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Development and in vitro characterization of epigallocatechin gallate-liquisolid compacts for oral drug delivery system

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Abstract
This study focused on developing liquisolid formulations of Epigallocatechin gallate (EGCG) to enhance its solubility, dissolution, and bioavailability. EGCG was formulated into six liquisolid systems (F-1 to F-6) using propylene glycol as a solvent, Avicel PH 102 as the carrier, and Aerosil 200 as the coating material. The formulations were prepared based on a mathematical model to optimize the carrier-to-coating ratio and liquid load factor. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) confirmed the absence of significant drug-excipient interactions. Flowability analysis showed that the formulations had suitable compressibility and flow properties for direct compression into tablets. Drug release studies in Simulated Gastric Fluid (SGF, pH 1.2) and Simulated Intestinal Fluid (SIF, pH 6.8) demonstrated that F-3 had the fastest release profile, reaching near 78% within 60 minutes, outperforming the direct compressible tablet (DCT) in both media. Scanning electron microscopy (SEM) revealed uniform drug distribution within the carrier matrix. The study concluded that the liquisolid approach, particularly formulation F-3, offers a promising strategy for improving the solubility and bioavailability of EGCG, making it a suitable candidate for oral delivery systems aimed at achieving rapid therapeutic effects.
Keywords: Liquisolid formulation, Epigallocatechin gallate (EGCG), Solubility enhancement, Drug release profile, Oral bioavailability

Introduction

Liquisolid compacts are considered to be one of the potential advanced formulations for improving solubility and bioavailability of poorly water-soluble drugs. This technique refers to the conversion of liquid medicines or substances in the form dissolved/suspended into non-volatile solvents, to free flowing and compressible powders. When combined with specific carrier and coating agents, the liquid medication is encapsulated within powders, which absorb the liquid without behaving as a solid dosage. The resulting formula can then be tableted or encapsulated, thus providing a solid dosage form with several advantages over conventional approaches. Increased bioavailability of poorly water-soluble drugs as a result of enhanced dissolution rates, wettability and surface area

available for drug release[12,18].

The concept of improving dissolution rates by the liquisolid compacts involves maintaining the drug in a solubilized or molecularly dispersed state following its conversion to solid state. The drug is present in liquid form which is easily available for absorption i.e. it interacts with Gastrointestinal fluids quicker than the solid formulations. The most important carriers are the large amount of carrier (e.g. Avicel pH 102 microcrystalline cellulose) and coating agents (such as colloidal silicon dioxide) (Aerosil 200), used by liquisolid systems to transform liquid formulations into dry powders suitable for direct compression. The carrier absorbs the liquid, while the coating material helps prevent the formation of agglomerates, thereby ensuring that the powder remains free-flowing. This approach not only facilitates better drug dissolution but also enhances the uniformity of dosage units, leading to more consistent therapeutic outcomes[6, 10, 15 and 19].

Epigallocatechin gallate (EGCG) is a major catechin found in green tea, known for its wide range of pharmacological activities, including potent antioxidant, anti-inflammatory, anti-cancer, and cardioprotective effects. These properties make EGCG a promising candidate for therapeutic use in various chronic conditions, such as cardiovascular diseases, cancer, and metabolic disorders. However, EGCG's clinical application is greatly hindered by its poor aqueous solubility and low oral bioavailability. EGCG has a tendency to degrade under physiological conditions, especially in the acidic environment of the stomach, leading to reduced stability and a lower fraction of the dose reaching systemic circulation. As a result, despite its beneficial properties, the therapeutic potential of EGCG remains underutilized due to challenges in formulating it into effective oral dosage forms.

The rationale for using liquisolid compacts as a delivery system for EGCG lies in their ability to address these solubility and stability challenges. Liquisolid compacts can enhance the dissolution rate of EGCG by incorporating it into a liquid vehicle like propylene glycol, which acts as a solubilizing agent. This increases the apparent solubility of EGCG, allowing for greater dissolution when the formulation comes into contact with gastrointestinal fluid [7]. Furthermore, by converting the solubilized EGCG into a solid powder, the liquisolid technique helps protect the compound from degradation, ensuring that a higher concentration reaches the site of absorption. This method has the potential to significantly enhance the pharmacokinetic profile of EGCG, making it more effective for clinical use [9, 13 and 19].

This study aims to develop and characterize EGCG-loaded liquisolid formulations to overcome the solubility limitations of EGCG and improve its bioavailability. By systematically optimizing formulation parameters such as the carrier-to-coating ratio and liquid load factor, the study seeks to achieve a formulation with optimal flow properties, compressibility, and dissolution rates. Additionally, the study evaluates the physical and chemical stability of the formulated liquisolid compacts, ensuring that the enhanced solubility does not compromise the integrity of EGCG. Ultimately, this research explores the potential of liquisolid technology as a viable strategy for delivering EGCG in a stable and bioavailable form, contributing to more effective therapeutic outcomes and broader applications of EGCG in health and medicine. Through this work, liquisolid compacts are positioned as an innovative solution for the formulation challenges associated with poorly soluble active pharmaceutical ingredients like EGCG, emphasizing their potential to transform the landscape of oral drug delivery.

