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GREEN TECHNIQUE: APPLICABILITY OF HYDROTROPIC SOLVENT FOR ENHANCEMENT OF SOLUBILITY OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

The great challenge in screening studies as well as formulation of new chemical entities is the solubilization of poorly soluble drugs. In order to improve the solubility of poorly water soluble drugs, hydrotropes were utilized. Water insoluble drugs rosuvastatin, Telmisartan, valsartan and nebivolol were selected for the study, and hydrotrpes sodium acetate, sodium citrate, sodium chloride and urea were prepared in the water in various strength 1%, 2.5%, 5% and 6%. Enhancement in solubility was carried out by measuring absorbance of solution on the UV-VIS spectrophotometer. Solubility profile graph were plotted in between absorbance and various strength of hydrotrope. Sodium acetate was found appreciable solvent for valsartan and sodium citrate was found beneficial solvent for rosuvastatin. During analytical method development and formulation development exploitation of hydrotropic solvent is the approach towards green technique.

KEYWORDS: rosuvastatin, Telmisartan, valsartan and nebivolol.

INTRODUCTION

Almost more than 90% drugs are orally administered. Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substance is highly dependent on solubility of that compound in aqueous medium. It is estimated that 40% of active new chemical entities identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble.[1]

The field of drug discovery and development plays a major role in the world and serves mankind. The great challenge in screening studies as well as formulation of new chemical entities is the solubilization of poorly soluble drugs. In order to improve the solubility of poorly water soluble drugs, a number of methodologies can be adopted.[2] The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[3] Hydrotropy is one of the solubility enhancement techniques which enhance solubility to many folds with use of hydrotropes like sodium acetate, sodium citrate, urea, sodium chloride etc.[4]

Hydrotropes with an amphiphilic molecular structure possess the ability to increase the solubility of sparingly soluble organic molecules in water. Simply the presence of a large quantity of one solute enhances the solubility of another solute. Hydrotropic agents are stated as ionic organic salts which help to increase or decrease the solubility of solute in a given solvent via 'salt in' or 'saltout' effects, respectively. Salts which show 'salt in' of non-electrolytes are called "hydrotropic salts" and the phenomenon is known as "hydrotropism". They do not exhibit any colloidal properties but they improve solubility by forming weak interaction with solute molecules.[1,5] A hydrotropic molecule interacts with a less water-soluble molecule via weak van der Waals interactions such as π–π or attractive dipole– dipole interaction.[4]

The solubility is defined according to Pharmacopoeia[6] in terms of number of milliliters of solvent required to dissolve 1g of solute and if the exact solubility are not known the Pharmacopoeia provides general term to describe a given range.

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

NEED OF SOLUBILITY

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.[3]

It is evident from the literature survey that more is the concentration of hydrotrope; more is the aqueous solubility of poorly water-soluble drugs. Therefore, highly concentrated solutions of hydrotropic agents were used in the present investigation. Distilled water was used in making hydrotropic solutions,

Characteristics of hydrotropes

• Completely dissolvable in water and essentially insoluble in the framework.

• Hydrotropes are surface dynamic and total in watery arrangement in light of their amphiphilic structure.

• Should not create any temperature when disintegrated in water.

• Cheap and simple accessibility.

• Nonlethal and non receptive.

• Insensitive to temperature impacts, when disintegrated in water.

• The dissolvable character being free of pH, high selectivity, and then no appearance of emulsification are the other one of kind points of interest of hydrotropes.[7]

Advantages of Hydrotropic Solubilization Technique

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
2. It only requires mixing the drug with the hydrotrope in water.
3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.[1]

Disadvantages of Hydrotropic solubilization Technique

1. By the excess use of hydrotropic agents problems associated with toxicity may arise.
2. The interaction between the drugs and hydrotropic agents may become weak.
3. The complete removal of water is not possible, because of the use of water as the solvent.[2]

DRUG INFORMATION

Rosuvastatin chemically is (*E*,3*R*,5*S*)-7-[4-(4-fluorophenyl)-2-[methyl (methylsulfonyl) amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid.[8,9,10] Rosuvastatin lowers triglycerides level significantly and used to lower LDL-C in familial and multifactorial hyperlipidaemia or combined familial and multifactorial hyperlipidaemia type IIb.[11,12] It is insoluble in water.[6]

Telmisartan is [4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] phenyl] benzoic acid[8,9,10] and it is sparingly soluble in dichloromethane, slightly soluble in methanol, practically insoluble in water.[6] It is orally active potent and specific antagonists of angiotensin II receptors. They are long acting angiotensin receptors antagonists.[11,12]

