WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 8, 833-845. Research Article ISSN 2277– 7105

HYDROTROPIC SOLUBILIZATION TECHNIQUE TO CHALLENGE THE SOLUBILITY OF POORLY WATER SOLUBLE DRUG VALSARTAN

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Article Received on
26 May 2016,

Revised on 17 June 2016,
Accepted on 08 July 2016

DOI: 10.20959/wjpr20168-6722

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ABSTRACT

Aqueous solubility is one of the major concerns during formulation development of new drug molecules. Drug efficacy as well bioavailability can be restricted by poor aqueous solubility of drugs. Previously, many techniques have been developed to enhance aqueous solubility of drug which showed promising advantage of increased potency as well reduced side effects. Hydrotropic solubilization is one of the enhancement techniques which enhance solubility of drug to many folds with the use of hydrotropes like sodium acetate, sodium benzoate, sodium citrate, urea etc. The key objective of current research work was to enhance aqueous solubility of very poorly water soluble drug, Valsartan using hydrotropic solubilization technique. Valsartan is an orally active antihypertensive drug which is poorly water soluble (0.021mg/ml) and has low bioavailability of 23%. Rationale to choose hydrotropic solubilization for Valsartan was that hydrotropic solution may enhance solubility of drug which in turn results in enhanced dissolution rate as well bioavailability. Solubility studies were performed using various concentrations of hydrotropic solutions of sodium acetate, sodium ascorbate, sodium benzoate, piperazine, etc. These solubility studies revealed that the solubility of drug was increased 62 hundred times when added to 5% piperazine anhydrous solution and marked its importance in pharmaceutical field. The reason for high solubility may be due to higher pH of piperazine solution which could dissolve valsartan being weakly acidic in nature.

KEYWORDS: Hydrotropy, solubility, valsartan, piperazine, sodium benzoate, solubility enhancement.

INTRODUCTION

Solubility is one of the important parameter for drug to achieve desired concentration in systemic circulation for showing effective pharmacological response. Drug response may be severely affected by poor aqueous solubility of drug which may also lead to unnecessary side effects. This is true for parenterally, topically as well orally administered drug dosage forms. Earlier, many techniques have been developed to enhance the aqueous solubility. These techniques include complexation, cosolvency, emulsions, liposomes, particle size reduction, solid state alteration, solid dispersions etc. Enhancement in aqueous solubility can thus be a valuable aid to increase efficiency or reduce dose and side effects for certain drugs.

Hydrotropy is one of the solubility enhancement techniques which enhances solubility by many folds with use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide etc. and have many advantages like, it does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system etc.[1]

The term 'Hydrotropy' was put forward by Carl Neuberg [2] to describe increase in solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. The term "solubility" is defined as maximum amount of solute that can be dissolved in a given amount of solvent.[3]

Hydrotropy refers to the ability of a concentrated solution of a chemical compound (usually alkali metal salts of organic acids) to increase the aqueous solubility of another compound (usually a sparingly soluble organic compound). Simply, it is a solubilization phenomenon wherein addition of large amount of second solute increases aqueous solubility of another solute and those compounds that have this property are called "Hydrotropes".

Solubility enhancement is one of the most significant parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Hydrotropy is one of the important solubility enhancement techniques that can be used to enhance solubilization of poorly water soluble drugs in folds by using various hydrotropic agents.[4]

Examples of various hydrotropic agents used as excipients to increase aqueous solubility of drug are urea, xylitol, nicotinamide, resorcinol, sodium benzoate and sodium *p*-hydroxy benzoate sodium salicylate, sodium acetate, piperazine, nicotinamide, Ibuprofen Sodium.[5-16] Selection of drug is based on major criteria of poor aqueous solubility and low bioavailability. As a result, Valsartan was selected as drug of interest. It is pharmacologically, a new potent orally active antihypertensive drug which selectively acts as angiotensin II antagonist acting on the AT1 receptor subtype. It is used to treat hypertension, heart failure and post-myocardial infarction.