Material and Methods

Drugs, Chemicals and Reagents

In this study, a variety of materials were employed to develop and optimize a liquid-solid system. Epigallocatechin gallate (EGCG), obtained from Resenta Pharma, India, served as the model drug due to its challenging solubility profile. Avicel PH 102, sourced from Sigma Aldrich, India was used as a carrier material, known for its excellent compressibility and flow properties, which are critical in solid dosage formulation. Aerosil 200, supplied by Sigma Aldrich, India, functioned as a coating agent to enhance the flowability of the powders, making it easier to process into tablets. Indion 414, provided by Ion Exchange Ltd., India, was incorporated as a super disintegrant to improve the dissolution rate, thereby enhancing the release profile of Epigallocatechin gallate (EGCG) from the formulated tablets. Propylene glycol, acquired Sigma Aldrich, India, was utilized as a non-volatile solvent, aiding in the solubilization of Epigallocatechin gallate (EGCG) within the liquid-solid matrix. Magnesium stearate, sourced from LobaChemie, India acted as a lubricant, facilitating the tableting process by reducing friction during compression. Dihydrogen phosphate, obtained from Merck, Germany, was used in the preparation of buffer

solutions required for dissolution studies, ensuring accurate pH conditions for in vitro testing. All other reagents and chemicals used throughout the study were of analytical grade, ensuring precision and consistency in the experimental procedures. The careful selection of these materials contributed significantly to the formulation's stability, compressibility, and enhanced bioavailability.

Mathematical Modelling for Design of Liquisolid Compacts

The formulation design of liquisolid compacts for Epigallocatechin gallate (EGCG) was based on the mathematical model described earlier [1]. This model provides a systematic approach for optimizing the ratios and quantities of excipients to ensure desirable flow properties and compressibility in the liquisolid systems.In this study, propylene glycol served as the liquid vehicle, while Avicel pH 102 (Microcrystalline Cellulose-MCC) and Aerosil 200 functioned as the carrier and coating materials, respectively. The concentration of EGCG in propylene glycol was evaluated at 20% w/w, 30% w/w, and 40% w/w. To optimize the formulation properties, the carrier-to-coating ratio (R) was selected as 10:1, 15:1, and 20:1. These ratios were chosen based on their potential to balance flowability and compressibility of the resultant powders.The excipients ratio (R) is defined by the relationship between the weights of the carrier (Q) and the coating (q) materials as follows:

$R=Q/q$ ---1

The liquid load factor (Lf) represents the weight ratio of the liquid medication (W) to the carrier powder (Q) in the liquisolid system. It is a critical factor in achieving an acceptably flowing and compressible powder and is defined by:

$Lf=W/Q$ ---2

The flowable liquid retention potential (Φ value) of the carrier and coating materials was used to calculate the necessary quantities of each ingredient. The relationship between the powder excipient ratio (R) and the liquid load factor (Lf) is expressed as:

$Lf=\Phi carrier+\Phi coating\ (1/R)$ ---3

In this equation, Φcarrier and Φcoating represent the Φ values of Avicel PH 102 and Aerosil 200, respectively. These values are crucial for determining the maximum amount of liquid that the powders can retain while maintaining flowability. The process begins with calculating the Lf using Equation (3) based on the chosen carrier-to-coating ratio (R). Once the Lf is determined, Equation (2) is used to calculate the required amount of carrier. Finally, the weight of the coating material is determined using Equation (1).The application of this model ensures that the EGCG-based liquisolid system is formulated with optimal ratios, enhancing the solubility and stability of EGCG while ensuring the powders remain easy to handle and compress into solid dosage forms. This method allows for a tailored approach to developing liquisolid systems that maximize the therapeutic efficacy of EGCG

Fabrication of a directly compressible tablet (DCT)

The preparation of a directly compressible tablet (DCT) containing Epigallocatechin gallate (EGCG) involved formulating a conventional physical mixture without the addition of any non-volatile liquid vehicle. The DCT formulation used 40 mg of EGCG, 200 mg of Avicel pH 102 as a directly compressible filler, 10 mg of Aerosil 200 as a flow-enhancing agent, 5% super disintegrant to facilitate rapid tablet disintegration, and 1% lubricant to reduce friction during compression. All the ingredients were thoroughly mixed in a mortar for 10 minutes to ensure uniform distribution of the components. The resulting mixture was then directly compressed into tablets using a Korsch EKO tablet compression machine (Germany). This method enabled the formation of tablets with consistent weight and uniformity, suitable for further evaluation of their physical and pharmacological properties [8, 14].

Solubility determination

Saturated solutions of Epigallocatechin gallate (EGCG) were prepared by adding an excess amount of the drug to the solvent, propylene glycol. The mixtures were shaken in a water shaker bath for 48 hours at 25°C, ensuring constant vibrations to facilitate maximum solubility. After the equilibration period, the solutions were filtered through a 0.45-micron filter to remove any undissolved particles. The filtered solutions were then appropriately diluted and analysed using a UV-visible spectrophotometer (Carry win UV, Varian, Australia) at a wavelength of 298 nm to determine the solubility concentration. In addition to the solubility determination in propylene glycol, the saturation solubility of EGCG was also evaluated in simulated gastric fluid (SGF) with pH 1.2 and simulated intestinal fluid (SIF) with pH 6.8. This assessment provided insights into the solubility behaviour of EGCG under

conditions that mimic the gastrointestinal environment, which is crucial for predicting the drug's absorption profile upon oral administration.

Evaluation of liquisolid formulations

Flow Properties:

The flowability of the liquisolid powders was assessed through parameters like angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio [16].

Angle of Repose: This measures the flow characteristics of the powder. A lower angle indicates better flowability.

Bulk and Tapped Density: These values help calculate compressibility indices, which provide insights into the packing ability of the powders.

Carr's Index and Hausner's Ratio: These indices were calculated to assess the flowability and compressibility of the liquisolid powders. Carr's index below 15% and a Hausner's ratio below 1.25 indicate good flow properties.

