

COMPRISING TELMISARTAN SOFT GELATIN CAPSULE AND SUSTAINED RELEASE HYDROCHLOROTHIAZIDE PELLETS FOR HYPERTENSION MANAGEMENT

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ABSTRACT :

OBJECTIVE :

The present study aimed to develop and evaluate a novel hybrid oral dosage form containing **immediate-release Telmisartan** and **sustained-release Hydrochlorothiazide**. The study was designed to combine both release characteristics within a single hard gelatin capsule. Preformulation studies were performed to evaluate the physicochemical properties and drug–excipient compatibility. Telmisartan soft gelatin formulations were developed to improve solubilization and rapid drug dissolution. Hydrochlorothiazide sustained-release pellets were developed to achieve prolonged drug release. The optimized formulations were combined and evaluated for physicochemical characteristics, drug content, dissolution behaviour, release kinetics and stability.

METHODS

Preformulation studies including solubility, FTIR and DSC compatibility studies were carried out for Telmisartan and Hydrochlorothiazide. Six Telmisartan softgel formulations (F1–F6) were prepared using PEG 400, propylene glycol, Tween 80 and MCT oil. The formulations were evaluated for appearance, clarity, drug content and in-vitro dissolution. Six Hydrochlorothiazide sustained-release pellet formulations were prepared by **extrusion–spheronization** using HPMC K100M and ethyl cellulose. The pellets were evaluated for

morphology, micromeritic properties, drug content and in-vitro drug release. The optimized Telmisartan softgel and Hydrochlorothiazide pellets were incorporated into a size '0' hard gelatin capsule and evaluated for dual-release behaviour and stability.

RESULTS

Among the Telmisartan formulations, **F6 was selected as the optimized formulation**, showing 99.60% drug content and 98.82% drug release at 60 min. Hydrochlorothiazide pellet formulation F6 showed spherical and smooth pellets with a drug content of 99.2%. The optimized pellets showed controlled drug release of 18.26% at 1 h and 99.18% at 12 h. The Korsmeyer–Peppas model showed the best fit with $R^2 = 0.9969$ and an n-value of 0.686. The final hybrid capsule showed satisfactory physical characteristics and drug contents of $99.4 \pm 0.5\%$ Telmisartan and $98.9 \pm 0.6\%$ Hydrochlorothiazide. Telmisartan showed rapid release of 98.14% at 60 min, whereas Hydrochlorothiazide showed prolonged release of 99.18% at 12 h.

CONCLUSION

The study successfully developed a **hybrid oral dosage form** combining immediate-release Telmisartan with sustained-release Hydrochlorothiazide.

Telmisartan softgel F6 provided rapid drug release, while Hydrochlorothiazide pellet F6 provided controlled and prolonged release.

The final hybrid capsule successfully maintained the intended biphasic IR/SR drug-release pattern. The formulation showed satisfactory physical integrity, drug content and dissolution performance. Accelerated stability studies for 3 months demonstrated that the formulation retained acceptable physical and dissolution characteristics.

The developed system therefore demonstrated technical feasibility as a single oral dosage form providing two independently controlled drug-release profiles.

1.INTRODUCTION

Hypertension is one of the major chronic cardiovascular disorders and requires long-term pharmacological management to maintain blood pressure within the desired therapeutic range. Effective treatment may require the use of antihypertensive agents with different mechanisms of action to achieve adequate and sustained blood-pressure control. Telmisartan, an angiotensin II receptor blocker, and Hydrochlorothiazide, a thiazide diuretic, represent two complementary approaches to antihypertensive therapy. The present research focuses on developing a novel dosage form that combines these two drugs with different release characteristics in a single oral dosage unit. Final thesis for Suriya

Telmisartan is characterized by poor aqueous solubility and is classified as a BCS Class II drug, making dissolution an important factor influencing its oral drug-release behaviour. Therefore, a formulation approach capable of improving drug solubilization and promoting rapid dissolution is desirable. In the present study, Telmisartan was incorporated into a soft gelatin capsule using a solubilized fill system containing suitable excipients. The softgel approach was selected to facilitate rapid release of Telmisartan and provide the intended immediate-release component of the formulation. Final thesis for Suriya

Hydrochlorothiazide has comparatively better aqueous solubility and can be incorporated into a polymer-controlled multiparticulate system to obtain prolonged drug release. Sustained-release pellets provide several formulation advantages, including controlled drug liberation and the possibility of obtaining a more consistent release profile. In this research, Hydrochlorothiazide pellets were developed using extrusion-spheronization with release-controlling polymers. The formulation variables were optimized to obtain uniform, mechanically stable pellets with appropriate flow characteristics and controlled drug-release behaviour. Final thesis for Suriya

The concept of the present work was therefore based on combining two independently designed delivery systems within a single dosage form. An immediate-release Telmisartan soft gelatin capsule was intended to provide rapid drug availability, whereas sustained-release Hydrochlorothiazide pellets were designed to maintain drug release over an extended period. The two optimized components were subsequently incorporated into a size “0” hard gelatin capsule. This hybrid configuration was designed to produce a dual-release profile consisting of rapid Telmisartan release followed by prolonged Hydrochlorothiazide release from the same oral dosage unit. Final thesis for Suriya

Preformulation studies were performed to establish the physicochemical characteristics of both drug substances and to determine their suitability for formulation development. Solubility studies, Fourier-transform infrared spectroscopy and differential scanning calorimetry were used to support formulation selection and assess drug-excipient compatibility. Analytical methods were also established for quantitative estimation of the drugs. Because the absorption characteristics of the two drugs overlapped in the combined system, simultaneous RP-HPLC analysis was employed for evaluation of the final hybrid formulation and dissolution samples. Final thesis for Suriya

The developed hybrid dosage form was evaluated comprehensively for its physical characteristics, drug content, integrity and in-vitro dissolution behaviour. The optimized Telmisartan softgel and Hydrochlorothiazide sustained-release pellets were assessed individually before incorporation into the final capsule. The final hybrid system was then examined to confirm that the combination of the two components did not adversely affect their respective release characteristics. Release kinetics were additionally studied to understand the mechanism governing Hydrochlorothiazide release from the pellet system. Final thesis for Suriya

Overall, the study was designed to demonstrate the technical feasibility of a hybrid oral dosage form capable of delivering two antihypertensive agents through independently controlled release mechanisms. The formulation combines the rapid-release advantage required for poorly soluble Telmisartan with the prolonged-release characteristics intended for Hydrochlorothiazide. Such a system provides a rational formulation strategy for incorporating different release profiles within a single oral dosage unit and was subsequently evaluated for its physicochemical performance and short-term accelerated stability.