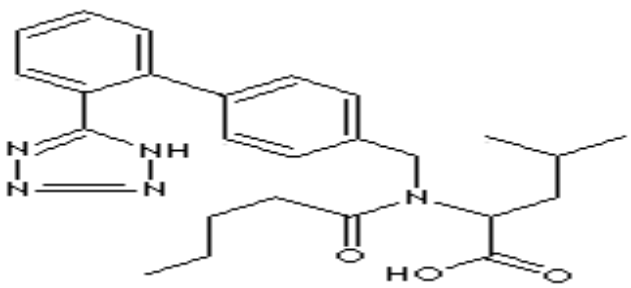
Valsartan is basically poorly water soluble drug and its aqueous solubility is reported to be less than 1 mg/ml (about 0.021mg/ml) but it is freely soluble in alcohols like methanol, ethanol. It belongs to BCS Class II. This drug is rapidly absorbed after oral administration having bioavailability of about 23% and its dose ranges from 80 to 320 mg per day. If solubility of this drug is increased, there is a chance of increased dissolution rate, early onset of action, bioavailability and reduction in daily dose administered. Keeping this point in view, the present research work is focused to enhance solubility of Valsartan using hydrotropic solubilization technique. The effect of hydrotropes like sodium acetate, sodium ascorbate, sodium benzoate, piperazine, etc. on the solubility of Valsartan was investigated.

MATERIALS

Valsartan was kindly gifted from Hetero Drugs, Hyderebad, India. Sodium ascorbate, Sodium gluconate, Piperazine anhydrous were purchased from Molychem, Mumbai, India. Sodium acetate, Sodium benzoate, Tri-sodium citrate dihydrate were purchased from Rankem, Haryana, India. Sodium salicylate was purchased from Loba Chemie, Mumbai. Urea and Ammonium acetate were purchased from Qualigens, Mumbai, India. All the chemicals and reagents used were of analytical grade.

DRUG PROFILE

Valsartan Structure



IUPAC Name

N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]-L-valine;

Synonyms: Diovan

Molecular Formula: C24H29N5O3

Molecular Weight: 435.52g/mole

Physical Properties

Color: white odorless crystalline powder

Melting point: 116 – 117°C

Solubility: Slightly soluble in water, freely soluble in ethanol, methanol.

Category: antihypertensive drug.

Dose and dosage form: Available as tablets and capsule dosage forms and dose ranges from 40, 80,160 to 320mg/day.[17]

Brand name: DIOVAN of Novartis Pharmaceuticals Corp, USA

STARVAL of RanbaxyPharmaceuticals, Himachal Pradesh, India

VALENT of Lupin Pharmaceuticals, Madhya Pradesh, India

METHODS

1. Identification of drug

a. UV Spectroscopic Characterization of Valsartan

Identification of Valsartan was done by UV Spectrophotometric method using Shimadzu Spectrophotometer UV-1800 (Shimadzu Corp., Japan).

About 50mg of Valsartan was added into 50ml volumetric flask. To this, 40ml of methanol was added and sonicated to dissolve the drug and final volume was made up with methanol to give final strength i.e. 1000µg/ml. From the above standard stock solution 2ml was transferred into 100 ml volumetric flask and diluted to mark with methanol to give concentration of 20µg/ml. The resulting solution was scanned in UV range (200nm-400nm).[18]

b. IR spectrometry

The IR analysis of the sample was carried out using IRAffinity-1 (Shimadzu Corp., Japan). In this instrument, diamond being the preferred choice for most applications because of its robustness and durability. Here, the solid material is placed onto the small crystal area and then the pressure arm is positioned over the crystal/sample area. Force is applied to the

sample, pushing it onto the diamond surface. Transmittance was measured from wave number 4000 cm^{-1} to 400^{-1} using Happ-Gensel apodization. IR spectrum of Valsartan was shown in Fig.1 and also various vibrations due to different movement of the molecules observed in IR spectrum were given in Table 1 for Valsartan.

2. Preparation of Calibration Curve of Valsartan in methanol (λmax 250nm)

Standard stock solution of Valsartan was prepared by dissolving 100mg of drug in 100ml of methanol (1000µg/ml). From the above stock solution 10 ml was taken and diluted up to 100ml in methanolic HCl (100µg/ml). From the above solution 0.4, 0.8, 1.2, 1.6 and 2ml was taken and diluted up to 10ml with methanol to get series of solutions in concentration range from 4 to 20 µg/ml of Valsartan. Absorbance was noted using UV- VIS Spectrophotometer at λmax of 250nm against blank (methanol). Calibration curve values of Valsartan in methanol (λmax 250 nm) were given in Table 2 and also graph was plotted as shown in Fig 2.