Differential Scanning Calorimetry (DSC):

DSC was employed to study the thermal behaviour of EGCG in the liquisolid formulations. This technique provides information about the melting point, crystallinity, and thermal stability of the drug.The DSC thermograms of pure EGCG, the individual excipients (e.g., Avicel pH 102, Aerosil 200), and the liquisolid formulations were compared. The disappearance or shift of the characteristic melting peak of EGCG in the liquisolid system indicates potential interaction between the drug and the excipients, suggesting the transformation of EGCG into an amorphous state, which could enhance its solubility [5].

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR analysis was used to investigate potential chemical interactions between EGCG and the excipients in the liquisolid formulations. This technique identifies characteristic functional groups and detects any shifts or changes in the peak positions, which may indicate interactions.The FTIR spectra of pure EGCG, excipients, and the liquisolid formulations were recorded, focusing on key absorption bands, such as those representing –OH, –NH, and aromatic groups in EGCG. Any significant changes or shifts in the spectra of the liquisolid formulations compared to pure components could suggest hydrogen bonding or other interactions, which may impact the stability and solubility of EGCG [2, 11].

X-ray Diffraction (XRD):

X-ray diffraction was carried out to investigate the crystalline or amorphous state of EGCG in the liquisolid formulations. The degree of crystallinity, can be determined by profile XRD patterns and is important due to it providing a linkage to the solubility and dissolution behaviour of the drug. Diffraction patterns of pure EGCG, individual excipients and liquisolid formulations were recorded. Usually, pure EGCG peaks showed a sharp profile characterized by single well-resolved signals associated with its crystalline phase nature. Complete disappearance or decreasing intensity of these peaks in the liquisolid formulation is indicative of decrease in crystallinity or conversion in amorphous form. Form the result of analysis, improved solubility and faster dissolution rates of EGCG in the liquisolid system are often linked to this change [2,5].

Scanning Electron Microscopy (SEM):

SEM analysis was conducted to visualize the surface morphology and particle size of the liquisolid formulations. This technique provides high-resolution images, enabling the examination of the physical appearance and structural characteristics of the formulations.SEM images of pure EGCG, the carrier and coating materials, and the liquisolid formulation were compared. The images provide insight into the surface texture, particle agglomeration, and the distribution of EGCG within the formulation. A smooth and uniform surface indicates proper incorporation of EGCG into the carrier matrix, while any visible crystalline structures could suggest incomplete solubilization or dispersion within the formulation[2,5].

Uniformity of Weight:

Tablets prepared from the liquisolid systems were evaluated for uniformity of weight to ensure consistent drug dosing. Twenty tablets were weighed individually, and the average weight was calculated. The deviation from the average weight was determined, with acceptable limits being within ±5% for tablets [17].

Hardness and Friability:

Hardness: This was tested using a hardness tester to ensure that the tablets could withstand handling and

transportation without breaking. Adequate hardness also ensures that the tablets do not disintegrate prematurely[17].

Friability: The friability test was conducted using a friabilator. A batch of pre-weighed tablets was rotated for a specified time, and the weight loss was calculated. A friability value below 1% indicates that the tablets have sufficient mechanical strength[17].

Disintegration Time:

The disintegration time of the tablets was tested using a disintegration apparatus in simulated gastric fluid (pH 1.2) at 37°C. This test ensures that the tablets break down into smaller particles within a suitable time frame to allow for rapid drug release in the gastrointestinal tract[3,17].

Drug Content Uniformity:

The uniformity of EGCG content in the tablets was determined by crushing ten tablets, taking a specific amount of powder equivalent to one tablet, and dissolving it in a suitable solvent. The solution was then filtered, diluted, and analyzed using a UV-visible spectrophotometer at 298 nm. The drug content should be within 90-110% of the labeled claim to ensure dose uniformity [3].

In vitro Dissolution Studies:

The dissolution profile of EGCG from the liquisolid tablets was studied using a USP Type II dissolution apparatus (paddle method) in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8). The release rate of EGCG was monitored over time, and samples were collected at predetermined intervals. These samples were filtered, diluted, and analysed by UV-visible spectrophotometry at 298 nm. The dissolution studies helped in comparing the release rate of EGCG from liquisolid formulations with that of conventional or directly compressible tablets. Enhanced dissolution indicates improved bioavailability potential for the liquisolid formulations [4].

Statistical analysis

The statistical analysis of the data obtained from the evaluation of liquisolid formulations containing Epigallocatechin gallate (EGCG) was essential to ensure the reliability and validity of the results. Data from different evaluation parameters, such as drug content, dissolution profile, disintegration time, and physical characteristics (e.g., hardness and friability), were presented as mean ± standard deviation (SD). This approach provided an accurate representation of the variation within each set of measurements, allowing for a clearer interpretation of the data. To compare the performance of different formulations, Analysis of Variance (ANOVA) was used. This statistical test helped to determine whether there were significant differences between the means of various formulations, such as those with different EGCG concentrations or carrier-to-coating ratios. A p-value of less than 0.05 was considered statistically significant, indicating that the observed variations between the formulations were unlikely to have occurred by chance. When ANOVA indicated overall significance, post-hoc tests, such as Tukey's Honest Significant Difference (HSD) test, were conducted to pinpoint which specific groups differed significantly from each other. The dissolution profiles of the liquisolid formulations were also analyzed to compare the release rates of EGCG. By evaluating the dissolution data statistically, it was possible to assess which formulations provided enhanced drug release, thus offering potential improvements in bioavailability. The statistical analysis played a crucial role in guiding the formulation optimization process, ensuring that the selected formulation offered the best balance between stability, dissolution rate, and overall efficacy.

