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Research Paper

Formulation and Evaluation of Fast Dissolving Tablets of Enalapril Employing Solid Dispersion Technique for Enhanced Solubility and Dissolution

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ABSTRACT

Enalapril, an angiotensin-converting enzyme (ACE) inhibitor commonly used to treat hypertension and congestive heart failure, has very low water solubility (3.5 mg/L) and exhibits poor oral bioavailability of around 28%, mainly due to its limited solubility and significant first-pass metabolism in the liver. This study aimed to develop and assess fast dissolving tablets (FDTs) of Enalapril by employing the solid dispersion method to improve its solubility, dissolution rate, and bioavailability. Solid dispersions of Enalapril with β-cyclodextrin were prepared using the kneading technique in drug-to-carrier ratios ranging from 1:1 to 1:5. These formulations were evaluated for yield, drug content, solubility, melting point, and dissolution in vitro. Fourier Transform Infrared (FTIR) spectroscopy showed no significant interactions between the drug and excipients in the optimized solid dispersion.Fast dissolving tablets were then formulated by direct compression of the solid dispersion, using croscarmellose sodium and crospovidone as superdisintegrants, PVP K-30 as a binder, saccharin for sweetness, and magnesium stearate and talc as lubricants and glidants. A total of nine formulations (F1–F9) were tested for various pre-compression (angle of repose, bulk and tapped density, Carr's index, Hausner's ratio) and post-compression parameters (weight variation, hardness, friability, thickness, drug content, wetting time, disintegration time, and in vitro drug release).Formulations containing crospovidone, especially those combined with sodium lauryl sulfate, demonstrated the fastest tablet disintegration within 75 seconds and the highest cumulative drug release, following zero-order release kinetics ($R^2 = 0.94–0.99$). Stability studies under accelerated conditions for one month confirmed that the optimized formulation maintained its physicochemical properties and dissolution profile.This research indicates that combining solid dispersion technology with fast dissolving tablet formulation is an effective way to enhance the solubility-limited

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bioavailability of Enalapril, facilitating a rapid onset of antihypertensive action without requiring water intake. This approach is particularly advantageous for pediatric, elderly, and patients with swallowing difficulties.

INTRODUCTION

Due to its ease of use, precise dosing, and high patient adherence, oral drug delivery remains the most favored method, comprising about 50-60% of all dosage forms. Among solid oral forms, tablets and capsules are the most widely used. However, many patients—especially children, elderly, bedridden individuals, and those with swallowing difficulties—struggle to swallow traditional tablets, particularly when water is not readily available, such as during travel, motion sickness, coughing, or allergic reactions. This has led to growing interest in tablets that dissolve rapidly in the mouth, known by various names like fast dissolving tablets (FDTs), mouth-dissolving tablets, melt-in-mouth tablets, **or** orodispersible tablets (ODTs)**.** According to the European Pharmacopoeia, an orodispersible tablet is one that disintegrates in the mouth within three minutes. When placed on the tongue, an FDT dissolves immediately, releasing the medicine to dissolve in saliva. Some drugs in this form may have enhanced bioavailability because part of the dissolved drug can be absorbed directly through the buccal, pharyngeal, and esophageal mucosa, reducing the impact of first-pass liver metabolism compared to traditional tablets.

Criteria for a fast dissolving drug delivery system

An ideal fast disintegrating tablet (FDT) should rapidly dissolve or break down in the mouth within seconds without requiring water. It must be compatible with methods to mask unpleasant tastes and strong enough to endure handling despite its naturally porous and lightweight structure. Additionally, it should leave minimal or no residue after use, be stable against changes in humidity and temperature, and be cost-effective to produce using conventional tablet-making and packaging machinery.

Techniques for preparing fast dissolving tablets

There are several methods used to manufacture fast-dissolving tablets (FDTs). Freeze-drying, also known as lyophilization, creates a porous and quickly dissolving amorphous structure but is costly, takes a long time, and produces fragile tablets that are challenging to package using standard methods. Tablet molding involves pressing a damp powder mixture gently to form a porous tablet that dissolves fast, although these tablets often lack sufficient strength. Spray drying combines a matrix material such as gelatin or mannitol with a superdisintegrant, resulting in tablets that break down in roughly 20 seconds. Sublimation uses volatile substances like camphor or ammonium bicarbonate that evaporate post-compression, leaving a porous tablet that disintegrates within 10 to 20 seconds. Among these techniques, direct compression stands out as the simplest and most cost-effective approach. It is widely favored due to the use of superdisintegrants and sugar-based ingredients that ensure quick tablet breakup and a pleasant taste.

Mechanism of action of superdisintegrants

Tablet breakdown with the help of superdisintegrants happens through four key processes:

- Swelling: The disintegrant takes in water and expands, which creates forces that break the tablet apart from within.
- Wicking or capillary action: Water moves into the tablet through tiny channels, weakening the bonds between the particles.