Hypertension is a common chronic cardiovascular disorder that requires effective and continuous pharmacological management. Telmisartan, an angiotensin II receptor blocker, and Hydrochlorothiazide, a thiazide diuretic, provide complementary antihypertensive effects. Telmisartan is a poorly water-soluble BCS Class II drug, making rapid dissolution an important consideration for its oral delivery. Therefore, a solubilized soft gelatin capsule was selected to improve the dissolution and provide immediate release of Telmisartan.

Hydrochlorothiazide was incorporated into sustained-release pellets to achieve controlled and prolonged drug release.

The pellets were developed using extrusion–spheronization with suitable release-controlling polymers to obtain uniform and stable multiparticulates.

The optimized Telmisartan softgel and Hydrochlorothiazide pellets were combined within a single size “0” hard gelatin capsule.

This hybrid dosage form was designed to provide rapid release of Telmisartan along with prolonged release of Hydrochlorothiazide from one oral dosage unit.

Preformulation, compatibility, physicochemical, drug-content and in-vitro dissolution studies were performed to optimize and evaluate the formulation.

The overall approach was intended to establish a technically feasible hybrid oral delivery system providing distinct immediate-release and sustained-release profiles for hypertension management.

Hypertension is a major chronic cardiovascular disorder requiring effective long-term pharmacological therapy. Telmisartan and Hydrochlorothiazide are antihypertensive agents with complementary therapeutic actions.

Telmisartan is a poorly water-soluble BCS Class II drug, for which rapid dissolution is important. A soft gelatin capsule was therefore selected to provide a solubilized and immediate-release formulation of Telmisartan. Hydrochlorothiazide was formulated as sustained-release pellets to provide controlled and prolonged drug release. The pellets were prepared using extrusion–spheronization with suitable release-controlling polymers. The optimized Telmisartan softgel and Hydrochlorothiazide pellets were incorporated into a single size “0” hard gelatin capsule. The hybrid system was designed to provide rapid release of Telmisartan and prolonged release of Hydrochlorothiazide from one dosage unit.

2.MATERIALS AND METHODS

2.1 Materials

The present investigation was carried out for the development of a hybrid oral dosage form containing **immediate-release Telmisartan soft gelatin capsules and sustained-release Hydrochlorothiazide pellets**. Telmisartan and Hydrochlorothiazide were selected as the active pharmaceutical ingredients. The soft gelatin shell consisted mainly of gelatin, glycerol, liquid sorbitol, purified water, methyl hydroxybenzoate, propyl hydroxybenzoate, titanium dioxide and iron oxide red. The Telmisartan liquid fill contained PEG 400, propylene glycol, Tween 80 and medium-chain triglyceride (MCT) oil. Final thesis for Suriya

For preparation of the Hydrochlorothiazide sustained-release pellets, microcrystalline cellulose PH 101, lactose monohydrate, HPMC K100M, ethyl cellulose and PVP K30 were used. HPMC K100M and ethyl cellulose served as the principal release-retarding polymers, while MCC PH 101 supported pellet formation and PVP K30 acted as a binder. Purified water was used as the granulating liquid during pellet preparation. Size “2” hard gelatin capsules were used for preliminary pellet dissolution testing, while size “0” block-orange hard gelatin capsules were selected as the outer shell for the final hybrid formulation. Final thesis for Suriya

Analytical and processing solvents included purified water, methanol, ethanol, 0.1 N hydrochloric acid, phosphate buffers, acetonitrile and potassium bromide. The major instruments employed during the study included an analytical balance, UV–Visible spectrophotometer, RP-HPLC system, FTIR spectrophotometer, differential scanning calorimeter, melting-point apparatus, USP dissolution apparatus II, friabilator, planetary mixer, extruder, spheroniser, tray dryer, sieve set, rotary-die soft gelatin encapsulation machine, sonicator and stability chamber. Final thesis for Suriya

2.2 Preformulation Studies

Preformulation investigations were performed before formulation development to establish the basic physicochemical characteristics of Telmisartan and Hydrochlorothiazide and to assist in selecting appropriate formulation components. The studies included evaluation of organoleptic properties, solubility behaviour and melting point. These preliminary investigations provided information useful for designing the immediate-release Telmisartan softgel and sustained-release Hydrochlorothiazide pellet systems. Final thesis for Suriya

The colour, odour, appearance and physical nature of each drug were examined visually using clean watch glasses against a white background. Solubility studies were conducted to understand the dissolution behaviour of the drug substances in selected solvents and aqueous media. Melting-point determination was performed using a digital melting-point apparatus, and the observed values were compared with the expected characteristics of the respective drug substances. The preformulation findings were subsequently used to guide the selection of the solubilized liquid fill and polymeric pellet matrix. Final thesis for Suriya

2.3 Analytical Method Development

UV–Visible spectrophotometry was employed for the quantitative estimation of the individual drugs. Telmisartan exhibited maximum absorption at approximately **296 nm**, whereas Hydrochlorothiazide showed maximum absorption around **274 nm**. Standard calibration solutions were prepared over the concentration range of **2–12 µg/mL**, and calibration curves were established for quantitative analysis. The analytical procedures were applied for drug-content determination and dissolution studies of the individual formulations. Final thesis for Suriya

For samples containing both drugs, simultaneous analysis by UV spectroscopy was considered unsuitable because of overlapping absorption characteristics. Therefore, a reversed-phase HPLC method was developed for simultaneous estimation of Telmisartan and Hydrochlorothiazide in the final hybrid formulation and dissolution samples. A C18 reverse-phase column with an aqueous buffer and organic solvent system was used, with UV/PDA detection. The method development considered specificity, linearity, accuracy, precision, detection and quantification limits, robustness and system suitability in accordance with the stated analytical approach. Final thesis for Suriya

2.4 Drug–Excipient Compatibility Studies

Compatibility studies were conducted to determine whether the selected excipients produced any significant physical or chemical interaction with Telmisartan or Hydrochlorothiazide. Fourier-transform infrared spectroscopy and differential scanning calorimetry were used as

complementary analytical techniques. Physical mixtures of the drugs with their proposed excipients were prepared in suitable ratios and stored in airtight containers protected from moisture and light before analysis. Final thesis for Suriya

For FTIR analysis, the samples were mixed with IR-grade potassium bromide and compressed to form pellets. Spectra were recorded over the range of **4000–400 cm⁻¹**, and the characteristic absorption bands of the pure drugs were compared with those of the corresponding drug–excipient mixtures. For DSC analysis, approximately 3–5 mg of sample was placed in aluminium pans and heated at a controlled rate under nitrogen atmosphere over a suitable temperature range. Changes in characteristic peaks, peak positions and thermal behaviour were examined to assess compatibility. Final thesis for Suriya