Results and discussion

Design of liquisolid systems using mathematical model

The table presents the composition of six different formulations (F-1 to F-6) of Epigallocatechin gallate (EGCG) prepared using a mathematical model for liquisolid systems. Each formulation contains a constant 35 mg dose of EGCG, with varying parameters that influence the overall formulation characteristics. The drug concentration remains constant at 25% w/w across all formulations, ensuring that the differences between the formulations arise from variations in the carrier-to-coating ratios, liquid load factors, and other excipient quantities rather than the amount of EGCG itself. The carrier-to-coating ratio (R) varies among the formulations, ranging from 10 in F-4 to 24 in F-3. This ratio determines the balance between the carrier (AvicelpH 102) and the coating (Aerosil 200) agents. A lower ratio, such as F-4 with R = 10, indicates a higher proportion of coating material relative to the carrier, while a higher ratio, such as F-3 with R = 24, indicates a greater amount of carrier. The ratio affects the

flowability and compressibility of the liquisolid systems, as well as the amount of each excipient required.
The liquid load factor (Lf) represents the ability of the carrier and coating materials to hold a certain amount of liquid vehicle while maintaining good flow properties, and it is inversely related to the carrier ratio. Formulation F-4, with the lowest carrier ratio (R = 10), has the highest Lf (0.491), meaning it can retain more liquid medication. Conversely, F-3, with the highest carrier ratio (R = 24), has the lowest Lf (0.298). These varying Lf values influence the amount of carrier required to produce a flowable powder, affecting the overall weight and volume of the final tablet.
Each formulation contains a consistent amount of 140 mg of propylene glycol, which serves as the non-volatile liquid vehicle for solubilizing EGCG. This consistency ensures that differences in Lf and carrier ratios directly impact the required amounts of carrier and coating materials. As the carrier ratio (R) increases, the amount of carrier (Avicel PH 102) increases, while the amount of coating (Aerosil 200) decreases. For instance, F-3 has 469.93 mg of Avicel pH 102 and 19.58 mg of Aerosil 200, compared to F-4 with 285.13 mg of Avicel pH 102 and 28.51 mg of Aerosil 200. The balance between the carrier and coating is critical for maintaining good flow properties and compressibility during tablet manufacturing. The amount of disintegrant (Indion 414) varies slightly across formulations, ranging from 35 mg in F-4 to 42 mg in F-3, facilitating the breakdown of tablets to ensure efficient drug release in the gastrointestinal tract. The lubricant (Mg Stearate) amounts also vary slightly, ranging from 6.0 mg in F-4 to 7.4 mg in F-3, aiding in preventing sticking during tablet compression and ensuring smooth production. The unit dose, representing the total weight of each tablet, varies from 494.65 mg in F-4 to 678.91 mg in F-3, influenced mainly by differences in the amount of carrier and coating materials required to maintain flowability at different Lf values. Formulations with higher carrier ratios, such as F-3, tend to have larger unit doses due to the increased amount of Avicel pH 102. Overall, the variations in carrier ratio (R) and liquid load factor (Lf) play a significant role in determining the physical properties and quality of the EGCG liquisolid formulations. A higher carrier ratio results in a greater amount of Avicel pH 102, enhancing compressibility but increasing the tablet's weight, while a lower ratio increases the proportion of coating material, improving flowability but potentially reducing compressibility. Adjusting these parameters allows formulators to optimize the EGCG release profile for desired therapeutic outcomes. This approach provides flexibility in designing formulations with tailored release characteristics, making it suitable for various clinical applications. The consistent use of 140 mg of propylene glycol ensures that differences in performance between formulations can be attributed to the optimized ratios and excipient adjustments rather than variability in the solvent content.

Table 1 Composition of EGCG liquisolid formulas prepared according to mathematical model (All liquisolid formulas contain 35 mg EGCG)

Parameters	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Drug Concentration in Liquid Medication (%w/w)	25	25	25	25	25	25
Carrier Ratio (R)	12	18	24	10	15	20
Liquid Load Factor (Lf)	0.436	0.344	0.298	0.491	0.381	0.326
Liquid Vehicle (mg) (PG)	140	140	140	140	140	140
Carrier Q (mg) (Avicel PH 102)	321.22	407.11	469.93	285.13	367.78	430.11
Coating Q (mg) (Aerosil 200)	26.77	22.62	19.58	28.51	24.52	21.51
Disintegrant (mg) (Indion 414)	36.0	39.0	42.0	35.0	37.5	40.0
Lubricant (mg) (Mg Stearate)	6.2	6.8	7.4	6.0	6.5	7.0
Unit Dose (mg)	530.19	615.53	678.91	494.65	576.29	638.61

Solubility

The table provides an overview of the solubility of Epigallocatechin gallate (EGCG) in different solvents, including Simulated Gastric Fluid (SGF, pH 1.2), Simulated Intestinal Fluid (SIF, pH 6.8), and Propylene Glycol (PG). Each solvent exhibits varying degrees of solubility, which has implications for the formulation and bioavailability of EGCG in different physiological environments. EGCG exhibits very low solubility in SGF, with

a solubility of 0.0087% w/w ± 0.000421. This low solubility can be attributed to the acidic nature of SGF, which limits the dissolution of EGCG. The limited stability of EGCG under acidic conditions is a challenge for oral formulations targeting absorption in the stomach. This low solubility can lead to poor bioavailability, making it necessary to consider formulation strategies that can enhance dissolution in acidic environments, such as using solubilizers or modifying the pH.

In SIF, which represents a more neutral pH condition, the solubility of EGCG is even lower at 0.0029% w/w ± 0.000233. This reduced solubility may be due to the neutral pH environment, which is less favourable for dissolving EGCG. The low solubility in SIF suggests that EGCG may have limited dissolution and absorption in the intestinal tract without the aid of solubilizing agents or formulation strategies like liquisolid systems. Enhancing solubility in SIF is critical, as the small intestine is a major site for drug absorption.

