Solubility Enhancement of Telmisartan Using Mixed Hydrotropy Approach

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Research Article

Article Info:
Received on:10/10/2015
Accepted on: 25/10/2015
Published on:21/11/2015

QR Code for mobile

Literati
Open Access

ABSTRACT :
The present study was aimed at enhancement of telmisartan solubility using mixed hydrotropy approach. Telmisartan is a angiotensin II receptor antagonist used as antihypertensive. The effect of various hydrotropes at fixed concentration (40%) was probed to screen suitable hydrotropes for further studies except piperazine anhydrous and sodium benzoate (20%). Moreover effect of selected hydrotropes at different concentrations (10%, 20%, 30%, 40%) and blends of hydrotropes (10%) on solubility of telmisartan was investigated. The results indicated remarkable enhancement in solubility with sodium benzoate and sodium salicylate respectively. The mixed hydrotropic solution BD (Urea, PEG 4000 PEG 6000) showed 15737 folds improved solubility though other blends also gave the comparable results. The interference of various solubilizers in spectrophotometric estimation of Telmisartan was examined and no interference was observed. The contribution of pH in Telmisartan solubility enhancement was negligible.

Keywords: Mixed hydrotropy, telmisartan, solubility, antihypertensive

INTRODUCTION:

Among the newly developed drug molecules, most of them are lipophilic in nature and poor solubility is one of the most difficult problem of these drugs. Hydrotropy is one of the advanced and most successful method, in which aqueous solubility of poorly water soluble drugs is increased by co-dissolving with other highly water soluble inert substances. Such agents used to increase the solubility of poorly water soluble drug in aqueous medium are known as hydrotropic agent or hydrotropes like Sodium Benzoate, Niacinamide, Sodium Citrate, Sodium Acetate and Urea.[1,2] Moreover blends of hydrotropes could be used to enhance the solubility of poorly water soluble drugs owing to synergistic or additive effect of solubilizers in combination known as mixed hydrotropy. Mixed hydrotropy tends to decrease the concentration of individual solubilizers and toxicity. Further, all the solubilizers used in the study are GRAS (Generally regarded as safe) listed.

Telmisartan is 4'-[1,4'-dimethyl-2-propyl [2,6'-bi-benzimidazole]-1'-yl] methyl 1,1'- biphenyl 2-carboxylic acid. It is practically insoluble in water; sparingly soluble in strong acid; soluble in strong bases. Telmisartan prescribed for the treatment of essential hypertension is a new Angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT1), with a binding affinity 3000 times greater for AT1 than AT2.

The aim of the present investigation is to increase the solubility of telmisartan by mixed hydrotropy approach.

MATERIALS AND METHODS

Telmisartan was obtained as gift sample from Shreya Ltd. Aurangabad, India. All other chemicals were of analytical grade. Deionized water was used during study and solutions were analyzed using Shimadzu 1700 double beam UV spectrophotometer.

Determination of equilibrium solubility of telmisartan

The equilibrium solubility of Telmisartan was determined in water, various solubilizers and solubilizer blends. The various solubilizers and cosolvents were screened to enhance the solubility of Telmisartan. Equilibrium solubility studies were performed according to a method developed by Higuchi and Connors.

Aqueous solutions of hydrotropes and cosolvents (40%) were prepared in deionized water. Sufficient excess amount of drug was added to amber coloured glass vials containing fixed volumes (10 ml) of the hydrotrope solution. The vials were sonicated for 1 to 2 hours at room temperature. The solutions were allowed to equilibrate for next 24 hours and centrifuged for 5 min (REMI, R 8C BL). The supernatants of each vial were filtered through Whatman filter paper (Grade 41). An aliquot of each filtrate was suitably diluted with deionized water and the resulting solutions were analyzed by UV spectrophotometer at 230 nm against blank. The Solubility enhancement ratio was calculated by using following equation.

Solubility enhancement ratio = Solubility in particular hydrotrope solution/solubility in water

Similarly Telmisartan solubility was determined using varying concentrations (10%, 20%, 30%) of selected solubilizers and blends of solubilizers (10%).

Interference of solubilizer in spectrophotometric estimation of telmisartan

Interference of solubilizers in the spectrophotometric estimation of ZAL was determined by dissolving known amount of drug and each solubilizer in deionized water. The absorbance was recorded against respective reagent

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doi: 10.15272/ajbps.v5i50.759

Conflict of interest: Authors reported none

blank at appropriate wavelength.

Effect of pH on solubility of telmisartan

The various phosphate buffers having pH 1.9, 3, 4, 4.8, 5.8, 6.8, 7.2, 7.8, 9.2, and 9.8 were prepared according to standard protocol. Sufficient excess amount of Telmisartan was added to amber coloured glass vials containing fixed volumes (10 ml each) of the respective buffers. The vials were sonicated for 1 to 2 hr at room temperature. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes. The supernatants of each vial were filtered through Whatman filter paper, filtrate was diluted suitably with deionized water and the resulting solutions were analyzed by UV spectrophotometer at 230 nm against blank solutions.