Valsartan chemically is N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine[8,9,10] and also it is angiotensin inhibiting drug. Practically insoluble in water.[6]

Nebivolol is cardioselective beta blocker with NO- mediated vasodilator properties. Nebivolol is effective in hypertension as well as cardiac heart failure. Drug generally block beta1 receptor in low dose and beta2 receptor in high dose.[11,12]

Chemically it is 1-(6-fluoro-3,4-dihydro-2*H*-chromen-2-yl)-2-[[2-(6-fluoro-3,4-dihydro-2*H*-chromen-2-yl)-2-hydroxyethyl]amino]ethanol[8,10] and sparingly soluble in dimethyl-formamide, slightly soluble in methanol[6]

All drugs chemical structure is shown in Fig No 1.

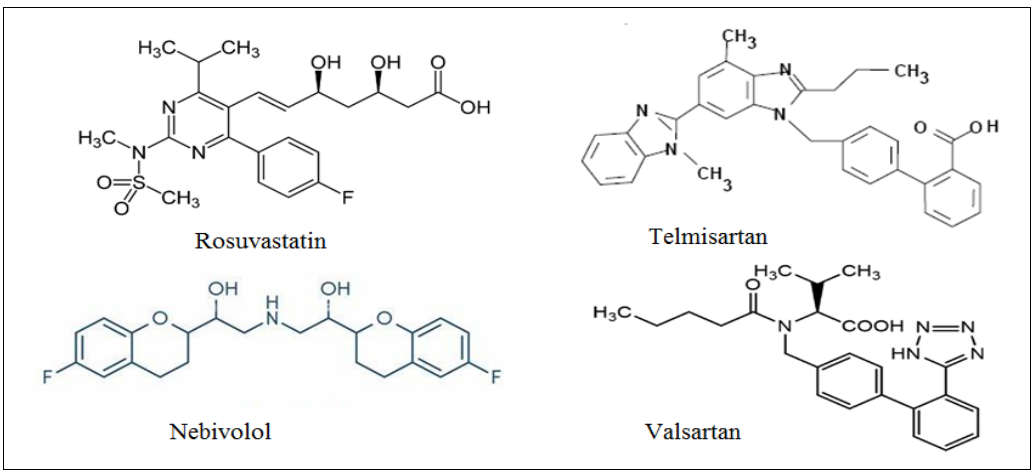

Fig No 1: Chemical structure of drug molecule.

MATERIALS AND METHOD

Hydrotropes sodium citrate, sodium acetate, sodium chloride and urea were selected for the research and drugs valsartan, telmisartan, nebivolol, rosuvastatin were for the enhancement of solubility. Distilled water is the solvent for making hydrotropes solution. Valsartan was procured from FDC Mumbai, nebivolol from Yarro chem., Mumbai and rosuvastatin, Telmisartan were procured from Micro Lab, Bangaluru.

Analysis was performed with a Shimadzu Double beam UV - Visible spectrophotometer (Shimadzu, Kyoto, Japan) with spectral bandwidth of 2 nm and wavelength accuracy of ± 1 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ±0.1 mg Model No. ER 200A was utilised for weighing and for degassing the solutions Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

METHODOLOGY

Another approach before developing the method was use of eco friendly or green solvent. Use of organic solvent and their disposal adversely affects on the earth's environment. Hydrotropic solvents sodium citrate, sodium acetate, sodium chloride and urea were used in strength of concentration from 1% to 6% and any enhancement in solubility was measured by recording absorbance at drugs respective λ_{max}.

1. Preparation of hydrotropic solvent

Each Hydrotropes was weighed with amount 1gm, 2.5gm, 5gm and 6gm and dissolved in separate glass container having distilled water to obtain 1% w/v 2.5%w/v, 5%w/v and 6%w/v hydrotrope strength solution.

2. Preparation of drug solutions

Prior solubility study was carried out by weighing 10 mg of drug and transfer into clean and dry test tube and added slowly 1% hydrotrope solution; addition was continued till a notable solubility was observed. Finally volume was made to 50 ml with the hydrotrope solution. Similarly the procedure was repeated with same quantity of drug and in each conc of hydrotropes. This procedure has given a broad study upon solubility of drug in all these selected hydrotropes.

Aliquot of the prepared solution was further diluted to obtain 20µg/ml drug and absorbance was measured against blank solution. In these way four different concentrations of drug was available in each hydrotrope solvent. Similarly the conc effect on solublization was studied by preparing the drugs solution in 2.5%, 5% and 6% hydrotropes.

3. Solubility study profile of drug

Absorbance of each drug was measured in four different concentration strength of hydrotrope; and graph was plotted in between absorbance against drug solutions in different concentration strength of hydrotrope. In this way a solubility profile curve of each drug in various strength of hydrotrpe was generated.

