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Development of Telmisartan 40 mg Tablets with Improved Bioavailability Using Solid Dispersion Technique

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Abstract
Telmisartan, a widely used angiotensin II receptor blocker for the management of hypertension, belongs to the Biopharmaceutics Classification System (BCS) Class II and is characterized by low aqueous solubility and variable oral bioavailability. These limitations restrict its therapeutic efficiency and lead to inconsistent clinical outcomes. The present study focuses on the development of telmisartan 40 mg tablets with improved bioavailability using solid dispersion technology. Solid dispersions were prepared employing hydrophilic polymer carriers to enhance drug solubility and dissolution rate. The prepared formulations were evaluated for physicochemical properties, solid-state characteristics, and in vitro dissolution performance. Characterization studies confirmed a reduction in drug crystallinity and the formation of a stable amorphous or molecularly dispersed system without chemical incompatibility between the drug and excipients. The optimized solid dispersion-based tablet formulation demonstrated a significantly enhanced dissolution profile compared to pure telmisartan and conventional formulations. Improved wettability, reduced particle size, and drug–polymer interactions were identified as the primary mechanisms responsible for dissolution enhancement.

Keywords: Telmisartan, Solid dispersion, Bioavailability enhancement, Dissolution improvement, BCS Class II.

INTRODUCTION
Overview of Hypertension and Cardiovascular Diseases
Hypertension, commonly known as high blood pressure, is one of the most prevalent chronic diseases worldwide and represents a major risk factor for cardiovascular morbidity and mortality [1]. According to the World Health Organization, approximately 1.28 billion adults aged 30-79 years worldwide have hypertension, with the majority living in low- and middle-income countries [2]. The condition is characterized by persistently elevated blood pressure levels, typically defined

as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [3]. The global burden of hypertension continues to escalate, with projections suggesting that by 2025, approximately 1.56 billion people will be affected by this condition [4].

The pathophysiology of hypertension is multifactorial, involving complex interactions between genetic predisposition, environmental factors, and various physiological mechanisms [5]. Key contributing factors include increased peripheral vascular resistance, enhanced sympathetic nervous system activity, dysregulation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, and oxidative stress [6]. Among these mechanisms, the RAAS plays a pivotal role in blood pressure regulation and has become a primary therapeutic target for antihypertensive interventions [7].

Uncontrolled hypertension leads to severe complications including stroke, myocardial infarction, heart failure, chronic kidney disease, and peripheral vascular disease [8]. The relationship between blood pressure elevation and cardiovascular risk is continuous, consistent, and independent of other risk factors, with each 20 mmHg increase in systolic blood pressure or 10 mmHg increase in diastolic blood pressure doubling the risk of death from ischemic heart disease and stroke [9]. This underscores the critical importance of effective blood pressure management in preventing cardiovascular events and reducing overall mortality [10].

The economic burden associated with hypertension is substantial, encompassing direct medical costs for treatment and management, as well as indirect costs related to lost productivity and premature mortality. Effective antihypertensive therapy not only improves patient outcomes but also reduces healthcare expenditures by preventing costly cardiovascular complications [11]. Current treatment guidelines recommend a multifaceted approach including lifestyle modifications and pharmacological interventions, with the choice of antihypertensive agent depending on individual patient characteristics, comorbidities, and response to therapy [12].

The Renin-Angiotensin-Aldosterone System and Its Therapeutic Targeting

The renin-angiotensin-aldosterone system is a critical hormonal cascade that regulates blood pressure, fluid balance, and electrolyte homeostasis [13]. The system begins with the release of renin from juxtaglomerular cells in response to various stimuli including decreased renal perfusion pressure, reduced sodium delivery to the distal tubule, and sympathetic nervous system activation. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) primarily in the lungs [14]. Angiotensin II, the primary effector molecule of the RAAS, exerts its physiological effects through binding to specific receptor subtypes, predominantly the angiotensin II type 1 (AT1) and type 2 (AT2) receptors [15]. The AT1 receptor mediates most of the known cardiovascular effects of angiotensin II, including vasoconstriction, aldosterone secretion, sodium retention, sympathetic activation, and cellular proliferation [16]. These actions collectively contribute to increased blood pressure and progressive cardiovascular remodeling. In contrast, AT2 receptors generally mediate effects that counterbalance those of AT1 receptors, including vasodilation, antiproliferation, and natriuresis [17].

