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Research Article

Hydrotropic Approach for the Enhancement of Telmisartan Solubility

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Telmisartan is a BCS Class II drug with low aqueous solubility and high permeability that exerts antihypertensive effects by selectively blocking angiotensin II type I receptors. However, its limited solubility in water restricts its oral bioavailability and therapeutic performance. Hydrotropy, a simple and economical solubilization technique, has gained attention as an effective approach to improve aqueous solubility of poorly soluble drugs. Unlike methods requiring organic solvents or complex formulations, hydrotropy utilizes safe, non-toxic, and non-flammable agents that enhance solubility through weak molecular interactions. In the present study, the hydrotropic technique was applied to telmisartan using sodium salicylate, sodium tartrate, urea, potassium acetate, and sodium benzoate as hydrotropic agents in different concentrations. These compounds are well-known for their ability to increase solubility by altering solvent properties and destabilizing the water structure. The results revealed an enhancement in the aqueous solubility and dissolution profile of telmisartan in the presence of the selected hydrotropes when compared with the drug alone. The percentage increase in solubility with urea was 1.08% (10%), 1.19% (20%), and 1.60% (30%); with sodium benzoate, it was 2.54% (10%), 3.41% (20%), and 4.07% (30%); with potassium acetate, 2.48% (10%), 3.07% (20%), and 3.796% (30%); with sodium salicylate, the enhancement was highest at 6.31% (10%), 6.68% (20%), and 7.07% (30%); and with sodium tartrate, it was 4.01% (10%), 5.61% (20%), and 6.56% (30%). Improved dissolution rates suggested the potential for increased bioavailability, since dissolution is the rate-limiting step for BCS Class II drugs. The study confirmed hydrotropy as a safe, practical, and efficient approach for enhancing telmisartan solubility and improving formulations of poorly water-soluble drugs.

Keywords: Telmisartan, solubility, hydrotrophy, urea, sodium benzoate, in-vitro release.

INTRODUCTION

Oral drug delivery is the most widely used route due to its convenience, cost-effectiveness, and high patient acceptability. However, the therapeutic effectiveness of orally administered drugs largely depends on their bioavailability, which is mainly governed by solubility and permeability. Poor aqueous solubility remains a major challenge in the development of oral dosage forms and is one of the primary reasons for low and variable bioavailability, particularly for BCS Class II drugs. [1] The therapeutic effectiveness of any drug depends on its bioavailability, defined as the fraction of the administered dose that reaches the systemic circulation and the site of action to elicit the desired pharmacological response. Drug bioavailability is mainly influenced by solubility and permeability, while other contributing factors include chemical stability, dissolution rate, and purity. Currently, only about 8% of new drug candidates exhibit both high solubility and high permeability. [2] One of the major challenges in oral dosage form design is poor bioavailability of drugs, which is governed by several factors such as solubility, permeability, dissolution rate, hepatic first-pass metabolism, and efflux mechanisms. Among these, low solubility and poor permeability are the most recurrent causes of inadequate oral bioavailability. In addition to oral formulations, solubility plays a critical role in other dosage forms such as parenteral formulations. [3] Poorly water-soluble drugs present significant