RESULT AND DISCUSSION

Each drugs absorbance in selected hydrotropic solvent was given in Table No 1.It was observed that rosuvastatin was shown good solubility in 2.5% sodium citrate (Fig No 2) solution and solubility was slowly decreased in sodium acetate, sodium chloride and urea solution.

Table No 1: Absorbance of drug in various strength of hydrotrope solution.

SR No	Name of Drug	Name of Hydrotrope	Absorbance of drug in conc of Hydrotropes			
			1 %	2.5 %	5 %	6 %
1	Rosuvastatin	Sodium citrate	1.1377	1.1401	0.8496	1.0239
		Sodium acetate	0.7845	0.8300	0.7849	0.6146
		Sodium chloride	-	0.5325	0.2499	-
		Urea	-	0.4896	0.3546	-
2	Valsartan	Sodium citrate	0.4700	0.4598	0.4459	0.5220
		Sodium acetate	0.5272	0.4310	0.5642	0.2670
		Sodium chloride	0.3105	0.1635	0.1495	-
		Urea	0.1086	0.0706	0.1302	-
3	Telmisartan	Sodium citrate	0.5950	0.5726	0.6050	0.5658
		Sodium acetate	0.2102	0.2134	0.2048	0.1641
		Sodium chloride	0.0229	0.1656	0.2620	0.1478
		Urea	0.1887	0.1827	0.2010	0.1855
4	Nebivolol	Sodium citrate	0.0651	0.0850	0.0336	0.0306
		Sodium acetate	0.1299	0.0994	0.0681	0.1229
		Sodium chloride	0.0497	0.0299	0.0431	0.0223
		Urea	0.1857	0.1442	0.1844	0.1818

The plotted graph in between absorbance against different concentration of hydrotrope for rosuvastatin is shown in Fig.No 3, The solubility profile curve of rosuvastatin in sodium citrate is the sign of enhanced solubility as compare to other hydrotropes.

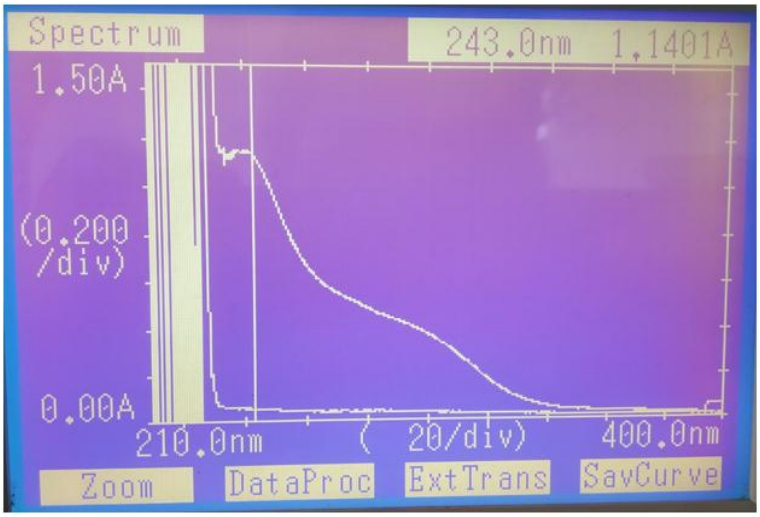

Fig No 2: UV spectra of Rosuvastatin in sodium citrate.

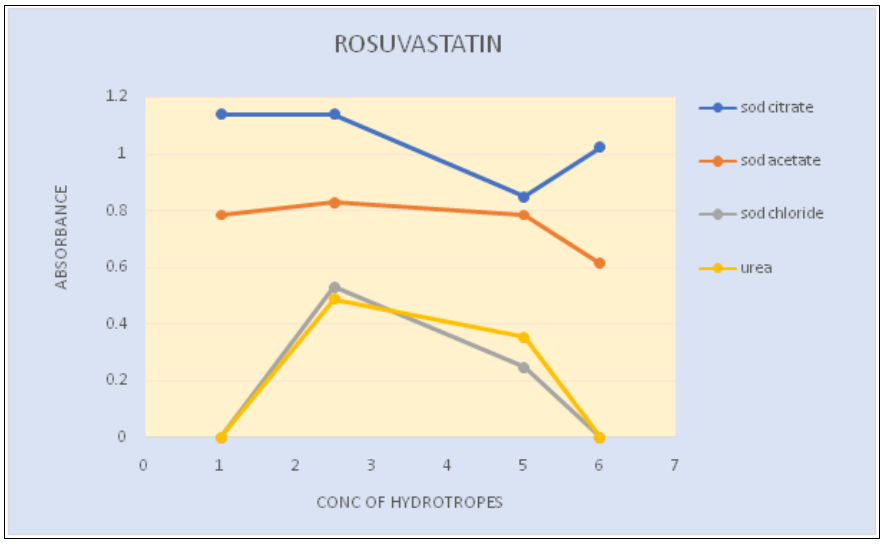

Fig No 3: Solubility profile of rosuvastatin in selected hydrotropes.

