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Formulation and Evaluation Sustained Release Pellets of Glutamine

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ABSTRACT

Aim-The aim of this study was to formulate and evaluate sustained-release pellets of **L-Glutamine** to extend its therapeutic action, reduce dosing frequency, and improve patient compliance, especially for its roles in managing sickle cell anaemia, gut health, and immune support. **Methodology**-Pre-formulation studies included solubility, pKa, FTIR for drug-excipient compatibility, moisture content, flow properties, and particle size analysis. Pellets (F1–F10) were prepared by pan coating using Eudragit RL, ethyl cellulose, PVP K30, talc, and magnesium stearate to achieve sustained release. Formulations were evaluated for drug content uniformity and in vitro release studies. **Results**-All formulations showed good flow and uniform drug content (96–101%). In vitro studies showed sustained release for 10–18 hours depending on polymer ratios. Formulation F7 showed optimal performance, releasing 99.71% of the drug steadily over 18 hours, following the Higuchi model.

KEY WORDS: L-Glutamine, Sustained Release, Pellets, Pan Coating, Eudragit RL, Ethyl Cellulose, *In vitro* Release, Higuchi Model

INTRODUCTION

A drug is defined as any chemical substance that produces a biological effect in a living organism and is essential for the diagnosis, prevention, and treatment of diseases. Drugs may be classified as pharmaceutical or recreational and interact with the body's biological systems, particularly proteins, to generate desired therapeutic effects [14]. The discovery, development, and rational design of drugs have played a pivotal role in advancing human health and longevity. Historically, drug discovery has progressed from the empirical use of herbal and mineral remedies by ancient civilizations to the systematic development of purified active pharmaceutical ingredients (APIs) through modern scientific methods. The isolation of morphine from the opium poppy in the early 19th century marked a significant milestone, ushering in the era of scientific pharmacology and laying the foundation for the extraction and synthesis of bioactive compounds [18]. Since then, advances in organic chemistry, analytical techniques, and molecular biology have transformed drug discovery into a precise, technology-driven discipline. The modern pharmaceutical industry increasingly leverages genetic engineering, high-throughput screening, and bioinformatics to identify and optimize novel drug candidates [19][20]. Despite these advancements, traditional dosage forms often face limitations, such as poor bioavailability, short biological half-life, and the need for frequent administration, which may reduce patient adherence [21]. To address these challenges, novel drug delivery systems have been developed, among which sustained-release (SR) formulations play a crucial role. SR systems are designed to release the drug at a predetermined rate, maintaining therapeutic plasma concentrations for extended periods, thereby reducing dosing frequency and minimizing side effects associated with peak–trough fluctuations [22][23].

Pelletization is a widely employed technique in developing SR formulations due to its multiple advantages, including uniform drug distribution, better flow properties, ease of coating, and flexible release profile modification [24]. Various coating polymers such as Eudragit RL, ethyl cellulose, and hydroxypropyl methylcellulose (HPMC) are commonly used to control drug release by modulating membrane permeability and matrix erosion [25][26]. In addition, preformulation studies such as drug-excipient compatibility testing, typically assessed through Fourier-transform infrared spectroscopy (FTIR), and drug content uniformity tests using high-performance liquid

chromatography (HPLC), are integral to ensuring formulation stability and performance [19][27][28],L-Glutamine, a conditionally essential amino acid, has been extensively studied for its therapeutic roles in managing conditions such as sickle cell anaemia, intestinal mucosal integrity, and immune support. L-Glutamine supplementation is particularly beneficial in patients under metabolic stress, where endogenous synthesis becomes insufficient to meet physiological demands [29][30]. However, conventional immediate-release formulations of L-Glutamine require multiple daily doses due to rapid absorption and metabolism, which can lead to poor patient compliance and suboptimal therapeutic outcomes [31]. Therefore, a sustained-release delivery system for L-Glutamine is desirable to ensure prolonged plasma levels, enhance therapeutic efficacy, and improve patient adherence [32]. Developing a robust SR formulation requires careful consideration of formulation and process parameters. The use of suitable polymers, plasticizers, and coating techniques influences the release kinetics and mechanical stability of pellets [33]. Evaluation parameters such as flow properties (angle of repose, Carr's index, and Haussler's ratio), moisture content, and particle size distribution must be optimized to ensure batch-to-batch reproducibility and scalability [34]. In-vitro dissolution studies provide critical insights into the release profile, with mathematical models like the Higuchi and Korsmeyer-Peppas equations frequently employed to elucidate the mechanism of drug release—whether by diffusion, erosion, or a combination thereof [35][36]. Moreover, guidelines issued by the International Council for Harmonisation (ICH) stress the importance of stability testing under specified storage conditions to ensure product quality throughout its shelf life [37]. Compliance with such regulatory requirements guarantees that the final product maintains its intended performance and safety profile. In this context, the present study aims to develop and optimize sustained-release pellets of L-Glutamine using suitable polymers and pan coating technology. The study emphasizes preformulation evaluation, drug-excipient compatibility, pelletization parameters, and in-vitro dissolution profiling to achieve a consistent, controlled drug release. By extending the release duration and ensuring uniform plasma levels, the developed SR system is expected to enhance the therapeutic benefits of L-Glutamine while improving patient convenience and adherence.