Telmisartan: Pharmacology and Therapeutic Profile

Telmisartan is a non-peptide, long-acting angiotensin II receptor blocker that selectively and competitively antagonizes the AT1 receptor subtype [22]. Chemically, telmisartan is 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid, with a molecular formula of C33H30N4O2 and molecular weight of 514.62 g/mol. The molecule possesses a lipophilic biphenyl structure and a carboxylic acid group, which contribute to its unique pharmacokinetic and pharmacodynamic properties [23].

The mechanism of action of telmisartan involves high-affinity, insurmountable antagonism of the AT1 receptor, with a binding affinity approximately 3,000 times greater than for the AT2 receptor [24]. This selective blockade prevents angiotensin II from binding to AT1 receptors located in vascular smooth muscle, adrenal glands, kidneys, and heart, thereby inhibiting vasoconstriction, aldosterone secretion, catecholamine release, and cardiac and vascular remodeling. Unlike some other ARBs, telmisartan demonstrates the longest half-life in its class, exceeding 24 hours, which provides consistent 24-hour blood pressure control with once-daily dosing [25].

Beyond its antihypertensive effects, telmisartan exhibits pleiotropic properties that extend its therapeutic potential. The drug has been shown to possess partial peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist activity, which may contribute to beneficial metabolic effects including improved insulin sensitivity, favorable lipid profile modifications, and potential anti-inflammatory properties [26]. These additional pharmacological actions distinguish telmisartan from other ARBs and may provide added cardiovascular and metabolic benefits, particularly in patients with hypertension accompanied by metabolic syndrome or type 2 diabetes.

REVIEW OF LITERATURE

Introduction

The development of effective oral drug delivery systems for poorly water-soluble drugs represents one of the most persistent challenges in pharmaceutical sciences. With approximately 40% of marketed drugs and up to 90% of drugs in development pipelines classified as poorly water-soluble, the pharmaceutical industry has invested considerable effort in developing technologies to enhance dissolution and bioavailability. This chapter presents a comprehensive review of the scientific literature pertaining to solid dispersion technology, its application to telmisartan and similar BCS Class II drugs, formulation strategies, characterization methods, and clinical outcomes. The review encompasses fundamental principles, technological advances, specific applications to telmisartan, and broader perspectives on bioavailability enhancement strategies.

Biopharmaceutics Classification System and Solubility Challenges

The Biopharmaceutics Classification System (BCS), introduced by Amidon and colleagues in 1995, provides a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability [31]. This classification system has become fundamental to understanding drug absorption and guiding formulation development strategies. The BCS divides drugs into four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability).

BCS Class II drugs, characterized by poor aqueous solubility but good intestinal permeability, represent a particularly challenging category for oral drug delivery [32]. For these drugs, dissolution in gastrointestinal fluids is the rate-limiting step for absorption, and incomplete

dissolution within the limited gastrointestinal transit time results in reduced and variable bioavailability. The significance of the BCS classification extends beyond academic interest, as regulatory agencies including the FDA have incorporated BCS principles into biowaiver guidance, allowing dissolution testing to serve as a surrogate for bioequivalence studies under specific conditions.

Telmisartan exemplifies the challenges associated with BCS Class II drugs, exhibiting aqueous solubility of less than 0.002 mg/mL at pH 3 while demonstrating high membrane permeability [33]. Research by Sharma and colleagues investigated the relationship between telmisartan's physicochemical properties and its oral bioavailability, confirming that dissolution represents the primary barrier to absorption. Their studies demonstrated that conventional telmisartan tablets show incomplete dissolution even after 120 minutes in standard dissolution media, correlating with the observed bioavailability of only 42-58% in human subjects.