difficulties in pharmaceutical dosage form development due to their slow dissolution rate and low bioavailability. [4] Since the dissolution rate is directly proportional to solubility, improving solubility leads to enhanced dissolution and bioavailability. Drugs administered orally are completely absorbed only when they possess adequate solubility in gastric fluids, thereby exhibiting good bioavailability. Thus, bioavailability is strongly dependent on drug solubility in aqueous environments and permeability across lipophilic membranes. [5] Therapeutic effectiveness depends on drug bioavailability, which is ultimately governed by solubility. Solubility is a key parameter required to achieve adequate drug concentration in systemic circulation for pharmacological response. [6] Despite advances in research and development, more than 40% of lipophilic drug candidates fail to reach the market due to poor bioavailability, even though they may possess promising pharmacodynamic activity. Drugs that do reach the market often require high doses to achieve therapeutic action. The primary objective of formulation and development is to deliver the drug to the site of action at an optimum dose. [7] Hydrotropy is a solubilization technique in which hydrotropic agents such as sodium benzoate, sodium acetate, urea, and sodium alginate enhance aqueous solubility of poorly soluble drugs through weak molecular interactions rather than micelle formation. [8] This phenomenon is concentration-dependent and does not involve chemical modification of the drug. Hydrotropes are widely used in pharmaceutical and industrial applications. [9] Mixed hydrotropy employs combinations of hydrotropic agents to achieve synergistic solubility enhancement while minimizing individual hydrotrope concentrations and associated toxicity. This approach offers a simple, effective, and safer alternative for solubilization of BCS Class II drugs such as telmisartan. [10] Telmisartan is classified as a BCS Class II drug due to its extremely low aqueous solubility (0.09 µg/mL) and dissolution rate-limited absorption. It is highly ionizable (pKa 4.45 ± 0.09) and exhibits pH-dependent solubility, being poorly soluble in acidic environments. [11] These properties lead to inconsistent absorption and suboptimal bioavailability (~43%). [12] Furthermore, marketed formulations such as MICARDIS® contain strong alkalizing agents that may compromise product stability. Therefore, development of a drug delivery system capable of enhancing solubility, dissolution, bioavailability, and stability of telmisartan is of significant interest. Various formulation strategies such as prodrugs, self-emulsifying systems, salt formation, particle size reduction, lipid-based systems, and cyclodextrin complexation have been explored. [13] The aim of the present study was to enhance the aqueous solubility and dissolution behavior of telmisartan, a BCS Class II drug, using the mixed hydrotropy approach, with the objective of improving its oral bioavailability.

MATERIALS AND METHODS:

MATERIALS

Telmisartan was obtained as gift sample from Hetero Labs Limited-Hyderabad, Telengana. Sodium Benzoate was procured Nice Chemicals Pvt Ltd., Edappally, Kochi. Sodium Salicylate and Urea Extrapure were purchased from S.D. Fine Chemicals Pvt. Ltd., Mumbai. Magnesium stearate was obtained from LOBA Chemie Pvt Ltd., Mumbai. Aerosil was from Hi Media Laboratories Pvt. Ltd., Mumbai. All materials were of analytical grade and used as received.

METHODS

Preformulation studies

Melting Point

Melting point determination of the pure drug was done, as it is a first point indication of purity of sample. Melting point of the drug was determined by taking a small amount of the drug in a capillary tube closed at one end and was placed in Thiel's melting point apparatus and the temperature at which the drug melts was noted. [14] Averages of triplicate readings were taken.

Identification (Scanning of drug-max)

10 and 20 µg/ml solutions of telmisartan in distilled water and hydrochloric acid buffer pH 1.2 respectively were scanned in UV range between 200-400 nm using UV-spectrophotometer against blank.

Solubility studies

Excess amount of the telmisartan was taken and dissolved in a measured amount of distilled water and 0.1 N hydrochloric acid pH 1.2, in a glass beaker separately to get a saturated solution. The solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. Then measured quantity of the filtered drug solution was withdrawn after 24 hrs and the concentration was measured spectrophotometrically at 297 nm. [15] Averages of triplicate reading were taken.

Saturation solubility of telmisartan in hydrotropic solution

For saturation solubility of telmisartan in hydrotropes, briefly, different stock solutions (10%, 20% and 30%) of urea, sodium benzoate, potassium acetate, sodium salicylate and sodium tartarate were prepared individually in distilled water. To 5 ml aliquot of these hydrotropes in glass vials, drug was added until saturation was achieved. Further, these vials were kept in an vortex mixture for 24 h. [16] The solubility enhancement ratio was determined spectrophotometrically at 295.5 nm using UV spectrophotometer using Eq. 1.