- Particle-particle repulsion: This involves electrostatic forces between particles, mainly seen in disintegrants that do not swell.
- Deformation recovery: Particles that were compressed during tablet manufacturing return to their original shape when exposed to water, generating stress that disrupts the tablet structure.

The most frequently used superdisintegrants—such as sodium starch glycolate, croscarmellose sodium, crospovidone, alginic acid, and calcium silicate—typically work through one or more of these methods.

Advantages *and limitations of fast dissolving tablets*

Fast Disintegrating Tablets (FDTs) provide several recognized benefits. They can be taken without water anytime and anywhere, making them especially convenient for patients on the move. They are suitable for elderly and pediatric patients, as well as those who are mentally ill, developmentally disabled, uncooperative, nauseous, or restricted in fluid intake. FDTs reduce the choking hazard linked to the physical blockage that conventional tablets may cause. They may also enhance drug bioavailability by allowing absorption through the mucosa of the mouth, throat, or esophagus before reaching the stomach, which decreases first-pass liver metabolism. Additionally, FDTs enable rapid therapeutic effects, which is crucial in conditions like motion sickness, sudden allergic or asthma attacks, and hypertensive emergencies.

However, these advantages come with some drawbacks. Due to their porous nature, FDTs often have less mechanical strength compared to traditional compressed tablets, necessitating careful handling and specialized packaging such as blister packs to avoid damage. Moreover, drugs with bitter or unpleasant tastes require extra taste-masking strategies since the medication dissolves directly on the tongue, exposing taste buds, unlike conventional tablets that bypass them.

Solubility and its enhancement

The therapeutic performance of an orally administered drug is governed largely by its aqueous solubility and, consequently, its dissolution rate, since only dissolved drug is available for absorption across the gastrointestinal membrane. Currently, only about 8% of new chemical entities possess both adequate solubility and permeability. The Noyes-Whitney equation, in its Nernst-Brunner form, $dc/dt = DA(Cs - Ct)/Vh$, illustrates that the dissolution rate can be enhanced by improving drug solubility in the dissolution medium, reducing the thickness of the diffusion layer, or increasing the effective surface area available for dissolution through particle-size reduction or improved wetting. Chemical strategies for solubility enhancement include salt and prodrug formation, while physical strategies include particle-size reduction (milling, micronization, nanonization), the use of surfactants and cosolvents, complexation with agents such as cyclodextrins, modification of the solid form (polymorphs, cocrystals), and the formation of solid dispersions.

Solid dispersion technique

Chiou and Riegelman defined a solid dispersion as the dispersion of one or more active ingredients in an inert carrier matrix in the solid state, prepared by the melting (fusion), solvent, or melting-solvent (kneading) method. In a solid dispersion, the poorly water-soluble drug is molecularly dispersed, or dispersed as amorphous or fine crystalline particles, within a hydrophilic carrier, which reduces drug crystallinity, increases the effective surface area, and improves wettability, thereby enhancing the dissolution rate. Hydrophilic carriers commonly employed for this

purpose include polyethylene glycols, polyvinylpyrrolidone (PVP) and cyclodextrins, the latter offering the additional advantage of true molecular inclusion complexation.

Patented fast dissolving tablet technologies

A number of proprietary FDT technologies have been developed and commercialized on the basis of the principles outlined above. Zydis technology (Catalent) produces a freeze-dried unit that dissolves on the tongue within 5 seconds by physically trapping the drug in a water-soluble saccharide/polymer matrix, offering pre-gastric absorption benefits but suffering from high manufacturing cost and fragility. Orasolv and Durasolv (CIMA Labs) rely on taste-masked, effervescent-assisted direct compression at low compaction force, giving disintegration times of 10-40 seconds, with Durasolv additionally offering greater tablet hardness (15-100 N) suitable for conventional bottling and blistering. WOWTAB (Yamanouchi) combines low- and high-mouldability saccharides to balance rapid dissolution with adequate hardness. Flashdose (Fuisz/Biovail) uses a flash-heat-processed, high-surface-area 'floss' matrix, while Flashtab (Prographarm) and Oraquick (K.V. Pharmaceuticals) rely on coated/taste-masked microcrystals and micro-mask microsphere technology, respectively, to combine taste masking with rapid disintegration. Other notable systems include Advatab, Pharmaburst and Frosta technology, each offering variations on the disintegrant/diluent blend and compaction strategy to optimize the balance between disintegration speed, mechanical strength and manufacturability. Direct compression, as used in the present study, was selected in preference to these more specialized (and generally costlier) technologies because it offers comparable disintegration performance for a solubility-enhanced drug candidate while remaining scalable on conventional tableting equipment.