Valsartan was shown good solubility in 1%, 2.5% sodium acetate solution (Fig No 4) and it was observed that moderate solubility was observed in 1%, 2.5% sodium citrate solution whereas drug shown poor solubility in sodium chloride and urea of concentration 1%. Plotted graph of valsartan absorbance in each concentration of hydrotrope against different hydrotrope is shown in Fig No 5. Solubility profile curve of valsartan shows that enhanced solubility was found in 5% sodium acetate solution.

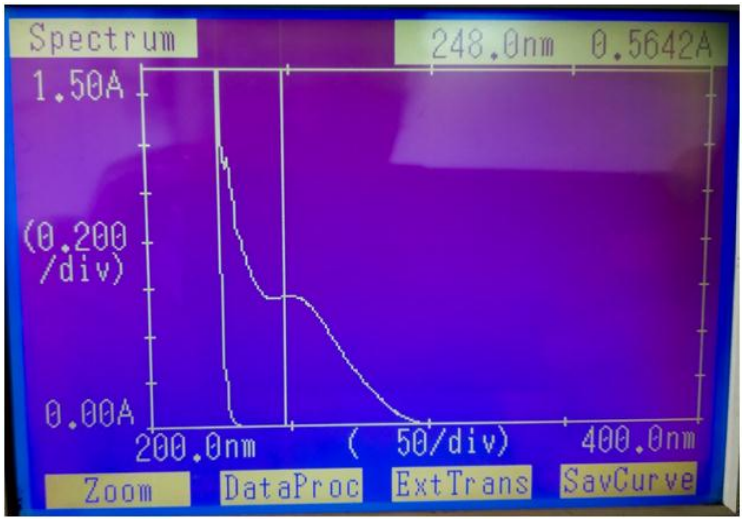

Fig No 4: UV spectra of valsartan in sodium acetate.

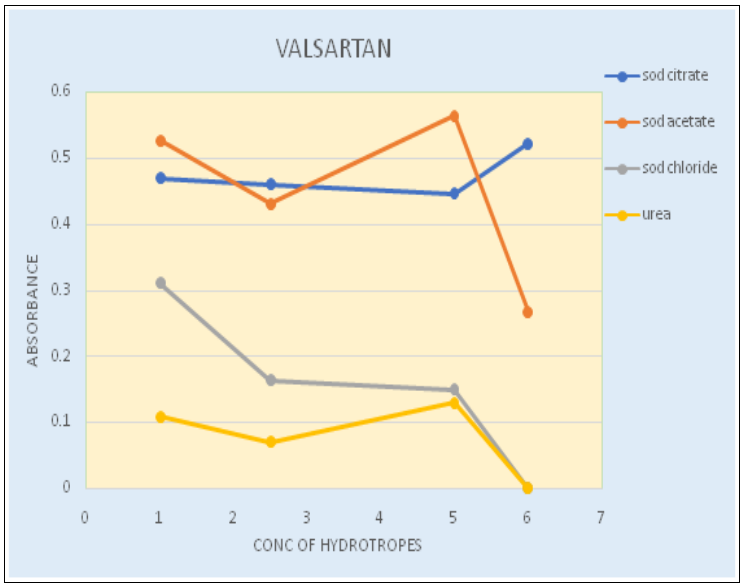

Fig No 5: Solubility profile of valsartn in selected hydrotropes.

Solubility of telmisartan in various concentration of each hydrotropic agent was studied and tabulated in Table No 1, it was found that telmisartan was insoluble in these selected hydrotropic agents; and solubility curve graph also shown poor solubility of Telmisartan Fig No 6.

