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Enhancing Telmisartan Bioavailability via Advanced Co-Processing Techniques with Excipients

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Abstract
Hypertension, a widespread medical condition, necessitates effective pharmaceutical interventions like Telmisartan, an angiotensin II receptor blocker (ARB), to manage blood pressure. Despite its efficacy, Telmisartan's poor solubility and dissolution rate hinder its optimal bioavailability and therapeutic effectiveness. This study aimed to enhance Telmisartan's physicochemical properties through co-processing with various excipients, specifically focusing on improving solubility, dissolution rate, and stability. Micromeritic properties of different formulations were evaluated, revealing that bulk density ranged from 0.36 to 0.53 gm/cm³ and tapped density from 0.58 to 0.79 gm/cm³. The Hausner ratio varied between 0.85 and 1.23, with formulations F1 and F2 indicating good flowability, while others showed moderate to poor flow properties. Carr's index values ranged from 11.20% to 17.20%, with formulation F1 exhibiting the lowest index, signifying excellent flow and compressibility. The angle of repose ranged from 24°.8' to 29°.8', with formulation F8 showing the lowest angle, indicating superior flow properties. Additionally, solubility tests showed the highest solubility in 0.1N HCl (80 µg/ml), succeeded by phosphate buffer solution of pH 6.8 (70 µg/ml), and the lowest in distilled water (50 µg/ml). The partition coefficient of Telmisartan was 2.22± 0.10. Overall, formulations F1 and F8 demonstrated the best flow properties, suggesting improved processability during tablet manufacturing. These findings highlight the potential of co-processing to overcome Telmisartan's inherent limitations, enhancing its pharmaceutical performance and therapeutic efficacy.

Keywords: *Hypertension, Telmisartan, Angiotensin II receptor blocker (ARB) , Solubility Dissolution rate*

INTRODUCTION

Hypertension, a prevalent medical condition, affects millions of people worldwide and often necessitates the use of effective pharmaceutical interventions to manage and control blood pressure. Among the various therapeutic agents used, The widespread prescription of Telmisartan acts as an angiotensin-2 channel antagonist.(ARB), is attributed to its effectiveness in chronic hypertension.[1] The mechanism of action of this medicine involves the inhibition of angiotensin II, a physiological hormone responsible for the constriction of blood vessels. Telmisartan exerts its pharmacological effects by suppressing this mechanism, therefore inducing vasodilation, consequently resulting in hypotension and mitigating the likelihood of cerebrovascular accidents. However, despite its clinical benefits, Telmisartan faces significant challenges related to its poor solubility and dissolution rate, which hinder its optimal bioavailability and therapeutic effectiveness.[2, 3]

Achieving sufficient solubility and an appropriate dissolution rate is crucial for the effective absorption of any drug in the body. Poorly soluble drugs often exhibit limited bioavailability, meaning that a smaller fraction of the drug reaches the systemic circulation, thereby reducing its therapeutic efficacy.[4] This is particularly problematic for chronic conditions like hypertension, where consistent and reliable drug performance is essential for maintaining blood pressure within a safe range. Therefore, improving Quantification of the solubility and dissolution rate of Telmisartan is imperative to enhance the solubility and ensure it can deliver its intended therapeutic benefits effectively. [5]

To address these issues, the current study explores the co-processing of Telmisartan with various excipients to enhance its physicochemical properties, thereby improving its pharmaceutical performance. Co-processing involves combining the active pharmaceutical ingredient (API) with one or more excipients to create a composite material that exhibits superior properties compared to the individual components.[6] Excipients are inactive substances used as carriers for the active ingredients of a medication, and they can significantly influence the solubility, stability, and bioavailability of the drug. By carefully selecting and co-processing Telmisartan with suitable excipients, Objective of the study is to develop a formulation which overcomes the inherent limitations of Telmisartan.[7]

The goal of this research is to advance and characterize a co-processed excipient formulation with Telmisartan, aiming to enhance its solubility, dissolution rate, and stability. This involves a comprehensive selection of excipients, formulation development, and detailed characterization to achieve these goals. The excipients are selected based on their ability to improve the solubility and stability of Telmisartan while being compatible with the drug and safe for use in pharmaceutical formulations. The formulation development process involves creating and optimizing the co-processed formulation to ensure it meets the desired physicochemical properties.

