ORIGINAL ARTICLE

Solubility and Dissolution Rate Enhancement of Poorly Soluble Telmisartan using Hydrotropy Method

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Abstract

Objectives: Drugs given by oral route will undergo dissolution followed by permeation then it reaches to blood. Low water solubility is the foremost issue that comes upon with the development of dosage forms for newly discovered drugs as well as old drugs. Telmisartan is a class II category drug under the biopharmaceutical classification system, which limits its bioavailability to about 40%. Hydrotropy method has several advantages compared to other methods such as cost-effectiveness, ease of process, compatibility, scalable, and flexibility to varieties of dosage forms. Henceforth, an attempt has been made to improve the solubility of telmisartan using the hydrotropy method. **Materials and Methods:** Three different hydrotropic agents (urea, mannitol, and lactose) in different concentrations (10–50%) were used to find the solubility of the drug. The design of an expert statistical tool was utilized to optimize the best concentration of hydrotropic agent for having maximum solubility of the drug. **Results:** In a 40% urea blend, the solubility was obtained approximately 25.87 times more than pure drug (0.003 mg/mL) which showed the potential of the hydrotropic agent. This obtained optimized batch was further characterized for drug release profile and other related parameters. The optimized concentration of urea showed 87.46 ± 0.17% of drug release in 8 h which is relatively higher than the plain drug release. **Conclusion:** Therefore, it can be concluded that the 40% concentration of urea as a hydrotropic agent showed to be a key factor for enhancement of solubility followed by dissolution of poorly soluble telmisartan drug.

Key words: Dissolution rate, hydrotropy method, solubility enhancement, telmisartan

INTRODUCTION

Drugs given by oral route will undergo dissolution followed by permeation then it reaches to blood. Drug dissolution rate, pre-systemic metabolism, and efflux process are a few of the vital factors responsible for creating the efficacy of drugs. The aqueous solubility in the gastric fluid is an important factor for new drug moieties.[1,2] This leads to unpredictable bioavailability and potential harmfulness to the body after final absorption through the gastric mucosa. Hence, the poor aqueous solubility of new drug moieties is the major task for the researchers.[3]

Apart from these aspects, any other factors such as an easy route for administration of drugs, satisfactory compliance from patients, cheap, non-sterile manufacturing requirements, and easiness in dosage form fabrication make this oral route as a route of choice for almost all drugs. Researchers all over the globe are working with many newer physical or chemical techniques for the improvement in the aqueous solubility of newly synthesized drugs.[4,5]

The methods include particle size reduction,[6] formulation of nanosuspension,[7] complexations with water-soluble molecules,[8] adjustment by altering the pH, conversion into salt form, use of surfactants, development of nanotechnology, and solid dispersions.[9-12]

The aqueous solubility is a prime importance in delivering the desired goal of the drug molecule. The above-mentioned

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method either in single or in combination can be utilized to improve the water solubility of the drug. The ideal method shall play a key role in significant improvement in bioavailability, reduction in dosing frequency, low production cost, and enhanced patient compliance.

Few techniques may be costly and time-consuming too, therefore the techniques with low cost and easiness in process shall be preferred over time. Among various techniques, Hydrotropy is the promising method to enhance aqueous solubility followed by dissolution characteristics of in-soluble drugs. The hydrotropy method has several advantages compared to other methods such as cost-effectiveness, ease of process, compatibility, scalable, and flexibility to varieties of dosage forms. The word "hydrotropy" was coined by the scientist Carl A. Neuberg in 1916. Hydrotropy is a process of solubilization that results in a rise in another's aqueous solubility of the solution by adding a large quantity of the second solute. The resultant product exhibited greater drug solubility in a dissolution media[13-16]. The hydrotropic agent has both hydrophilic and hydrophobic parts in their structure. At high concentrations, hydrotropic agents can form micelles in the solvent. These micelles have a hydrophilic shell and a hydrophobic core. The poorly soluble drug molecules can partition into the hydrophobic core of the micelles. As a result of the solubilization and micelle formation, the solubility of the poorly soluble drug in the solvent is significantly enhanced.

Telmisartan is a blocker for the angiotensin II receptor and is basically used for the treatment of hypertension. Telmisartan is a class II category drug under the biopharmaceutical classification system (BCS), which limits it in achieving desirable bioavailability.[17-19]

Therefore, the aim of the present research work is to improve the aqueous solubility of telmisartan followed by its dissolution rate using the hydrotropy method.

MATERIALS AND METHODS

Materials

Telmisartan was gifted by Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat, India. Various hydrotropic agents such as Urea, lactose, and mannitol were procured from LobaChemiePvt Ltd., Mumbai, Maharashtra, India. Other compounds used in this study were of analytical acceptable grade.

