A Comparative Study on Interactions and Influence of Alkalizers on Dissolution Rate of Telmisartan

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ABSTRACT

For preformulation studies in formulation development, compatibility studies are crucial. Telmisartan is an angiotensin II receptor blocker [ABRs]. It is also used in the treatment of heart attack and stroke. It is a BCS class II drug. Since telmisartan's solubility is pH-dependent, a few alkalizing agents are utilized to speed up the solubility and dissolution process. The objective of this study was to enhance the solubility of telmisartan. Alkalizing agents such as magnesium hydroxide, sodium bicarbonate, aluminium hydroxide, and barium carbonate are used. Telmisartan solid dispersions with the selected alkalinising agents were formulated by employing a kneading technique and subjected to IR spectral, HPLC and in-vitro dissolution studies. Magnesium hydroxide was found to be preferable compared to other alkalizers based on docking, IR spectral and HPLC techniques and *in-vitro* dissolution studies. The results demonstrated the enhanced solubility of telmisartan with magnesium hydroxide and sodium lauryl sulphate at ratios. This study concluded that addition of alkalising agent like magnesium hydroxide improves solubility of class – II drugs.

Key Words: *Telmisartan, Docking studies, HPLC, FTIR, Solid dispersions*

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INTRODUCTION

Telmisartan is a class of angiotensin II receptor blockers. It functions by preventing the action of specific natural substances that narrow blood arteries, letting blood flow more freely and the heart pump more effectively. It is also used in the treatment of heart attack and stroke [1-6]. According to the BCS classification, telmisartan is classified as a class II drug, i.e., highly permeable but poorly soluble [7]. Excipient compatibility screening is widely accepted as a crucial step in the development process. Telmisartan is a pH-dependent solubility drug [7]. So, it has more solubility in alkaline pH. To improve the solubility, alkalizers such as magnesium hydroxide, sodium bicarbonate, aluminium hydroxide, and barium carbonate are used. The alkalizing agents are incorporated into the drug by using the solid dispersion method by kneading technique. Drug-excipient mixtures are packed in blister packs and stored at 40^0c for 15 days. The blends were analysed with HPLC and FTIR [8-15]. Drug solubility, stability, dissolution rate and bioavailability may alter as a result of interactions between active ingredient and inactive excipients in a solid form. Excipients are typically used to improve process parameters and effectiveness. Due to telmisartan's poor flow characteristics and inability to dissolve in water, required excipients are added and compatibility studies were perfomed.

This article explains how alkalizers are employed to improve the solubility of telmisartan. This study's objective was to assess telmisartan's physical and chemical stabilities and rate of dissolution when combined with excipients.

MATERIALS AND METHODS

Telmisartan, Magnesium hydroxide, sodium bicarbonate, aluminium hydroxide, barium carbonate, Sodium lauryl

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sulphate, potassium dihydrogen phosphate, triethylamine, orthophosphoric acid, HPLC grade acetonitrile and HPLC grade methanol for HPLC purpose.

Procedure for docking

Docking is a Structure-based technique which attempts to find the best match between two molecules. Docking studies were conducted for telmisartan and Mg $(OH)_2$ by using the software PubChem for the selection of telmisartan and RCSB-PDB for Mg ions and sodium bicarbonate. The software Chimera, Auto Dock and Discovery Studio are responsible for carrying out these docking studies [16-19].

Method of preparation

1. Preparation on solid dispersion:

The solid dispersion of telmisartan with alkalizing agents like magnesium hydroxide, sodium bicarbonate, aluminium hydroxide, and barium carbonate was prepared by using the kneading method in the ratio of 1:1 by employing acetone as solvent. The solid dispersion of telmisartan with alkalizing agent magnesium hydroxide was also prepared by using the kneading method in the ratios of 1:3 and 1:5. The formulated solid dispersions were air dried and passed through sieve no 60 and kept in a desiccator for further use.