Enalapril

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor class, indicated in the management of hypertension, congestive heart failure and nephropathy, and in reducing cardiovascular mortality in high-risk individuals. Following hepatic biotransformation it is converted to its active diacid metabolite, enalaprilat, a potent competitive inhibitor of ACE that blocks the conversion of angiotensin I to angiotensin II, thereby reducing peripheral vascular resistance and aldosterone-mediated sodium and water retention. Enalapril is practically insoluble in water (approximately 3.5 mg/L) and exhibits an oral bioavailability of only about 60% for the parent drug (approximately 28% is often cited for the therapeutic bioavailability accounting for hepatic conversion), attributable to its poor aqueous solubility and appreciable first-pass metabolism. Since hypertensive emergencies and acute angina demand a rapid onset of pharmacological action, and parenteral administration is not always practicable, there is a clear rationale for developing a non-parenteral, solubility-enhanced, rapidly disintegrating oral dosage form of Enalapril that permits fast absorption into the systemic circulation without the need for water.

LITERATURE REVIEW:

A substantial body of literature supports the use of superdisintegrant-based direct compression and solid dispersion technology for the formulation of fast dissolving/sublingual tablets of antihypertensive and other actives. Aher et al. reviewed FDTs as a preferred option for pediatric and geriatric patients unable to swallow

conventional tablets. Batra and Sardana reviewed sublingual delivery of antihypertensive drugs, noting that low bioavailability due to first-pass metabolism is the principal barrier to oral antihypertensive therapy and that sublingual/fast dissolving routes can improve both bioavailability and onset of action. Narasimhulu et al. developed a 10 mg sublingual lisinopril tablet with a disintegration time competitive with the innovator product. Patel et al. prepared felodipine sublingual tablets from a β-cyclodextrin/poloxamer 407 solid dispersion combined with the superdisintegrant Kyron T-314, achieving 87% drug dissolution within 15 minutes and a disintegration time of 22 seconds. Srilatha et al. and Sramika et al. similarly optimized sublingual tablets of atenolol and nimodipine, respectively, using croscarmellose sodium, crospovidone and sodium starch glycolate, reporting disintegration times in the range of 22-46 seconds and near-complete drug release within 15-30 minutes.

Several other workers have combined solid dispersion with fast dissolving tablet technology specifically to address poorly water-soluble drugs. Kumar et al. and Singh et al. reported that solid dispersions prepared with PEG and PVP carriers reduced drug crystallinity and improved wettability, translating into faster dissolution than the pure drug or a simple physical mixture. Verma et al. formulated fast dissolving tablets of Enalapril maleate by direct compression, confirming, through compatibility studies, the absence of any interaction between drug and excipients, and demonstrating rapid disintegration with an improved release profile. Gupta et al. and Namitha et al. reviewed the various solid dispersion techniques and concluded that their combination with fast dissolving tablet technology offers a synergistic improvement in solubility, dissolution rate, bioavailability and patient compliance, provided that formulation variables such as drug-to-carrier ratio and superdisintegrant type and concentration are carefully optimized. This body of evidence provided the rationale and the methodological framework for the present investigation.

Further supporting this rationale, Chowdary and Aishwarya formulated paracetamol FDTs comparing crospovidone, croscarmellose sodium and sodium starch glycolate along with a co-processed pregelatinized starch-PEG-Aerosil excipient, concluding that superdisintegrant selection had a greater influence on disintegration time than diluent choice. Savita and Sethi demonstrated that natural sweetening agents such as stevia leaf powder could be used to mask the bitterness of metoclopramide hydrochloride in an FDT formulation without compromising disintegration performance, an approach of relevance to the saccharin-sweetened formulation used in the present study. Biraju et al. optimized glipizide FDTs using croscarmellose sodium with PVP K-30 as binder and demonstrated comparability with the marketed conventional formulation after one-month accelerated stability testing at 25°C/60% RH and 40°C/75% RH, a protocol broadly similar to that adopted here. Collectively, these reports confirm that (i) superdisintegrant type and concentration are the dominant formulation variables governing FDT disintegration and dissolution performance, (ii) solid dispersion or complexation technology can be combined with FDT formulation without compromising tablet mechanical properties, and (iii) accelerated stability testing over 30 days is an established and sufficient preliminary indicator of short-term formulation robustness prior to more extended studies.

AIM AND OBJECTIVES:

Aim: To formulate and evaluate fast dissolving tablets of Enalapril using the solid dispersion method in order to enhance its solubility, dissolution rate and overall bioavailability.