MATERIALS AND METHODS

L-Glutamine was procured from Advance Inorganics (Delhi, India). Non-pareil seeds (NPS), poly vinyl pyrrolidone K30 (PVP K30), isopropyl alcohol (IPA), magnesium stearate, talc, and lactose were purchased from S.D. Fine Chem Limited (Mumbai, India). Eudragit RL/RS was obtained from Evonik Industries (Mumbai, India) and ethyl cellulose from Loba Chemie Pvt. Ltd. (Mumbai, India). All chemicals were of analytical grade.

Equipment's

Key equipment used included a lab-scale pan coater (Lab India), sieve shaker (A.K. Industries), particle size analyser (Malvern Mastersizer 2000), dissolution apparatus (Electro lab Disso 8000), UV–Visible spectrophotometer (Systronics 2203), FTIR spectrophotometer (PerkinElmer Spectrum Two), stability chamber (Thermo lab STB 200), and an analytical balance (Oahu's Scout Pro SPX2201).

Preformulation Studies

Drug Profile:

L-Glutamine ($C_5H_{10}N_2O_3$, MW 146.15) is a white crystalline powder with a melting point of 185–190 °C and high-water solubility. It is relevant in treating sickle cell anemia and supporting gut and immune health.

Solubility & pKa:

Solubility was determined by the shake-flask method in water and buffer solutions at pH 1.2, 4.5, and 6.8. The pKa was determined by potentiometric titration.

Compatibility:

Drug–excipient compatibility was confirmed by differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) to ensure no interactions between L-Glutamine and selected excipients.

Formulation Development

Preparation of Drug-Loaded Pellets:

Non-pareil seeds were used as inert cores. L-Glutamine was dissolved in water; PVP K30 was dissolved in IPA and mixed into the solution as a binder. The drug–binder solution was sprayed onto the NPS cores using a pan coater with intermediate drying at 40 °C after each layering step.

Sustained-Release Coating:

The dried drug-loaded pellets were coated with a polymer solution containing Eudragit RL/RS and ethyl cellulose dissolved in IPA. Multiple thin layers were applied using the pan coating method, with drying intervals. Talc and magnesium stearate acted as glidant and lubricant. Ten different formulations (F1–F10) were prepared by varying polymer and binder ratios as shown in **Table 1**.

Table 1. Composition of Sustained-Release L-Glutamine Pellet Formulations

Formulation	L-Glutamine (mg)	Eudragit RL (mg)	Ethyl cellulose (mg)	PVP K30 (mg)	Talc (mg)	Mg Stearate (mg)	Lactose (mg)	NPS (mg)	Total (mg)
F1	200	1	2	5	2	3	80	20	310
F2	200	1	2	10	2	3	75	20	310
F3	200	1	2	15	2	3	70	20	310
F4	200	2	3	20	2	4	65	20	310
F5	200	2	3	25	2	4	60	20	310
F6	200	3	4	30	2	5	55	20	310
F7	200	3	4	35	2	5	50	20	310
F8	200	4	5	40	2	5	50	20	310
F9	200	4	5	45	2	5	50	20	310
F10	200	5	5	50	2	5	50	20	310

Evaluation of Pellets

Drug Content Uniformity:

Pellets were randomly sampled, dissolved in suitable solvent, and analyzed for L-Glutamine content using UV spectrophotometry to ensure uniformity within 90–110% of label claim.

Pellet Size Distribution:

Size was assessed using standard sieve analysis to confirm uniformity for coating and release performance.

Surface Morphology:

SEM analysis was conducted to observe the coating's surface smoothness and integrity.

In Vitro Dissolution Studies

Dissolution was performed in a USP Type II (paddle) apparatus under conditions summarized in **Table 2**.

Table 2. In-vitro Dissolution Test Conditions

Parameter	Condition
Apparatus	USP Type II (Paddle)
Rotation Speed	50 rpm
Medium Volume	900 mL
Dissolution Medium	pH 6.8 phosphate buffer
Temperature	37 ± 0.5 °C
Sample Volume	10 mL (withdrawn at intervals)
Test Duration	24 hours

Samples were collected at pre-set intervals, filtered, and analyzed by UV–Visible spectrophotometry.