Methods

Solubility enhancement by different hydrotropy methods

Single hydrotropy

The aqueous solubility of the drug was determined in three different hydrotropic agents, namely lactose, urea, and mannitol at a concentration of 10%, 20%, 30%, 40%, and 50% of each, using purified water as solvent at a temperature of 25°C ± 1°C. The additional quantity of drug was mechanically shaken with 10 mL of each concentration of hydrotropic agents' solution kept in a volumetric flask, to get a saturated mixture. An equilibrium was achieved by 12 h continuous stirring on a mechanical stirrer. The centrifugation of the mixture was carried out at 2000 rpm for 20 min followed by filtration. The aliquots after suitable dilution with water were analyzed under UV spectrophotometer at 228 nm.[20]

Mixed hydrotropy

The procedure of solubility study was repeated using the combination of two hydrotropic agents at a temperature of 25°C ± 1°C. The two hydrotropic agents with different ratios were mixed in water to get a mixture of hydrotropic agents. The previously saturated drug solution was added to the above mixture. The mixture was processed and solubility was analyzed by the same method discussed above.[21,22]

Optimization through the design of experiment (DoE) statistical tool

The experiments were designed using DoE software (Version 10.0.1.0). The DoE software was utilized to study interactions between different variables as well as the fulfilment of the desired responses. For the selection of the optimum quantity of hydrotropes, a factorial design was applied by use of one factor with one center point optimization method.[23] A total of seven trials were performed as per the suggestions of the software. The concentration (%) of urea was selected as an independent variable (X_1) and solubility of the drug was considered a dependent variable (Y_1) based on primary trials. The layout of the design is shown in Table 1.

Preparation of solid dispersion

The accurate weight amount of the hydrotropic agent was dissolved in the required volume of warm water using a teflon-coated magnetic bead on a high-speed magnetic stirrer. The drug was added to the above mixture after the complete dissolution of the hydrotropic agent in water. The temperature was maintained at 55–60°C to evaporate water. The wet solid dispersion was formed once most of the water was evaporated. This wet mixture was kept on several watch glasses placed in a hot air oven which was maintained at 50 ± 2°C for complete drying. The resultant solid dispersions were crushed with a glass pestle mortar and then passed through sieve# 60. The product was carefully stored in well tight glass bottle.[11,12]

Table 1: The statistical design for optimization

Independent factor (X_1)	Level		Dependent factor (Y_1)
Concentration of urea (% w/v)	Low	High	Solubility (mg/mL)

In vitro dissolution studies

The dissolution profile of the hydropic mixture was compared with the pure drug. The USP type-II apparatus was utilized to study the dissolution profile using a rotating paddle method. The prepared solid dispersion (equivalent to 40 mg of drug) and plain drug (40 mg) were placed into the hard gelatin capsules (size 2). The 900 mL of distilled water was considered a dissolution medium. The paddle was set at 50 rpm and the temperature was adjusted at 37°C ± 0.5°C. The samples of 5 mL of volume were withdrawn at every 1 h time intervals up to 8 h, filtered, and analyzed after suitable dilution using a UV spectrophotometer at 228 nm.[24,25]

Drug excipient compatibility study

The Fourier Transform Infra-Red spectrophotometer (FTIR) (IRAffinity-1: Shimadzu Corporation, Japan) was used to check any interaction between the drug and excipients. The FTIR spectrum was studied for the mixture (Sample: KBr, in ratio 1:300) in the recommended range (4000–400 cm-1) using FTIR spectrophotometer.[24]

Stability study

The optimized hydrotropic mixture was placed in glass vials for specific stability conditions at 25 ± 1°C/60 ± 5% RH and 40 ± 1°C/75 ± 5% RH in a precise stability cabinet for the duration of 3 months as per ICH guidelines. The formulations were analyzed for physical appearance and % drug release at every 1 month.[24,26]

RESULTS AND DISCUSSION

Solubility study by single hydrotropy method

The equilibrium solubility of Telmisartan was carried out with different hydrotropic agents. All hydrotropes such as lactose, urea, and mannitol are capable of improving the solubility of the drug to some extent as shown in Table 2. The maximum aqueous solubility was achieved with 40% w/v urea solution. This showed a 25.86-fold significant increment in drug solubility with urea compared to solubility in water. The urea may reach a maximum equilibrium at 40% w/v therefore 50% w/v urea solution did not show any significant improvement in solubility. Hence, hydrotrope with 40% w/v solution was considered for further optimization.

Solubility study by mixed hydrotropy method

To verify further improvement in solubility, various blends of hydrotropic agents were also studied. The total strength of hydrotropic agents was kept constant at 40% w/v. All the hydrotropic combinations were also found to have increments in drug solubility as shown in Table 3. The 40% w/v blend comprised urea: lactose at a ratio of 35:5 showed the highest solubility but it did not have any significant difference with the solubility obtained with single hydrotropy urea 40% w/v solution. Therefore, urea with 40% w/v solution was considered for further optimization.

