FORMULATION AND EVALUATION OF ENTERIC COATED TABLET OF BROMELAIN AND QUERCETIN FOR ENHANCED THERAPEUTIC EFFICACY IN VARICOSE VEIN

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Abstract : Chronic venous insufficiency (CVI) and varicose veins are progressive vascular disorders driven by sustained venous hypertension, severe oxidative stress, and chronic inflammation. Conventional oral therapies often suffer from poor patient compliance and significant limitations, such as the enzymatic degradation of active agents in the gastric environment. This study aimed to design, formulate, and evaluate an advanced enteric-coated tablet delivering a synergistic combination of bromelain and quercetin. Core tablets containing 250 mg each of bromelain and quercetin were prepared via direct compression and coated with pH-dependent Eudragit L100. Comprehensive preformulation, FTIR, and DSC studies confirmed chemical compatibility. The optimized formulation (Batch B3-E) exhibited excellent mechanical strength, robust acid resistance, and controlled intestinal release. This targeted oral delivery system effectively shields sensitive actives from gastric degradation, offering a promising, non-invasive therapeutic strategy for venous disorders.

IndexTerms - Bromelain, Quercetin, Enteric Coating, Eudragit L100, Chronic Venous Insufficiency, Release Kinetics, Varicose Veins.

1. Introduction

Varicose veins and chronic venous insufficiency (CVI) represent a major global health challenge, affecting approximately 25% of the adult population worldwide. The underlying pathophysiology involves complex inflammatory cascades, continuous oxidative stress, localized accumulation of pro-inflammatory cytokines, and proteolytic degradation of the extracellular matrix by matrix metalloproteinases (MMPs). While conventional treatments range from compression stockings to invasive surgical techniques, they frequently exhibit severe limitations, including high recurrence rates, procedural risks, and failure to address the underlying molecular mechanisms driving disease progression.

Bromelain, a proteolytic enzyme complex derived from Ananas comosus, and quercetin, a naturally occurring bioflavonoid, possess potent synergistic anti-inflammatory, antioxidant, and fibrinolytic properties. Together, they are capable of addressing the multi-pathway pathology of CVI. However, oral administration of unshielded bromelain and quercetin faces significant biopharmaceutical barriers. Bromelain is severely hindered by rapid enzymatic inactivation in the aggressive acidic environment of the stomach, while quercetin exhibits poor aqueous solubility and extensive first-pass metabolism.

To overcome these limitations, the present study was undertaken to develop a robust, pH-dependent enteric-coated tablet system utilizing Eudragit L100. This formulation provides complete gastric protection and ensures targeted, sustained intestinal release of the active ingredients, maximizing systemic therapeutic efficacy.

2. Materials and Methodology

2.1 Materials

Bromelain and Quercetin were procured as high-purity active pharmaceutical ingredients. Eudragit L100 and Hydroxypropyl Methylcellulose Phthalate (HPMC-P) were obtained as functional enteric coating polymers. Microcrystalline Cellulose (Avicel), Sodium Starch Glycolate (SSG), Magnesium Stearate, Starch, Triethyl citrate, and Talc were utilized across all experimental procedures.

2.2 Preformulation and Compatibility Studies

Organoleptic evaluations, melting point determinations, and solubility profiling across various pH media were conducted. Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) analyses were performed on pure APIs and physical mixtures stored under accelerated stability conditions (40°C/75% RH) for 30 days to investigate potential drug-excipient interactions.

2.3 Formulation of Core Tablets and Enteric Coating Process

Core tablets containing a fixed dose of 250 mg each of bromelain and quercetin were prepared via direct compression to avoid thermal and solvent degradation. The optimized core batch (B3) was subjected to pan-coating using an organic solution containing Eudragit L100 (5% w/w), triethyl citrate, and talc dissolved in an isopropyl alcohol-water (60:40) solvent system. Tablets were pre-warmed at 40°C–45°C and sprayed iteratively until a uniform 5% to 8% weight gain was achieved, followed by curing.

figure 1: physical appearance of the finalized enteric coated tablet formulation labeled from optimized batches batch1 to batch8

2.4 In Vitro Dissolution and Release Kinetics Modeling

In vitro drug release was evaluated using a USP Type II dissolution apparatus at 50 rpm and 37°C ± 0.5°C. Acid resistance testing was performed in 0.1 N HCl (pH 1.2) for 120 minutes. Subsequently, tablets were transferred to pH 6.8 phosphate buffer for 90 minutes. Release data were fitted into Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models to determine release kinetics and mechanisms.