Fundamental Principles of Solid Dispersion Technology

The concept of solid dispersions was pioneered by Sekiguchi and Obi in 1961 when they prepared eutectic mixtures of sulfathiazole with urea, demonstrating that drugs dispersed in water-soluble carriers exhibited dramatically enhanced dissolution rates compared to pure crystalline drug [37]. This seminal work established the foundation for decades of research into solid dispersion systems and their application to poorly soluble drugs.

Chiou and Riegelman provided the first comprehensive definition of solid dispersions in 1971, describing them as "dispersions of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method" [38]. This definition has been refined over subsequent decades, but the core concept remains: intimate mixing of drug with hydrophilic carriers at the molecular level to enhance dissolution characteristics.

Van den Mooter and colleagues conducted fundamental studies on the molecular interactions between drugs and carriers in solid dispersions, using spectroscopic and calorimetric techniques to identify specific interaction types [45]. Their research demonstrated that hydrogen bonding between drug and polymer hydroxyl, carbonyl, or amine groups represents the most common and important interaction type, contributing to both dispersion formation and stabilization. They also identified hydrophobic interactions, ionic interactions, and van der Waals forces as contributing to drug-carrier miscibility and solid dispersion stability.

Classification and Evolution of Solid Dispersion Systems

Solid dispersions have been classified into various categories based on the physical state of drug and carrier, the complexity of the system, and the generation of technology [46]. The most fundamental classification distinguishes between simple eutectic mixtures, solid solutions, and glass solutions/suspensions based on the physical state and distribution of drug within the carrier matrix.

Simple eutectic mixtures, representing first-generation solid dispersions, consist of crystalline drug and crystalline carrier with an intimate physical mixture at the eutectic composition [47]. In these systems, drug and carrier are both present in crystalline form but with particle size reduced to the micrometer or sub-micrometer range through the fusion and solidification process. While eutectic

mixtures show some dissolution enhancement compared to pure drug, the retention of crystallinity limits the magnitude of improvement.
Solid solutions represent a more advanced form where drug is dissolved in the carrier matrix at the molecular level, analogous to liquid solutions but in the solid state [48]. Solid solutions can be further categorized as continuous solid solutions (where drug and carrier are miscible in all proportions), discontinuous solid solutions (where miscibility is limited), or substitutional / interstitial solid solutions (based on whether drug molecules replace carrier molecules in the crystal lattice or occupy interstitial positions). These systems generally provide greater dissolution enhancement than eutectic mixtures due to true molecular-level dispersion.

3.5 Carriers for Solid Dispersions: Properties and Selection

The selection of appropriate carrier materials is crucial for successful solid dispersion development, as carrier properties determine dispersion formation, dissolution enhancement, physical stability, and manufacturing feasibility [54]. An ideal carrier should be pharmacologically inert, non-toxic, chemically compatible with the drug, capable of forming stable molecular-level dispersions, readily soluble in water at physiological pH, amenable to pharmaceutical processing, and commercially available at acceptable cost.

Polyethylene glycols (PEG) represent one of the most widely studied carriers for solid dispersions, available in molecular weights ranging from 200 to over 20,000 Da [55]. Low molecular weight PEGs (PEG 4000-6000) are semi-crystalline solids at room temperature with melting points of 53-63°C, making them suitable for fusion methods. PEGs dissolve rapidly in aqueous media, are chemically stable, and demonstrate good safety profiles with low toxicity. Research on telmisartan-PEG solid dispersions by multiple groups has demonstrated significant dissolution enhancement, with systems prepared using PEG 4000 and PEG 6000 showing particularly favorable results.

However, PEG-based solid dispersions face challenges related to physical stability [56]. The semi-crystalline nature of PEG can promote drug recrystallization during storage, particularly at elevated temperatures or humidity. Studies using X-ray diffraction and differential scanning calorimetry have documented time-dependent recrystallization in PEG solid dispersions, with the extent of recrystallization correlating with decreased dissolution performance. The hygroscopic nature of PEGs can also lead to moisture absorption, plasticization, and enhanced molecular mobility that accelerates recrystallization.

