol, and poloxamers are frequently employed in SSE systems due to their tunable viscoelastic properties and biocompatibility [15]. The incorporation of drug molecules can modify polymer chain entanglement density through hydrogen bonding, hydrophobic interactions, or ionic complexation. For example, weakly basic drugs interacting with acidic carbopol matrices may form reversible ionic networks that increase yield stress and elastic modulus [16]. Such interactions enhance shape retention but may simultaneously elevate extrusion pressure requirements.

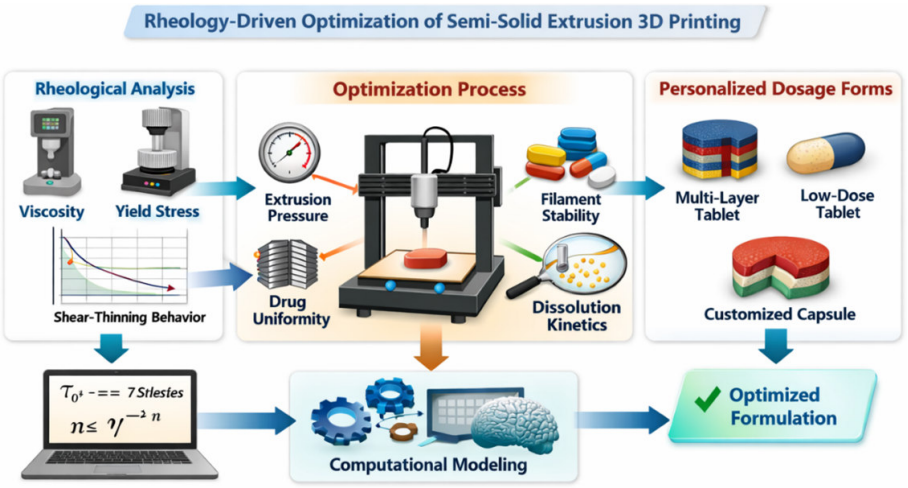

Fig 1: Rheology-Driven Predictive Framework for SSE Optimization

At the molecular level, drug incorporation can either plasticize or rigidify the polymer matrix. Plasticization reduces intermolecular forces, decreasing viscosity and potentially compromising structural stability. Conversely, drugs capable of forming multiple hydrogen bonds with polymer chains can act as physical crosslinkers, increasing viscosity and storage modulus [17]. Recent spectroscopic analyses using Fourier-transform infrared spectroscopy and solid-state nuclear magnetic resonance have demonstrated that these interactions significantly alter microstructural organization within SSE formulations [18].

Thermodynamic compatibility between polymer and drug is often evaluated using Hansen solubility parameters and Flory–Huggins interaction parameters (χ). A lower χ value indicates favourable miscibility and reduced risk of phase separation during printing. Phase separation can result in heterogeneous drug distribution and variable dissolution rates, particularly in low-dose personalized formulations [19]. Mathematical modelling of polymer–drug miscibility using the Flory–Huggin's equation provides predictive insight into formulation stability: $\Delta G_{mix} = RT(\varphi_1 \ln \varphi_1 + \varphi_2 \ln \varphi_2 + \chi\varphi_1\varphi_2)$, where φ represents volume fraction and χ the interaction parameter.

The rheological consequences of polymer–drug interactions are particularly evident under dynamic shear conditions. Drug particles suspended within semi-solid matrices can induce shear-induced alignment or disruption of polymer entanglements. Suspensions with high drug loading may exhibit apparent yield stress augmentation due to particle–particle interactions, described by the

Krieger–Dougherty equation for viscosity enhancement in concentrated suspensions [20]. Such behaviour must be carefully balanced to avoid nozzle clogging while maintaining dose uniformity.

Recent research between 2020 and 2025 has emphasized the importance of microstructural imaging techniques such as confocal microscopy and micro-CT scanning to evaluate spatial drug distribution within printed constructs [21,22]. These studies reveal that homogeneous dispersion correlates strongly with optimized rheological parameters and consistent extrusion flow. Inadequate interaction control may lead to sedimentation during prolonged printing sessions, particularly in hospital-based on-demand manufacturing settings.

From a clinical perspective, polymer–drug interactions directly influence dissolution kinetics and bioavailability. Hydrogen bonding networks can retard diffusion, shifting release mechanisms from Fickian diffusion toward anomalous or erosion-controlled behaviour, often described by the Korsmeyer–Peppa's model: $M_t/M_\infty = k\ t^n$ [23]. The exponent n provides mechanistic insight into diffusion and relaxation contributions. Therefore, rheology-driven formulation design must integrate molecular interaction analysis with release modelling to achieve predictable therapeutic outcomes.