Propylene Glycol (PG) shows a significantly higher solubility of EGCG at 5.351% w/w ± 0.543, making it a suitable solvent for formulating EGCG into liquisolid systems. This high solubility enables the preparation of a more concentrated liquid medication, which can be incorporated into a liquisolid formulation to enhance the overall bioavailability of EGCG. The use of PG in liquisolid formulations helps in overcoming the solubility limitations seen in SGF and SIF, providing a vehicle that can maintain a higher concentration of dissolved EGCG, thus improving its availability for absorption in the gastrointestinal tract. The solubility of EGCG varies significantly across different solvents, with the highest solubility observed in PG and the lowest in SIF. These differences highlight the challenges in formulating EGCG for oral delivery. While its solubility in aqueous media like SGF and SIF is low, using solubilizing agents such as PG in liquisolid systems can help enhance the dissolution and bioavailability of EGCG. Such formulation strategies are crucial for ensuring that EGCG can achieve therapeutic levels in the body despite its inherently poor solubility in physiological fluids.

Table 2 Solubility of EGCG in various solvents

Solvent	**Solubility (%w/w)**	**± S.D.**	**Notes**
Simulated Gastric Fluid (SGF, pH 1.2)	0.0087	± 0.000421	Low solubility due to acidic conditions; limited stability.
Simulated Intestinal Fluid (SIF, pH 6.8)	0.0029	± 0.000233	Lower solubility in neutral conditions, indicating reduced dissolution.
Propylene Glycol (PG)	5.351	± 0.543	Significantly higher solubility, making it ideal for solubilizing EGCG.

Precompression evaluation

The table presents the flowability parameters of six different liquisolid formulations (F-1 to F-6), including the Angle of Repose (Ɵ), Compressibility Index (%), and Hausner's Ratio. These parameters are critical for evaluating the flow properties and compressibility of powders during the manufacturing of tablets, influencing both the efficiency of the production process and the quality of the final product.

Angle of Repose (Ɵ)

The Angle of Repose is a measure of the flowability of powders, with lower values indicating better flow properties. In the table, the angles of repose for the formulations range from 26.83° (F-3) to 39.42° (F-4).F-3 exhibits the best flowability with an angle of repose of 26.83° ± 0.232, indicating that this formulation can flow more easily and uniformly into the tablet die during compression. This helps ensure consistency in tablet weight and drug content.On the other hand, F-4, with an angle of repose of 39.42° ± 0.617, has the poorest flowability among the formulations. This could lead to challenges in achieving uniform filling during the compression process, potentially resulting in weight variation and inconsistent drug content.

Compressibility Index (%)

The Compressibility Index measures the ability of a powder to decrease in volume under pressure, with lower values (typically below 15%) indicating good flow properties. The formulations in the table have compressibility indices ranging from 9.22% (F-3) to 15.33% (F-4).F-3, with a compressibility index of 9.22% ± 0.114, demonstrates the best compressibility, making it ideal for forming tablets with good mechanical strength and

uniformity.F-4, with a compressibility index of 15.33% ± 0.403, is on the higher end of the range, indicating a less efficient packing of particles. This could result in tablets with less consistent mechanical properties and may require more careful control during compression.

Hausner's Ratio:

Hausner's Ratio is another indicator of powder flowability, calculated as the ratio of tapped density to bulk density. A ratio below 1.25 generally indicates good flow properties, while values above 1.25 suggest poorer flow.The values of Hausner's Ratio for the formulations range from 0.578 (F-4) to 0.657 (F-3). Although all formulations fall below 1.25, F-4, with a value of 0.578 ± 0.020, suggests better flow properties relative to its compressibility, which might be beneficial in certain production conditions.F-3, with a Hausner's Ratio of 0.657 ± 0.021, indicates that while it has good overall flowability, it may experience slightly more resistance to packing compared to F-4. However, its superior angle of repose and compressibility index compensate for this, making it a well-balanced formulation for tablet production.Flowability parameters of liquisolid formulations identify F-3 as having the best flow among them accompanied by good compressibility in terms, indicating that it is a promising candidate to be formulated into successful tablet. The lower angle of repose and compressibility index indicate uniform weight and amount of drug content can be manageable during compression. F-4, however, provides a good Hausner's Ratio compared to the angle of repose and therefore be easier to process in some manufacturing. Formulations with good flow properties (F-3, F-2) are often preferred as they may reduce the risks of sticking and clogging during the tableting process - which can result in highly variable tablet quality.

Table 3 Flowability parameters of prepared liquisolid tablets.

Formulations	Angle of Repose (Ɵ) *	Compressibility Index (%) *	Hausner's Ratio*
F-1	35.02 ± 0.743	14.50 ± 0.411	0.586 ± 0.019
F-2	29.18 ± 0.406	10.22 ± 0.355	0.644 ± 0.020
F-3	26.83 ± 0.232	9.22 ± 0.114	0.657 ± 0.021
F-4	39.42 ± 0.617	15.33 ± 0.403	0.578 ± 0.020
F-5	34.22 ± 0.551	11.82 ± 0.421	0.624 ± 0.021
F-6	30.69 ± 0.307	10.36 ± 0.332	0.641 ± 0.021

Mean ± SD*

Differential scanning calorimetry

The DSC thermogram of pure EGCG (Fig. 1) displayed a sharp endothermic peak at 221°C, corresponding to its melting point, indicating the crystalline nature of the compound. The sharpness of this peak suggests a high degree of crystallinity in the pure drug. The DSC thermogram of the direct compressible tablet (DCT) containing EGCG (Fig.1) showed the presence of this characteristic endothermic peak at a slightly reduced intensity, which suggests that EGCG remains in its crystalline form within the DCT without significant interaction with the excipients. However, in the DSC thermogram of the liquisolid formula (Fig.1), the characteristic melting endotherm of EGCG at 221°C was notably absent or appeared as a broad peak. This disappearance of the crystalline peak indicates that EGCG may have transitioned into an amorphous or molecularly dispersed state in the liquisolid formulation. Such a transition is often associated with enhanced solubility, as the amorphous state of a drug typically exhibits better dissolution properties compared to its crystalline counterpart.