3. Result and Discussion

3.1 Preformulation and Compatibility Findings

FTIR Preformulation & Compatibility: The FTIR spectra confirmed the structural identity of the pure active pharmaceutical ingredients and their physical mixtures.

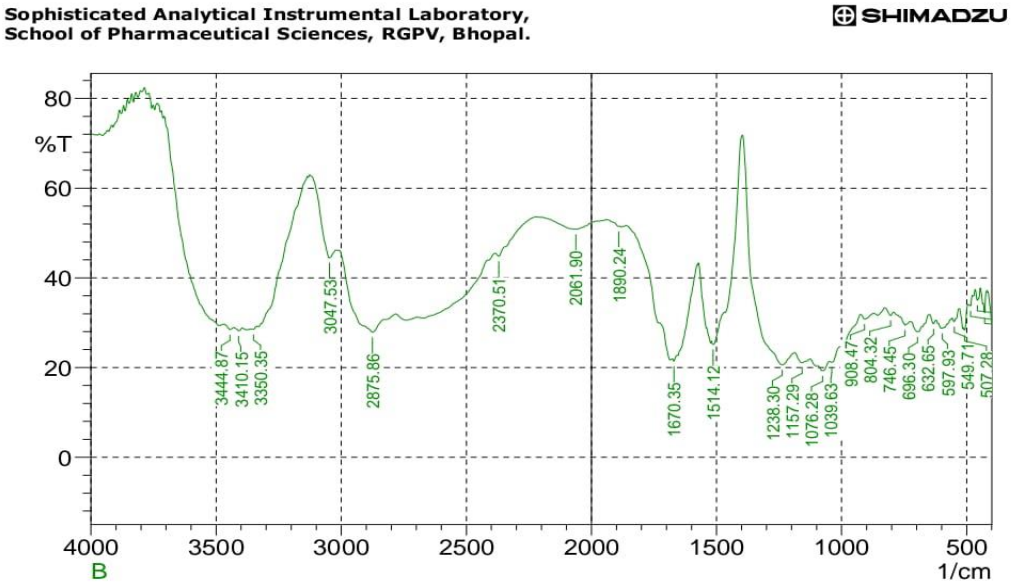

figure 2: ftir spectrum of bromelain

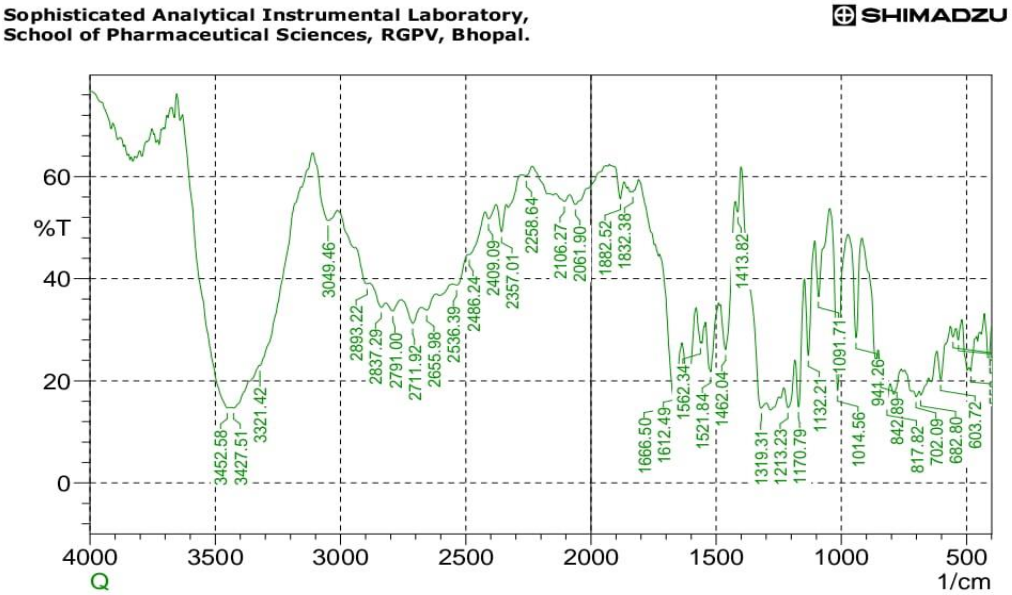

figure 3: ftir spectrum of quercetin

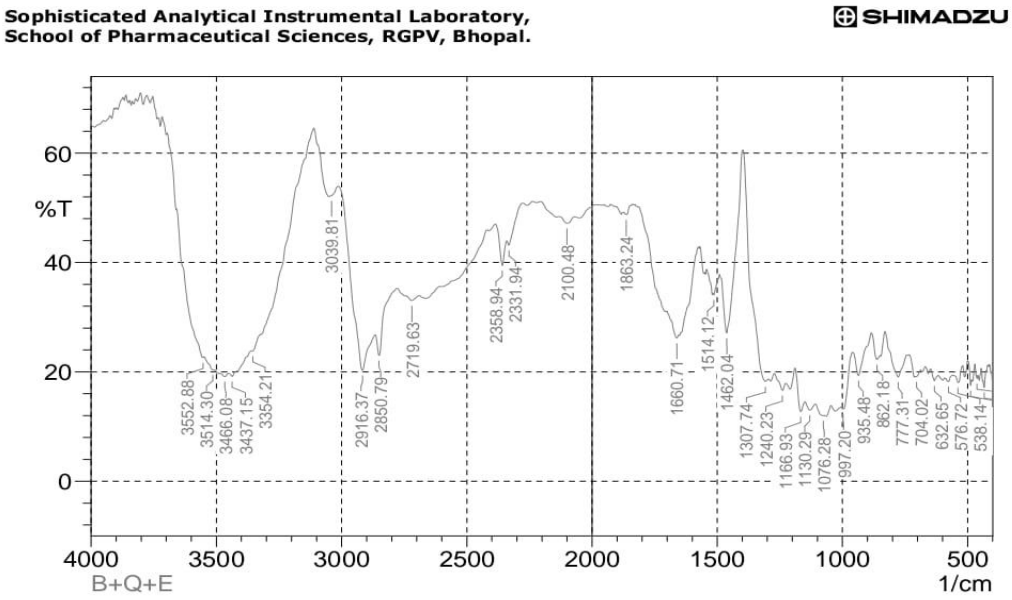

figure 4: ftir spectrum of physical mixture (bromelain + quercetin + excipients)

table 1: ftir peak values of bromelain

Peak Position	Functional Group / Vibration
3410.15 cm^{-1}	O–H or N–H stretching (Hydroxyl or amide group)
2875.86 cm^{-1}	C–H stretching (Aliphatic)
2370.51 cm^{-1}	N≡C or –C≡N stretching / possible impurities
1670.35 cm^{-1}	C=O stretching (Amide I band – peptide linkage)
1076.28 cm^{-1}	C–O stretching (Alcohol or ester group)
696.30 cm^{-1}	Aromatic C–H bending or skeletal vibrations

table 2: ftir peak values of quercetin

Peak Position	Functional Group / Vibration
3452.58 cm^{-1}	O–H stretching (phenolic or hydroxyl group)
2791.00 cm^{-1}	C–H stretching (aliphatic)
2061.90 cm^{-1}	C≡C or C≡N stretching
1612.49 cm^{-1}	C=C stretching (aromatic ring) / C=O stretching (conjugated)
1319.31 cm^{-1}	C–O stretching (phenolic or ether linkage)
1041.56 cm^{-1}	C–O–C stretching (ether) or C–O alcohol group
682.80 cm^{-1}	Aromatic C–H bending

table 3: ftir peak values of physical mixture

Peak Position	Functional Group / Vibration
3437.15 cm^{-1}	O–H stretching (phenolic or hydroxyl group)
2850.79 cm^{-1}	C–H stretching (aliphatic)
2100.48 cm^{-1}	C≡C or C≡N stretching
1660.71 cm^{-1}	C=C stretching (aromatic ring) / C=O stretching
1076.28 cm^{-1}	C–O stretching (phenolic or ether linkage)
632.65 cm^{-1}	Aromatic C–H bending