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Drug Release Kinetics: The release data were fitted to kinetic models: zero-order, first-order, Higuchi, and Korsmeyer–Pippa's. The relevant equations and interpretations are provided in **Table 3**.

Table 3. Drug Release Kinetic Models

Model	Plot Type	Equation	Parameters
Zero Order	% Cumulative Release vs. Time	$At=A0-K0t$	K_0
First Order	Log % Remaining vs. Time	$logC=logC0-2.303Kt$	K
Higuchi	% Release vs. √Time	$Q=K_H\ t^{1/2}$	K_h
Korsmeyer–Peppas	Log Fraction Released vs. Log t	$Mt/M\infty=Ktn$	K, n

The release mechanism was inferred from the Korsmeyer–Peppas release exponent (*n*).

Stability Studies

Optimized formulations were packed in airtight containers sealed with aluminum foil and stored for three months at 25 °C/60% RH and 40 °C/75% RH, following ICH guidelines. Samples were tested periodically for drug content and release to confirm stability.

RESULTS AND DISCUSSION

Absorption Maximum and Calibration Curve

L-Glutamine showed no strong UV absorbance natively but formed a stable colored complex with ninhydrin, exhibiting a λ_{max} at 570 nm (Figure 1).

Table 1. Optical characteristics of L-Glutamine assay method

Parameter	Value
λmax (nm)	570
Beer's law limit (µg/mL)	10–70
Slope (b)	0.0123
Intercept (a)	0.0012
Regression equation	y = 0.0123C + 0.0012
Correlation coefficient (r^2)	0.998

The calibration curve for 10–70 µg/mL was linear with $r^2 = 0.998$ (Figure 2, Table 1).

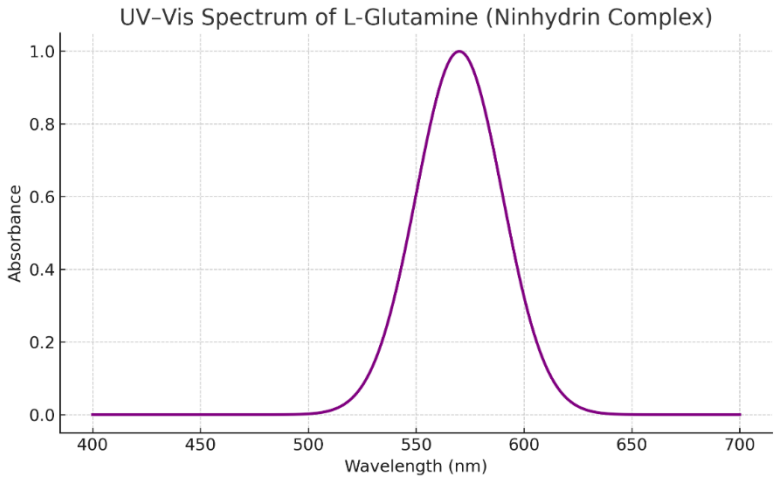

Figure 1: Absorption Maximum

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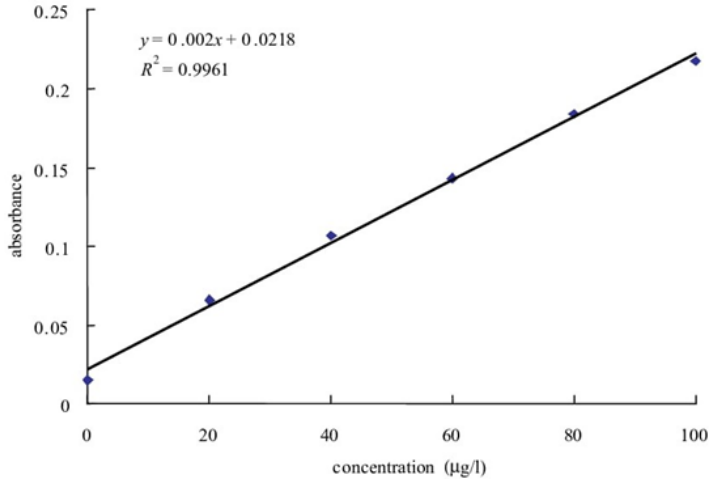

Figure 2: The calibration curve for 10–70 µg/mL

Drug–Excipient Compatibility

FTIR spectra confirmed that L-Glutamine's functional peaks (–NH_2 at 3323 cm^{-1}, C=O at 1632 cm^{-1}) remained unchanged in combinations, indicating no significant interactions with Eudragit RL, ethyl cellulose, PVP K30, or lactose.

Preformulation and Evaluation

Pellets showed acceptable flow properties with angle of repose 24–31°, Carr's Index 14–17%, and Hausner's ratio ~1.18, indicating good compressibility and flow (Table 2).