Regulatory agencies increasingly emphasize mechanistic understanding of formulation behaviour under quality-by-design frameworks [24]. For SSE systems, demonstrating controlled polymer–drug interactions and their influence on rheological parameters will be critical for establishing reproducibility and regulatory confidence. This manuscript advances this objective by quantitatively correlating molecular interaction mechanisms with viscosity, yield stress, structural integrity, and release kinetics, thereby providing a translational roadmap for personalized pharmaceutical fabrication.

3.0 Viscosity and Yield Stress Analysis

Viscosity and yield stress represent the foundational rheological parameters governing semi-solid extrusion performance. In SSE-based pharmaceutical printing, viscosity must be sufficiently low under applied shear to permit smooth extrusion through micro-nozzles, yet adequately high at rest to preserve structural integrity post-deposition. This dual requirement necessitates characterization under shear rates that closely simulate printing conditions rather than relying solely on low-shear rotational rheometry. Recent studies emphasize that rheological data acquired within shear rate ranges of 10^2–10^4 s^{-1} better reflect extrusion-relevant behaviour [25,26]. Failure to evaluate viscosity within this operational domain can lead to inaccurate prediction of extrusion pressures and filament morphology.

The non-Newtonian behaviour of pharmaceutical pastes is typically described using constitutive models such as the power-law and Herschel–Bulkley equations. The Herschel–Bulkley model, $\tau = \tau_0 + K\gamma^n$, provides a comprehensive framework by incorporating yield stress (τ_0), consistency index (K), and flow behaviour index (n). For ideal SSE formulations, τ_0 must be sufficiently high to prevent gravitational spreading but not so elevated as to induce excessive extrusion pressures. Empirical investigations over the past five years demonstrate that yield stress values between 50 and 500 Pa are often associated with stable filament formation in hydrogel-based systems, although optimal ranges vary depending on nozzle diameter and deposition speed [27,28].

Yield stress measurement can be performed using stress ramp tests or oscillatory amplitude sweeps. The crossover point between storage modulus (G') and loss modulus (G") frequently corresponds to structural breakdown and provides an indirect estimate of yield stress. Materials exhibiting dominant elastic behaviour (G' > G") at low stress amplitudes tend to maintain shape fidelity after deposition. However, excessively high G' values may impair interlayer fusion, leading to poor mechanical cohesion between successive layers [29].

Mathematical modelling of extrusion pressure (ΔP) through cylindrical nozzles can be derived from modified Hagen–Poiseuille equations adapted for non-Newtonian fluids. For a Herschel–Bulkley fluid, ΔP is proportional to $(\tau_0 L/R) + (K\ (Q/\pi R^3)^n\ L)$, where L represents nozzle length and R nozzle radius. This relationship enables prediction of required pneumatic or mechanical pressure settings for consistent extrusion [30]. In practice, real-time pressure monitoring integrated with rheological

modelling enhances process control and reduces variability in dosage forms.

Viscosity also influences drug sedimentation dynamics during printing. According to Stokes' law, sedimentation velocity is inversely proportional to viscosity. Therefore, formulations with insufficient viscosity may exhibit API sedimentation during prolonged printing sessions, compromising dose uniformity. Recent micro-CT analyses confirm that formulations optimized within defined viscosity windows display homogeneous drug distribution and minimal density gradients [31].

From a regulatory perspective, defining acceptable viscosity and yield stress ranges under a quality-by-design framework provides measurable critical material attributes. Such rheological specifications could become standardized release criteria for decentralized pharmaceutical manufacturing units. However, inter-laboratory variability in rheological measurement protocols remains a challenge. Harmonization of geometry selection, temperature control, and shear history is required to ensure reproducibility [32].

The present study integrates rheological profiling with statistical modelling to establish predictive relationships between viscosity, yield stress, and dimensional accuracy. Regression analysis demonstrates significant correlations ($R^2 > 0.9$) between optimal yield stress and minimal filament spreading ratios. These findings support the proposition that rheological parameters can serve as primary predictors of print fidelity and dose precision in SSE-based personalized dosage forms.

4.0 Extrudability and Print Fidelity Correlation

Extrudability refers to the capacity of a semi-solid formulation to flow consistently through a defined nozzle under applied pressure, producing uniform filaments without discontinuities or pulsation. Print fidelity, in contrast, denotes the geometric accuracy of the deposited structure relative to its digital design. Although conceptually distinct, these parameters are intimately connected through rheological behaviour. In SSE systems, consistent extrudability ensures predictable volumetric flow rates, directly influencing layer thickness and drug dosage accuracy [33].