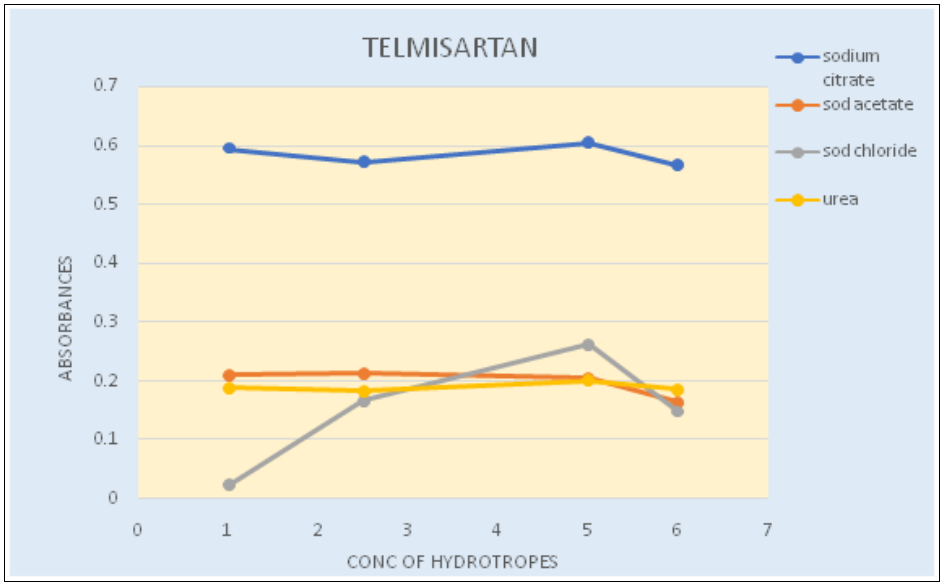

Fig No 6: Solubility profile of telmisartan selected hydrotropes.

Similarly Nebivolols study and obtained data were tabulated in Table No 1. It was found that nebivolol was insoluble in all these hydrotropes of various concentration levels. The graph of absorbance against concentration of nebivolol in these agents at various concentration is shown in Fig No 4. The graph confirms insolubility of nebivolol in these agents However, Nebivolol shown solubility in co-solvent ethanol. Solubility curve profile of nebivolol is shown in Fig No 7.

The calculated solubility of drug in the hydrotropic solution is tabulated in Table No 2. Valsartan solubility was found in sodium acetate solution in the conc 0.1%.

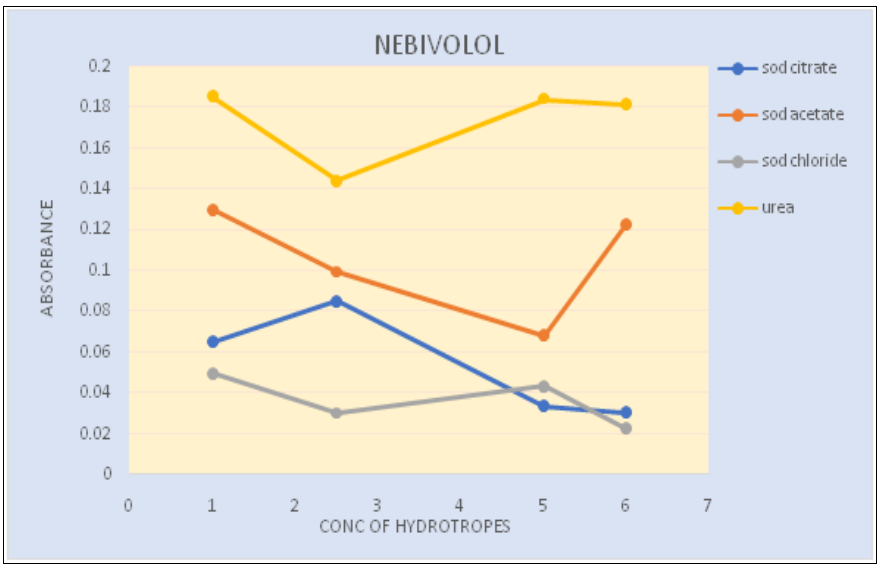

Fig No 7: Solubility profile of nebivolol in selected hydrotropes.

Table No 2: Calculated solubility of drug in suitably found hydrotrope.

Sr No	Name of drug	Conc. of Hydrotropes in %	Amount of Drug(mg)	Volume of solvent (ml)	Solubility (%w/v)
1	Nebivolol	1% Urea	10	7	0.14
2	Rosuvastatin	2.5% Sodium Citrate	10	12	0.08
3	Valsartan	5%Sodium Acetate	10	10	0.1

CONCLUSION

It was concluded that sodium acetate is the suitable hydrotrope for solubility of valsartan and sodium citrate is beneficial solvent for enhancement of solubility of rosuvastatin. Sometime Lower concentration of hydrotrope solvents are beneficial over the higher concentration.

We could say these two hydrotropes are ecofriendly solvent for these two drugs and by using these solvent formulations can be developed which would have more bio availability. During method development or technique use of ecofriendly instead of organic solvents could be rational green approach.

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