Statistical analysis

Statistical analysis of data was performed by one way analysis of variance (ANOVA) followed by Dunnet and Tukey Krammer test, with significance level set at 0.05. The data was expressed as mean ± S.D. (Graph Pad INSTAT 3.10)

Results and discussion

The equilibrium solubility of telmisartan in various solubilizers was determined and result indicates remarkable increase in solubility with sodium benzoate, sodium salicylate, piperazine anhydrous, and urea. The results are presented in Table I. The results were compared by Dunnet test and indicates statistically significant differences in solubility (P<0.05) between water and above solubilizers. In this study piperazine anhydrous and sodium benzoate were used at 20 % level because above 20% drug was precipitated and exact determination of solubility was difficult. These solubilizers with maximum solubility were used for further study.

Sr. No.	Solubilizer solution (40%)	Solubility (mg/ml)	Solubility enhancement ratio
1	PA(20%)	214.28	6200.39
2	SC	0.4145	11.996
3	SA	0.7184	20.788
4	U	10.642	307.95
5	SS(20%)	943	27285.8
6	SB	1286.8	37235.01
7	PC	1.027	29.734
8	PEG 200	0.485	14.054
9	PEG 400	0.0985	2.850
10	PEG 600	0.1603	4.638
11	PEG 4000	0.5226	15.1232
12	PEG 6000	0.7325	21.195
13	Niacinamide	115.806	3350.88

Table 1: Solubility of telmisartan in various hydrotropic agents

The significant improvement in solubility was obtained using high concentration of hydrotropic agents. However such high concentration is not acceptable and may precipitate toxicity. The toxicity could be avoided by reducing the concentration of individual solubilizers. Hence hydrotropic agents were used at 10% concentration in combinations to enhance the solubility of telmisartan. The aim of this study was to investigate the effect of blend containing solubilizers on solubility of telmisartan. Initially solubility was estimated in blend containing three solubilizers keeping total concentration 10%. The results indicated substantial increase in solubility in each blend and blend BD showed maximum solubility as shown in Figure. 1. Also statistically significant difference in solubility was observed (P<0.05) in comparison with water. This may be attributed to synergistic effects of solubilizers in combination and order of this effect was BD > BC > BB > BA > BE>BF (Table 2).

Blend codes	Solubilizer (% w/v)						Equilibrium solubility (mg/ml)	Solubility enhancement ratio
	SB	SS	PA	U	PEG 4000	PEG 6000		
BA	3.33	3.33	3.33	-	-	-	34.188	989.23
BB	**-**	**-**	**3.33**	**3.33**	**3.33**	**-**	**71.285**	**2062.64**
BC	**-**	**-**	**3.33**	**3.33**	**3.33**	**-**	**188.571**	**5456.33**
BD	**-**	**-**	**-**	**3.33**	**3.33**	**3.33**	**543.888**	**15737.5**
BE	3.33	-	-	-	3.33	3.33	10.651	308.188
BF	3.33	3.33	-	-	-	3.33	9.697	280.59

Table 2: solubility of telmisartan in mixture of three solubilizers

SB: sodium benzoate, , PA: Piperazine anhydrous, SS: sodium salicylate, Urea

Similarly solubility was investigated in blend containing more than three solubilizers keeping total concentration 10% and blend AE exhibited utmost solubility of 378.57 mg/ml with 10954 folds enhancement in solubility (Table 3, Figure 1). Each blend showed statistically significant difference in solubility when compared with each other and water (P<0.05). This may be owing to synergistic effect of solubilizers in combination.

Blend codes	Solubilizer (% w/v)						Equilibrium solubility (mg/ml)	Solubility enhancement ratio
	SB	SS	PA	U	PEG 4000	PEG 6000		
AA	2.5	2.5	2.5	2.5	-	-	10.338	299.13
AB	2.5	2.5	2.5	-	-	2.5	5.950	172.18
AC	2.5	2.5	-	-	2.5	2.5	1.235	35.743
AD	2.5	-	-	2.5	2.5	2.5	3.376	97.708
AE	-	-	2.5	2.5	2.5	2.5	378.57	10954.03
AF	-	2.5	2.5	2.5	2.5	-	52.11	1507.54

Table 3: Solubility of telmisartan in mixture of different solubilizers.

The interference of solubilizers in spectrophotometric estimation of zaltoprofen was investigated and from results it was evident that solubilizers did not interfered in estimation. It can solely attributed to the fact that wavelength of maximum absorption (λ_{max}) of drug, 230 nm was not shifted.

The contribution of pH in solubility enhancement was probed using buffers of wide pH range and results indicate that solubility was increased with increase in pH. However effect of pH on solubility enhancement was negligible.

CONCLUSION:

Aqueous solubility is a major concern for number of drugs and lead to bioavailability problems. However this problem can be conquered using mixed hydrotropy technique. Solubility of poorly water soluble drug telmisartan was increased remarkably using mixed hydrotropy. Solubility was enhanced significantly with increase in concentration of solubilizers. However blends of solubilizers exhibited substantial increase in solubility at low concentration owing to synergistic effect in combination. Furthermore this technique could be exploited to increase the solubility of poorly water soluble drugs using GRAS listed solubilizers in future.

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Cite this article as:
Phulzalke S.B, Kate B.A, Bagade M. Y. Solubility Enhancement of Telmisartan Using Mixed Hydrotropy Approach. Asian Journal of Biomedical and Pharmaceutical Sciences, 5(50), 2015, 37-39.