Objectives:

1. To characterize the drug and excipients and study drug-excipient interaction by FTIR spectroscopy.
2. To prepare and evaluate solid dispersions of Enalapril with β-cyclodextrin as carrier.
3. To formulate fast dissolving tablets of the optimized Enalapril solid dispersion using superdisintegrants by the direct compression method.
4. To evaluate the developed formulations for pre-compression (flow) and post-compression (physical, mechanical and release) properties.
5. To study the in vitro drug release profile and release kinetics of the optimized formulations.
6. To assess the short-term accelerated stability of the optimized formulation.

MATERIALS AND METHODS:

Drug and excipient *profile*

Enalapril (chemical name: (2S)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid; molecular formula $C_{20}H_{28}N_2O_5$; molecular weight 376.45 g/mol) is a white to off-white crystalline powder belonging to the ACE-inhibitor/antihypertensive category, administered orally at doses ranging from 2.5 mg to 40 mg per day depending on indication. It is slightly soluble in water but freely soluble in methanol and ethanol, shows approximately 60% oral bioavailability and 50-60% plasma protein binding, undergoes hepatic conversion to its active metabolite enalaprilat (biological half-life ~11 hours), and is contraindicated in pregnancy, bilateral renal artery stenosis and in patients with a history of ACE-inhibitor-associated angioedema. Croscarmellose sodium and crospovidone, the two superdisintegrants employed, are cross-linked cellulose and cross-linked polyvinylpyrrolidone derivatives respectively, both practically insoluble in water and used at 2-6% w/w to promote disintegration principally by wicking (croscarmellose) or capillary action with minimal swelling (crospovidone). PVP K-30 served as a dry binder, saccharin as a sweetening/taste-masking agent, and magnesium stearate (0.25-5% w/w) and talc (1-10% w/w) as lubricant and glidant, respectively, to improve powder flow and reduce die-wall friction during compression.

Materials *and equipment*

Enalapril solid-dispersion-grade drug substance was procured as a gift sample from Mankind Pharma Pvt. Ltd. Croscarmellose sodium and crospovidone were obtained from Well Manor Pvt. Ltd. and Leben Life Sciences, respectively. PVP K-30 was procured from Research Lab Fine Chem Industry. Saccharin, magnesium stearate and talc were obtained from institutional laboratory stock. β-cyclodextrin, sodium lauryl sulphate and all other reagents and solvents used were of analytical grade. The major equipment used in the study is listed in Table 1.

Table 1: Major equipment used in the study

Equipment	Specification/Model
UV/Visible double-beam spectrophotometer	LABINDIA 3000+
Fourier Transform IR spectrophotometer	SHIMADZU
Tablet compression machine (mini press)	Karnavati Engineering Pvt. Ltd.
Tablet dissolution tester (USP)	Electrolab TDT-08L

Equipment	Specification/Model
Tablet hardness tester	Pfizer type
Friability test apparatus (double drum)	Omega
Tablet disintegration test apparatus	Omega Scientific Industries
Tap density apparatus	Omega
Hot air oven	Rolex
Electronic balance	Wensar

Preformulation studies

The melting point of Enalapril was determined by the capillary method using a Thiele's melting point apparatus. Standard calibration curves of Enalapril were constructed in pH 6.8 phosphate buffer using a LABINDIA double-beam UV-visible spectrophotometer (UVWIN software) over the wavelength range 200-400 nm. Drug-excipient compatibility was assessed by Fourier Transform Infrared (FTIR) spectroscopy (SHIMADZU) using the KBr pellet method over the range 4000-400 cm-1, comparing the spectrum of pure Enalapril with that of physical mixtures containing (a) crospovidone, sodium lauryl sulphate, PVP K-30, maize starch, magnesium stearate and talc (Mixture A), and (b) croscarmellose sodium in place of crospovidone (Mixture B).

Preparation of Enalapril solid dispersion

Solid dispersions of Enalapril with β-cyclodextrin were prepared by the kneading method in five molar ratios (1:1, 1:2, 1:3, 1:4 and 1:5). The drug and carrier were wetted with a 1:1 methanol-water mixture and kneaded thoroughly for 30 minutes in a glass mortar. The resulting paste was dried under vacuum for 24 hours, after which the dried mass was scraped, crushed, pulverized and passed through a No. 100 sieve (150 µm), and the solid dispersion (coded RSDI-RSDV) was stored in a desiccator for further evaluation.

Evaluation of solid dispersion

The prepared solid dispersions were evaluated for process yield, angle of repose, bulk density, compressibility (Carr's index), moisture uptake, total drug content, phase-solubility behaviour, melting point and in vitro dissolution in pH 6.8 phosphate buffer using a USP XXIII paddle-type dissolution apparatus (50 rpm, 37 ± 0.5°C), with drug release monitored spectrophotometrically at 212 nm.