Drug - excipient compatibility study

In the current research, the active pharmaceutical ingredient and the solid dispersions formulated with different alkalisers (binary mixtures) and the ternary system comprising the drug, alkaliser and surfactant were analysed with HPLC and FTIR techniques. The blends containing telmisartan and magnesium hydroxide (1:1), telmisartan and sodium bicarbonate (1:1), telmisartan and aluminium hydroxide (1:1), telmisartan and barium carbonate (1:1), telmisartan and magnesium hydroxide (1:5), telmisartan and sodium lauryl sulphate (1:0.3), and telmisartan with magnesium hydroxide + sodium lauryl sulphate (1:5:0.3) were transferred into glass bottles and stored at 40^0 C for 15 days and then subjected to following studies.

Ftir spectral studies

FTIR spectra for pure drug, alkalizing agents and preformulation mixtures were recorded by scanning in the range of 600-4000 cm−1 using a **BRUKER** FTIR spectrometer [20-22].

Hplc studies

The blends were analysed by RP-HPLC method specified in pharmacopoeia [23].

- *Solvent preparation*

5 ml of triethylamine was diluted to 2000 ml with water to prepare buffer solution.80 volumes of above buffer solution and 20 volumes of HPLC-grade methanol were mixed to prepare solvent.

- *Mobile phase preparation*

2.72g of potassium dihydrogen phosphate was dissolved in 1000 ml of water, added 2 ml of triethylamine and pH was adjusted to 2.4 using orthophosphoric acid. 60 volumes of above buffer solution and 40 volumes of HPLC-grade acetonitrile were mixed to prepare mobile phase.

Standard preparation

40 mg of telmisartan drug was weighed accurately and transferred into a 100 ml volumetric flask, 20 ml of solvent was added and sonicated for 15 min. Volume was made up to the mark with the solvent.0.1 ml of above solution was diluted to 100 ml with solvent to prepare standard.

- *Sample preparation*

Powder equivalent to 40 mg of telmisartan drug was transferred into a 100 ml volumetric flask, 20 ml of solvent was added and sonicated for 15 min. Volume was made up to the mark with the solvent.0.1 ml of above solution was diluted to 100 ml with solvent to prepare sample.

- *System suitability*

The telmisartan standard solution was injected into the chromatograph repeatedly five times. From the observed chromatogram, various system suitability parameters such as tailing factor, theoretical plates and % RSD of the peak area were calculated with the Spinchrome CFR software.

Procedure

Separate injections of 20 µL each of the diluent, standard, and sample preparations were loaded in to the BDS Hypersil C18 (250 X 4.6 mm), 5µ column, which was maintained at room temperature. Injections were run for 15 minutes, the mobile phase's flow rate was held constant at 1.5 ml/min. The sample was detected at 298nm [23], and the chromatograms were recorded. Percentage assay of the telmisartan was calculated by using the following formula

$$\%\text{Assay} = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard dilution}}{\text{Sample dilution}} \times \frac{\text{Potency}}{100} \times 100 \quad (9)$$

Invitro dissolution studies

Preparation of dissolution medium

Invitro dissolution studies were carried out by using USP dissolution test apparatus II. Dissolution tests were done separately for the pure drug and the formulation. Pure drugs and the formulation powder containing drug equivalent to 40 mg of pure drug were used for dissolution studies. Dissolution was carried out in 900ml of phosphate buffer pH 7.5 at rpm 75 and the temperature 37± 0.5ºc. Samples were collected every 5 minutes. The samples were assayed spectrometrically At 296 nm [23, 24].

RESULTS AND DISCUSSION

The purpose of this study is to increase the *invitro* dissolution rate of telmisartan by using alkalizing agents. Docking studies for the telmisartan with $Mg(OH)_2$ have more binding energy compared to sodium bicarbonate. FT-IR Spectra comprising a mixture of pure telmisartan, and its binary mixtures are shown in **Figures 1 and 2**. It indicated that there is an interaction between the drug and the binary mixtures. At 3059.5 cm^{-1}, a prominent peak was obtained for pure telmisartan whereas telmisartan in combination with binder mixtures showed no such peak at the above value which indicates considerable interaction of telmisartan with the binder mixture. The hydroxyl group present in the pure telmisartan disappears in binary mixtures and forms a new bond with the excipients. Hence, it confirms the stability of the drug in its solid dispersion.