2.5 Development of Telmisartan Soft Gelatin Capsules

The immediate-release Telmisartan component was developed as a liquid-filled soft gelatin capsule because Telmisartan has poor aqueous solubility. Six formulations, designated **F1–F6**, were prepared by varying the proportions of PEG 400, propylene glycol, Tween 80 and MCT oil while maintaining the Telmisartan dose at **20 mg** and the total fill weight at **120 mg**. The formulation design allowed the effect of the co-solvent, surfactant and oil ratios on the physical characteristics and dissolution performance of the drug to be investigated. Final thesis for Suriya

The soft gelatin shell was prepared using gelatin as the principal film-forming material together with glycerol and liquid sorbitol as plasticizing agents. Methyl hydroxybenzoate and propyl hydroxybenzoate were incorporated as preservatives, while titanium dioxide and iron oxide red were used for opacity and colour. The shell ingredients were mixed and heated under controlled conditions, followed by filtration, gelatin incorporation, vacuum mixing and deaeration to obtain a homogeneous gelatin mass suitable for encapsulation. Final thesis for Suriya

For preparation of the Telmisartan fill, the accurately weighed drug was first incorporated into PEG 400 and mixed thoroughly. Propylene glycol was then added gradually with continuous stirring, followed by Tween 80 and MCT oil. The mixture was homogenized until a clear or uniformly dispersed system was obtained, and entrapped air was removed by sonication or standing. The prepared liquid fill was subsequently encapsulated using the **rotary-die soft gelatin encapsulation technique**, followed by drying, inspection and removal of defective capsules. Final thesis for Suriya

The prepared softgel formulations were examined for general appearance, weight variation, fill-weight uniformity, shell thickness, drug content, disintegration, leakage, moisture content and physical stability of the fill. Drug content was determined by dissolving an accurately measured quantity of the fill in a suitable solvent followed by filtration, dilution and UV spectrophotometric analysis. In-vitro dissolution testing was carried out using USP dissolution apparatus II, and the release of Telmisartan was monitored over the specified period. Final thesis for Suriya

2.6 Development of Hydrochlorothiazide Sustained-Release Pellets

The sustained-release Hydrochlorothiazide component was prepared as matrix-type pellets using the **extrusion–spheronization technique**. Six formulations, F1–F6, were prepared with a fixed Hydrochlorothiazide quantity of **25 mg per 100 mg solid formulation**. MCC PH 101 and lactose were used as pelletization aid and diluent, respectively, while increasing concentrations of HPMC K100M and ethyl cellulose were incorporated to modify the drug-release rate. PVP K30 was maintained as the binder. Final thesis for Suriya

The required quantities of Hydrochlorothiazide, MCC, lactose, HPMC K100M and ethyl cellulose were accurately weighed and dry blended for approximately 10–15 minutes. PVP K30 was separately dissolved in purified water to prepare the binder solution. The binder solution was gradually added to the dry mixture under continuous mixing until a cohesive, plastic and non-sticky wet mass suitable for extrusion was obtained. Final thesis for Suriya

The prepared wet mass was passed through a **1.0 mm perforated screen** to produce cylindrical extrudates. These extrudates were immediately transferred to the spheroniser and processed at approximately **800–1200 rpm for 5–10 minutes** to convert them into spherical pellets. The wet pellets were subsequently dried in a tray dryer or hot-air oven at **40–50°C for 4–6 hours** until a constant weight was achieved. The dried material was sieved, and the desired **0.5–1.2 mm** size fraction was collected and stored in airtight containers under suitable conditions. Final thesis for Suriya

The Hydrochlorothiazide pellets were evaluated for appearance, shape, surface characteristics, particle-size distribution and micromeritic properties. Flow characteristics were assessed using angle of repose, bulk density, tapped density, Carr’s compressibility index and Hausner ratio. Mechanical strength was examined by friability testing, while drug content was determined by extracting the drug from an accurately weighed quantity of pellets followed by filtration, dilution and UV analysis. Final thesis for Suriya

For dissolution testing, the required quantity of pellets was accurately filled into size “2” hard gelatin capsules to obtain a suitable unit-dose test system. The capsules were subjected to in-vitro dissolution testing using USP apparatus II at **37 ± 0.5°C**. Samples were withdrawn at predetermined intervals, replaced with fresh dissolution medium, filtered and analysed for Hydrochlorothiazide. The release data were subsequently examined using suitable mathematical models, including zero-order, first-order, Higuchi and Korsmeyer–Peppas models. Final thesis for Suriya

2.7 Development of the Hybrid Capsule

After optimization of the individual components, the Telmisartan softgel and Hydrochlorothiazide sustained-release pellets were combined to produce the final hybrid dosage form. One optimized Telmisartan softgel containing **20 mg Telmisartan** was combined with the quantity of Hydrochlorothiazide pellets corresponding to **25 mg drug**. A **size “0” block-orange hard gelatin capsule** was selected because it provided sufficient internal space to accommodate both components without damaging the softgel or compressing the pellets. Final thesis for Suriya

The hard gelatin capsule was separated into its body and cap. One optimized Telmisartan softgel was carefully positioned inside the capsule body, followed by accurate filling of the required quantity of Hydrochlorothiazide sustained-release pellets around the softgel. Care was taken to avoid pellet crushing, overfilling or deformation of the softgel. The capsule cap was then fitted securely, and the finished units were visually inspected for proper locking, leakage and deformation. Final thesis for Suriya

2.8 Evaluation of the Final Hybrid Capsule

The final hybrid capsules were evaluated for external appearance, capsule locking, weight variation, component integrity and drug content. Individual capsules were visually inspected for uniformity of colour, shape and surface finish and for the absence of cracks, dents or deformation. Weight variation was assessed using randomly selected capsules, while the contents of selected units were analysed for Telmisartan and Hydrochlorothiazide to assess dose uniformity. Final thesis for Suriya

The in-vitro dissolution behaviour of the final hybrid capsule was studied using a two-stage approach to demonstrate the intended **immediate-release/sustained-release (IR/SR)** characteristics. Telmisartan release from the softgel component was monitored during the initial phase, while Hydrochlorothiazide release from the polymeric pellets was followed over an extended period. The combined dissolution samples were analysed using the developed simultaneous RP-HPLC procedure to distinguish and quantify both drugs accurately. Final thesis for Suriya

Finally, the optimized hybrid formulation was subjected to accelerated stability testing at **40 ± 2°C and 75 ± 5% relative humidity for three months**. Samples were evaluated at predetermined intervals for physical appearance, weight characteristics, drug content and dissolution performance. The stability study was intended to determine whether the formulation maintained its physical integrity and the desired immediate-release and sustained-release characteristics during storage.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 Organoleptic Properties

Telmisartan and Hydrochlorothiazide were examined for their basic physical characteristics before formulation development. Both drugs appeared as white to off-white, odourless crystalline powders. Telmisartan was found to be non-hygroscopic, whereas Hydrochlorothiazide showed slight hygroscopicity during prolonged exposure to atmospheric conditions. No visible discoloration, abnormal particles or other physical defects were observed. The findings indicated that both drug substances were physically suitable for further formulation development.