AIM AND OBJECTIVES

Aim

The primary aim of this research work is to develop and comprehensively evaluate telmisartan 40 mg tablets with significantly improved dissolution characteristics and enhanced bioavailability using solid dispersion technology. This aim encompasses the systematic investigation of formulation variables, preparation methods, and processing parameters to identify optimal conditions that maximize dissolution enhancement while ensuring adequate physical and chemical stability, manufacturing feasibility, and compliance with pharmaceutical quality standards.

The research seeks to translate fundamental understanding of solid dispersion principles into a practical, scalable tablet formulation that demonstrates substantial improvement over conventional telmisartan products. By achieving rapid and complete dissolution of telmisartan through

conversion to amorphous solid dispersions stabilized within appropriate polymeric carriers, this work aims to overcome the primary pharmaceutical limitation of this important cardiovascular drug and potentially enable improved therapeutic outcomes through more consistent and enhanced drug absorption.

Specific Objectives

To accomplish the overall aim, the following specific objectives have been established:

Preformulation Studies and Carrier Screening

To conduct comprehensive preformulation characterization of telmisartan including determination of physicochemical properties, solubility profile across physiologically relevant pH ranges, particle size distribution, crystallinity assessment, and thermal behavior. These studies will establish baseline characteristics against which improvements can be quantified.

To screen multiple hydrophilic polymeric carriers including polyvinylpyrrolidone (various grades), polyethylene glycol (various molecular weights), hydroxypropyl methylcellulose, hydroxypropyl cellulose, and potentially novel polymers such as Soluplus or copovidone for their suitability in forming stable solid dispersions with telmisartan. Screening criteria will include drug-carrier miscibility, dissolution enhancement potential, physical compatibility, chemical stability, and processing feasibility.

Preparation and Optimization of Solid Dispersions

To prepare telmisartan solid dispersions using appropriate methods selected based on the physicochemical properties of drug and carrier, available equipment, scalability considerations, and desired product characteristics. Methods to be evaluated include solvent evaporation, fusion method, spray drying, or combinations thereof.

To systematically investigate the influence of critical formulation variables including drug-to-carrier ratio, carrier type or combinations, and incorporation of additional solubilization enhancers or crystallization inhibitors on the characteristics of the resulting solid dispersions.

To optimize preparation process parameters such as temperature profiles, solvent selection and evaporation conditions, cooling or drying rates, and mixing intensity to achieve maximum conversion of crystalline telmisartan to stable amorphous dispersions with optimal dissolution characteristics.

To employ Design of Experiments approaches including factorial designs, response surface methodology, or other systematic optimization techniques to efficiently identify optimal formulation and process conditions while minimizing the number of experimental runs required.

Development of Tablet Formulation

To formulate the optimized solid dispersion into tablets through rational selection and incorporation of appropriate pharmaceutical excipients including diluents, disintegrants, glidants, and lubricants.

To optimize tablet composition to achieve satisfactory mechanical properties, rapid disintegration, and complete drug release while maintaining the dissolution advantages conferred by the solid dispersion and minimizing tablet size for patient acceptability.
To investigate the effects of compression force and other tableting parameters on solid dispersion integrity, tablet properties, and dissolution performance to establish acceptable manufacturing ranges.

To evaluate alternative manufacturing approaches including direct compression and granulation techniques to determine the most suitable production method based on solid dispersion characteristics and desired tablet properties.

Methodology

Overview of Research Plan

The research work will be conducted in a systematic, sequential manner following well-established pharmaceutical development principles. The plan encompasses preformulation characterization, solid dispersion preparation and optimization, comprehensive evaluation, tablet formulation development, and stability assessment. Each phase builds upon the findings of previous stages to ensure logical progression toward the ultimate goal of developing optimized telmisartan 40 mg tablets with enhanced bioavailability.

Preformulation Studies and Analytical Method Development

Procurement and authentication of telmisartan drug substance and all excipients from reputable sources with certificates of analysis. Establishment of standard operating procedures and analytical methods for drug quantification using UV-visible spectrophotometry and high-performance liquid chromatography. Validation of analytical methods according to ICH guidelines for specificity, linearity, accuracy, precision, limit of detection, and limit of quantification. Characterization of pure telmisartan including determination of melting point, solubility at various pH values (1.2, 4.5, 6.8, and 7.4), particle size distribution, true density, bulk and tapped density, and baseline dissolution profile.