3. Solubility studies of Valsartan

The solubility of Valsartan was determined in distilled water and various aqueous and non aqueous solvents. The various types of solubility studies include Qualitative solubility, Quantitative solubility, pH dependent solubility study and hydrotropic solubilization study.

a. Qualitative solubility study

Qualitative solubility analysis for Valsartan was done by dissolving 10mg of drug in 10 ml of solvent (aqueous/ non aqueous) taken in conical flask. Various solvents used for the solubility study were distilled water, acetone, ethanol, methanol, chloroform etc. After shaking, the samples were examined for the presence of any undissolved suspended particles and clarity. The results of qualitative solubility of Valsartan in various solvents were reported in Table 3.

b. Quantitative solubility study

Quantitative solubility analysis for Valsartan was done by taking 10ml solvent and dissolving excess amount of solute in selected solvent taken in conical flask till saturated solution was obtained. Various solvents used for solubility study were water, acetone, chloroform, methanol and ethanol. The conical flasks were stoppered and agitated in thermostatically controlled orbital shaker (Tanco, Pitampura, New Delhi, India) at 25±1°C. After 24hrs equilibrium was attained and the samples were filtered through Whatman filter paper (No.1). The individual samples were analyzed after suitable dilution to determine concentration of drug dissolved using UV-VIS spectrophotometer.[5] The quantitative solubility of drug in

various solvents was reported in Table 4.The experiment was conducted in triplicate and the average values were noted.

c. pH dependent solubility study

The pH dependent solubility of Valsartan was determined using phosphate buffers ranging from pH 1.2 to 10. These buffer solutions were prepared using freshly boiled and cooled distilled water. These solutions were filtered through Whatman filter paper (No.1) and kept in tightly closed glass bottles. Here, excess quantity of drug was added to a series of screw capped 15ml glass vials containing 10ml of phosphate buffer solutions (of varying pH like pH 1.2, 2.2, 4.6, 5.8, 7.4, 8, 9 and 10) until saturated solution was obtained. The vials were mechanically shaken at room temperature for 24 hrs, in thermostatically controlled orbital shaker (Tanco, Pithampura, Delhi) at 25±1°C. These suspensions were filtered through Whatman filter paper (No.1).[5] Aliquots of filtrate obtained were diluted with distilled water and analyzed using UV spectrophotometer at 250nm against blank. The solubility study was carried out in triplicate and observation was given in Table 5.

4. Solubility study using hydrotropes

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Various hydrotropes were selected to study solubility of Valsartan and those include sodium acetate, sodium ascorbate, sodium benzoate, sodium salicylate, sodium gluconate, urea, piperazine anhydrous, ammonium acetate, tri-sodium citrate dihydrate. Aqueous solutions of these hydrotropes of different concentrations were prepared by dissolving their required quantities in water. Hydrotropes or hydrotropic agents are molecules having planar hydrotropic structure brought into solution by a polar group. Hence it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is not necessarily anionic, can act as hydrotropic agent.[19]

An excess quantity of drug was added to a series of screw capped 15ml glass vials containing 10ml of hydrotropic solutions until saturated solution was obtained. The vials were mechanically shaken at room temperature for 12 hrs, in thermostatically controlled orbital shaker (Tanco, Pithampura, Delhi) at 25±1°C. These suspensions were filtered through Whatman filter paper (No.1).[5] Aliquots of filtrate obtained were diluted with suitable quantity of required solvent and analyzed using UV spectrophotometer at 250nm. The solubility study was carried out in triplicate and observation was given in Table 6.

5. Solubility enhancement ratio determination

Solubility enhancement ratio is another parameter that determines the extent to which the drug is soluble in a particular solvent compared to that of water. The solubility enhancement ratios were calculated and given in Table 7.