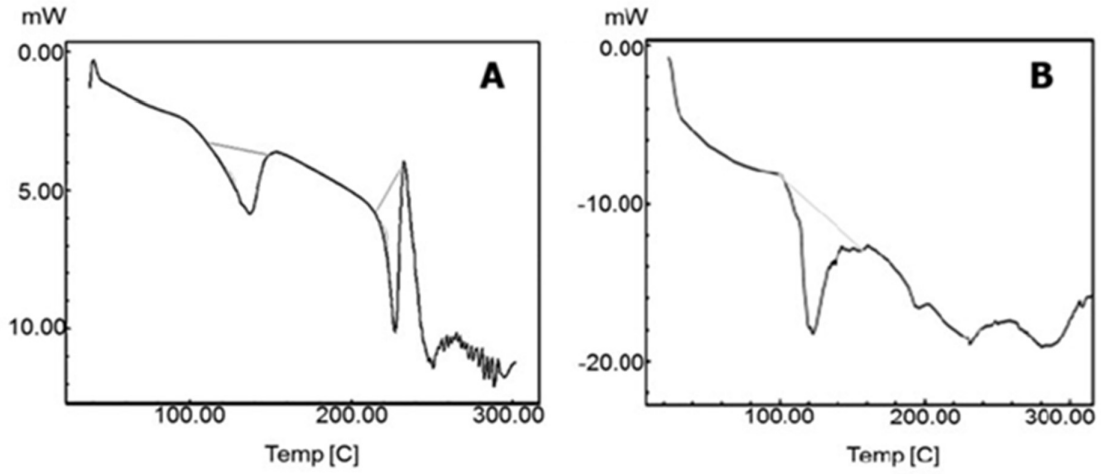

Fig. 1 DSC thermogram of pure EGCG (A) and Liquisolid formulation (B)

Fourier transform spectroscopy

The FTIR spectrum of pure EGCG (Fig.2) displayed characteristic peaks that indicate the presence of specific functional groups. Notable peaks included a strong O-H stretching vibration at 3370 cm^{-1}, which corresponds to the phenolic hydroxyl groups present in EGCG. Additionally, peaks were observed at 1610 cm^{-1} and 1520 cm^{-1}, which are attributed to C=C stretching vibrations of the aromatic rings. A characteristic C=O stretching vibration was noted at 1685 cm^{-1}, indicative of the carbonyl groups presents in EGCG.The FTIR spectrum of the direct compressible tablet (DCT) containing EGCG (Fig. 2) retained these characteristic peaks, albeit with reduced intensity. This reduction suggests that there was no significant interaction between EGCG and the excipients used in the DCT, indicating that the structural integrity of EGCG was maintained in the formulation.In contrast, the FTIR spectrum of the liquisolid formula (Fig.2) showed the absence of the prominent O-H stretching peak at 3370 cm^{-1}. This suggests that hydrogen bonding may have occurred between the phenolic hydroxyl groups of EGCG and the hydroxyl groups of the liquid vehicle (propylene glycol) in the liquisolid formulation, potentially contributing to enhanced solubility and stability of EGCG in the formulation.

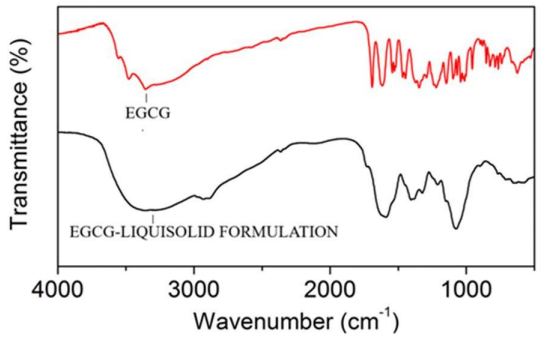

Fig. 2 FTIR spectrum of pure EGCG and Liquisolid formulation

Scanning electron microscopy

The SEM images of pure EGCG (Fig.3) show4ed well-defined, needle-like crystals, reflecting its crystalline nature. The surface morphology was characterized by sharp edges and smooth surfaces, typical of crystalline compounds. SEM analysis of the direct compressible tablet (DCT) containing EGCG (Fig.3) revealed that the drug particles were embedded within the tablet matrix, maintaining their crystalline shape with some degree of surface irregularity, indicating minimal interaction between EGCG and the excipients in the DCT.In contrast, the SEM images of the liquisolid formulation (Fig.3) showed a significant change in the morphology of EGCG. The

sharp crystalline structures of EGCG were no longer visible, with the particles appearing more homogenously distributed and coated with the carrier material. The smooth, uniform surface observed in the liquisolid formulation suggests that the liquid vehicle has been adsorbed onto the carrier matrix, leading to a more molecularly dispersed form of EGCG. This change in surface morphology is consistent with enhanced dissolution properties, as the molecular dispersion can increase the surface area available for interaction with the dissolution medium.