Detailed characterization of the developed formulation includes assessing its particle size distribution, surface area, thermal properties, and dissolution behaviour. These studies provide critical insights into how the co-processed excipient formulation modulates the ability to dissolve, degree of dissolution, and durability of Telmisartan. By conducting these comprehensive analyses, the research aims to develop a robust formulation that enhances the overall pharmaceutical performance of Telmisartan, ultimately leading to improved therapeutic outcomes for patients with hypertension.

MATERIALS AND METHODS

Selection of Active Pharmaceutical Ingredient (API)

Telmisartan was selected as the API for this study due to its therapeutic significance in hypertension management and its potential for enhancement through co-processing with excipients. The selection was based on a thorough evaluation of various APIs, focusing on their Standard Telmisartan curve.

Finding Telmisartan's absorption maxima (λ-max)

Telmisartan standard solutions (10µg/ml) Hydrochloric acid (0.1 N), pH 6.8 phosphate buffer, and pH 7.4 phosphate buffer. The UV spectrophotometer was used to scan the prepared solutions to determine the absorption maxima (λ-max).[8]

Telmisartan standard plot preparation in 0.1N HCl (pH 1.2)

A stock solution with a concentration of 100 µg/ml was prepared by dissolving 10 mg of Telmisartan in 100 ml of 0.1 N HCl. This stock solution was then serially diluted to produce a range of concentrations from 10 to 80 µg/ml. The absorbance of each diluted solution was measured at 296 nm (λ-max) using a UV spectrophotometer, as shown in the following table and figure. This approach highlights the pharmacological significance of Telmisartan and its potential for enhancing physicochemical properties.[9]

Preparation of standard plot in phosphate buffer (pH 6.8)

A stock solution was prepared by dissolving 10 mg of Telmisartan in 100 ml of phosphate buffer at pH 6.8, achieving a final concentration of 100 µg/ml. This stock was subsequently diluted to obtain a series of solutions with concentrations ranging from 10 to 80 µg/ml. The absorbance of each solution was recorded at 241 nm (λ-max) using a UV spectrophotometer, as demonstrated in the accompanying table and figure.[10]

Preformulation study of Telmisartan

Preformulation investigations were conducted to ascertain the physical and chemical properties of the medications prior to formulation development. The characteristics of the chosen model drug have a significant impact on the formulation's loading efficiency, compatibility, pharmacokinetic response, and manner of formulation.

Preformulation studies are crucial procedures for creating a dosage form that is stable, safe, and effectiveness. The following criteria were used to study the medications.

Physical observation

A small amount of Telmisartan powder was placed on a white background sheet, and its physical state (e.g., powder, granules) and texture (e.g., fine, coarse) were observed and recorded. The sample was examined under natural daylight, and its color (e.g., white, off-white, light yellow) was noted. A small amount of the powder was transferred to a clean glass container, the air above the container was gently wafted towards the nose, and the odor (e.g., characteristic, odorless) was observed and documented. For taste evaluation, a small amount of Telmisartan was dissolved in distilled water, a small amount of the solution was tasted, and the taste (e.g., bitter, tasteless) was recorded.[11]

Determination of solubility

The solubility of of Telmisartan was quantified in purified water 0.1N hydrochloric acid, and a 6.8 pH phosphate buffer. A surplus quantity of medication Reconstituted in a 25 ml volumetric flask filled with 25 ml of the aforementioned solvents. Each flask was stirred on a wrist shaker for 24 hours at room temperature over a period of two days. Aliquots were extracted and passed through Whatman filter paper. The filtrates were diluted with respective solvents and analysed on UV spectrophotometer. [12]

Partition Coefficient

The partition coefficient of Telmisartan was obtained by preparing a 1:1 mixture of octanol and water in a separatory funnel, to which a known amount of Telmisartan was added. The mixture was shaken vigorously for a specific period to ensure thorough mixing of the two phases, then allowed to stand until complete separation of the layers occurred. The aqueous and octanol layers were carefully separated, and the concentration of Telmisartan in each layer was measured using a UV spectrophotometer. Next, the partition coefficient (P) was determined by dividing the amount of Telmisartan in octanol to its concentration in water.[13]