Solubility enhancement ratio was calculated by using following formula:

Solubility enhancement ratio = Solubility in hydrotropic solution/ Solubility in water

RESULTS AND DISCUSSION

1. Identification of drug

a. UV Spectroscopic Characterization of Valsartan

UV spectroscopic analysis for the drug was performed and in spectrum valsartan showed absorbance maximum at 250 nm. UV analysis of Valsartan was carried out in methanol as the drug was completely soluble in methanol.

b. IR spectrometry

The characteristic peaks in IR spectra represent various functional groups present in the each molecule of drug and were assigned to establish the identity of drug sample, Valsartan (Table 1). The IR Spectra of Valsartan was shown in Fig.1.

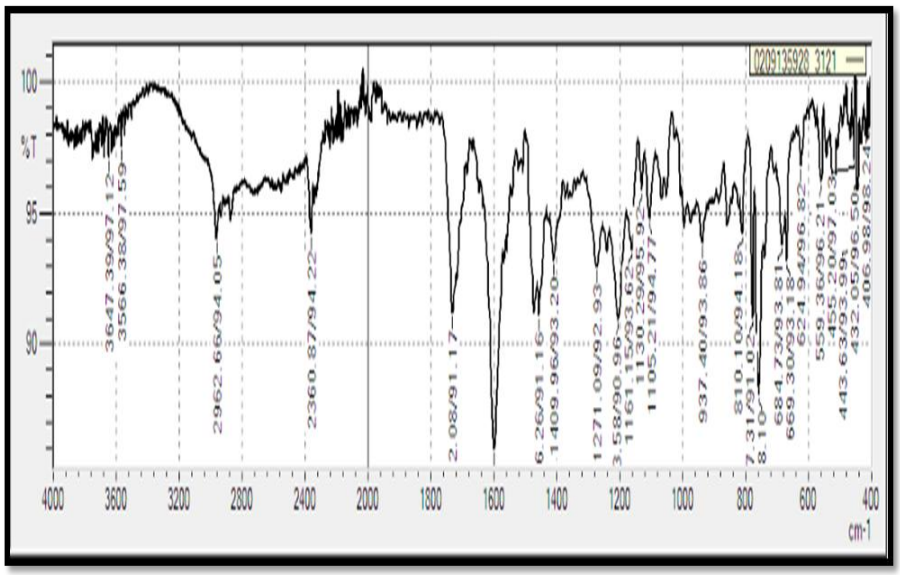


Fig 1: Infrared spectrum of Valsartan drug sample.

The following table represents various peaks corresponding to different functional groups in Valsartan.

Table 1: Interpretation of IR spectrum of Valsartan

Standard peaks (cm^{-1})	Group	Observed peak (cm^{-1})
3700-3500	N-H amide stretch	3566.38
3000-2950	Aromatic cyclic enes	2962.66
1750-1700	CO group of acid	1732.08
1600-1450	C=C aromatic	1456.26
1450-1400	Carbonyl group	1409.96
1300-1250	Hydroxyl group	1271.09
850-800	C-H bending (aromatic)	810.10
800-700	C-C bending	758.02

All the peaks values were found to be nearer to standard values that confirmed the purity of Valsartan drug sample.

2. Preparation of calibration curve of Valsartan in methanol (λmax 250nm)

Calibration curve in of Valsartan was plotted using methanol at λmax of 250nm and the readings were shown in Table 2. Figure 2 depicts the linear standard curve of Valsartan including the graph equation.

Table 2: Calibration curve of Valsartan in methanol (λmax 250nm).