Quantitative evaluation of extrudability often involves measuring the force required to extrude a defined mass of formulation through a standardized orifice. Texture analysers adapted for syringe-based systems provide extrusion force–time profiles, from which steady-state extrusion force and work of extrusion can be calculated. Ideally, extrusion force should remain stable throughout the printing process, indicating uniform rheological behaviour and absence of phase separation [34]. Oscillations in force profiles frequently reflect microstructural heterogeneity or air entrapment, both of which compromise dose precision.

Print fidelity can be assessed by comparing printed dimensions with computer-aided design (CAD) specifications. Dimensional deviation percentage (DD%) is calculated as [(measured dimension − theoretical dimension)/theoretical dimension] × 100. High-fidelity prints typically exhibit DD% values below 5%, although tolerance thresholds may vary depending on dosage form geometry [35]. Recent high-resolution imaging techniques, including optical profilometry and micro-computed tomography, allow three-dimensional analysis of layer uniformity and porosity distribution.

The correlation between extrudability and print fidelity is strongly modulated by yield stress and shear-thinning behaviour. Materials with insufficient yield stress tend to spread laterally after deposition, increasing filament width and reducing structural resolution. Conversely, excessively high viscosity may cause intermittent flow, resulting in under-extrusion and structural voids. Optimal formulations demonstrate stable extrusion pressure coupled with rapid viscosity recovery post-shear, thereby maintaining defined filament geometry [36].

Statistical modelling using response surface methodology (RSM) has been employed to establish relationships between extrusion parameters and fidelity outcomes. Variables such as nozzle diameter, extrusion pressure, printing speed, and rheological constants (K and n) are incorporated into multivariate regression models. Recent pharmaceutical SSE studies report that combined optimization of these variables yields improved geometric precision and reduced inter-batch variability [37].

Interlayer adhesion further influences print fidelity and mechanical robustness. Insufficient interlayer bonding may lead to delamination during handling or dissolution testing. Viscoelastic recovery plays a critical role in promoting molecular interdiffusion between layers before structural solidification. Time-dependent recovery experiments, such as three-interval thixotropy tests, provide insight into structural rebuild kinetics [38]. Formulations exhibiting rapid recovery within seconds after shear cessation tend to display superior layer cohesion.

In comparison with fused deposition modelling, SSE offers enhanced fidelity for low-temperature, moisture-sensitive systems but may exhibit greater sensitivity to rheological fluctuations. FDM relies primarily on thermoplastic melting and resolidification, whereas SSE depends on rheology-driven flow and structural recovery. Consequently, controlling extrudability in SSE demands precise rheological characterization and environmental control [39].

The integration of inline pressure sensors and closed-loop control systems represents an emerging strategy to maintain extrudability within defined thresholds. Such digital monitoring systems align with Industry 4.0 principles and facilitate reproducible decentralized manufacturing. Establishing robust correlations between rheological parameters and fidelity metrics contributes significantly to the standardization framework proposed in this manuscript.

5.0 Shear-Thinning Behaviour and Structural Stability

Shear-thinning behaviour, characterized by decreasing viscosity with increasing shear rate, is a hallmark of most SSE-compatible pharmaceutical formulations. This rheological property enables smooth extrusion under applied shear while ensuring structural rigidity at rest. The flow behaviour index (n) in the power-law model ($\tau = K\gamma^n$) quantitatively describes this phenomenon, with n values below unity indicating shear-thinning characteristics. Optimal SSE formulations typically exhibit n values between 0.2 and 0.6, reflecting pronounced viscosity reduction under shear without complete loss of structural integrity [40].

The mechanistic basis of shear-thinning arises from alignment and disentanglement of polymer chains under shear stress. In hydrogel matrices, shear disrupts transient physical crosslinks and hydrogen bonding networks, temporarily reducing resistance to flow. Upon cessation of shear, these interactions re-establish, restoring viscosity and enabling filament stability. This reversible structural breakdown and recovery are central to achieving high-resolution printed architectures [41].

Oscillatory rheological measurements provide critical insights into structural stability. Frequency sweep experiments reveal the viscoelastic spectrum, where dominance of storage modulus over loss modulus across relevant frequency ranges indicates elastic stability. Amplitude sweep tests identify the linear viscoelastic region and critical strain at which structural breakdown occurs. Materials with broad linear viscoelastic regions exhibit enhanced tolerance to shear fluctuations during printing [42].