3.1.2 Solubility Studies

The solubility behaviour of Telmisartan and Hydrochlorothiazide was studied in different solvents and aqueous media. Telmisartan was practically insoluble in distilled water, while Hydrochlorothiazide showed comparatively better aqueous solubility. Telmisartan was freely soluble in methanol and soluble in ethanol, whereas Hydrochlorothiazide showed good solubility in methanol and moderate solubility in ethanol. In 0.1 N HCl, Telmisartan showed slight solubility, while Hydrochlorothiazide was soluble. These findings supported the selection of a solubilized soft gelatin formulation for Telmisartan and a polymer-controlled sustained-release pellet system for Hydrochlorothiazide.

3.1.3 Melting Point Determination

The observed melting point of Telmisartan was **261–263°C**, which was close to its reported value. Hydrochlorothiazide exhibited a melting range of **267–270°C**, also consistent with reported values. The relatively narrow melting ranges indicated reproducible thermal behaviour of both drug substances. These results provided preliminary confirmation of the identity and physical characteristics of the drugs. The melting point data were also used as reference values for interpretation of the subsequent DSC studies.

3.2 Analytical Method Development

Methanol was selected as the analytical solvent because it produced clear and stable solutions of both Telmisartan and Hydrochlorothiazide. The maximum absorption wavelength was found to be **296 nm for Telmisartan** and **274 nm for Hydrochlorothiazide**. Calibration curves were prepared over the concentration range of **2–12 µg/mL**. Telmisartan showed an excellent correlation coefficient of **$R^2 = 0.9993$** , while Hydrochlorothiazide showed **$R^2 = 0.9999$** . The results demonstrated good linearity and supported the use of the developed UV method for quantitative estimation.

Since the two drugs exhibited overlapping spectral characteristics in the combined formulation, simultaneous estimation by individual UV wavelengths was not considered sufficient for the final hybrid dosage form. Therefore, an RP-HPLC method was used for simultaneous analysis of Telmisartan and Hydrochlorothiazide in the hybrid capsule and dissolution samples. This provided appropriate separation and quantification of both active ingredients.

3.3 Drug–Excipient Compatibility Studies

FTIR and DSC studies were carried out to determine the compatibility of the selected excipients with Telmisartan and Hydrochlorothiazide. The characteristic functional-group peaks of both drugs were retained in their respective optimized formulation blends, with no major disappearance or formation of new peaks. This indicated the absence of significant chemical interaction between the drugs and selected excipients under the conditions studied.

DSC analysis further supported the FTIR findings. Telmisartan showed a melting peak near **262.8°C**, while its optimized formulation blend showed only a minor shift to approximately **261.5°C**. Hydrochlorothiazide showed a melting peak around **268.4°C**, while the optimized blend showed approximately **267.1°C**. The observed shifts were small and accompanied by modest reductions in enthalpy, without new thermal events or eutectic formation.

Overall, the FTIR and DSC findings indicated satisfactory compatibility between the drugs and their selected excipients. Therefore, the excipients were considered suitable for further development of the Telmisartan softgel and Hydrochlorothiazide sustained-release pellet formulations.

3.4 Development and Evaluation of Telmisartan Soft Gelatin Capsule

Six Telmisartan soft gelatin formulations, designated **F1–F6**, were prepared using different proportions of PEG 400, propylene glycol, Tween 80 and MCT oil. The Telmisartan concentration was maintained at 20 mg in all formulations. The formulations were evaluated for physical appearance, clarity, drug content and in-vitro dissolution behaviour.

3.4.1 Physical Appearance and Clarity

A progressive improvement in clarity and fluidity was observed from F1 to F6. F1 appeared slightly viscous and turbid, whereas F2 showed improved clarity. F3 and F4 were clear, F5 was fluid and clear, and F6 produced a **clear, transparent and highly fluid formulation**. The improvement was attributed to the combined solubilizing and wetting effects of PEG 400, propylene glycol and Tween 80, along with the reduced relative proportion of MCT oil.

3.4.2 Drug Content

The drug content of the Telmisartan formulations ranged from **96.2% to 99.6%**. F1 showed the lowest drug content, whereas F6 exhibited the highest value of **99.6%**. All formulations remained within the applied acceptance range. The progressive increase in drug content was consistent with improved clarity and uniformity of the optimized formulation.

3.4.3 In-Vitro Dissolution Study

Telmisartan release increased progressively from F1 to F6. At 60 minutes, the cumulative drug release was **78.16% for F1** and increased to **98.82% for F6**. F5 also showed a high release of 94.37%, demonstrating the positive influence of the co-solvent and surfactant system. The higher release from F6 was associated with improved solubilization, wetting and dispersion of Telmisartan within the dissolution medium.

3.4.4 Selection of Optimized Formulation

Based on physical appearance, clarity, drug content and dissolution behaviour, **F6 was selected as the optimized Telmisartan soft gelatin formulation**. It showed a clear and transparent fill, drug content of **99.60%** and drug release of **98.82% at 60 minutes**. Therefore, F6 was selected for incorporation into the final hybrid capsule.

3.4.5 Comparison with Marketed Product

The optimized Telmisartan F6 softgel was compared with a marketed Telmisartan 20 mg tablet. F6 showed faster dissolution, with **60.72% release at 10 minutes** compared with **38.46%** for the marketed tablet. At 60 minutes, F6 achieved **98.82% release**, compared with **96.74%** for the marketed product. The difference factor and similarity factor were **$f_1 = 20.0$ and $f_2 = 40.4$** , respectively, indicating a different and faster dissolution profile for the developed softgel.