Table 2: Solubility study using single hydrotropy method

Hydrotropic agent	Concentration (w/v)				
	10%	20%	30%	40%	50%
	Solubility±SD (mg/mL)				
Lactose	0.0110±0.0010	0.0103±0.0003	0.0074±0.0002	0.0089±0.0001	0.0090±0.0002
Urea	0.0080±0.0020	0.0305±0.0003	0.0483±0.0020	0.0776±0.0004	0.0769±0.0003
Mannitol	0.0060±0.0020	0.0137±0.0007	0.0140±0.0005	0.0083±0.0003	0.0080±0.0001

All values are expressed as mean±SD, *n*=3

Table 3: Solubility study using mixed hydrotropy method

Hydrotropic agent % (w/v)		Solubility (mg/mL)		
A	B	Blend of Urea: Lactose	Blend of Urea: Mannitol	Blend of Lactose: Mannitol
5	35	0.0082±0.0004	0.0072±0.0020	0.0069±0.0010
10	30	0.0150±0.0003	0.0095±0.0005	0.0095±0.0003
15	25	0.0175±0.0005	0.0205±0.0006	0.0085±0.0005
20	20	0.0368±0.0010	0.0295±0.0020	0.0098±0.0004
25	15	0.0394±0.0002	0.0350±0.0002	0.0161±0.0005
30	10	0.0470±0.0005	0.0420±0.0050	0.0153±0.0020
35	5	0.0743±0.0003	0.0695±0.0040	0.0105±0.0010

All values are expressed as mean±SD, *n*=3

Optimization

The equilibrium solubility of telmisartan was carried out with the help of the statistical tool. All batches were able to improve the solubility of telmisartan. The utmost solubility was obtained in batch TEL 7 with a 25.87-fold enhancement compared to plain drug solubility in water. The layout of all batches is shown in Table 4. The surface plot also suggested that as the concentration of urea increases, the solubility of the drug is, respectively, increased. The data are depicted in Figure 1.

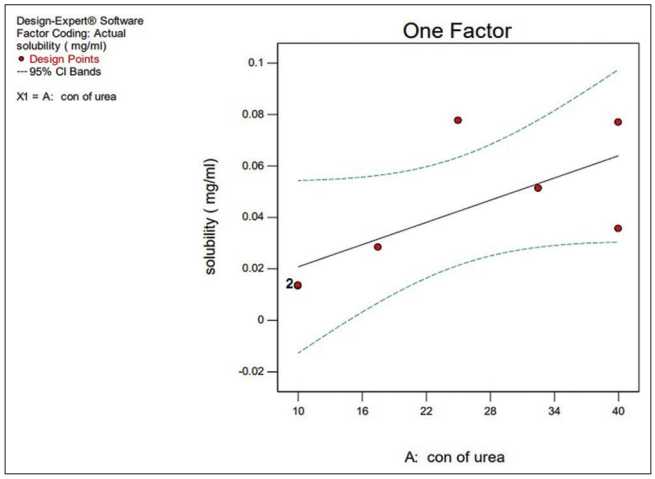

Figure 1: Contour plot for one factorial design

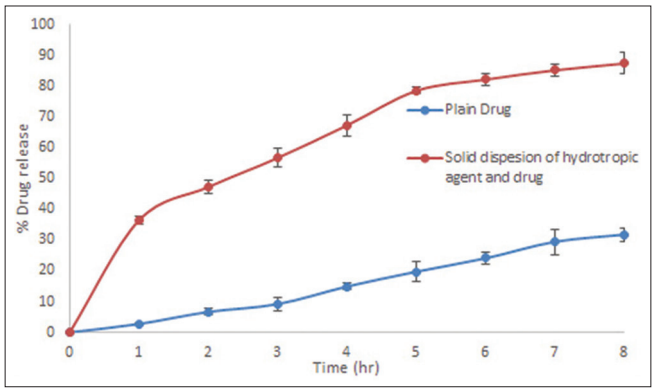

Figure 2: Dissolution profile between plain drug and hydrotropic blend of drug

In vitro dissolution studies

The dissolution profile of the hydrotropic mixture was compared with the plain drug. It was found that the hydrotropic solid dispersion of telmisartan and urea has a faster dissolution rate than that of pure telmisartan. The plain drug showed only 31.83±2.14% of drug whereas the blend of drug with hydrotropic agent showed comparatively higher 87.46 ± 3.48% drug release at the end of 8 h. Such hydrotropic agents may diffuse the drug molecules passively into the dissolution medium and enable the drug particles to be easily dispersed in the dissolution medium, hence a faster dissolution rate can be obtained in case of solid dispersion as compared to plain telmisartan. The data are depicted in Figure 2.