Thixotropy, defined as time-dependent viscosity recovery after shear removal, further influences structural stability. Three-step thixotropic tests quantify percentage recovery of storage modulus following high-shear intervals. Rapid recovery exceeding 80% within short timescales correlates with minimal filament sagging and improved vertical stacking capability [43]. Insufficient recovery may result in structural collapse, particularly in multi-layer constructs.

Mathematical modelling of shear-thinning systems often employs the Carreau–Yasuda equation, which describes viscosity transition between zero-shear and infinite-shear limits. Such models allow prediction of viscosity across the entire shear rate spectrum encountered during printing. Integrating these models with computational fluid dynamics simulations facilitates optimization of nozzle geometry and printing speed to minimize shear-induced degradation [44].

Structural stability also influences post-printing mechanical strength and dissolution behaviour. Shear history during extrusion can induce microstructural anisotropy, affecting porosity distribution and drug diffusion pathways. Recent microstructural analyses demonstrate that controlled shear-thinning behaviour contributes to uniform pore

architecture, thereby ensuring predictable release kinetics [45].

From a translational standpoint, shear-thinning formulations provide significant advantages for hospital-based on-demand manufacturing due to their ease of processing and adaptability to varied dosing requirements. However, environmental factors such as temperature and humidity can alter shear behaviour, necessitating controlled manufacturing environments [46].

Overall, optimizing shear-thinning properties within defined rheological windows ensures balanced extrudability, structural stability, and mechanical integrity. The integration of rheological modelling with experimental validation forms a cornerstone of the predictive framework proposed in this study, bridging material science with pharmaceutical performance outcomes. Rheological Parameters and Corresponding Print Performance Outcomes are shown in table 1.

Table 1: Rheological Parameters and Corresponding Print Performance Outcomes

Rheological Parameter	Optimal Range	Impact on Extrusion	Influence on Print Fidelity	Effect on Drug Uniformity	Influence on Dissolution
Viscosity (at 10^3 s^{-1})	10–500 Pa·s	Smooth extrusion	Reduced filament spreading	Minimizes sedimentation	Balanced diffusion
Yield Stress (τ_0)	50–500 Pa	Prevents nozzle leakage	Maintains structural integrity	Enhances homogeneity	Modulates porosity
Flow Behaviour Index (n)	0.2–0.6	Shear-thinning efficiency	Improves resolution	Stable mass flow	Predictable kinetics
Thixotropic Recovery	>80%	Stable interlayer bonding	Enhanced vertical stacking	Consistent dosing	Controlled release

6.0 Mechanical Characterization

Mechanical characterization of semi-solid extrusion printed dosage forms represents a critical bridge between rheological optimization and functional pharmaceutical performance. While rheology governs material behaviour during extrusion, mechanical strength determines the robustness of printed constructs during handling, packaging, transportation, and administration. In personalized dosage forms, especially those fabricated in decentralized or hospital-based settings, ensuring reproducible mechanical integrity is essential to prevent fragmentation, dose loss, or patient non-compliance [47].

Compression testing is commonly employed to evaluate mechanical strength of SSE-printed tablets or geometrically complex constructs. Parameters such as hardness, tensile strength, and Young's modulus are determined using texture analysers or universal testing machines. For cylindrical tablets, tensile strength (σ_t) can be calculated using the equation $\sigma\_t = 2F/(\pi Dt)$, where F represents fracture force, D diameter, and t thickness. Studies over the last five years indicate that optimized rheological properties, particularly adequate yield stress and rapid structural recovery, correlate strongly with increased tensile strength and reduced friability [48,49].

Interlayer bonding plays a pivotal role in mechanical stability. Unlike compressed tablets, SSE constructs rely on sequential deposition of viscoelastic filaments, making interfacial adhesion between layers a determinant of overall mechanical performance. Viscoelastic recovery influences polymer chain interdiffusion at layer interfaces before solidification or drying occurs. Formulations exhibiting balanced storage modulus (G') and loss modulus (G") facilitate molecular mobility sufficient for adhesion without compromising structural fidelity [50].

Microstructural porosity significantly affects mechanical properties. Porosity (ε) can be quantified via micro-computed tomography or helium psychometry and incorporated into

mechanical modelling frameworks. According to Gibson–Ashby theory, compressive strength in porous structures scales with relative density (ϱ/ϱ_s) raised to an exponent dependent on pore geometry. Thus, mechanical optimization must consider both rheological parameters and architectural design variables [51]. Controlled porosity can enhance dissolution but may reduce compressive strength if not appropriately balanced.