4.5 Development and Evaluation of Hydrochlorothiazide Sustained-Release Pellets

Six Hydrochlorothiazide sustained-release pellet formulations, F1–F6, were prepared using extrusion–spheronization with progressively increased concentrations of HPMC K100M and ethyl cellulose. The formulations were evaluated for morphology, flow properties, drug content and in-vitro drug-release characteristics. Final thesis for Suriya

3.5.1 Physical Appearance and Morphology

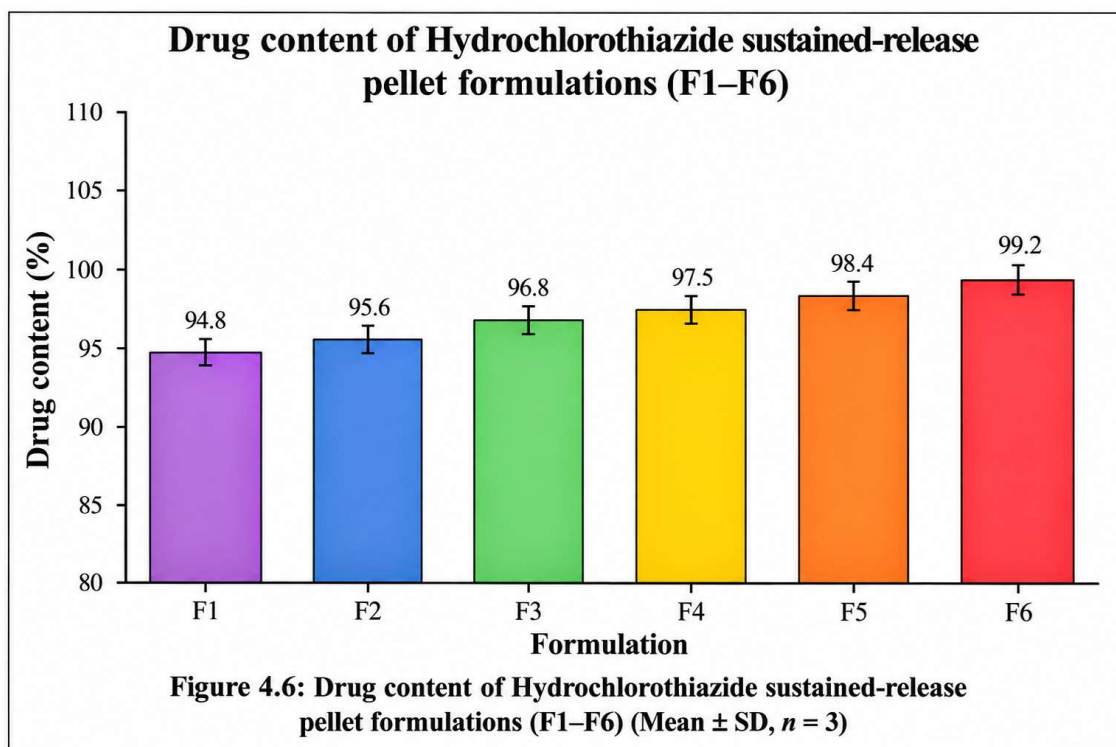
F1 showed irregular-to-spherical pellets with a slightly rough surface, while F2 showed improved pellet formation. F3 and F4 produced spherical and smooth pellets, whereas F5 showed dense pellets with good mechanical characteristics. F6 produced **spherical, smooth and relatively uniform pellets**, indicating the best overall morphology. The improved morphology was associated with increased polymer concentration and better cohesiveness of the wet mass during spheronization.

3.5.2 Flow Properties

The flow properties improved progressively with increasing polymer concentration. The angle of repose decreased from **29.5° in F1 to 24.5° in F6**. Carr's index decreased from **18.2% to 11.8%**, while the Hausner ratio decreased from **1.22 to 1.13**. These results indicated improved flow behaviour of the optimized formulation. The spherical and smooth morphology of F6 contributed to reduced interparticle friction and improved handling during capsule filling.

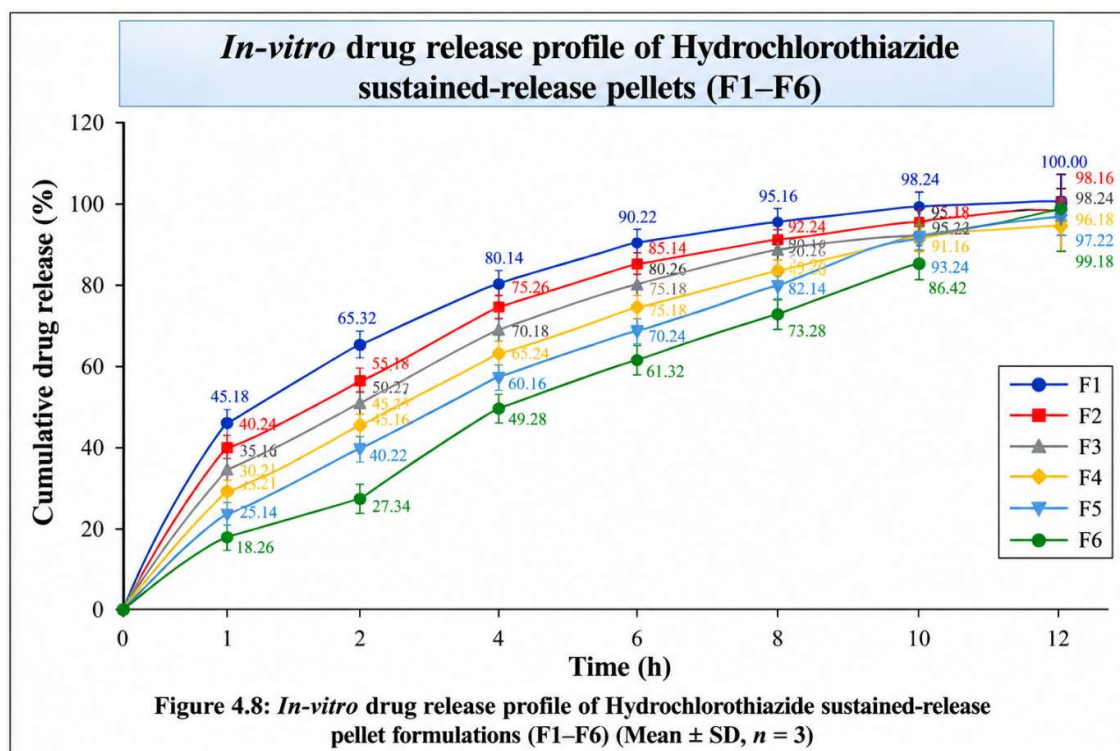
3.5.3 Drug Content

The Hydrochlorothiazide content ranged from **94.8% in F1 to 99.2% in F6**. All formulations were within the specified acceptance range. F6 showed the highest drug content, which was associated with improved wet-mass cohesiveness and more uniform distribution of the drug within the pellet matrix at higher polymer concentrations.