This study aims to establish a straightforward, accurate, and precise HPLC method for the analysis of telmisartan preformulations. The column used in this approach was the widely used BDS Hypersil C18 (250 X 4.6 mm), 5µ column, and the detection wavelength was 298 nm.

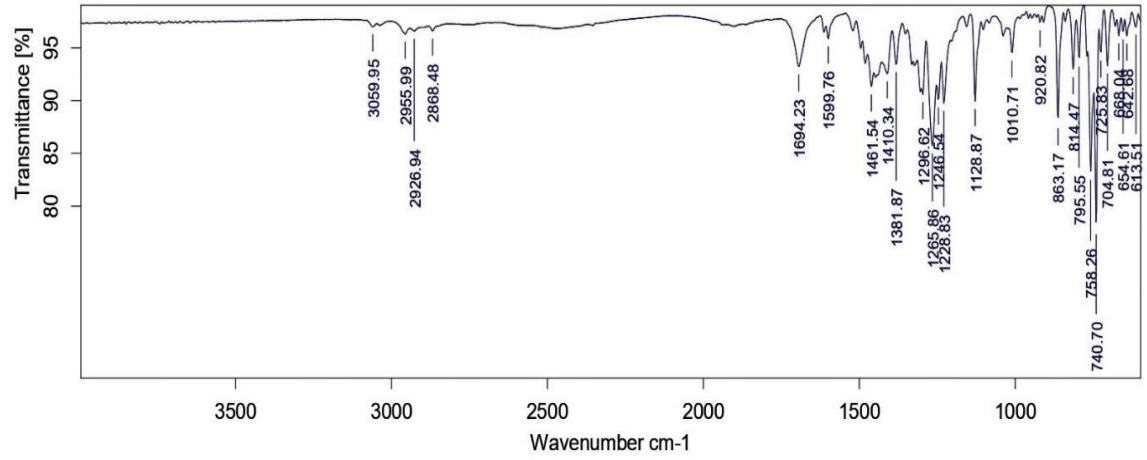

Figure 1. IR Spectra for Telmisartan

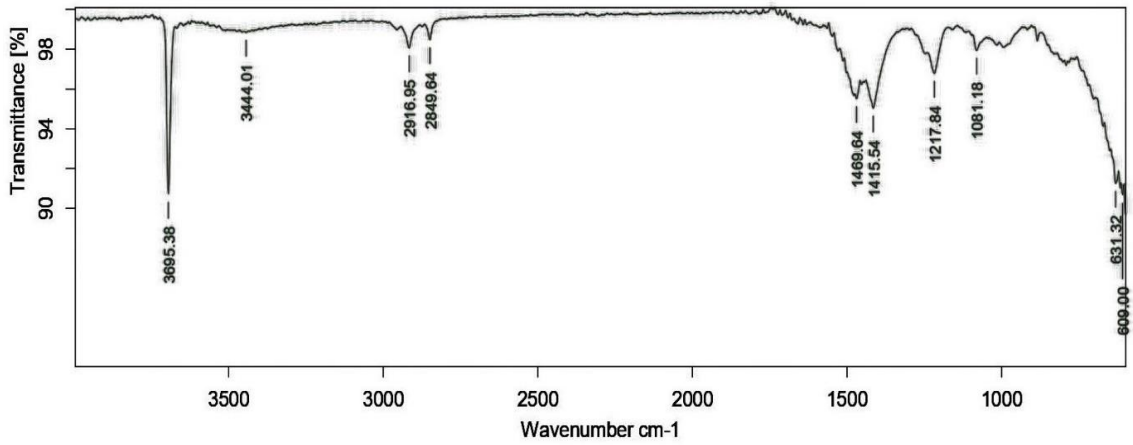

Figure 2. IR Spectra for Telmisartan + magnesium hydroxide + sodium lauryl sulphate