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in water}} \quad \text{…….(1)}$$

Preparation of solid dispersion containing hydrotropic agent

Hydrotropic solid dispersions were prepared as per Jain et al. Briefly, 1:2 ratio of drug: hydrotrope were used. In a minimum quantity of water, the hydrotropic agents (sodium salicylate and sodium tartrate) were dissolved separately at a temperature of 80 ^{0}C - 90 ^{0}C followed by slow addition of the drug until a semi solid mass was obtained, which was further scrapped and dried in an oven at 50 ^{0}C in a watch glass and later passed through 60 # sieve. Talc, aerosil and magnesium stearate were used to prepare the blend for the telmisartan hydrotrophy complex capsule. [17]

Drug content

The drug content of telmisartan solid dispersions was determined by dissolving accurately weighed amounts (100 mg) of powdered solid dispersion in 100 ml of methanol and stirring on a magnetic stirrer for 10 min. It was filtered through a membrane filter (0.45 µm), and drug content was determined at 295.5 nm by UV-spectrophotometer. [18]

In-vitro dissolution study of capsules containing solid dispersion of telmisartan and hydrotropic agent

In-vitro dissolution of capsules containing solid dispersion of telmisartan and hydrotropic agent (sodium salicylate and sodium tartrate) was carried out using USP type-I dissolution apparatus. Briefly, 900 ml of 0.1 M hydrochloric acid was used as the dissolution medium with the basket speed at 100 rpm and 37 0C ± 0.5 0C. At predetermined time intervals, 10 ml of aliquot was filtered and subjected to UV spectrometric analysis. Equal volume of dissolution medium was added at each time interval to maintain sink condition. [17]

Fourier Transform Infrared Spectroscopy studies (FTIR)

The Pure drug and selected formulations (F1) were subjected for FTIR analysis to check the compatibility/interaction between the drug and excipients. The samples were scanned over a range of 4000-400 cm-1 using FTIR. Spectra were analysed for any interactions.

RESULTS AND DISCUSSION

Preformulation studies

In the first phase of study, drug fluconazole was subjected to various preformulation studies namely melting point, identification and solubility. The results are shown in Table 3.

Melting Point

The melting point of telmisartan pure drug was determined by open capillary method and it was found to be 267 ºC.

Identification (Scanning of drug – λmax)

The UV absorption maxima for telmisartan was found to be 295.5 nm in distilled water and 0.1N Hydrochloric acid solution (pH 1.2). This was close to the reported value 297 nm. [19]

Solubility studies

Telmisartan is a class II category drug under the biopharmaceutical classification system and has poor aqueous solubility, especially in the physiological pH range (3-7), which limits its bioavailability. The saturation solubility of pure drug in water was found to be 0.0014 mg/ml which was close to the reported value of 0.0015 mg/ml.

Saturation solubility of telmisartan in hydrotropic solution

In the present study, various hydrotropic agents namely urea, sodium benzoate, potassium acetate, sodium salicylate, and sodium tartrate were evaluated for their ability to enhance the aqueous solubility of telmisartan, a poorly water-soluble drug. These hydrotropes were tested at three different concentrations: 10%, 20%, and 30% w/v. A clear concentration-dependent enhancement in the solubility of telmisartan was observed with all hydrotropic agents. Specifically:

- Urea increased the solubility from 1.08% to 1.60%,
- Sodium benzoate from 2.54% to 4.07%,
- Potassium acetate from 2.48% to 3.79%,
- Sodium salicylate from 6.31% to 7.07%, and
- Sodium tartrate from 4.01% to 6.56%,

as the concentration of each hydrotrope increased from 10% to 30%. (Table 1)