Concentration(µg/ml)	Absorbance
0	0
4	0.187
8	0.412
12	0.614
16	0.846
20	1.06

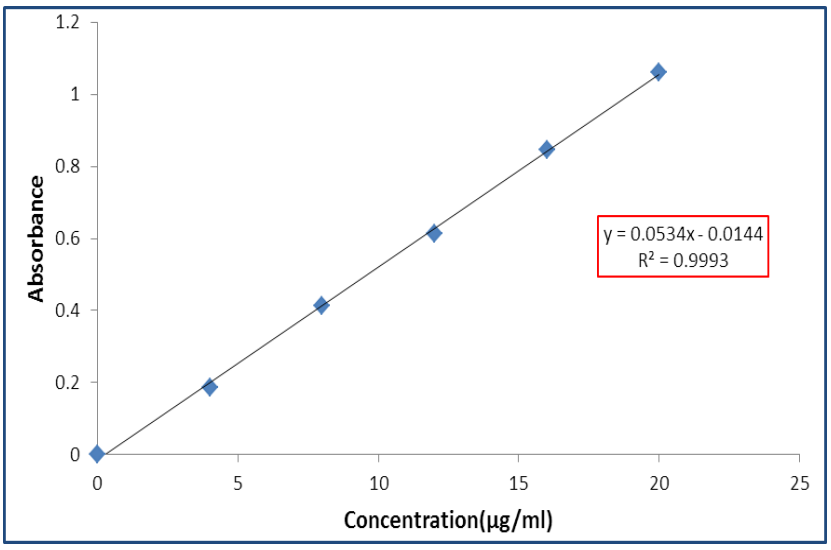


Fig 2: Linear calibration curve of Valsartan in methanol (λmax 250nm)

3. Solubility studies of Valsartan

Solubility studies were performed for Valsartan and the results were explained in detail as follows.

a. Qualitative solubility study

Different solvents were used for the solubility determination like distilled water, acetone, ethanol, methanol, chloroform, etc. to determine the solubility of drug.

Table 3: Qualitative solubility of Valsartan in various solvents.

Solvent	Solubility of Valsartan
Distilled water	Slightly soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Chloroform	**S**oluble
Acetone	**S**oluble
Ethyl acetate	Soluble
Dichloromethane	Soluble
0.1N HCl	Practically insoluble
0.1 N NaOH solution	Soluble
7.4pH phosphate buffer	Soluble

b. Quantitative solubility study

The quantitative solubility of Valsartan determined in different solvents and the results were illustrated in Table 4.

Table 4: Quantitative solubility of Valsartan in various solvents.

Sl. No	Solvent	Solubility* of Valsartan
1	Distilled Water	0.021mg/ml
2	Ethanol	0.214 g/ml
3	Methanol	0.275 g/ml
4	7.4pH phosphate buffer	0.965mg/ml
5	Ethyl acetate	55.74 mg/ml
6	Chloroform	67.86 mg/ml
7	Dichloromethane	36.11 mg/ml
8	Acetone	76.29 mg/ml

***Average of three determinations*

c. pH dependent solubility study

The pH dependent solubility of Valsartan in phosphate buffers ranging from pH 1.2 to 10 were shown in Table 5. Valsartan was found to be more soluble at higher pH indicating acidic nature of drug.

Table 5: pH dependent solubility of drugs in phosphate buffers of pH ranging from 1.2 to 10.

Solvent (water and different pH of PB)	Valsartan solubility* (mg/ml)
Distilled water	0.0212
1.2	0.089
2.2	0.102
4.6	0.262
6.8	0.535
7.4	0.965
8	1.016
9	1.134
10	1.152

*****Average of three determinations, PB indicates Phosphate buffer*

Solubility of Valsartan in water was 0.021 mg/ml and that of in that of pH 10 was 1.152 mg/ml and hence solubility of Valsartan in pH 10 was increased by 55 folds compared to that of solubility in distilled water.

4. Solubility study using hydrotropes

The results of hydrotropic solubilization of Valsartan in individual concentrations of hydrotropes were shown in Table 6 and it was also represented in graphical form in Fig 3.

Table 6: Solubility of Valsartan in various hydrotropic solutions.

Sl.No	Hydrotropic solution	Solubility* of Valsartan in mg/ml			
		5%(w/v)	10%(w/v)	20%(w/v)	30%(w/v)
1	Sodium acetate	14.4326	29.824	58.745	85.581
2	Sodium ascorbate	0.7036	1.4062	2.0248	3.7144
3	Sodium benzoate	6.6486	12.286	21.564	33.842
4	Sodium salicylate	0.4112	0.7826	1.3952	2.1626
5	Sodium gluconate	0.3527	0.5922	1.0326	1.5959
6	Tri-sodium citrate dihydrate	12.342	25.986	48.748	72.244
7	Urea	0.8929	1.7223	3.5225	4.9267
8	Ammonium acetate	12.547	27.246	52.622	79.865
9	Piperazine anhydrous	132.24	224.78	425.42	638.12

*****Average of three determinations*

Among the different hydrotropes used, solubility of Valsartan was found to be higher in Piperazine anhydrous > Sodium acetate > Ammonium acetate > Tri-sodium citrate dihydrate > Sodium benzoate > Urea > Sodium ascorbate > Sodium salicylate > Sodium gluconate.