Formulation of fast dissolving tablets

Fast dissolving tablets equivalent to 20.2 mg of Enalapril solid dispersion were prepared by the direct compression method using a Mini Press-1 tablet machine. Nine formulations (F1-F9) were designed to evaluate the influence of superdisintegrant type (croscarmellose sodium vs. crospovidone) and concentration, and the effect of incorporating sodium lauryl sulphate as a wetting agent, as summarised in Table 2. PVP K-30 was used as binder, saccharin as sweetening agent, and magnesium stearate and talc as lubricant and glidant, respectively. All ingredients were passed through a No. 60 sieve, blended and compressed directly into tablets.

Table 2: Composition of Enalapril fast dissolving tablet formulations (quantity in mg per tablet)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Enalapril solid dispersion	20.2	20.2	20.2	20.2	20.2	20.2	20.2	20.2	20.2
Croscarmellose sodium	6	12	18	-	-	-	-	-	-
Crospovidone	-	-	-	6	12	18	18	18	18
Sodium lauryl sulphate	-	-	-	-	-	-	1	2	3
PVP K-30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Saccharin	15	15	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3

Evaluation of powder blends (pre-compression parameters)

The powder blends of all nine formulations were evaluated for angle of repose (funnel method), bulk density and tapped density (graduated cylinder method, 100 tappings), Carr's index [(tapped density - bulk density)/tapped density x 100] and Hausner's ratio (tapped density/bulk density) as indices of flowability and compressibility.

Evaluation of tablets (post-compression parameters)

The compressed tablets were evaluated for weight variation (20 tablets, electronic balance), hardness (Pfizer hardness tester), friability (Roche friabilator, 25 rpm, 4 minutes, % loss = [(W1-W2)/W1] x 100), thickness and diameter (Vernier caliper), and drug content uniformity (UV spectrophotometry at 271 nm following extraction in pH 6.8 phosphate buffer). Wetting time and in vitro disintegration time were determined using a Petri dish/tissue paper method and a tablet disintegration test apparatus, respectively. In vitro dissolution studies were carried out in 900 mL of pH 6.8 phosphate buffer using USP Apparatus II (paddle, 50 rpm, 37 ± 0.5°C), with samples withdrawn at 5-minute intervals and analysed spectrophotometrically at 271 nm, replacing withdrawn volumes with fresh medium to maintain sink conditions. Dissolution data were fitted to zero-order and first-order kinetic models, and the model giving the higher correlation coefficient (R2) was taken as the best-fit model. The optimized formulation was subjected to accelerated stability studies at 40°C ± 2°C/75% ± 5% RH for 30 days as per ICH guidelines, and re-evaluated for physical appearance, drug content and dissolution profile.

RESULTS AND DISCUSSION:

Preformulation studies

Enalapril was obtained as a white, crystalline, odourless powder that complied with its reported organoleptic characteristics. Its melting point was found to be 108-110°C, in close agreement with the reported value of 109°C, confirming the identity and purity of the sample. The drug exhibited a solubility of 72.2 µg/mL in water and 80.41 µg/mL in pH 6.8 phosphate buffer, consistent with its classification as a practically water-insoluble drug. UV scanning of Enalapril in pH 6.8 phosphate buffer showed an absorption maximum (λmax) at 221 nm, which was used as the analytical wavelength; the resulting calibration curve was linear over the range 4-20 µg/mL with a

regression equation of y = 0.0257x + 0.0055 and a correlation coefficient (R2) of 0.9994, confirming adherence to Beer-Lambert's law.

Drug-excipient compatibility (FTIR)

The characteristic FTIR absorption bands of Enalapril - C-H stretch (2933.73 cm-1), ester C=O stretch (1741.72 cm-1), amide C=O stretch (~1649 cm-1), CH3 bending (1375 cm-1) and C-O stretch (~1184 cm-1) - were retained without significant shift, broadening or disappearance in the spectra of both Mixture A (with crospovidone) and Mixture B (with croscarmellose sodium), and in the spectrum of the Enalapril-β-cyclodextrin solid dispersion, which additionally showed the expected O-H stretch (3508.27 cm-1) contributed by the cyclodextrin carrier. The absence of any new peaks or loss of characteristic drug peaks confirmed that there was no significant chemical interaction between Enalapril and the selected excipients, supporting the physical and chemical stability of the proposed formulation.

Evaluation of Enalapril solid dispersion

Complexation of Enalapril with β-cyclodextrin markedly improved its aqueous solubility, from 72.6 µg/mL for the pure drug to 97.50 µg/mL for the optimized solid dispersion (an increase of approximately 34%), with a phase-solubility stability constant of 122 µg/mL. The melting point of the solid dispersion shifted substantially, to 244-246°C, consistent with the formation of an inclusion/solid-state complex rather than a simple physical mixture. Process yield across the five drug-carrier ratios ranged from 94.78% to 97.56%, drug content from 94.04% to 98.23%, and moisture uptake from 4.0% to 4.5%, all within acceptable pharmacopoeial limits (Table 2).