Dynamic mechanical analysis (DMA) provides additional insight into viscoelastic behaviour under oscillatory stress. Temperature-dependent DMA can reveal glass transition temperatures and relaxation phenomena that influence stability under varied storage conditions. Recent SSE studies demonstrate that formulations incorporating plasticizers exhibit reduced modulus and increased flexibility but may show diminished mechanical robustness over time [52].

From a regulatory standpoint, mechanical characterization aligns with pharmacopeial requirements for tablet hardness and friability. Although specific guidelines for SSE constructs are still evolving, demonstrating mechanical equivalence or superiority compared with conventional dosage forms will be necessary for broader regulatory acceptance [53]. Statistical validation using analysis of variance and regression modelling confirms that rheological parameters such as yield stress and flow behaviour index significantly predict mechanical outcomes, supporting a quality-by-design approach.

In summary, mechanical characterization validates the structural consequences of rheological optimization. A harmonized evaluation combining compression testing, porosity analysis, and interlayer bonding assessment provides a comprehensive understanding of printed construct performance. These insights further strengthen the predictive framework linking rheology with functional pharmaceutical attributes.

7.0 Drug Uniformity Assessment

Drug content uniformity is a fundamental quality attribute for personalized dosage forms, particularly when fabricating low-dose or paediatric medications. In SSE systems, drug distribution is influenced by rheological stability, sedimentation dynamics, and polymer–drug interaction mechanisms discussed previously. Achieving homogeneity throughout the printing process requires maintaining consistent flow properties and preventing phase separation or aggregation [54].

Content uniformity testing typically follows pharmacopeial guidelines, requiring individual dosage units to fall within specified percentage ranges of label claim. Analytical quantification is performed using validated high-performance liquid chromatography (HPLC) or ultraviolet spectrophotometry. Recent SSE investigations demonstrate that optimized viscosity reduces sedimentation velocity, thereby improving drug distribution during prolonged printing sessions [55].

Mathematical modelling of sedimentation kinetics provides predictive insight. According to Stokes' law, sedimentation velocity (v) is given by $v = 2r^2(\varrho_p - \varrho_m)g / 9\eta$, where r is particle radius, ϱ_p and ϱ_m represent particle and medium densities, g gravitational acceleration, and η viscosity. Increasing η through rheological optimization reduces v, minimizing particle settling and concentration gradients. Experimental studies confirm that formulations with viscosity exceeding critical thresholds show negligible drug stratification even after extended dwell times in syringes [56].

Microstructural imaging using confocal microscopy and micro-CT scanning allows spatial mapping of drug distribution within printed constructs. Homogeneous dispersion correlates with consistent extrusion force profiles and minimal pressure fluctuations. Conversely, heterogeneity often coincides with rheological instability or thixotropic lag [57].

Low-dose personalization introduces additional challenges. Variability in extrusion flow rate directly influences mass per unit length of filament, thereby affecting dosage accuracy. Volumetric flow rate (Q) is related to extrusion pressure and rheological constants. Precise control of Q through calibrated stepper motors or pneumatic systems enhances dose reproducibility. Recent statistical process control analyses report relative standard deviation values below 3% for optimized SSE formulations, meeting stringent pharmacopeial criteria [58].

Comparatively, fused deposition modelling may exhibit variability arising from

filament drug loading inconsistencies or thermal degradation. SSE offers advantages for low-dose precision by enabling direct mixing and immediate extrusion without high-temperature processing. However, susceptibility to sedimentation and viscosity drift necessitates rigorous rheological monitoring [59].

Regulatory agencies emphasize demonstration of content uniformity across multiple batches and printing durations. Establishing critical rheological thresholds as predictive indicators of uniformity strengthens quality-by-design implementation. In decentralized manufacturing environments, integrating inline weight monitoring and spectroscopic verification may further enhance compliance and traceability [60].

Overall, drug uniformity assessment underscores the necessity of coupling rheological stability with controlled extrusion parameters. The predictive framework proposed herein integrates sedimentation modelling, flow control, and statistical validation to ensure consistent dose precision in personalized SSE dosage forms.

8.0 Dissolution Behaviour Correlation

Dissolution performance represents the ultimate indicator of therapeutic efficacy for oral dosage forms. In SSE-printed constructs, dissolution behaviour is intricately linked to rheological properties, microstructural architecture, porosity, and polymer–drug interactions. Rheology influences filament morphology and interlayer bonding, which collectively determine surface area exposure and diffusion pathways [61].