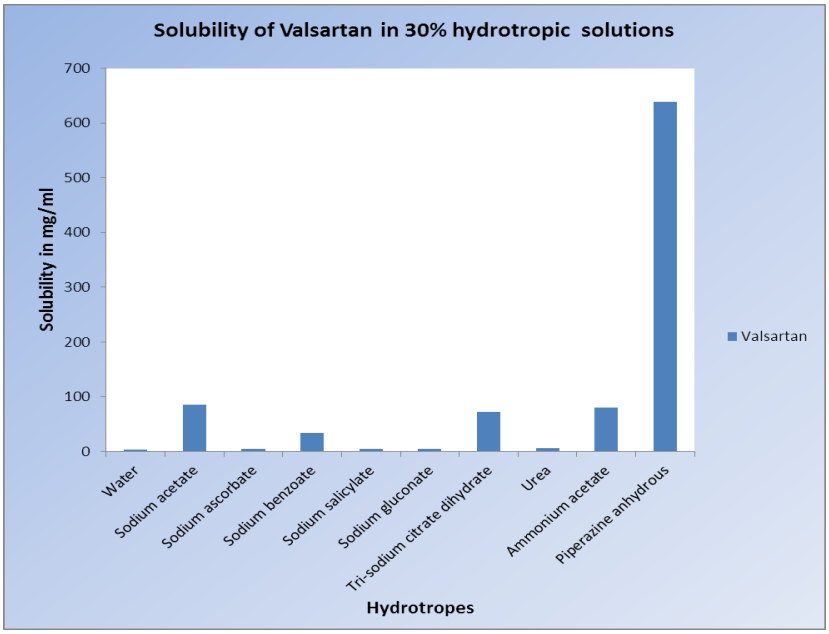


Fig 3. Solubility of Valsartan in 30% hydrotropic solutions.

5. Solubility enhancement ratio determination

Solubility enhancement ratios for Valsartan in various hydrotropic solutions were determined and the results were reported in Table 7.

Table 7: Solubility enhancement ratio of Valsartan in various hydrotropic solutions

Sl.No	Hydrotropic solution	Solubility enhancement ratio of Valsartan			
		5%(w/v)	10%(w/v)	20%(w/v)	30%(w/v)
1	Sodium acetate	680.78	1406.79	2770.99	4036.84
2	Sodium ascorbate	33.189	66.3301	95.5094	175.208
3	Sodium benzoate	313.61	579.528	1017.17	1596.32
4	Sodium salicylate	19.396	36.9150	65.8113	102.009
5	Sodium gluconate	16.637	27.9339	48.7075	75.2783
6	Tri-sodium citrate dihydrate	582.17	1225.75	2299.43	3407.74
7	Urea	42.117	81.241	166.16	232.36
8	Ammonium acetate	591.83	1285.1	2482.16	3767.2
9	Piperazine anhydrous	6237.7	10602	20066.9	30100.4

Solubility of Valsartan was enhanced in 30% hydrotropic solutions of Piperazine anhydrous, Sodium acetate, Ammonium acetate, Tri-sodium citrate dihydrate , Sodium benzoate. For Valsartan, the highest solubility was observed in 30% Piperazine anhydrous solution and the solubility enhancement ratio was observed as 30,100 compared to that of water.

Piperazine anhydrous is a well known hydrotropic agent used to increase solubility of many poorly water soluble drugs like nimesulide.[5]

CONCLUSION

It can be concluded that the concept of hydrotropic solubilization technique is novel, safe, eco-friendly and economic for enhancing bioavailability of poorly water-soluble drugs. Here, miraculous enhancement in solubility of Valsartan was observed in hydrotropic solution of piperazine anhydrous that marked its importance in pharmaceutical field where solubility of poorly water soluble drugs has been a critical step in production of dosage forms.