Table 3: Physicochemical evaluation of Enalapril solid dispersions (Mean ± SD, n = 3)

Batch	Drug:Carrier	Yield (%)	Angle of Repose (°)	Compressibility (%)	Moisture Uptake (%)	Drug Content (%)
Pure drug	-	-	21.80 ± 1.3	16.84 ± 1.2	4.0 ± 0.9	97.70 ± 0.9
RSD I	1:1	97.56 ± 1.1	21.00 ± 0.9	15.0 ± 1.5	4.2 ± 1.1	98.23 ± 0.7
RSD II	1:2	95.45 ± 1.4	22.56 ± 1.5	15.64 ± 1.3	4.2 ± 1.2	96.23 ± 1.2
RSD III	1:3	96.02 ± 1.1	22.36 ± 0.7	16.98 ± 1.4	4.3 ± 1.1	94.75 ± 1.5
RSD IV	1:4	97.45 ± 0.9	21.81 ± 1.3	15.79 ± 1.3	4.4 ± 1.3	96.56 ± 1.4
RSD V	1:5	94.78 ± 1.5	22.25 ± 0.8	15.70 ± 1.2	4.5 ± 1.2	94.04 ± 1.6

In vitro dissolution of the solid dispersion batches (SD1-SD5) in pH 6.8 phosphate buffer confirmed a ratio-dependent enhancement in release rate, with the 1:1 ratio (SD1) releasing 97.86% of Enalapril within 40 minutes, compared with only 73.06% release from the pure drug over the same period. Increasing the proportion of β-cyclodextrin beyond the 1:1 ratio did not further improve dissolution and, in fact, produced a modest decline in release rate, most likely because of the increasing bulk and viscosity of the carrier-rich matrix limiting water penetration. The 1:1 drug-carrier ratio (RSD I) was therefore selected as the optimized solid dispersion for incorporation into the fast dissolving tablet formulations.

The time-dependent dissolution profile of the five solid dispersion batches (SD1-SD5, corresponding to RSD I-RSD V) in pH 6.8 phosphate buffer over 50 minutes is summarised in Table 3a, and clearly illustrates the ratio-dependent decline in release

rate as the proportion of β-cyclodextrin was increased beyond the 1:1 ratio.

Table 3a: Dissolution profile of Enalapril solid dispersion batches SD1-SD5 in pH 6.8 buffer (% drug release)

Time (min)	SD1 (1:1)	SD2 (1:2)	SD3 (1:3)	SD4 (1:4)	SD5 (1:5)
0	0	0	0	0	0
10	38.00	20.34	15.20	13.20	10.43
20	58.76	25.31	25.70	20.34	12.50
30	86.68	43.63	38.06	25.31	18.24
40	97.86	66.73	56.70	43.80	25.34
50	-	80.24	67.81	47.27	38.54

Pre-compression parameters

The angle of repose of the powder blends for F1-F9 ranged from 21.80° to 28.81°, bulk density from 0.300 to 0.344 g/cm3, and tapped density from 0.480 to 0.560 g/cm3. Carr's index ranged from 13.79% to 34.85% and Hausner's ratio from 1.21 to 1.73, indicating that flow properties ranged from fair to poor across the batches, with formulations containing crospovidone together with sodium lauryl sulphate (F7-F8) generally showing comparatively better compressibility than the croscarmellose-based batches (Table 4). Although flow was not uniformly excellent, all blends were compressible into tablets of acceptable weight uniformity under the direct compression conditions employed, and the modestly elevated Carr's index values observed for some batches are consistent with the fine, low-bulk-density nature of superdisintegrant-rich blends generally reported for FDT formulations.

Table 4: Flow properties of powder blends F1-F9 (Mean ± SD, n = 3)

Formulation	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.3412 ± 0.013	0.5601 ± 0.062	34.85 ± 1.83	1.647 ± 0.238	21.80 ± 1.22
F2	0.3412 ± 0.013	0.5265 ± 0.088	33.83 ± 1.63	1.549 ± 0.304	23.26 ± 0.87
F3	0.3002 ± 0.010	0.5185 ± 0.032	20.91 ± 4.82	1.730 ± 0.146	26.56 ± 0.84
F4	0.3442 ± 0.015	0.5033 ± 0.038	26.92 ± 1.88	1.372 ± 0.089	23.42 ± 0.73
F5	0.3281 ± 0.031	0.4907 ± 0.069	31.82 ± 2.20	1.511 ± 0.299	22.17 ± 1.42