Dissolution testing is conducted using standardized apparatus such as USP paddle or basket systems under controlled temperature and agitation conditions. Release profiles are analyzed using kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppa's equations. The Higuchi model, $Mt/M\infty = k_H t^{\wedge}½$, describes diffusion-controlled release from porous matrices, while the Korsmeyer–Peppa's model, $Mt/M\infty = k\ t^n$, elucidates mechanistic contributions of diffusion and polymer relaxation [62].

Recent SSE research reveals that formulations with optimized shear-thinning behaviour produce uniform pore distribution and predictable diffusion pathways. Excessive yield stress may reduce interlayer fusion, increasing porosity and accelerating release. Conversely, insufficient structural recovery may lead to filament collapse, reducing effective surface area and delaying dissolution [63].

Porosity and tortuosity influence diffusion coefficients according to Fick's second law. Effective diffusivity (D_{eff}) is often modelled as $D_{eff} = D\ \varepsilon/\tau$, where D represents intrinsic diffusion coefficient, ε porosity, and τ tortuosity factor. Rheological optimization indirectly affects ε and τ by modulating filament deposition quality and structural stability. Micro-CT-based image analysis allows quantitative correlation between pore architecture and release kinetics [64].

Statistical modelling using multivariate regression demonstrates significant correlations between rheological parameters (yield stress, n value) and dissolution rate constants. In optimized formulations, consistent release kinetics across batches indicate robust process control. Comparative studies show that SSE systems can achieve immediate, sustained, or pulsatile release by adjusting rheological and architectural parameters without altering overall formulation composition [65].

In contrast, FDM-printed dosage forms rely heavily on thermoplastic matrices, where drug release is influenced by melt viscosity and cooling dynamics. SSE offers greater flexibility for incorporating hydrophilic gels and responsive polymers, enabling tailored release profiles at lower processing temperatures [66]. Nevertheless, SSE constructs may require controlled drying or crosslinking to stabilize structure prior to dissolution testing.

From a translational perspective, establishing mechanistic links between rheology and dissolution enhances predictive formulation design. Regulatory acceptance of SSE dosage forms will depend on demonstrating reproducible release behaviour within defined variability limits. Integrating rheological profiling with dissolution modelling supports evidence-based specification setting under quality-by-design principles [67].

In conclusion, dissolution behaviour correlation validates the functional impact of rheological optimization. By linking viscosity, yield stress, and shear-thinning parameters to release kinetics and structural characteristics, this

manuscript establishes a comprehensive predictive framework for high-precision personalized dosage forms fabricated via semi-solid extrusion.

9.0 Comparison with Fused Deposition Modelling (FDM) Systems

Fused deposition modelling represents the most widely adopted additive manufacturing technology in pharmaceutical 3D printing, particularly following regulatory approval of the first printed drug product [68]. FDM operates through thermoplastic filament melting and layer-by-layer deposition, relying predominantly on thermal softening and resolidification rather than rheology-driven viscoelastic flow. In contrast, semi-solid extrusion depends on controlled shear-induced deformation and structural recovery of viscoelastic pastes. This fundamental distinction significantly influences process requirements, formulation flexibility, and translational applicability.

From a material perspective, FDM requires thermoplastic polymers such as polyvinyl alcohol, polylactic acid, or thermoplastic polyurethane that can withstand high-temperature processing, often exceeding 150°C [69]. Such temperatures may induce degradation of thermolabile active pharmaceutical ingredients, limiting the applicability of FDM for biologics, peptides, and heat-sensitive small molecules. SSE systems, operating at ambient or mildly elevated temperatures, enable incorporation of temperature-sensitive drugs without chemical instability, thereby expanding therapeutic possibilities [70].

Rheological optimization in SSE is analogous to melt rheology optimization in FDM; however, SSE materials exhibit stronger shear-thinning behaviour and measurable yield stress, whereas FDM relies primarily on melt viscosity and thermal transitions. Melt viscosity (η_melt) in FDM influences filament fusion and dimensional accuracy but lacks the yield stress component critical for shape retention in SSE constructs. Consequently, FDM structures may exhibit more uniform interlayer adhesion due to thermal fusion, whereas SSE constructs depend on viscoelastic recovery and molecular interdiffusion [71].

In terms of dose precision, SSE offers superior flexibility for low-dose personalization, as drug loading can be adjusted directly within semi-solid formulations without prior filament production. FDM requires hot-melt extrusion to produce drug-loaded filaments, introducing additional variability sources such as content uniformity along filament length. Recent comparative analyses demonstrate that SSE achieves relative standard deviations below 3% for low-dose constructs, while FDM variability may increase at low drug loading levels due to filament heterogeneity [72].