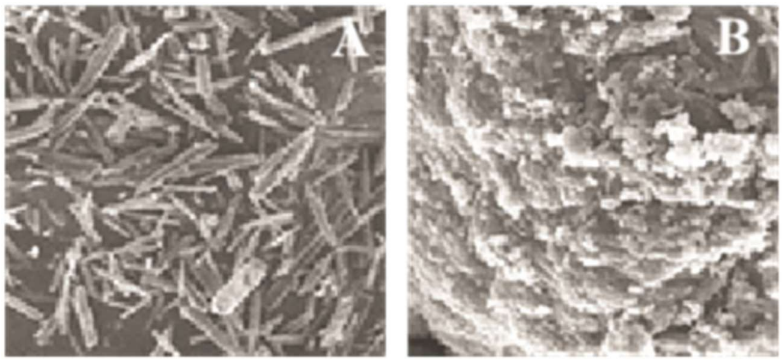

Fig. 3 SEM images of pure EGCG and Liquisolid formulation

Post compression studies of liquisolid compacts

The table provides insights into the physical properties and performance of six liquisolid formulations (F-1 to F-6) by assessing parameters such as hardness, friability, content uniformity, and disintegration time. These properties are critical for ensuring the quality, stability, and effectiveness of the tablets.

Hardness (kg/cm²):

Tablet hardness is a measure of its mechanical strength. The values range from 5.85 kg/cm² (F-4) to 6.74 kg/cm² (F-3), indicating the ability of the tablets to withstand handling and transportation without breaking.Formulation F-3 exhibits the highest hardness (6.74 ± 0.469 kg/cm²), suggesting good resistance to mechanical stress, while F-4 has the lowest hardness (5.85 ± 0.529 kg/cm²), which may result in a slightly more brittle tablet.

Friability (%):

Friability indicates the tablet's ability to resist abrasion. Lower values suggest better resistance to breaking and chipping. All formulations show friability values below 1%, which is within acceptable limits for pharmaceutical tablets.F-3 has the lowest friability (0.228%), indicating excellent resistance to wear, while F-4 has the highest friability (0.468%), which could make it more prone to surface damage during handling.

Disintegration Time (sec):

Disintegration time measures how quickly a tablet breaks down into smaller particles in a dissolution medium. The disintegration times vary significantly, ranging from 37 seconds (F-3) to 92 seconds (F-4).F-3 disintegrates the fastest (37 ± 0.950 seconds), which may contribute to a quicker onset of drug action, making it suitable for immediate-release formulations. On the other hand, F-4 has a much longer disintegration time (92 ± 2.500 seconds), indicating that it may take longer to release the drug, potentially impacting the rate of absorption.

Content Uniformity (%):

What it implies is, that each tablet (unit dose) should contain a proper quantity of active drug. All formulations are nearly 100% for content uniformity values reflects good consistency of drug distribution within each tablet. F-3 has the highest content uniformity (100.03%) i.e., each tablet provides exact potency it is meant for. F-4 exhibited the least content uniformity (93.26 %) which still falls under acceptable limit but demonstrates marginal variation in drug contents.

Examination of these data demonstrated that formulation F-3 is near optimal with high hardness, low friability, fast disintegration and good content uniformity. This renders it appropriate for fast drug release but high structural strength in handling. However, F-4 has a lower hardness and higher disintegration time compared to others that can be potentially useful for formulations with modified release profile. These results emphasize the necessity for optimizing these parameters in order to reach establish therapeutic goals and guarantee constant tablet quality.

Table 4 Hardness, friability, content uniformity and disintegration time of liquisolid formulas

Formulations	Hardness (kg/cm^2) *	Friability (%)	Disintegration Time (sec) *	% Content Uniformity
F-1	6.39 ± 0.539	0.428	71 ± 2.240	95.05
F-2	6.65 ± 0.509	0.318	42 ± 1.710	96.51
F-3	6.74 ± 0.469	0.228	37 ± 0.950	100.03
F-4	5.85 ± 0.529	0.468	92 ± 2.500	93.26
F-5	6.35 ± 0.499	0.398	76 ± 2.600	97.69
F-6	6.68 ± 0.409	0.308	71 ± 1.390	96.55

Mean ± SD*

In-vitro drug release

The provided graphs depict the drug release profiles of different formulations (F-1 to F-6) and the direct compressible tablet (DCT) in Simulated Gastric Fluid (SGF, pH 1.2) and Simulated Intestinal Fluid (SIF, pH 6.8) over a time range of 10 to 80 minutes, with drug release capped at 78%.

Drug Release in SGF:

In the SGF (pH 1.2) graph, formulations F-1, F-2, and F-3 show relatively faster drug release compared to DCT. F-3, in particular, reaches the highest release rate among the formulations, approaching 70% release by 60 minutes. DCT exhibits the slowest release profile, likely due to its lower disintegration rate in acidic conditions, which limits the dissolution of the drug. The gradual increase in release for F-1, F-2, and F-3 suggests that these formulations are more efficient in releasing EGCG in the acidic medium of SGF compared to DCT, providing a potential advantage for formulations targeting faster onset of action.

Drug Release in SIF:

In the SIF (pH 6.8) graph, formulations F-1 to F-6 display a more rapid release compared to their performance in SGF, consistent with the improved solubility and dissolution of EGCG in a neutral environment. F-3 once again shows the fastest release rate, reaching 78% at an earlier time point, followed closely by F-2 and F-4. The other formulations, including F-5 and F-6, demonstrate a similar trend but with slightly slower release kinetics. The DCT formulation shows a much slower release profile, highlighting its limitations in achieving quick drug release in both acidic and neutral conditions. The data indicates that formulations F-1 to F-6, especially F-3, are better suited for rapid release in the intestinal environment, making them ideal for conditions where a quick therapeutic effect is desired after oral administration.