Formulation	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F6	0.3001 ± 0.031	0.5007 ± 0.024	15.64 ± 1.70	1.211 ± 0.223	28.36 ± 0.46
F7	0.3251 ± 0.010	0.4804 ± 0.070	21.98 ± 2.01	1.341 ± 0.237	28.81 ± 1.26
F8	0.3201 ± 0.021	0.5288 ± 0.069	13.79 ± 0.20	1.235 ± 0.246	23.48 ± 1.60
F9	0.3011 ± 0.071	0.5124 ± 0.069	33.75 ± 1.72	1.290 ± 0.239	25.52 ± 1.20

Post-compression parameters

All nine formulations met pharmacopoeial requirements for weight variation (148.0-151.65 mg, well within the ± 7.5% limit for tablets of this weight range), hardness (2.6-3.4 kg/cm2), friability (0.17-0.47%, all below the 1% USP limit), thickness (3.2-3.7 mm), diameter (6.8-7.3 mm) and drug content (93.25-99.85%), confirming that a mechanically robust fast dissolving tablet could be achieved despite the low compression force typically required for rapid disintegration (Table 3).

Table 5: Post-compression evaluation of Enalapril fast dissolving tablets (Mean ± SD)

Batch	Weight Variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Drug Content (%)	DT (sec)	WT (sec)
F1	150.00 ± 1.15	3.4 ± 0.2	3.5 ± 0.10	0.281	96.26 ± 0.23	75	68
F2	149.35 ± 1.76	3.3 ± 0.26	3.2 ± 0.12	0.170	99.85 ± 3.60	80	75
F3	151.65 ± 1.09	3.2 ± 0.25	3.4 ± 0.25	0.325	94.62 ± 5.45	80	55
F4	149.95 ± 2.06	2.6 ± 0.20	3.5 ± 0.17	0.180	97.98 ± 1.88	125	98
F5	149.50 ± 2.21	3.0 ± 0.26	3.6 ± 0.31	0.303	98.67 ± 0.93	105	61
F6	151.12 ± 2.11	2.9 ± 0.26	3.4 ± 0.31	0.403	96.95 ± 1.88	100	65
F7	148.00 ± 2.15	3.4 ± 0.26	3.3 ± 0.19	0.410	93.25 ± 3.88	75	65
F8	149.99 ± 1.45	3.0 ± 0.26	3.5 ± 0.40	0.470	98.98 ± 1.88	80	76
F9	150.15 ± 1.25	3.2 ± 0.26	3.7 ± 0.80	0.430	97.00 ± 2.82	83	76

DT: Disintegration time; WT: Wetting time

Disintegration time ranged from 75 to 125 seconds and wetting time from 55 to 98 seconds. Formulations F1 and F7 (containing 4% w/w croscarmellose sodium and 12% w/w crospovidone with sodium lauryl sulphate, respectively) showed the fastest disintegration (75 seconds), whereas F4, which contained the lowest concentration of crospovidone without any wetting agent, disintegrated most slowly (125 seconds). This confirms that both the type and concentration of superdisintegrant, as well as the presence of a wetting agent, substantially influence disintegration performance, with

crospovidone's capillary wicking action being augmented by the surfactant action of sodium lauryl sulphate.

In vitro drug release and kinetics

Cumulative drug release at 40 minutes ranged from 82.88% (F1) to 98.75% (F6), with formulations containing 18 mg crospovidone (F6, F8, F9) consistently releasing more than 93% of the drug within 40 minutes, appreciably faster than the croscarmellose-based formulations (Table 6). This can be attributed to crospovidone's highly porous, non-gelling swelling behaviour, which promotes rapid water uptake and disintegration without the formation of a viscous gel layer that could retard drug release, as can occur with croscarmellose sodium at higher concentrations. Release was also consistently faster in the presence of sodium lauryl sulphate (F7-F9 vs. F6), confirming that improved wetting of the hydrophobic drug-carrier matrix translates directly into a faster onset of dissolution, in agreement with the Noyes-Whitney relationship discussed earlier.

Table 6: Percent cumulative drug release (% CDR) from formulations F1-F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	9.24	4.33	10.80	20.70	19.80	31.50	9.00	19.80	19.80
10	17.42	12.50	18.05	43.30	32.15	51.45	18.35	39.60	39.70
15	44.42	40.30	26.25	52.55	48.51	58.95	34.35	54.30	54.30
20	58.33	53.42	43.50	69.90	66.51	63.75	58.80	71.70	71.70
30	73.06	81.24	73.40	77.50	86.15	93.60	73.55	85.65	84.70
40	82.88	86.15	85.55	94.15	97.60	98.75	90.17	95.30	93.25

Fitting of the dissolution data to zero-order and first-order kinetic models (Table 7) showed higher R2 values for the zero-order model (0.947-0.996) than for the first-order model (0.858-0.985) for most formulations, indicating that drug release from the optimized Enalapril fast dissolving tablets predominantly follows zero-order kinetics, i.e., a constant rate of drug release independent of the residual drug concentration in the tablet, a release pattern that is generally desirable for achieving a consistent and predictable pharmacological response.