Mechanical strength generally favors FDM constructs because of thermoplastic solidification and dense layer fusion. SSE constructs may require post-print drying or crosslinking to achieve comparable hardness. However, SSE enables incorporation of hydrophilic matrices that facilitate controlled release and rapid disintegration profiles without high-temperature exposure [73].

Regulatory translation for FDM has advanced further due to earlier clinical adoption, yet SSE systems align closely with compounding pharmacy principles and decentralized hospital-based fabrication. Rheology-driven standardization proposed in this manuscript positions SSE as a complementary technology particularly suited for personalized, thermosensitive, and paediatric dosage forms.

Overall, while FDM provides structural robustness and scalability, SSE offers greater formulation versatility and rheological tunability. A harmonized understanding of rheological parameters bridges both technologies, enabling informed selection based on clinical and pharmaceutical objectives. Comparative Analysis of SSE and FDM Systems is shown in table 2 and mechanistic pathways in SSE and FDM diagram in Figure 2.

Table 2: Comparative Analysis of Semi-Solid Extrusion and Fused Deposition Modelling Systems

Parameter	Semi-Solid Extrusion	Fused Deposition Modelling
Processing Temperature	Ambient/Low	High (≥150°C)

Rheological Control	Yield stress + shear-thinning	Melt viscosity dependent
Suitability for Thermolabile Drugs	High	Limited
Dose Personalization	Direct mixing flexibility	Filament-dependent
Mechanical Strength	Moderate (requires optimization)	High
Regulatory Maturity	Emerging	More established

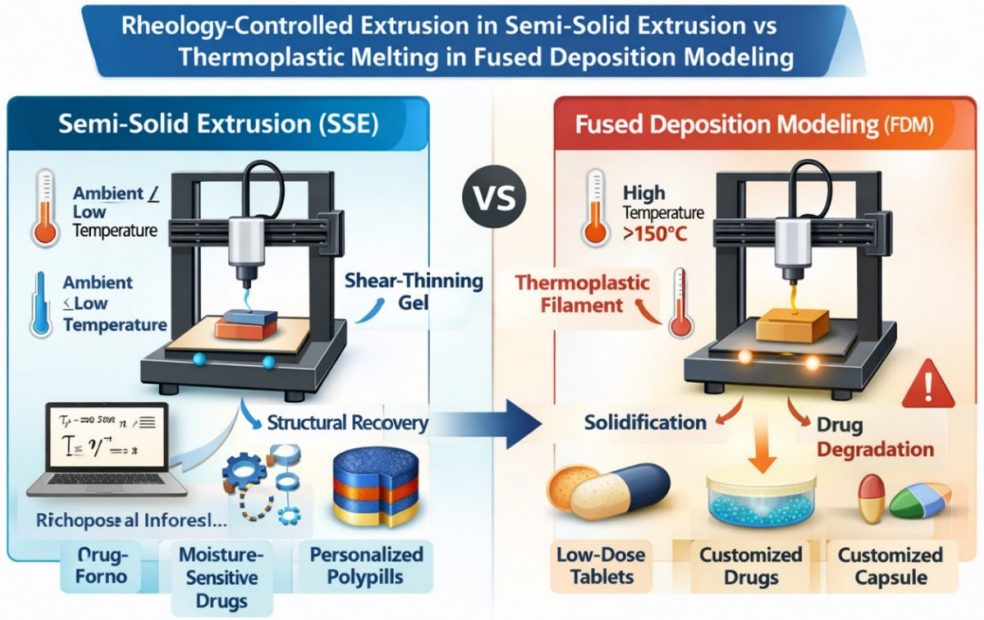

Fig 2: Comparative Mechanistic Pathways in SSE vs FDM

10.0 Standardization Framework for Rheology-Guided SSE Fabrication

The absence of harmonized rheological benchmarks remains a primary obstacle to widespread adoption of SSE in pharmaceutical manufacturing. A structured standardization framework must integrate critical material attributes (CMAs), critical process parameters (CPPs), and critical quality attributes (CQAs) under a quality-by-design paradigm [74].

Critical material attributes include viscosity at defined shear rates, yield stress, flow behaviour index (n), storage modulus (G'), and thixotropic recovery percentage. These parameters should be measured under standardized temperature and shear history conditions to ensure reproducibility. Establishing acceptable specification ranges derived from statistically validated experimental data provides predictive assurance of print fidelity and dose precision [75].