3.5.4 In-Vitro Drug Release

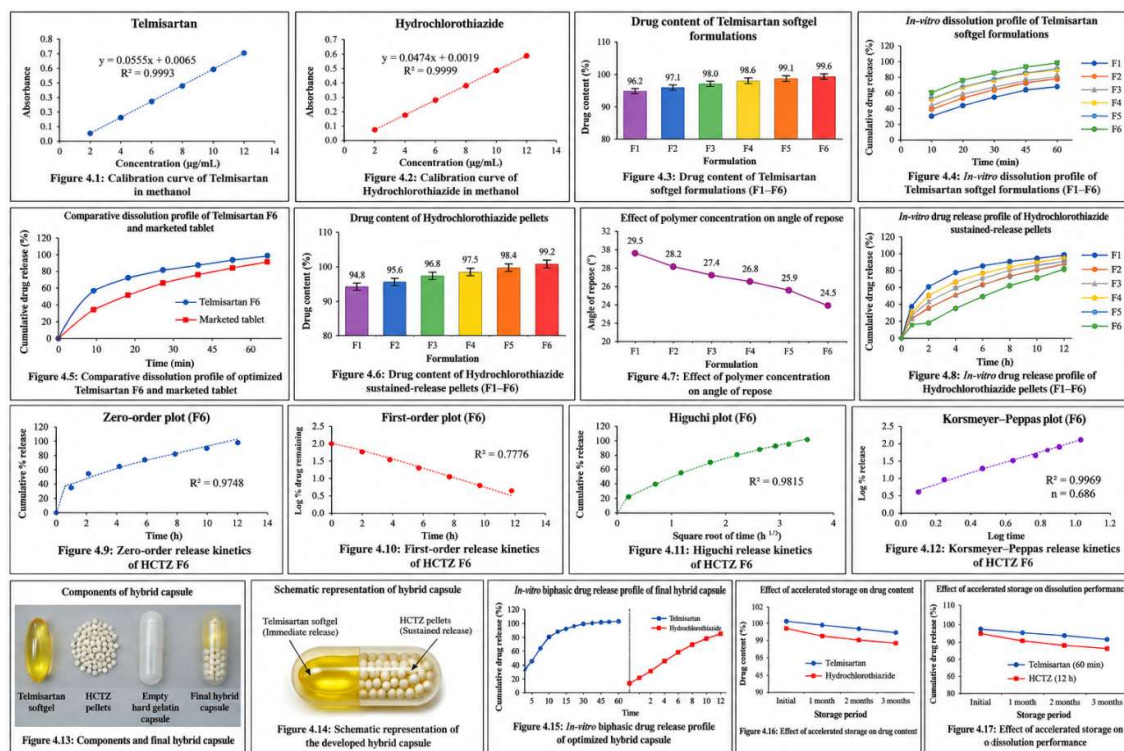
The dissolution results demonstrated a clear polymer concentration-dependent reduction in Hydrochlorothiazide release. F1 released **45.18% at 1 hour** and reached complete release by 12 hours, whereas F6 released only **18.26% at 1 hour** and gradually increased to **99.18% at 12 hours**. The slower release from F6 was attributed to the combined barrier-forming effects of HPMC K100M and ethyl cellulose.



3.5.5 Drug-Release Kinetics

The release kinetics of optimized F6 pellets were evaluated using different mathematical models. The **Korsmeyer–Peppas model showed the highest correlation coefficient ($R^2 = 0.9969$)**, followed by the Higuchi model with $R^2 = 0.9815$ and zero-order model with $R^2 = 0.9748$. The first-order model showed a lower correlation coefficient of $R^2 = 0.7776$.

The Korsmeyer–Peppas release exponent was $n = 0.686$, indicating anomalous or non-Fickian drug transport. This suggested that Hydrochlorothiazide release was controlled by a combination of drug diffusion and polymer relaxation/erosion. The hydration and swelling of HPMC K100M together with the barrier effect of ethyl cellulose contributed to the sustained-release mechanism.



3.6 Development and Evaluation of Final Hybrid Capsule

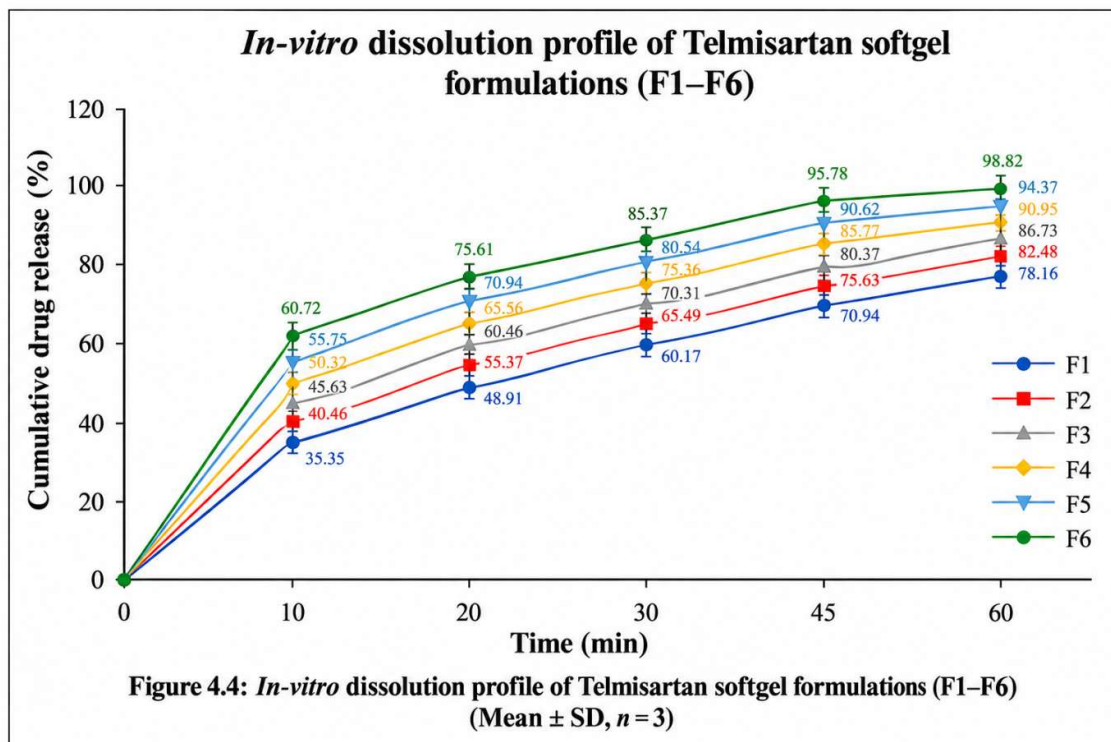
The optimized Telmisartan softgel F6 and Hydrochlorothiazide pellet F6 were incorporated into a single **size '0' hard gelatin capsule**. The final capsules exhibited a smooth and uniform appearance with satisfactory capsule-locking integrity. The average capsule weight was 260 ± 3 mg, with weight variation of $\pm 2.1\%$, and the pellet fill weight was 120 ± 2 mg.