Table 7: Regression coefficients (R2) for zero-order and first-order release kinetics (F1-F9)

Formulation	Zero-order R2	First-order R2
F1	0.9806	0.9849
F2	0.9602	0.9582
F3	0.9473	0.9437
F4	0.9812	0.9506
F5	0.9960	0.9271
F6	0.9488	0.8578

Formulation	Zero-order R2	First-order R2
F7	0.9813	0.9469
F8	0.9935	0.9867
F9	0.9887	0.9860

It is also noteworthy that hardness and friability, though inversely related to disintegration rate in principle, did not compromise the disintegration performance of any of the nine formulations in this study, since all batches were compressed at a deliberately low compaction force characteristic of direct-compression FDT manufacture; this confirms that an adequately robust tablet (friability < 0.5%, hardness 2.6-3.4 kg/cm2) could be achieved without sacrificing the target disintegration time of under 130 seconds for any formulation, and under 90 seconds for the crospovidone/SLS-based batches. From a patient-acceptability standpoint, the low compaction force together with the inclusion of saccharin as a sweetening and taste-masking agent would also be expected to confer an acceptable in-mouth feel, although a dedicated taste-panel evaluation was outside the scope of the present in vitro study.

Selection of optimized formulation

Considering disintegration time, wetting time, friability, drug content uniformity, extent of cumulative drug release and adherence to zero-order kinetics collectively, formulation F8 (18 mg crospovidone with 2 mg sodium lauryl sulphate) emerged as the optimized batch, combining a disintegration time of 80 seconds, friability below 0.5%, drug content of approximately 99%, and 95.30% cumulative drug release within 40 minutes with an excellent zero-order fit (R2 = 0.9935).

Accelerated stability study

The optimized formulation showed no visible change in physical appearance after 30 days of storage at 40°C ± 2°C/75% ± 5% RH. Drug content changed only marginally, from 99.23% before storage to 99.17% after storage, and the in vitro dissolution profile after stability testing was virtually superimposable on the initial profile, confirming that the formulation retained its physicochemical integrity and release characteristics under accelerated storage conditions.

Limitations and scope for future work

The present study was limited to in vitro evaluation of solubility, disintegration and dissolution behaviour and a 30-day accelerated stability study; it did not include in vivo pharmacokinetic, bioavailability or taste-evaluation studies, which would be necessary to fully translate the observed in vitro advantages into demonstrated clinical benefit. In addition, the Enalapril-β-cyclodextrin solid dispersion was characterized only by melting point, phase-solubility and FTIR spectroscopy; complementary techniques such as differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) would provide further confirmation of the extent of drug amorphization/complexation achieved. Long-term stability studies (6-24 months) under ICH long-term and intermediate storage conditions, together with a comparative in vivo bioavailability study against the marketed conventional Enalapril tablet, are recommended as the logical next steps in the development of this formulation.

SUMMARY AND CONCLUSION

Enalapril, an ACE inhibitor used widely in the management of hypertension and congestive heart

failure, is practically insoluble in water and subject to substantial first-pass hepatic metabolism, both of which limit its oral bioavailability and delay the onset of its antihypertensive effect. In the present investigation, a solid dispersion of Enalapril with β-cyclodextrin, prepared by the kneading method in a 1:1 drug-to-carrier ratio, was found to enhance aqueous solubility by approximately 34% relative to the pure drug. This optimized solid dispersion was successfully incorporated into fast dissolving tablets by the direct compression method using crospovidone and croscarmellose sodium as superdisintegrants. FTIR studies confirmed the absence of any significant drug-excipient interaction, supporting formulation stability. Of the nine formulations developed, those based on crospovidone, particularly in combination with sodium lauryl sulphate as a wetting agent, exhibited the most favourable combination of rapid disintegration, acceptable mechanical strength and near-complete, zero-order drug release within 40 minutes. The optimized formulation retained its physical, chemical and dissolution characteristics on accelerated stability testing.

It may therefore be concluded that the combination of solid dispersion technology with fast dissolving tablet formulation represents an effective strategy for overcoming the solubility-limited bioavailability of Enalapril, offering the additional clinical advantage of rapid disintegration in the oral cavity without the need for water. Such a formulation could be of particular value for pediatric, geriatric and dysphagic hypertensive patients, and in situations demanding a prompt onset of antihypertensive action. Further in vivo pharmacokinetic and bioavailability studies, together with long-term stability studies, are warranted to fully establish the clinical translatability of the optimized formulation.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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