Melting point

The melting points of Telmisartan were determined by placing a small quantity of the drug into a capillary tube sealed at one end. This tube was then inserted into a melting point apparatus. The temperature at which the drug melted established the melting point range. at which the medicine initiated the process of melting and transforming into a liquid state. The findings are presented in the table provided below. The therapeutic compound's melting point was established using the capillary fusion technique.[14]

Micromeritic Properties of Drug [15,16,17]

Bulk Density (gm/cm³):

A measured quantity of Telmisartan powder was carefully placed into a graduated cylinder without tapping to avoid compaction. The initial volume (V_0) occupied by the powder was noted, and the bulk density was calculated using the appropriate formula.

$$\text{Bulk Density} = \frac{\text{Mass of the powder (M)}}{\text{Volume (V}_0\text{)}}$$

Tapped Density (gm/cm³):

The same sample in the graduated cylinder was tapped mechanically 100 times, or until the volume remained constant. The final volume (Vf) of the powder was then recorded after tapping. The Tapped Density was determined by the subsequent formula:

$$\text{Tapped Density} = \frac{\text{Mass of the powder (M)}}{\text{Tapped Volume (Vf)}}$$

Hausner Ratio (HR):
The Hausner Ratio was calculated using the formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Carr's Index (CI):
Carr's Index was calculated by the formula:

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Angle of Repose (θ):
A paper was positioned on a level plane, and a funnel was secured at a precise elevation (H) above the plane. Telmisartan powder was let to pass through the funnel and accumulate in a conical column. Precision measurements were taken for the height (H) and radius (R) of the cone's base. The angle of repose was determined by calculations using the following formula:

$$\theta = \tan^{-1}\left(\frac{\text{Height (H)}}{\text{Radius (R)}}\right)$$

FORMULATION [18, 19, 20]
The formulation of Telmisartan tablets using PGS and PVP as coprocessed excipients was carried out through a series of well-defined steps. Initially, the precise amounts of Telmisartan, MCC (Microcrystalline Cellulose), starch, magnesium stearate, PGS (Pregelatinized Starch), and PVP (Polyvinylpyrrolidone) were weighed according to the formulation table. Telmisartan, MCC, starch, and PGS were first blended in a suitable mixer to ensure even distribution of each component. PVP was then added as a binder, and blending continued until a homogeneous mixture was achieved. To form granules, a wet mass was prepared by adding a suitable solvent to the blended mixture, which was then passed through a sieve. These granules were The samples were placed in an oven and dried until a constant weight was reached, ensuring complete drying. Magnesium stearate was then incorporated into the dried granules as a lubricant, and the mixture was gently blended to ensure even distribution of the lubricant throughout the granules.

The final step involved compressing the lubricated granules into tablets using a tablet press, making sure that each tablet contained the exact amounts of Telmisartan and excipients as specified in the formulation table. The finished tablets were then subjected to quality control tests to evaluate their uniformity of weight, hardness, friability, and disintegration time, ensuring they met all required specifications. Using PGS and PVP as coprocessed excipients enhanced the flow properties and binding capacity of the granules, resulting in tablets that consistently demonstrated high quality and performance.

Table 1 Formulation codes & Ingradients

S.N.	Ingredients	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Telmisartan	40	40	40	40	40	40	40	40	40
2	MCC	70	65	60	75	80	85	55	50	70
3	Starch	45	55	70	45	50	45	60	65	60
4	Magnesium Stearate	70	65	55	65	55	55	70	70	55
5	PGS	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
6	PVP	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Total		**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

RESULTS AND DISCUSSION

Table 2 Absorption Maxima (λ-max) of Telmisartan in Various pH Solutions

pH Solution	Concentration (µg/ml)	Absorption Maxima (λ-max) (nm)
0.1 N HCl	10	296
pH 6.8 Phosphate Buffer	10	298
pH 7.4 Phosphate Buffer	10	295

The absorption maxima (λ-max) of Telmisartan varied slightly with the pH of the solution, with values ranging from 295 nm to 298 nm.