Formulations F-1, F-2, and F-3 outperform the DCT in both SGF and SIF, achieving faster drug release rates due to their optimized formulation properties. This can be attributed to their improved solubilization and disintegration characteristics, which are beneficial for enhancing bioavailability. F-3 is consistently the fastest in both environments, suggesting its potential for delivering a more immediate therapeutic effect compared to the other formulations. The slower release profile of the DCT highlights the challenges of achieving rapid dissolution without formulation modifications, suggesting that the liquisolid approach used in the F-series is more effective for enhancing the release of EGCG in varying pH conditions.

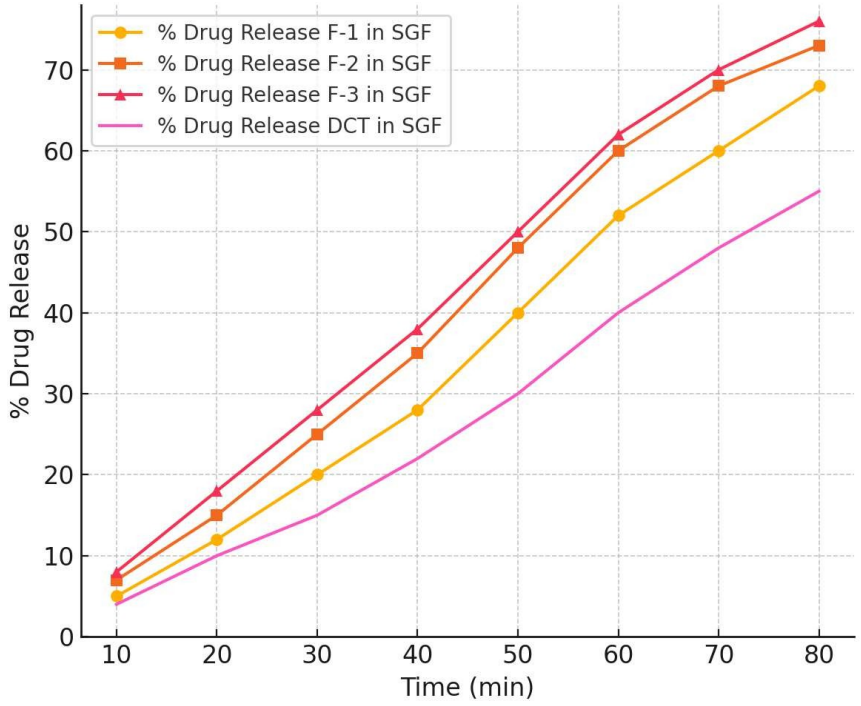

Fig. 5 The drug release profile of different formulations (F-1, F-2, F-3, and DCT) in Simulated Gastric Fluid (SGF, pH 1.2).

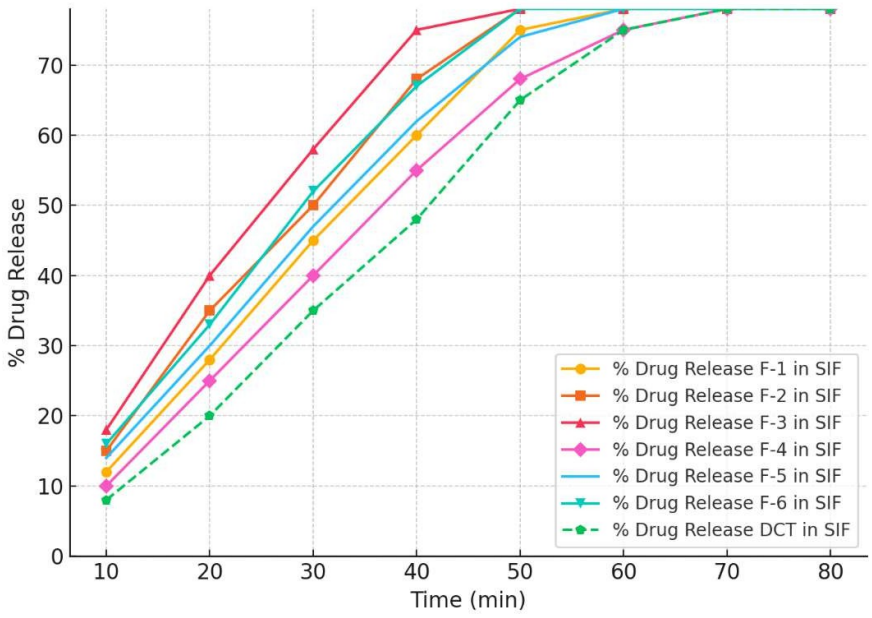

Fig. 6 The drug release profile of different formulations (F-1 - F-6, and DCT) in Simulated Gastric Fluid (SIF, pH 6.8).

Conclusion

The research successfully developed and characterized liquisolid formulations of EGCG using a systematic approach to optimize the formulation parameters. The use of propylene glycol as a solvent, combined with a well-defined carrier-to-coating ratio, allowed for the creation of formulations with improved flowability, compressibility, and dissolution properties. Differential scanning calorimetry (DSC) and FTIR analyses confirmed the compatibility of the drug with excipients, while X-ray diffraction (XRD) indicated a reduction in EGCG crystallinity, potentially enhancing its solubility. Drug release studies revealed that formulations F-1 to F-6, particularly F-3, significantly enhanced the dissolution rate of EGCG compared to the direct compressible tablet (DCT). F-3 demonstrated superior release characteristics in both acidic and neutral conditions, achieving nearly complete release within the stipulated time frame. The findings highlight that liquisolid formulations can be an effective strategy for overcoming the solubility challenges associated with EGCG, making it more suitable for oral administration. Overall, this study provides a promising formulation approach that can be applied to other poorly soluble drugs, contributing to improved therapeutic outcomes and patient compliance in oral drug delivery systems.

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Declaration of competing interest Authors declare that they have no competing interest.

Data availability The source data for all figures are available upon request from the corresponding author.

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