Drug excipient compatibility study

The compatibility study was performed using FTIR spectroscopic analysis. All spectra were compared with the spectrum of the drug to check any interactions. No major changes were observed in the functional groups' telmisartan in the spectrum of a blend of hydrotropic agent and drug. The characteristic peaks in the hydrotropic blend showed the spectrums for functional groups C-O, C-N, O-H, and C=O at 1228.71 cm^{-1}, 1269.22 cm^{-1}, 1458.25 cm^{-1}, and 181.04 cm^{-1}, respectively. Hence, it was considered that there was no interaction took place in between the drug and excipients used for the solubility enhancement method and they were compatible with each other. The spectrums are displayed in Figure 3.

Stability study

The stability study was conducted at specified atmospheric conditions. The result after 3 months showed that the optimized blend of hydrotropic agent, urea and telmisartan, does not have any significant changes as compared to the initial data. Therefore, it can be said that the prepared blend is stable and showed satisfactory data after the stability period. The data are shown in Table 5.

Table 4: Layout of various batches under the design of experiments

Batch code	Levels	Independent variable – X_1 (%)	Dependent variable – Y_1 (mg/mL)
TEL 1	−1	10	0.0133±0.0002
TEL 2	−1	10	0.0136±0.0003
TEL 3	−0.5	17.5	0.0284±0.0002
TEL 4	0	25	0.0356±0.0004
TEL 5	0.5	32.5	0.0513±0.0002
TEL 6	1	40	0.0769±0.0004
TEL 7	1	40	0.0776±0.0005

All values are expressed as mean±SD, *n*=3

Table 5: Stability data of optimized hydrotropic blend of urea and telmisartan

Time (months)	25±1°C/60±5% RH		40±1°C/75±5% RH	
	Physical appearance	% Drug release	Physical appearance	% Drug release
0	White free-flowing powder	87.46±3.48	White free-flowing powder	87.46±3.48
1		88.03±2.33		86.12±1.27
2		85.98±4.04		86.06±1.37
3		86.79±3.11		85.94±2.65

Values are expressed as mean±SD, *n*=3

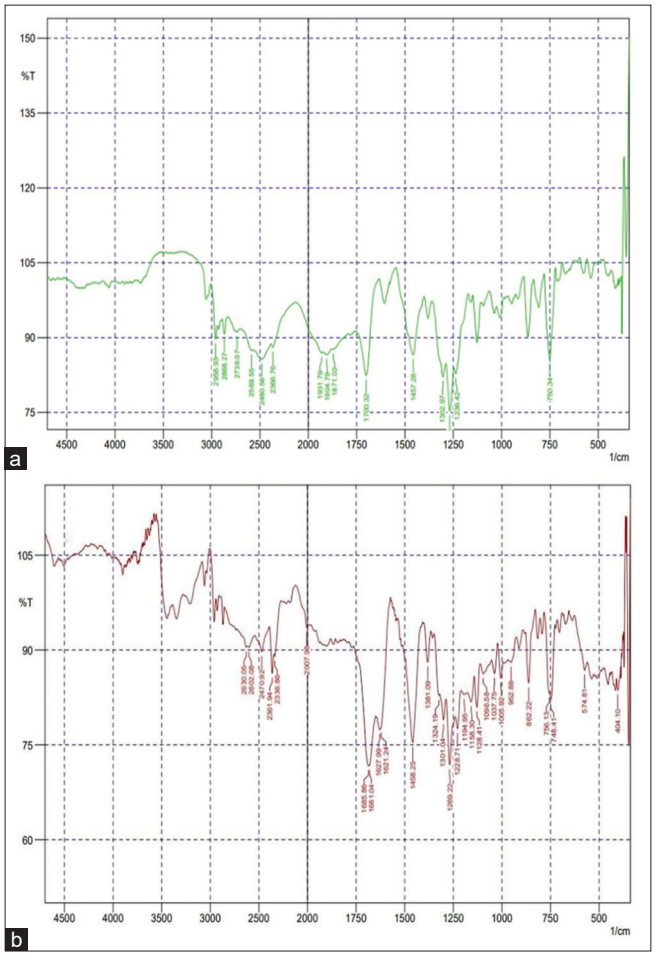

Figure 3: Fourier-transform infrared spectroscopy spectrum (a) plain telmisartan and (b) hydrotropic blend of urea and telmisartan

CONCLUSION

Telmisartan drug was selected for this project to improve the solubility by the hydrotropy method. The present research work concludes that the solubility of BCS class II drugs such as telmisartan can be improved by avoiding the use of organic solvents with the help of the hydrotropic method. An effort was executed to improve 25.87 times higher solubility of telmisartan using a blend of 40% w/v urea and drug followed by a significant enhancement in dissolution profile. At the end, it can be concluded that the hydrotropy method can be utilized at large extent in enhancing solubility followed by the dissolution profile of poorly water-soluble drugs.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest.

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