Critical process parameters encompass extrusion pressure, nozzle diameter, printing speed, and environmental conditions such as humidity. Mathematical modelling linking rheological constants to extrusion pressure allows predictive adjustment of CPPs. For example, real-time monitoring of pressure deviations beyond defined thresholds can trigger corrective action to maintain consistent volumetric flow rates [76].

Critical quality attributes include dimensional accuracy, mechanical strength, drug content uniformity, and dissolution kinetics. Multivariate regression and design-of-experiments approaches enable correlation of CMAs and CPPs with CQAs. Recent literature demonstrates that response surface modelling effectively identifies optimal rheological windows minimizing dimensional deviation and maximizing uniformity [77].

Regulatory considerations necessitate reproducibility, traceability, and documentation

of rheological characterization. Agencies increasingly emphasize mechanistic understanding rather than empirical optimization. Demonstrating consistent rheology-performance relationships supports validation protocols and facilitates technology transfer between facilities [78].

Integration of digital twins and computational fluid dynamics simulations further enhances standardization. Predictive modelling platforms incorporating Carreau–Yasuda or Herschel–Bulkley equations allow simulation of extrusion behaviour under varying conditions. Such digital frameworks align with Industry 4.0 and decentralized pharmaceutical production strategies [79].

The proposed standardization framework establishes rheology as a quantifiable, predictive cornerstone of SSE fabrication. Adoption of harmonized measurement protocols and statistical validation methodologies will accelerate regulatory confidence and clinical implementation.

11.0 Clinical Translation

Clinical translation of SSE-fabricated personalized dosage forms depends on demonstrable safety, efficacy, and reproducibility. Personalized medicine demands precise dose tailoring for populations such as paediatrics, geriatrics, and patients with polypharmacy requirements. Rheology-driven optimization ensures accurate dosing, consistent release profiles, and structural robustness suitable for clinical handling [80].

Hospital-based decentralized manufacturing represents a key translational opportunity. SSE printers installed within pharmacy departments can fabricate patient-specific doses on demand. However, such implementation requires validated rheological specifications and quality assurance systems. Integration of inline weight verification and spectroscopic analysis strengthens compliance with pharmacopeial standards [81].

Clinical advantages of SSE include the ability to fabricate multi-compartment constructs, modulate release profiles, and accommodate drug combinations without extensive industrial infrastructure. Additionally, low-temperature processing minimizes degradation risk, expanding therapeutic applicability to biologics and heat-sensitive molecules [82].

Challenges remain in scaling from bench to bedside. Variability in environmental conditions may influence rheology and extrusion consistency. Therefore, climate-controlled printing environments and operator training are essential. Furthermore, long-term stability studies under International Council for Harmonisation conditions must validate structural and chemical integrity over defined storage periods [83].

Economic considerations also influence translation. While SSE reduces material waste and supports small-batch manufacturing, initial equipment and validation costs must be justified through improved patient outcomes and workflow efficiency. Emerging cost-effectiveness analyses suggest that personalized dosing reduces adverse drug reactions and improves adherence, potentially offsetting implementation costs [84].

Ultimately, successful clinical translation requires interdisciplinary collaboration between pharmaceutical scientists, clinicians, regulatory bodies, and engineers. Rheology-driven standardization provides a scientifically robust foundation to support such integration.

12.0 Future Scope

Future research directions in rheology-driven SSE optimization encompass advanced material design, real-time monitoring technologies, and artificial intelligence integration. Development of smart polymers exhibiting stimuli-responsive rheology may enable adaptive extrusion behaviour tailored to specific geometries or release requirements [85].

Machine learning algorithms trained on rheological and printing datasets could predict optimal parameter combinations, reducing experimental burden and accelerating formulation development. Data-driven modelling approaches integrating shear-thinning indices, yield stress values, and structural recovery metrics may generate predictive printability maps

Microstructural characterization using advanced imaging modalities will refine understanding of pore architecture and its influence on dissolution kinetics. Coupling rheological modelling with diffusion simulations may yield comprehensive predictive platforms for personalized dosage design [86, 87].

Establishing international consensus on rheological characterization methods will enhance comparability across research centers and manufacturing sites [88].

In conclusion, rheology-driven optimization represents a transformative strategy for advancing semi-solid extrusion toward standardized, high-precision personalized pharmaceutical manufacturing. By correlating viscosity, yield stress, shear behaviour, structural stability, and therapeutic performance, this manuscript provides a mechanistic and translational roadmap for future development.

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