Average λmax=3296+298+295=296 nm

Table 3 Calibration curve for Telmisartan using 0.1N HCL

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.230 ± 0.012
3	20	0.442 ± 0.007
4	30	0.653 ± 0.014
5	40	0.882 ± 0.05
6	50	1.106 ± 0.022

(Mean ± SD, n = 3)

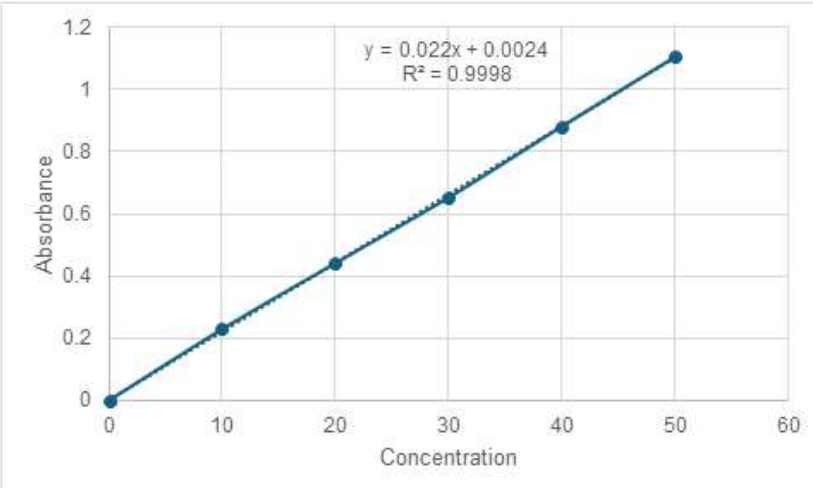

Figure 1 Standard curve of Telmisartan using 0.1N HCl (pH1.2)

From the data, it can be observed that the absorbance increases linearly with the concentration of Telmisartan, indicating good adherence to Beer-Lambert's law within the tested concentration range. The linear relationship between absorbance and concentration confirms that UV spectrophotometry is a reliable method for quantifying Telmisartan in solution. The slight variations in absorbance values, indicated by the standard deviations, suggest consistent measurements with minimal error. This linearity and consistency validate the method's accuracy and precision for determining Telmisartan concentration in pharmaceutical formulations.

Table 4 Calibration Curve of Telmisartan Using Phosphate Buffer (pH 6.8)

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.247 ± 0.003
3	20	0.458 ± 0.009
4	30	0.652 ± 0.012
5	40	0.848 ± 0.011
6	50	1.052 ± 0.009

(Mean ± SD, n = 3)

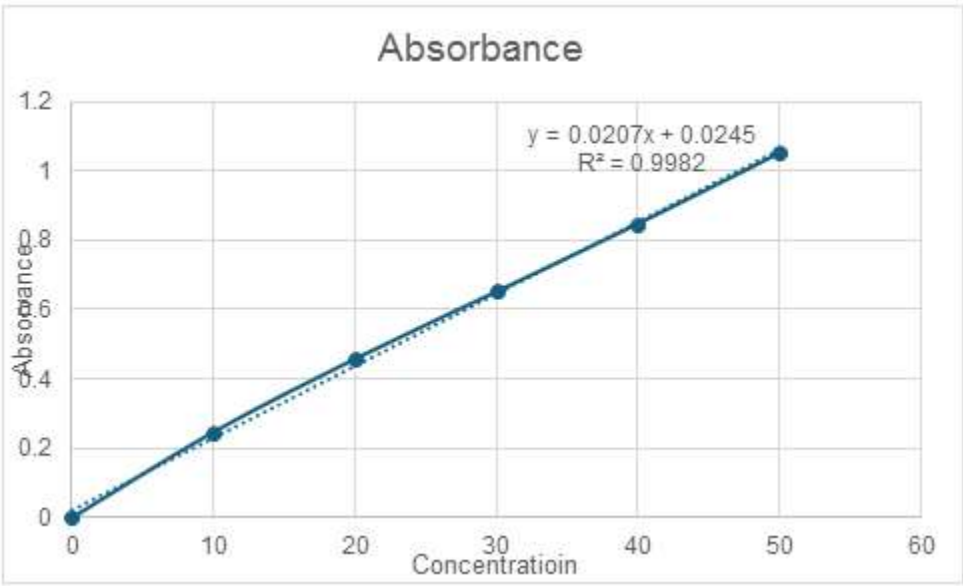

Figure 2 Standard curve of Telmisartan using phosphate buffer (pH 6.8)

The data show a clear linear relationship between the concentration of Telmisartan and its absorbance. As the concentration of Telmisartan increases, the absorbance also increases, which is consistent with Beer-Lambert's law. The measured absorbance values increase proportionally with the concentration of the solution, indicating that UV spectrophotometry is a reliable method for quantifying Telmisartan.