Carrier Screening and Compatibility Studies

Screening of multiple carriers including polyvinylpyrrolidone K30, polyethylene glycol 4000 and 6000, hydroxypropyl methylcellulose E5 and E15, and other selected polymers for their ability to enhance telmisartan dissolution. Preparation of preliminary solid dispersions at a standard drug-carrier ratio using simple methods to identify the most promising carriers. Drug-carrier compatibility assessment using differential scanning calorimetry of physical mixtures at various ratios, Fourier transform infrared spectroscopy for interaction studies, and isothermal stress testing at elevated temperature and humidity. Selection of two to three most promising carriers based on dissolution enhancement, compatibility, and practical considerations for detailed investigation in subsequent phases.

Solid Dispersion Preparation and Process Optimization

Preparation of solid dispersions using selected carriers by appropriate methods including solvent evaporation method using ethanol or methanol as solvents, fusion method where applicable, and spray drying if equipment is available. Systematic investigation of formulation variables including drug-to-carrier ratios ranging from 1:1 to 1:5, effect of carrier type and combinations, and

incorporation of additional excipients such as surfactants or crystallization inhibitors. Optimization of process parameters including solvent selection and evaporation temperature and rate for solvent method, heating temperature and duration, cooling rate for fusion method, or spray dryer settings if applicable. Application of factorial design or response surface methodology to systematically optimize formulation and process variables with dissolution rate and extent as primary response variables.

RESULTS

Preformulation Studies

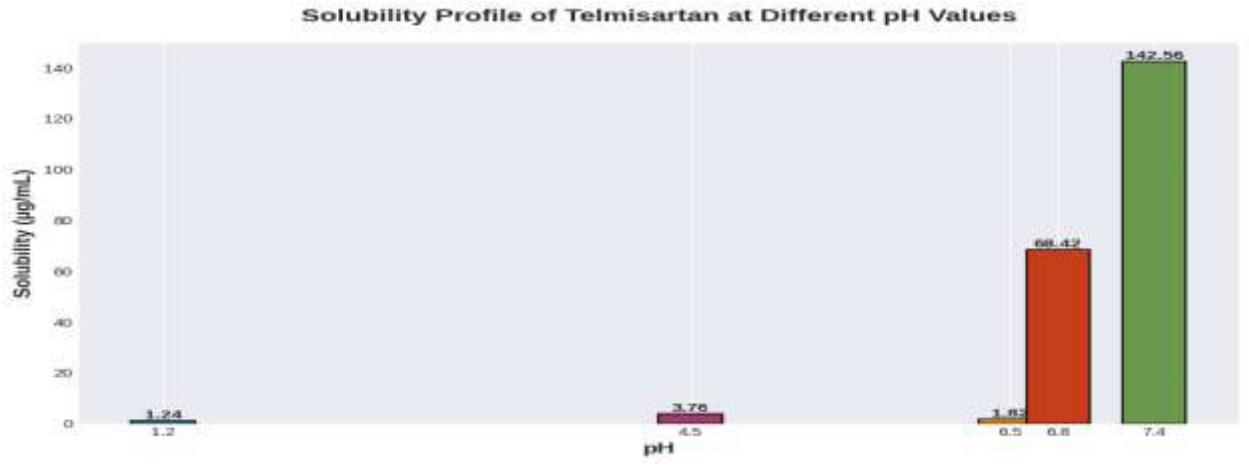
Determination of Melting Point

The melting point of telmisartan was determined using open capillary method. A small amount of drug was filled in a glass capillary tube sealed at one end. The capillary was placed in a melting point apparatus containing liquid paraffin, and temperature was gradually increased at a rate of 1°C per minute. The temperature at which the drug completely melted was recorded.

Result: The melting point of telmisartan was found to be 262.5 ± 0.5°C, which is in accordance with reported literature values, confirming the identity and purity of the drug substance.