Detailed analysis of the functional group peak positions highlights the Amide I band at 1670.35 cm^{-1} for Bromelain and the phenolic O–H at 3452.58 cm^{-1} for Quercetin. In the formulation spectra, these principal peaks remained unaltered—exhibiting combined peaks at 3437.15 cm^{-1} and 1660.71 cm^{-1}. The persistence of key functional groups confirms chemical compatibility between the drugs and the selected excipients.

DSC Thermal Analysis: To further validate stability, Differential Scanning Calorimetry (DSC) was performed.

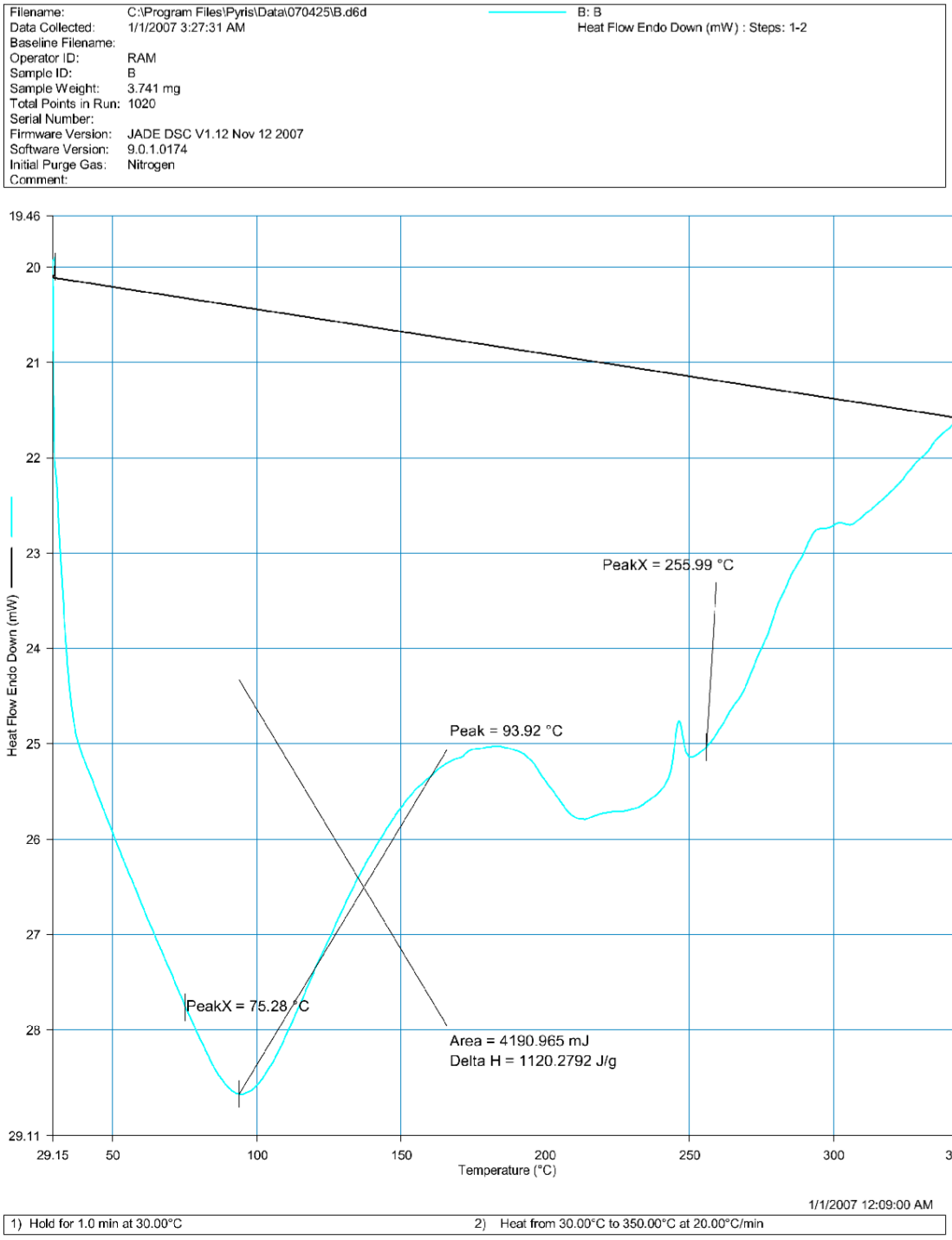

figure 5: dsc thermogram of bromelain