Each capsule contained one intact Telmisartan softgel without leakage, rupture or deformation. The drug content was $99.4 \pm 0.5\%$ for **Telmisartan** and $98.9 \pm 0.6\%$ for **Hydrochlorothiazide**. These results demonstrated satisfactory incorporation and uniformity of both components in the final dosage form.

3.6.1 In-Vitro Dual-Release Study

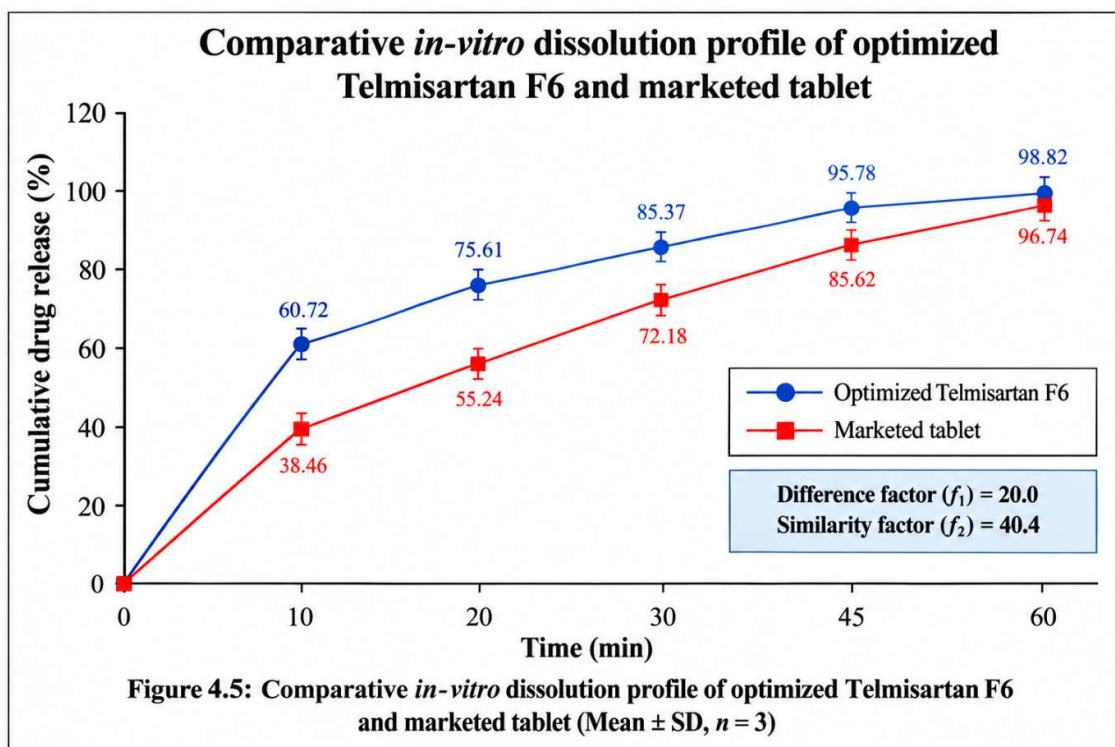
The final hybrid capsule showed the intended biphasic release pattern. Telmisartan exhibited rapid release, reaching **75.16% at 15 minutes, 90.12% at 30 minutes, 98.14% at 60 minutes and 99.12% at 2 hours**. This confirmed the immediate-release behaviour of the Telmisartan softgel component.

Hydrochlorothiazide showed controlled release, with **18.26% release at 1 hour, 49.28% at 4 hours, 73.28% at 8 hours and 99.18% at 12 hours**. The release profile was comparable to that of the optimized standalone pellet formulation. Therefore, incorporation of both components into the same capsule did not show an apparent adverse effect on their individual release characteristics.



3.6.2 Comparison with Intended Release Profile

The developed hybrid capsule achieved the intended release objectives. Telmisartan showed rapid release of approximately **98% within 60 minutes**, whereas Hydrochlorothiazide demonstrated prolonged release reaching approximately **99% at 12 hours**. Thus, the final dosage form successfully combined an immediate-release component and a sustained-release multiparticulate component within a single oral dosage unit.



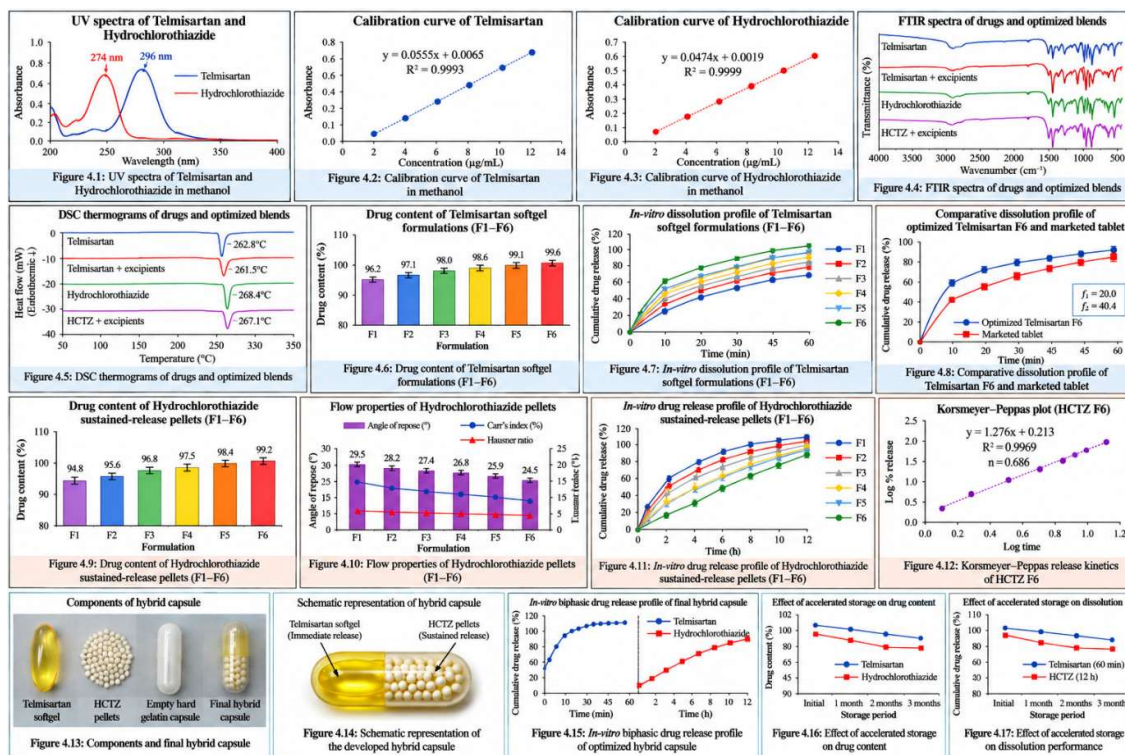
3.7 Stability Studies of Optimized Hybrid Capsule

The optimized hybrid capsule was subjected to accelerated stability conditions of $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for **three months**. The formulation was evaluated for physical appearance, weight variation, drug content and dissolution behaviour at different storage intervals.