Chromatographic procedures must be suitable for the system, and the system's repeatability must be sufficient for the analysis to be carried out. Prior to the conduct of the compatibility research at each condition, system suitability was undertaken. The diluent, standard, and sample preparations were each injected individually six

times. Results of the system suitability tests are compiled. The telmisartan peak's tailing factor was discovered to be 1.2. For telmisartan and its binary combinations, the average of the theoretical plates was discovered to be 8499.75. The results of the system suitability tests were within USP guidelines. The results revealed that the observed results were found to be statistically significant (P>0.05).

In **Figure 3** the chromatogram of the standard medication at 40 degrees was displayed. The unidentified contaminants were detected at a retention time (tr) of 7.04 min after the pure medication was eluted. (t_r): 2.6, 3.2 & 5.4 min respectively.

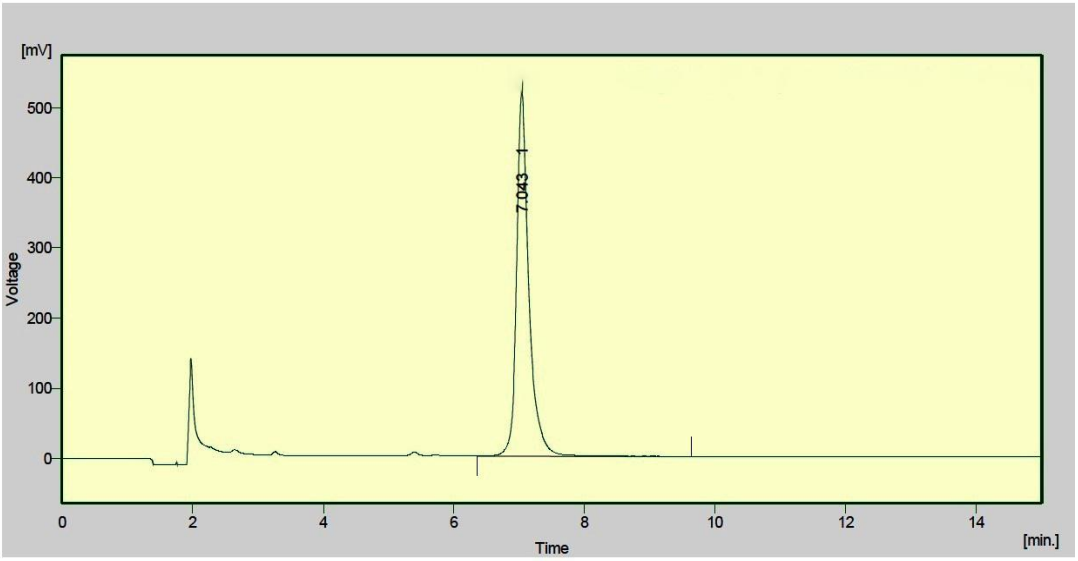

Figure 3. Chromatogram for Telmisartan

The chromatograms corresponding to the binary mixtures are shown in **Figures 4 and 5**. A Chromatogram for the mixture of telmisartan with magnesium hydroxide, and sodium lauryl sulphate showed in **Figure 6**. The drug with the excipient mixture was eluted at a retention time (t_r) of 11.49 min and the unknown impurities were observed at a retention time (t_r): of 3.1, 4.2 & 8.3 min respectively. Based on the above data the retention time for telmisartan is shifted from 7.044 to 11.493. This indicates that there is interaction between the drug and the excipient. The retention time for the formulation is due to an increase in aqueous solubility and due to interaction with the alkalizers used, or maybe both.