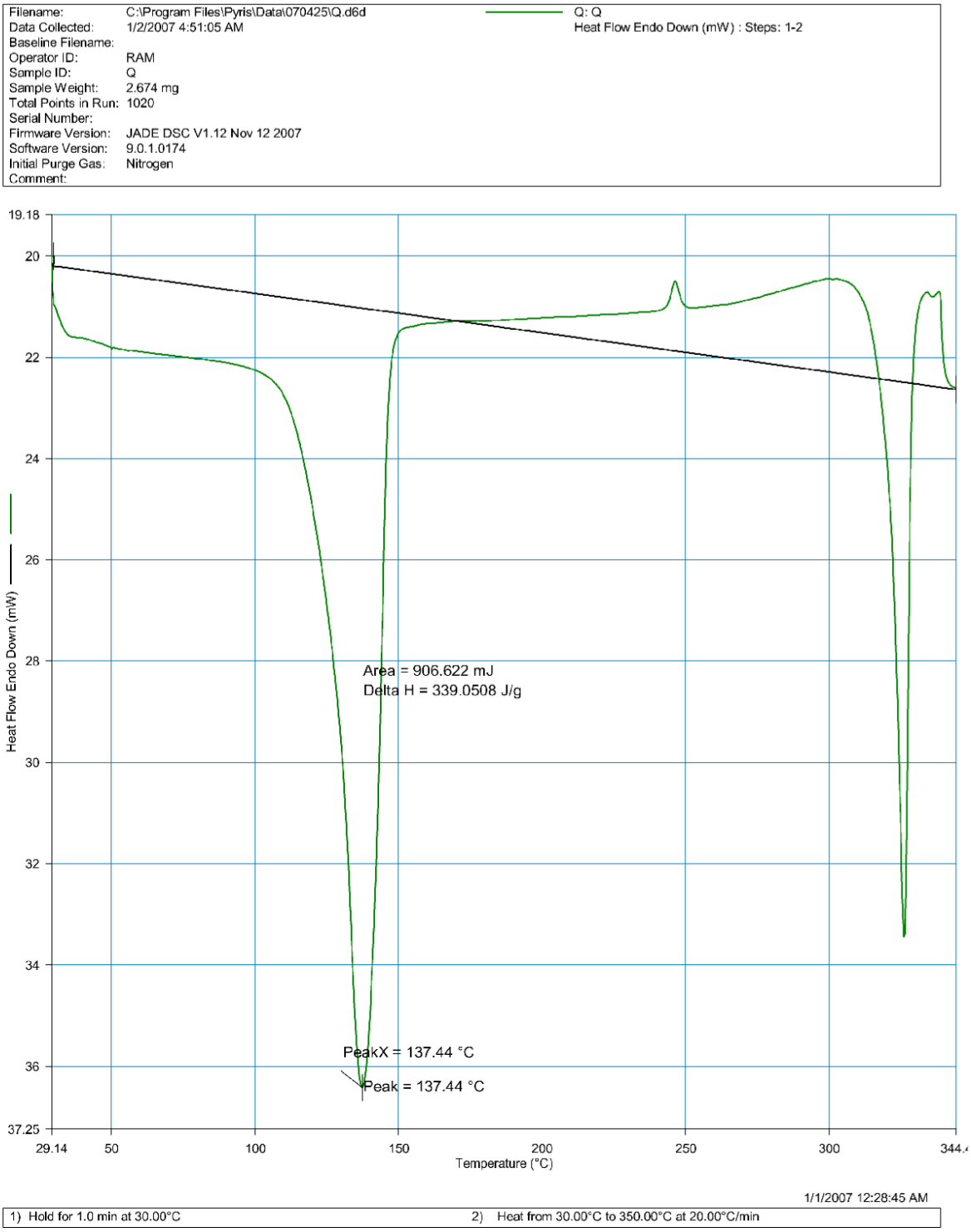

figure 6: dsc thermogram of quercetin

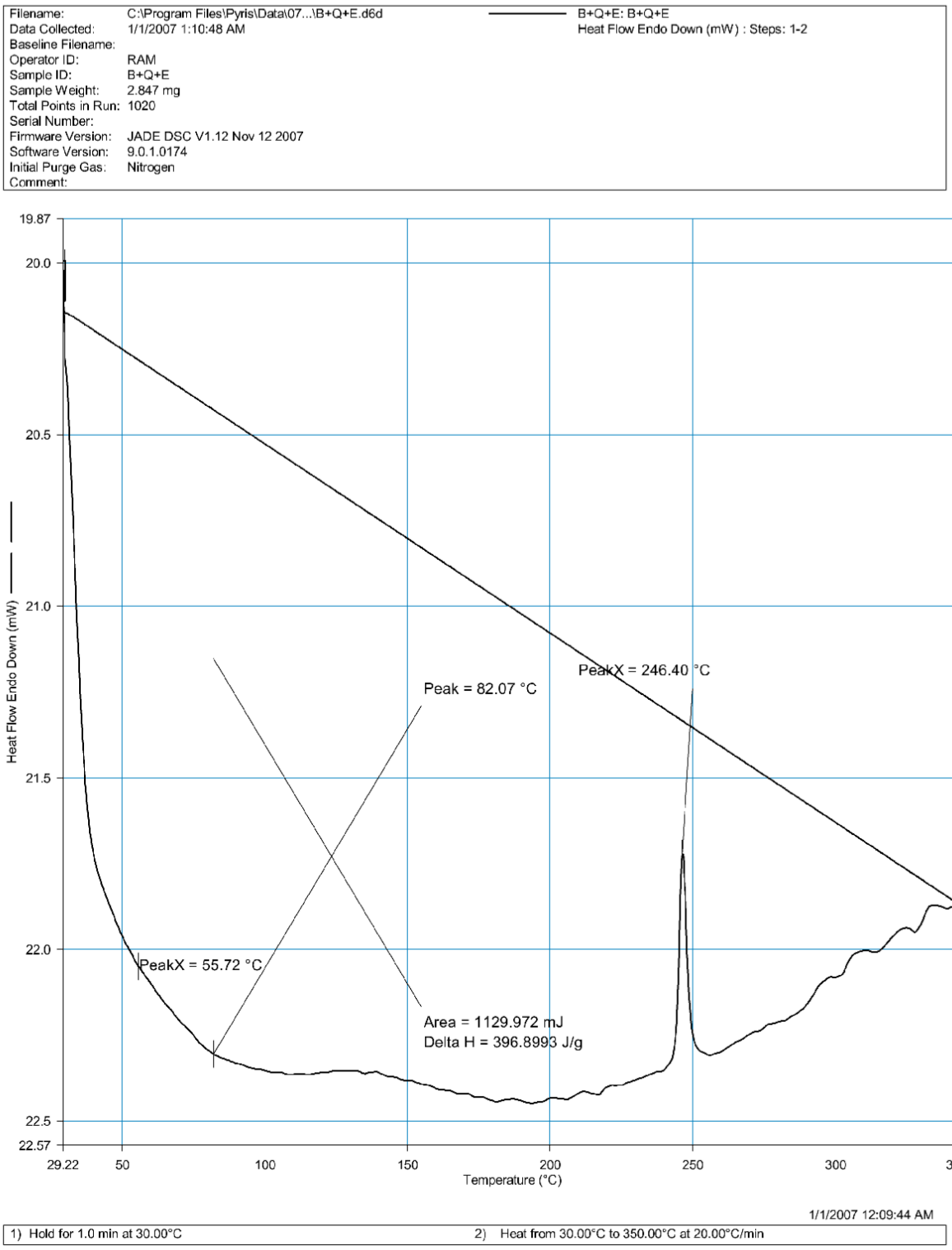

figure 7: dsc thermogram of physical mixture (bromelain + quercetin + excipients)

The DSC thermograms displayed distinct endothermic events for the individual components. Bromelain exhibited a characteristic denaturation endotherm at 75–80°C, while Quercetin displayed a sharp crystalline melting peak at 135–140°C. In the final physical mixture, these peaks were observable without the generation of new exothermic or endothermic variations. The preservation of individual thermal events confirms solid-state compatibility and thermal stability within the formulation matrix.