Individually, there was a 1.60-fold, 4.07-fold, 3.79-fold, 7.07-fold, and 6.56-fold increase in the solubility in case of 30% urea, sodium benzoate, potassium acetate, sodium salicylate, and sodium tartrate solutions, respectively. The enhancement in solubility can be attributed to the hydrotropic solubilization phenomenon, wherein hydrotropes facilitate drug solubilization through mechanisms such as self-aggregation, hydrogen bonding, and π-π interactions. According to H.A.Ali and H.A. Omer [20] hydrotropes may form non-micellar molecular aggregates in aqueous solutions, which can encapsulate hydrophobic drug molecules, thereby improving their apparent solubility. Among the hydrotropes studied, sodium salicylate and sodium tartrate demonstrated the highest solubilizing capacity for telmisartan, indicating their superior hydrotropic potential. This could be due to their structural compatibility with the drug molecule and the ability to form more stable solute-hydrotrope complexes.

Table 1: Saturation solubility of telmisartan in hydrotropic solution

Telmisartan hydrotropic solutions	Concentration of hydrotropic solution	Absorbance at 295.5 nm	Conc (µg/ml)	% of increase in solubility of drug
Solubility of drug in water alone	------	0.443	0.411	------
Drug + Urea	10%	0.479	0.445	1.08%
	20%	0.531	0.493	1.19%
	30%	0.712	0.661	1.60%
Drug + Sodium benzoate	10%	1.128	1.048	2.54%
	20%	1.512	1.405	3.41%
	30%	1.807	1.679	4.07%
Drug + Potassium acetate	10%	1.102	1.024	2.48%
	20%	1.364	1.267	3.07%
	30%	1.682	1.563	3.79%
Drug + Sodium salicylate	10%	2.799	2.601	6.31%
	20%	2.960	2.750	6.68%
	30%	3.135	2.913	7.07%
Drug + Sodium tartrate	10%	1.780	1.654	4.01%
	20%	2.450	2.311	5.61%
	30%	2.907	2.701	6.56%

Overall, all hydrotropic solutions showed significantly enhanced solubility of telmisartan compared to distilled water, suggesting that hydrotropy is an effective strategy for improving the aqueous solubility of poorly water-soluble drugs like telmisartan. This approach may be particularly valuable in the formulation of oral or parenteral dosage forms where drug solubility is a limiting factor.

Solid dispersion of telmisartan containing hydrotropic agent

Hydrotropic solid dispersions of telmisartan were prepared in a 1:2 drug-to-hydrotrope ratio (sodium salicylate or sodium tartrate) by dissolving the hydrotrope in minimal water at 80–90 °C, followed by gradual drug addition to form a semi-solid mass. The mass was dried at 50 °C, sieved (60#), and blended with talc, aerosil, and magnesium stearate for capsule formulation.

Characterization of solid dispersion and its dosage form

Drug content

The drug content was found to be 170 µgm/ml for telmisartan and sodium salicylate solid dispersion and 160 µgm/ml for telmisartan and sodium tartrate solid dispersions. (Table 2)

Table 2: Drug content of solid dispersion of telmisartan and hydrotropic agent

Solid dispersion	Drug Content (µg/ml)
Telmisartan and sodium salicylate	170
Telmisartan and sodium tartrate	160

In-vitro Dissolution of capsules containing solid dispersion

In case of solid dispersion of telmisartan with sodium salicylate, nearly 83% in-vitro drug release was observed within 300 min whereas in telmisartan with sodium tartarate, about 92% drug release was achieved, for the same time period. Telmisartan in presence of hydrotropic agents exhibited an enhanced dissolution. The improved dissolution may be attributed to the solubilizing effect of the hydrotropic dispersion that makes the drug get solubilized into aggregates which encapsulate the drug molecules. This efficient encapsulation leads to faster wetting of drug molecules that achieves a higher drug release, leading to an increase in the oral bioavailability. This clearly indicates that sodium tartrate solid dispersion exhibited faster dissolution compared to sodium salicylate solid dispersion, which may be due to the enhanced wetting and solubilization effect of sodium tartrate.