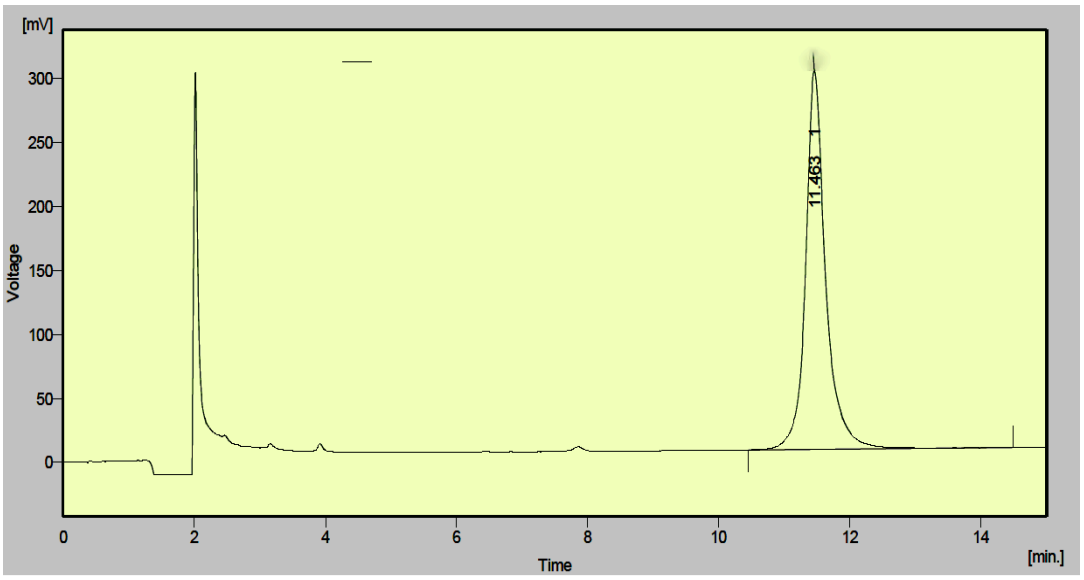

Figure 4. Chromatogram for Telmisartan + Magnesium hydroxide

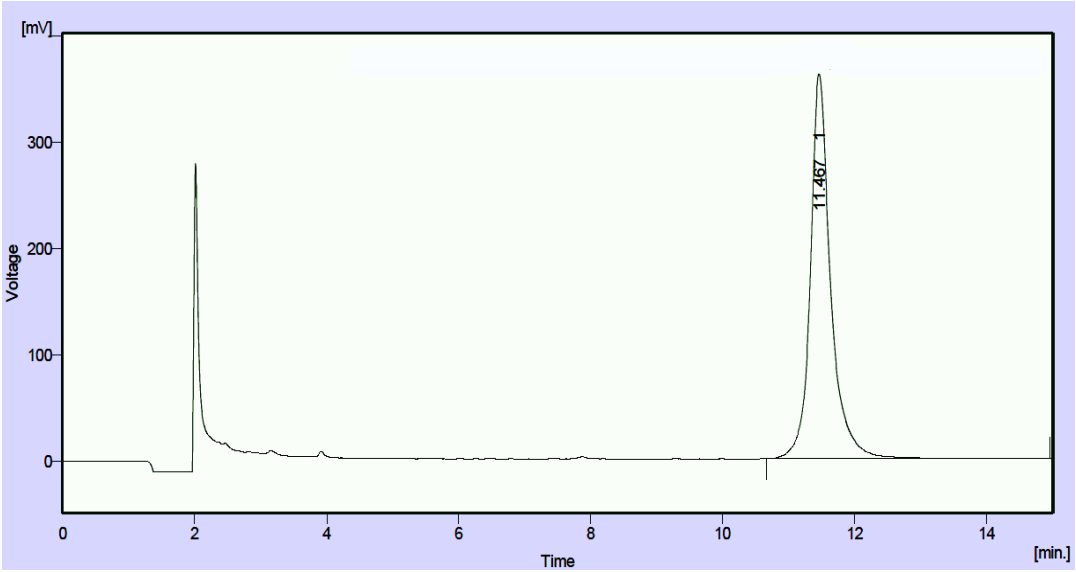

Figure 5. Chromatogram for Telmisartan + sodium lauryl sulphate

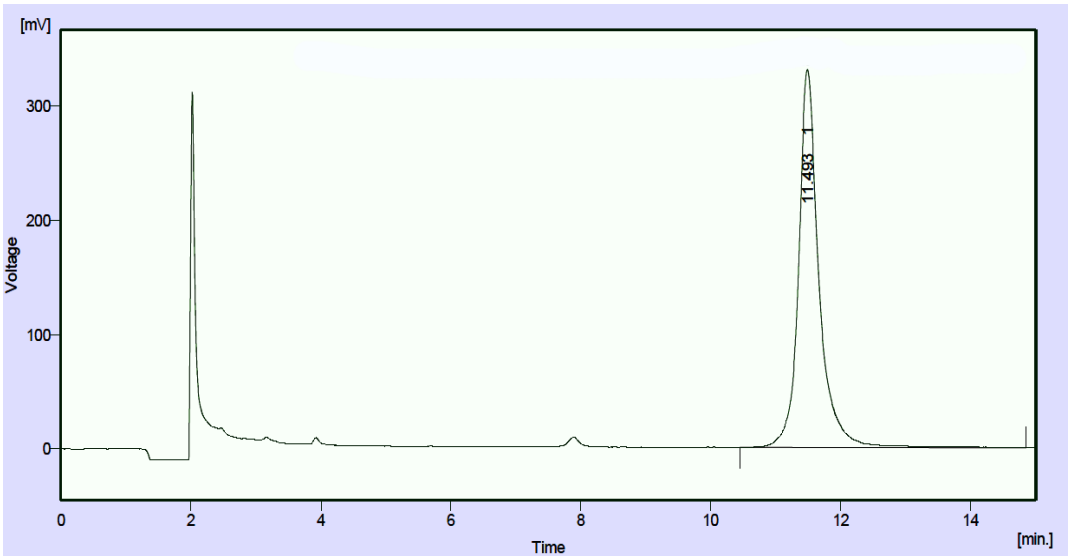

Figure 6. Chromatogram for Telmisartan + Magnesium hydroxide + Sodium lauryl sulphate

The dissolution studies were conducted for pure drug and with the optimized blend. The dissolution parameters such as dissolution efficiency and dissolution rate for pure drug, binary mixtures and ternary mixture were computed form the dissolution data and presented in **Table 1**. The dissolution parameters were futhur treated statistically with one way ANNOVA and the differences in dissolution parameters were found to be statistically significant ($p>0.05$).

Table 1. Dissolution data of Telmisartan and Alkalizers

Alkalizing agents	DE_{15}	K values
Telmisartan	5.25	0.7154
Magnesium hydroxide	58.33	6.1177
Barium carbonate	29.85	3.0883
Sodium bicarbonate	46.70	4.8343
Aluminium hydroxide	40.10	4.403
Magnesium hydroxide (1:3)	5.91	0.620
Magnesium hydroxide (1:5)	11.33	1.1881
Sodium lauryl sulphate	13.47	1.4319

CONCLUSION

The above comparative study of drug and excipient mixture is responsible for the enhancement of solubility of the telmisartan. As telmisartan is a BCS class II drug and is pH-dependent, we used different alkalizing agents like magnesium hydroxide, sodium bicarbonate, aluminium hydroxide and barium carbonate. The results demonstrated that the stability of Telmisartan with magnesium hydroxide has better solubility among the

alkalizing agents. The *invitro* dissolution data is shown in **Table 1**.

The FTIR studies show that there is an interaction between the drug and excipient mixture. HPLC studies show that there is an interaction between the drug and excipient mixture, so it shows the shifting of retention time for binary mixture compared to pure drug. Here it shows the increase in aqueous solubility and interaction with the alkalizers used, or maybe both. Hence it is responsible for the enhancement of the *invitro* dissolution rate of the telmisartan.

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Conflict of interest: None

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Ethics statement: None

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