3.2 In-Vitro Drug Release & Kinetic Profiles

The optimized Batch B3-E was subjected to rigorous dissolution testing, exhibiting a controlled and sustained drug release profile perfectly tailored for enteric delivery.

table 4: in-vitro cumulative drug release profile of optimized batch b3-e

Time (min)	Dissolution Medium	Cumulative Drug Release (%)
30	0.1 N HCl (pH 1.2)	2.0
60	0.1 N HCl (pH 1.2)	2.5
90	0.1 N HCl (pH 1.2)	3.0
120	0.1 N HCl (pH 1.2)	3.5
135	pH 6.8 Phosphate Buffer	35.0
150	pH 6.8 Phosphate Buffer	60.0
165	pH 6.8 Phosphate Buffer	78.0
180	pH 6.8 Phosphate Buffer	89.0
210	pH 6.8 Phosphate Buffer	98.0

As detailed in Table 28, the formulation possesses remarkable gastric resistance, restricting drug release to ≤ 3.5% in 0.1 N HCl over 120 minutes. Upon transfer to the simulated intestinal fluid, the polymer dissolved efficiently, achieving an optimal intestinal release of 98% in pH 6.8 buffer over 210 minutes.

Combined Formulation Kinetic Plots:

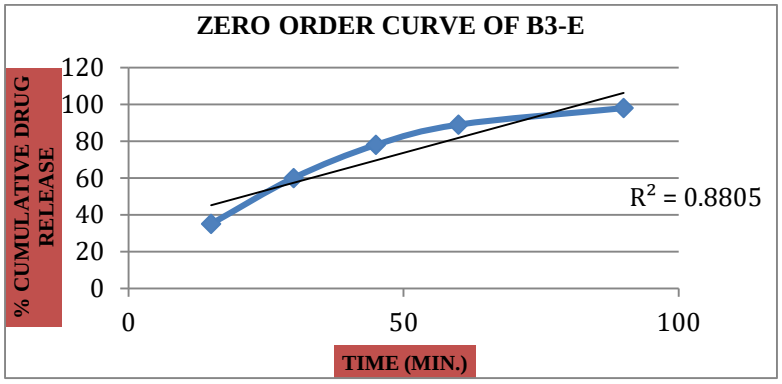

figure 8: zero order drug release profile of enteric coated tablet (b3-e)

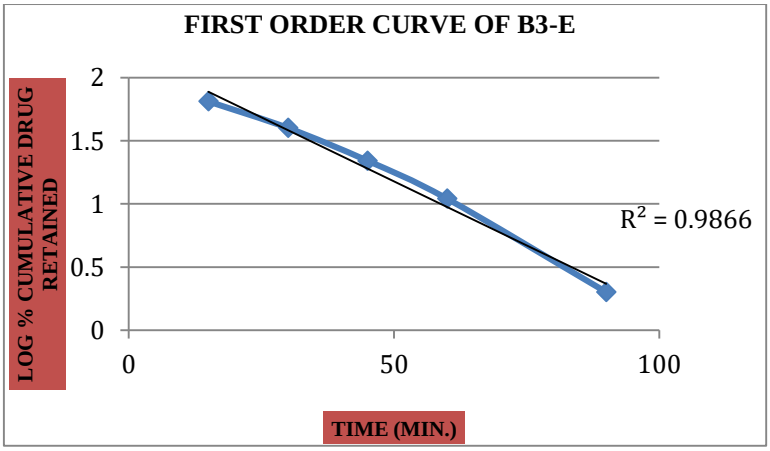

figure 9: first order drug release profile of enteric coated tablet (b3-e), $r^2 = 0.986$