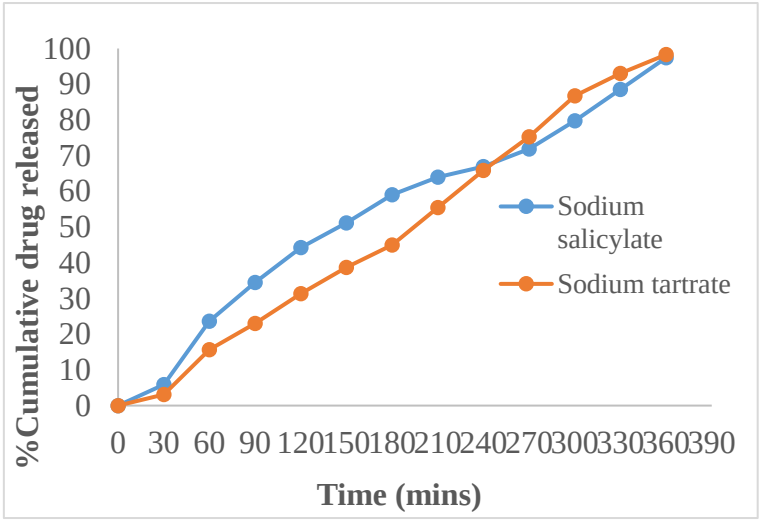

Fig. 1: % CDR of capsules containing solid dispersion of telmisartan and hydrotropic agent (Sodium salicylate and Sodium tartrate)

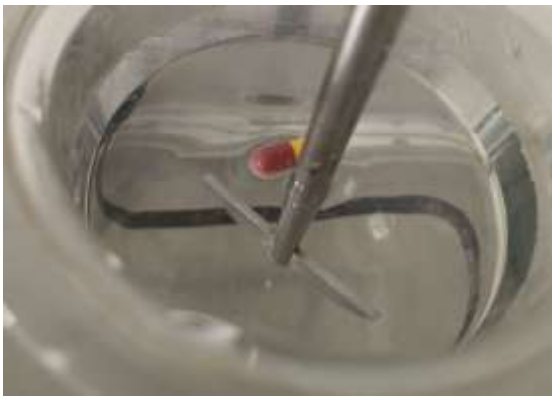

Fig. 2: Dissolution of capsules containing solid dispersion of telmisartan and hydrotropic agent (sodium tartrate)

Fourier Transform Infrared Spectroscopy studies (FTIR)

FTIR spectrum of telmisartan showed characteristic peaks at 3457.36 cm^{-1}, 3391.73 cm^{-1} (O–H stretching), 3070.47 cm^{-1} (aromatic C–H stretching), 2962.24 cm^{-1} and 2850.00 cm^{-1} (aliphatic C–H stretching), 1720.10 cm^{-1} and 1690.23 cm^{-1} (C=O stretching of –COOH group), 1645.74–1608.12 cm^{-1} (C=C and C=N stretching), 1584.89–1458.68 cm^{-1} (C=C ring stretching), 1374.00 cm^{-1} (O–H bending), 1289.78 cm^{-1} (C–X stretching), and 806.91–739.81 cm^{-1} corresponding to substituted benzene rings, which indicates the purity of telmisartan. In addition, no major interactions were visible as the characteristic functional peaks of telmisartan were present. In case of telmisartan and sodium tartarate solid dispersion, the FTIR spectra showed all characteristic peaks of the drug with slight shifts, suggesting physical interactions without chemical modification. Similarly, telmisartan and sodium salicylate solid dispersion exhibited the major peaks of telmisartan, indicating the stability of the drug in hydrotropes.