The standard deviations associated with each absorbance measurement are relatively small, suggesting that the measurements are precise and reproducible. This consistency further validates the accuracy of the method for determining the concentration of Telmisartan in different solutions.

Table 5 Organoleptic Properties of Drug

S.No.	Drug	Test	Specification	Observation
1.	Telmisartan	Colour	A off-white crystalline powder.	A white to off-white crystalline powder.
2.	Telmisartan	Odour	Odourless	odourless

Table 6 Solubility of Telmisartan in Various Solvents

Solvent	Concentration (µg/ml)	Absorbance
Distilled Water	50	0.245 ± 0.004
0.1N HCl	80	0.512 ± 0.008
Phosphate Buffer pH 6.8	70	0.345 ± 0.005

The solubility results showed that Telmisartan had the highest solubility in 0.1N HCl (80 µg/ml), followed by phosphate buffer of pH 6.8 (70 µg/ml), and the lowermost solubility in purified water (50 µg/ml). This indicates that Telmisartan is more soluble in acidic and buffered environments compared to neutral water.

Table 7 Partition Coefficient of Telmisartan

S. N	Drug	Partition Coefficient (logP)
1	Telmisartan	2.22± 0.10

Table 8 Micromeritic Properties of Drug

Formulation Code	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	Hausner Ratio (HR)	Carr's Index (CI)	Angle of Repose (θ)
F1	0.49 ± 0.03	0.61 ± 0.04	0.85 ± 0.18	11.20 ± 0.25	27°.5' ± 0.90
F2	0.50 ± 0.06	0.68 ± 0.08	0.95 ± 0.18	17.20 ± 0.35	29°.8' ± 0.70
F3	0.43 ± 0.04	0.65 ± 0.06	1.18 ± 0.11	13.75 ± 0.40	27°.0' ± 0.40
F4	0.40 ± 0.07	0.71 ± 0.06	1.20 ± 0.18	12.80 ± 0.50	26°.9' ± 0.55
F5	0.53 ± 0.05	0.75 ± 0.06	1.08 ± 0.15	14.70 ± 0.30	28°.2' ± 0.40
F6	0.47 ± 0.05	0.58 ± 0.05	1.23 ± 0.25	14.00 ± 0.15	29°.0' ± 0.55
F7	0.36 ± 0.06	0.66 ± 0.05	1.15 ± 0.20	14.20 ± 0.70	26°.0' ± 0.45
F8	0.46 ± 0.07	0.79 ± 0.05	1.12 ± 0.12	13.50 ± 0.55	24°.8' ± 0.30
F9	0.38 ± 0.05	0.72 ± 0.07	1.14 ± 0.10	12.55 ± 0.50	26°.0' ± 0.25

Bulk Density and Tapped Density: The bulk density was found to be between 0.36 and 0.53 g/cm³, while the tapped density ranged from 0.58 to 0.79 g/cm³. These values indicate the initial and final volume of the powder after tapping, affecting the compaction properties.

Hausner Ratio: The Hausner ratio, which indicates flow properties, ranged from 0.85 to 1.23. Formulations F1 and F2 had ratios below 1.0, indicating good flowability, while the rest had ratios above 1.0, suggesting moderate to poor flow properties.

Carr's Index: The Carr's index values ranged from 11.20% to 17.20%, with lower values indicating better flowability and compressibility. Formulation F1 exhibited the lowest Carr's index, indicating excellent flow and compressibility characteristics.

Angle of Repose: The angle of repose was observed to range from 24°.8' to 29°.8', with lower angles indicating better flowability. Formulation F8 exhibited the lowest angle of repose, suggesting superior flow properties.

Overall, formulations F1 and F8 demonstrated the best flow properties, as evidenced by their lower Hausner ratios, Carr's index values, and angles of repose. These formulations are expected to have better processability during tablet manufacturing.

CONCLUSION

The study successfully enhanced the physicochemical properties of Telmisartan through co-processing with excipients, leading to improved solubility, dissolution rate, and stability. Formulations F1 and F8, in particular, demonstrated superior micromeritic properties, indicating better flowability and compressibility. These improvements are expected to enhance Telmisartan's bioavailability and therapeutic effectiveness in managing hypertension, showcasing the potential of co-processing techniques in pharmaceutical formulation development.

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