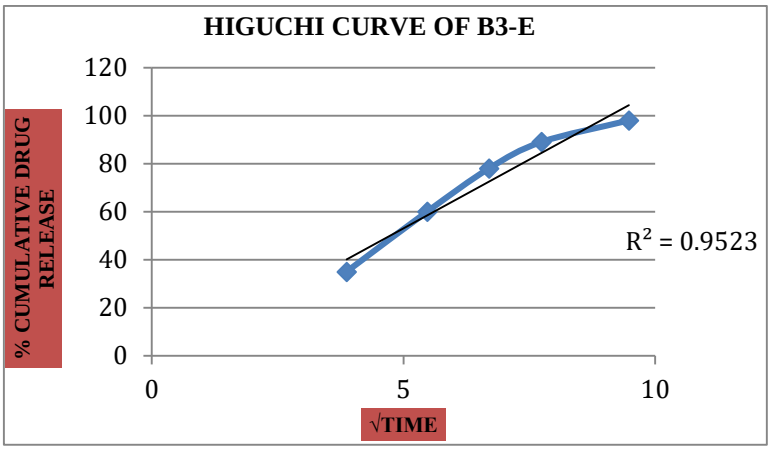

figure 10: higuchi drug release profile of enteric coated tablet (b3-e), $r^2 = 0.952$

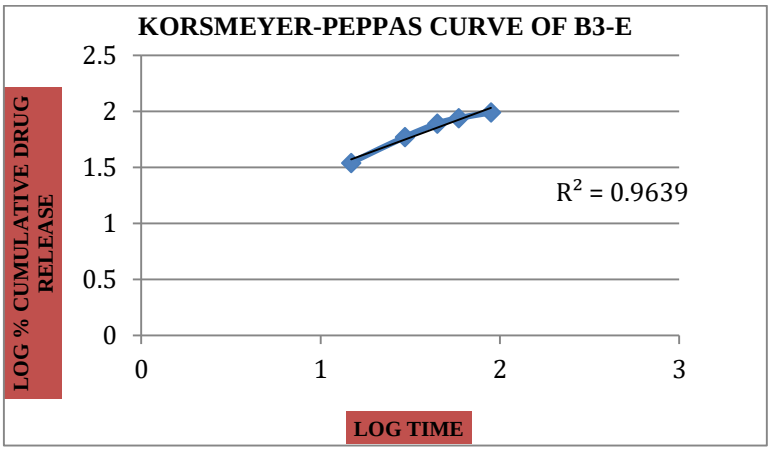

figure 11: korsmeyer-peppas drug release profile of enteric coated tablet (b3-e), $r^2 = 0.963$

table 5: regression coefficient (r^2 values) for bromelain and quercetin

Model	Bromelain (R^2)	Quercetin (R^2)
Zero Order	0.996	0.996
First Order	0.913	0.918
Higuchi	0.989	0.973
Korsmeyer-Peppas	0.991	0.996

Mathematical kinetic modeling of the dissolution data demonstrates an exceptional fit with the Zero-order kinetic model ($R^2 = 0.996$ for both Bromelain and Quercetin individually). This indicates that the formulation successfully delivers the active drugs at a constant, concentration-independent rate, ensuring steady therapeutic blood levels and reducing peak-and-trough fluctuations. Furthermore, Korsmeyer-Peppas analysis highlights high correlation values for both compounds. This confirms that drug release follows anomalous non-Fickian diffusion driven by diffusion and matrix relaxation.

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