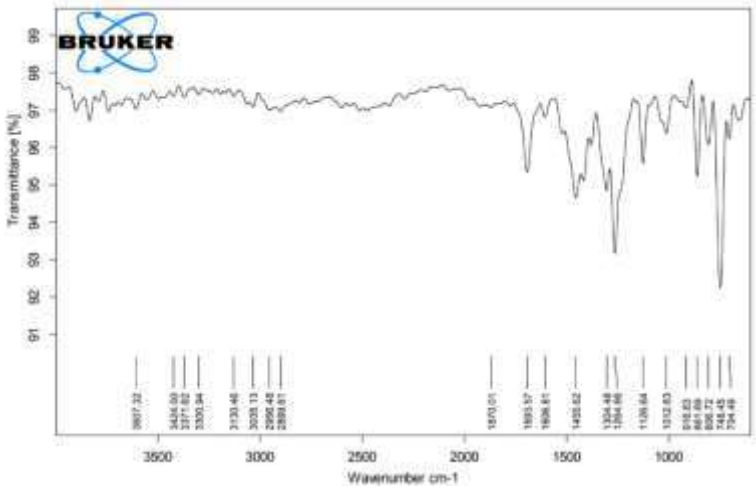

Fig. 3: FTIR of telmisartan pure drug

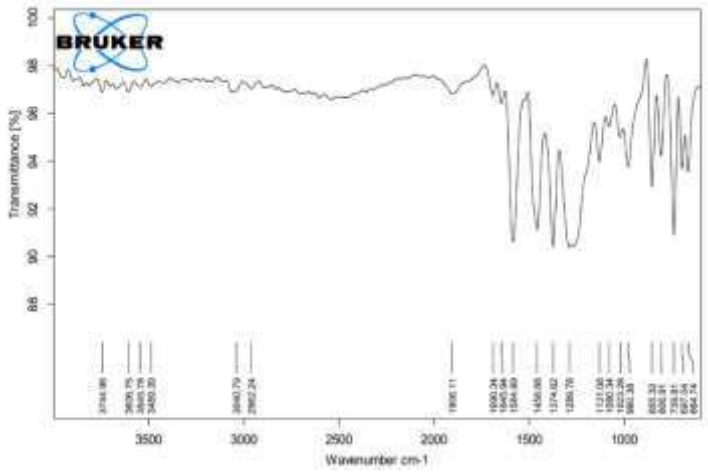

Fig. 4: FTIR of telmisartan with hydrotrope (sodium tartarate)

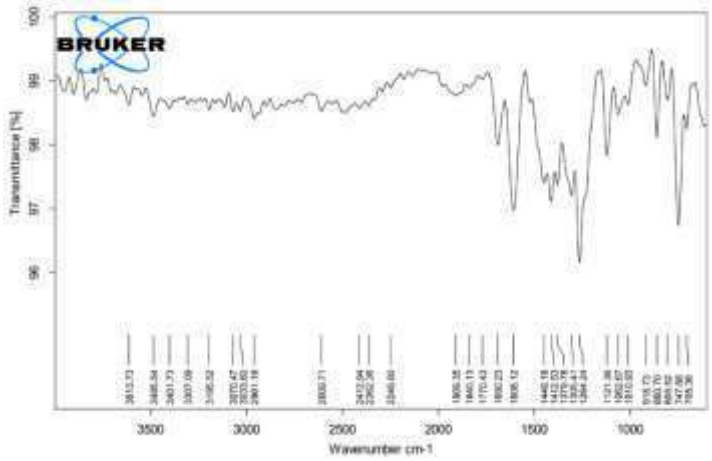

Fig. 5: FTIR of telmisartan with hydrotrope (sodium salicylate)

CONCLUSION:

In conclusion, hydrotropy proved to be a simple, effective, and economical strategy for overcoming the solubility limitations of telmisartan. This approach holds significant potential for formulation development of poorly soluble drugs. Future studies focusing on stability and in-vivo evaluation will help to confirm the pharmaceutical advantages of these hydrotropic dispersions.

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