Actually, low aqueous solubility was the major concern for Valsartan; hence by the use of hydrotropic solubilization technique not only solubility, dissolution rate increased but also there would be good scope of increase in bioavailability of Valsartan. As a result, daily dose, frequency of administration as well other side effects related to Valsartan would be minimized to a great extent.

ACKNOWLEDGEMENTS

The authors are grateful to Department of Pharmaceutics, Swami Vivekanand College of Pharmacy for providing the facilities to perform research work and they also declare that they have no conflict of interest.

FUNDING

The authors are very thankful to MPCST (M.P.Council of Science & Technology), Bhopal for funding this project work.

REFERENCES

1. Purwa J, Achhrish G, Shweta S, Meghal P. Solubility enhancement techniques with special emphasis on hydrotrophy. Int J Pharm Pro Res, 2010; 1(1): 34-45.
2. Neuberg, C. Hydrotropy, Biochem. Z, 1961; 76: 107–109
3. Osol A. (Eds.) In: “Remington’s Pharmaceutical sciences,” Easton Pennsylvania, Mack Publishing Company, 1990; 18: 203.
4. Lurdhu MK, Manohar BS. An ecofriendly spectroscopic method for estimation of etraverine by using hydrotropic agents. World J Pharm Pharm Sci, 2015; 4(3): 655-62.
5. Agrawal S, Pancholi SS, Jain NK, Agrawal GP. Hydrotropic solubilization of nimesulide for parenteral administration. Int J Pharm, 2004; 274(1-2): 149-55.
6. Jain AK. Solubilization of indomethacin using hydrotropes for aqueous injection. Eur J Pharm Biopharm, 2008; 68(3): 701-14.

7. Girishpai K, Divya S, Sreenivasa RM, Lalit K, Vamshi KT. Solubility Enhancement of Norfloxacin by Hydrotropy Technique. Int J Pharm Pharm Sci, 2014; 6(8): 395-97.
8. Jaya S, Umadevi SK, Sai V, Manisha L, Rajeswari G, Kasturibai B. Solubility enhancement of candesartan cilexetil by using different hydrotropic agents. Eur J Pharm Med Res, 2015; 2(1): 339-53.
9. Jain N.K, Agrawal RK. Formulation of aqueous injection of carbamazepine. Pharmazie, 1990; 45(3): 221-22.
10. Hussain MA, Dilucio RC, Maurin MB. Complexation of moricizine with nicotinamide and evaluation of complexation constants by various methods. J Pharm Sci, 1992; 82(1): 77-9.
11. Jayakumar C, Antony BM, Arunodhaya N, Nagendra GN. Solubility enhancement of theophylline drug using different solubilization techniques. Int J Pharm Cli Sci, 2012; 2(1): 7-10.
12. Rasool AA, Hussain AA, Dittert LW. Solubility enhancement of some water insoluble drugs in presence of nicotinamide and related compounds. J Pharm Sci, 1991; 80(4): 387-94.
13. Shravan KP, Dinesh K, Amol PW, Avinash SD. Solubility enhancement of ibuprofen using hydrotropic agents. Int J Pharm Life Sci, 2012; 2(2): 542-45.
14. Varma MM, Pandit JK. Influence of urea and xylitol on the dissolution rate of flurbiprofen. Ind Pharmacist, 2005; 4: 97-9.
15. Maheshwari RK, Deswal S, Aher R, Wanare G, Jawade S, Indurkhya A, Jagwani. Ibuprofen Sodium: A Novel Hydrotropic Agent for estimation of poorly water-soluble drugs. J Appl Chem Res, 2009; 10: 56-60.
16. Maheshwari RK, Chaturvedi SC, Jain NK. Application of hydrotropy in spectrophotometric determination of pharmaceutical dosage forms. Ind drugs, 2005; 42: 760-3.
17. http://www.drugbank.ca/drugs/DB00177
18. Sivasankara Rao G, Venkat Rao S, Vardhan SVM, Ramachandran D. Development and validation of new UV-spectrophotometric assay method for valsartan in pure and in formulations. J Cli Pharm Res, 2013; 5(7): 229-32.
19. Saleh A.M, El-Khordagui LK. Hydrotropic agents: a new definition. Int J Pharm, 1985; 24: 231.