No significant changes were observed in colour, shape, surface appearance or overall capsule integrity. There was no visible cracking, deformation, softgel leakage or pellet aggregation during the study. Weight variation increased only slightly from $\pm 2.1\%$ **initially to $\pm 2.7\%$ after three months**, indicating satisfactory physical stability.

Telmisartan content decreased from **99.4% to 98.3%**, while Hydrochlorothiazide content decreased from **98.9% to 97.8%** after three months. Both drug contents remained within the reported specification. The changes were relatively small and did not indicate substantial deterioration during the investigated accelerated storage period.

The dissolution characteristics were also substantially maintained. Telmisartan release at 60 minutes decreased from approximately **98% to 95%**, while Hydrochlorothiazide release at 12 hours decreased from approximately **99% to 94%**. Despite these minor changes, the formulation retained its intended immediate-release and sustained-release characteristics.



3.8 Summary of Results and Discussion

The preformulation studies established the physicochemical characteristics and solubility behaviour of Telmisartan and Hydrochlorothiazide and provided the basis for selection of suitable formulation approaches. Analytical studies showed excellent linearity for both drugs, while FTIR and DSC investigations indicated satisfactory drug–excipient compatibility.

Among the Telmisartan formulations, **F6 was selected as the optimized softgel**, showing 99.6% drug content and 98.82% release at 60 minutes. Among the Hydrochlorothiazide formulations, **F6 was selected as the optimized sustained-release pellet**, exhibiting spherical morphology, favourable flow properties, 99.2% drug content and 99.18% release at 12 hours.

The final hybrid capsule successfully combined both optimized formulations and produced a distinct biphasic release pattern. Telmisartan was rapidly released, while Hydrochlorothiazide was released gradually over 12 hours. The formulation also demonstrated satisfactory physical integrity and drug content.

Overall, the results demonstrated the **technical feasibility of combining immediate-release Telmisartan softgel and sustained-release Hydrochlorothiazide pellets within a single hard gelatin capsule**. The accelerated stability study further indicated satisfactory short-term physical, chemical and dissolution stability under the investigated conditions.

4.CONCLUSION

The present research work successfully demonstrated the development and **in-vitro evaluation of a novel hybrid oral dosage form** comprising an immediate-release Telmisartan soft gelatin capsule and sustained-release Hydrochlorothiazide pellets incorporated into a single hard gelatin capsule. The formulation was designed to provide rapid release of Telmisartan together with controlled and prolonged release of Hydrochlorothiazide.

The optimized **Telmisartan F6 softgel** exhibited a clear and transparent appearance, satisfactory drug content of **99.6%**, and rapid drug release of **98.82% within 60 minutes**. The selected excipient system consisting of PEG 400, propylene glycol, Tween 80 and MCT oil was therefore suitable for achieving the desired immediate-release characteristics.

The optimized **Hydrochlorothiazide F6 pellets** showed spherical and smooth morphology, favourable flow properties and a high drug content of **99.2%**. The formulation provided controlled drug release, with **18.26% release at 1 hour and 99.18% at 12 hours**. The Korsmeyer–Peppas model provided the best fit ($R^2 = 0.9969$) with an **n-value of 0.686**, indicating anomalous/non-Fickian drug-release behaviour involving diffusion and polymer relaxation/erosion.

The optimized Telmisartan softgel and Hydrochlorothiazide pellets were successfully combined in a **size “0” hard gelatin capsule**. The final hybrid capsule showed satisfactory physical integrity, drug content and reproducible filling. Most importantly, it demonstrated the intended **biphasic release profile**, with Telmisartan reaching **98.14% release at 60 minutes**, while Hydrochlorothiazide reached **99.18% release at 12 hours**. Accelerated stability studies conducted at **40 ± 2°C/75 ± 5% RH for three months** showed no significant deterioration in physical appearance or capsule integrity. Both drug contents remained within the reported specifications, while the immediate-release behaviour of Telmisartan and sustained-release behaviour of Hydrochlorothiazide were substantially retained.

Overall conclusion

Thus, the study established the **technical feasibility of a single hybrid capsule capable of providing immediate release of Telmisartan and sustained release of Hydrochlorothiazide**. The developed system successfully combined two independently optimized release profiles without apparent adverse interference between the components. However, the present findings are based on in-vitro and short-term accelerated stability studies; further **formal analytical validation, full ICH-compliant stability studies and pharmacokinetic/bioavailability evaluation** are required before further development of the formulation.

5.ACKNOWLEDGEMENTS

I express my sincere and heartfelt gratitude to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai**, for providing me with the opportunity to pursue the **Master of Pharmacy in Pharmaceutics** and to undertake this research work.

I am deeply grateful to **Dr. Mariyappan G., M.Pharm., Ph.D., Professor & Head, Department of Pharmaceutics, Pallavan Pharmacy College, Kolivakkam, Kanchipuram**, for his valuable guidance, constant encouragement, constructive suggestions and continuous support throughout the course of this research work.

I sincerely thank the **Management and Principal of Pallavan Pharmacy College** for providing the necessary facilities, laboratory infrastructure and academic support required for the successful completion of this dissertation.

I extend my sincere thanks to all the **teaching and non-teaching staff members of the Department of Pharmaceutics** for their valuable assistance, cooperation and encouragement during the experimental work.

I also express my gratitude to the **laboratory staff and technical personnel** for their support and assistance during the formulation, evaluation and analytical studies carried out as part of this research.

I am thankful to my **friends and classmates** for their encouragement, cooperation and support throughout my postgraduate studies and during the completion of this dissertation.

Finally, I express my deepest gratitude to my **parents, family members and well-wishers** for their unconditional love, prayers, encouragement and constant support, which gave me the strength and motivation to successfully complete this work.

Above all, I thank the Almighty God for giving me the strength, wisdom and perseverance to complete this research work successfully.

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