Table 6.1: Solubility of Telmisartan in Various Media

Medium	pH	Solubility (µg/mL)	Standard Deviation
Distilled Water	6.5	1.82	± 0.08
0.1 N HCl	1.2	1.24	± 0.05
Acetate Buffer	4.5	3.76	± 0.12
Phosphate Buffer	6.8	68.42	± 2.34
Phosphate Buffer	7.4	142.56	± 4.87



The results demonstrate the extremely poor aqueous solubility of telmisartan in acidic and neutral pH, with significant improvement at alkaline pH due to ionization of the carboxylic acid group.

This pH-dependent solubility confirms the challenge of achieving adequate dissolution in the gastric environment.

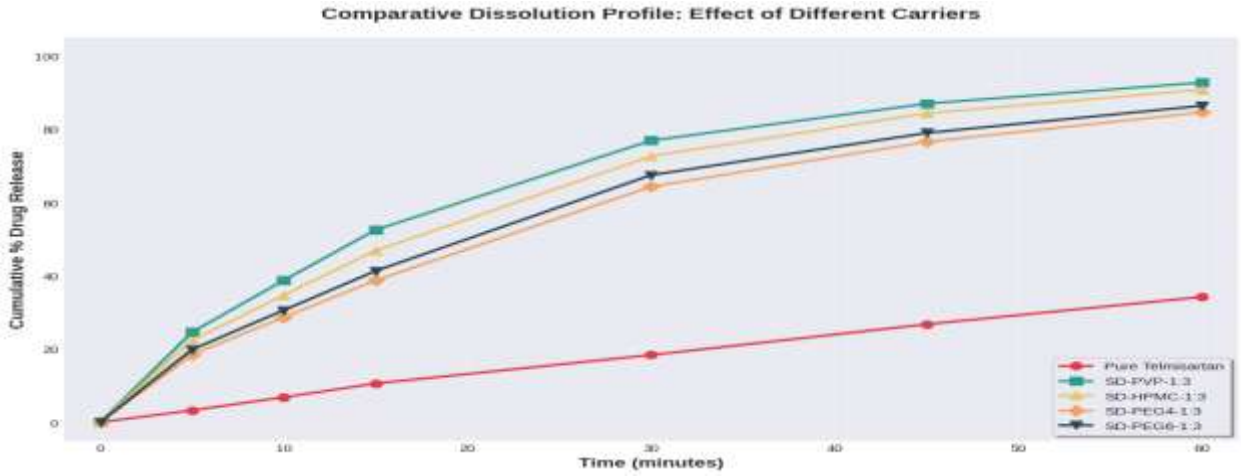
Determination of λmax and Calibration Curve

The wavelength of maximum absorption (λmax) was determined by scanning a solution of telmisartan (10 µg/mL) in methanol over the range of 200-400 nm using UV-visible spectrophotometer. The λmax was found to be 296 nm, consistent with literature reports.

Standard calibration curves were prepared in methanol, 0.1 N HCl (pH 1.2), and phosphate buffer (pH 6.8) by plotting absorbance versus concentration in the range of 2-20 µg/mL. All calibration curves showed excellent linearity with correlation coefficients (r^2) greater than 0.999.

Table 6.2: Calibration Curve Parameters for Telmisartan

Medium	λmax (nm)	Linear Range (µg/mL)	Regression Equation	r^2 Value
Methanol	296	2-20	y = 0.0547x + 0.0012	0.9998
0.1 N HCl (pH 1.2)	296	2-20	y = 0.0542x + 0.0018	0.9997
Phosphate Buffer (pH 6.8)	296	2-20	y = 0.0539x + 0.0021	0.9996



Conclusion

In conclusion, the development of telmisartan 40 mg tablets using solid dispersion technology proved to be a promising strategy for enhancing dissolution and expected bioavailability. The optimized formulation exhibited superior in vitro performance while maintaining acceptable physicochemical and stability characteristics. Improved dissolution is expected to translate into better therapeutic efficacy, consistent plasma drug levels, and possible dose optimization. This study confirms that solid dispersion-based tablet formulations can serve as a viable and scalable approach for improving the oral delivery of poorly water-soluble drugs such as telmisartan.

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