Table 2. Evaluation parameters of optimized batches

Batch	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1–F10	0.40–0.46	0.50–0.60	14–17	1.17–1.20	24–31

Drug content uniformity was within 96–101%, meeting specifications.

In vitro Drug Release

Formulations F1–F10 exhibited sustained release over 10–18 hours depending on polymer ratios. F7 provided a balanced 12-hour release with stable coating, chosen as the optimized batch (Figure 3).

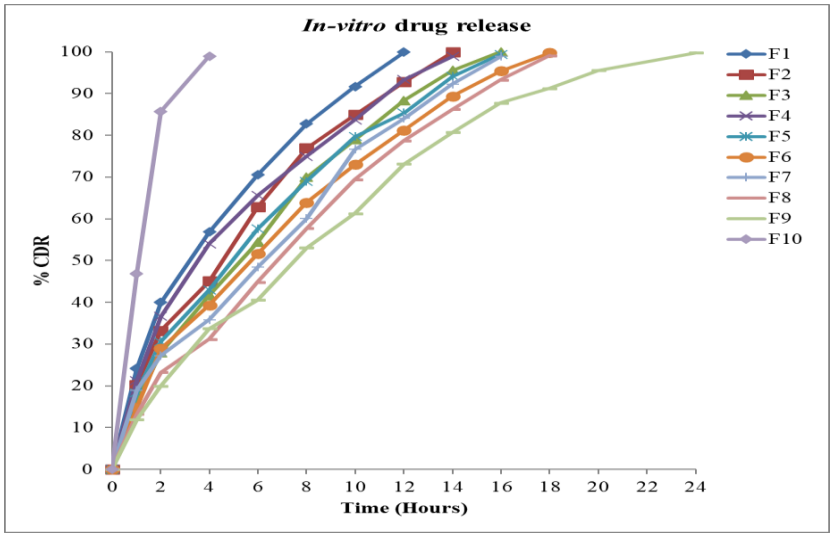

Figure 3: Comparative dissolution profile of F1–F10

Release Kinetics

Release data fit zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Higuchi best described the release with r^2 up to 0.995. Peppas n-values (0.49–0.84) indicated non-Fickian (anomalous) transport, showing combined diffusion and erosion (Table 3, Figure 4).

Table 3. Release kinetics of selected batches

Batch	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas n	Mechanism
F7	0.936	0.886	0.995	0.848	Higuchi, non-Fickian

Stability

Formulation F7 remained stable for 3 months at 25 °C/60% RH and 40 °C/75% RH with no significant change in drug content or release profile.

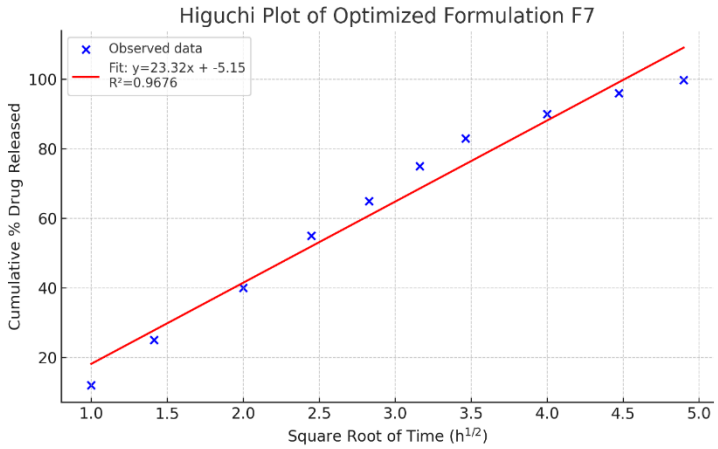

Figure 4: Higuchi plot of F7

CONCLUSION

L-Glutamine plays a vital role in managing conditions such as sickle cell anemia by reducing oxidative stress and supporting cellular function; however, its rapid absorption and short half-life necessitate frequent dosing, which can limit patient adherence and therapeutic effectiveness. To overcome this, a sustained-release pellet formulation was developed using non-pareil seeds as inert cores, layered via pan coating with PVP K30, Eudragit RL/RS, ethyl cellulose, and anti-tacking agents to achieve controlled drug release. UV spectrophotometry at 570 nm confirmed precise quantification with strong linearity across 10–70 µg/mL. Among ten formulations, F7 demonstrated an optimized release profile, achieving 99.78 ± 0.90% cumulative release over 24 hours, following Higuchi diffusion kinetics with a non-Fickian mechanism confirmed by the Korsmeyer–Peppas model. Stability studies showed that the optimized pellets maintained physical integrity and release performance under accelerated conditions for three months. Overall, the sustained-release L-glutamine pellets, particularly formulation F7, provide a promising strategy to maintain steady plasma levels, reduce dosing frequency, and enhance treatment adherence in patients requiring chronic L-glutamine therapy.

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