

**A COMPARATIVE SOLUBILITY ENHANCEMENT STUDY OF ROSUVASTATIN
USING SOLUBILIZATION TECHNIQUES**Pankaj Nainwal*¹, Priyanka Sinha¹, Amandeep Singh¹, Deepak Nanda¹, D.A.Jain²¹Dev Bhoomi Institute of Pharmacy and Research, Dehradun, Uttarakhand² Director Research, Department of Pharmaceutical Sciences, Bhagwant University, Ajmer,
Rajasthan***Corresponding address:** pankajherbs@gmail.com, Fax.No.0135-26944245

ABSTRACT : Solid dispersion of Rosuvastatin was prepared by solvent evaporation method; PEG (Polyethylene glycol) 4000, mannitol and urea were used as carriers. Hydrotropic studies were carried out using different hydrotropic agents (sodium acetate, sodium benzoate and salicylate) and Micellar solubilization was carried out using different surfactant solutions (sodium lauryl sulphate, tween 80 and cetrimide). The solubility enhancement of Rosuvastatin by different solubilization technique was observed in decreasing order as hydrotropic solubilization > solid dispersion > micellar solubilization. It was observed that the solubility increased with the increase in the concentration of hydrotropic agents and amongst the various hydrotropic agents used the solubility was Rosuvastatin was enhanced greatest to 55 folds with sodium salicylate. This increase may be attributed due to aggregation of the hydrotropic molecules and inclusion of one of these aggregates at high concentration probably by reacting to form an associated product as a result of hydrogen bonding.

Key words: Solubility, Rosuvastatin Solid dispersion, Hydrotropy, Micellar solubilization.

INTRODUCTION

Now days, the drugs which exist and those being discovered are of synthetic origin and have limitation of poor water solubility. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, etc. Rosuvastatin calcium, Synonyms 7-{4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxy hept-6-enoic acid. Average weight of rosuvastatin Average: 481.538. Monoisotopic: 481. 168284538. Rosuvastatin is approved for the treatment of high [LDL cholesterol \(dyslipidemia\)](#), total cholesterol ([hypercholesterolemia](#)), and/or [triglycerides \(hypertriglyceridemia\)](#). In February 2010, Rosuvastatin was approved by the FDA for the primary prevention of cardiovascular events. Poor water soluble drug, such as Rosuvastatin face problem of low bioavailability as their dissolution is rate limiting factor¹. So, it becomes a requirement to improve solubility of Rosuvastatin to formulate it as dosage form. Therefore present work is aimed towards enhancing the solubility, dissolution thereby bioavailability of Rosuvastatin by using different technique such as solid dispersion, hydrotropic solubilization and micellar solubilization and results obtained were compared for better solubility profile of Rosuvastatin In 1971 Chiou and Riegelman defined solid dispersion as “A dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent evaporation or melt-solvent method”. Solid dispersion when exposed to aqueous media, the carrier is dissolved; the drug is released as very fine colloidal particles² and widely used to increase intrinsic solubility or dissolution and further the bioavailability of drug^{3,4}.

Various carriers can be used for solid dispersion preparation which includes polyethylene glycol, poly vinyl pyrrolidone, urea, mannitol, poloxamers etc. Solid dispersion can be prepared by conventional methods such as solvent evaporation method, fusion method and melt solvent method and novel methods used for preparation includes super critical fluid technology, electrospinning, spray drying, lyophilization and melt extrusion method⁵. Neuberg in 1916 first introduced the concept of hydrotropy. Hydrotropy may be defined as a phenomenon in which water solubility of poorly water soluble compounds may be increased several folds by use of diverse groups of hydrophilic solutes called hydrotropes⁶. In other words hydrotropic solubilization is the addition of large amount of additives, in presence of which the aqueous solubility of the solute shows multifold enhancement⁷. This approach can be conveniently applied to wide range of water insoluble compounds. Hydrotropes commonly used includes sodium benzoate, sodium acetate, sodium salicylate, nicotinamide, urea, trisodium citrate, sodium ascorbate, piperazine, caffeine etc⁸⁻¹⁰. Hydrotropy is used for solubility enhancement of different class of drugs such as anti- tumor, anti- viral, anti-inflammatory, antipyretic and analgesic drugs, xanthine derivatives etc^{9,10}. Hydrotropy is successfully applied for solubility enhancement of nimmeslide¹¹, riboflavin⁸, nifedipine¹², xanthine derivatives like theophylline and caffeine¹³. Micellar solubilization is used as an efficient tool for solubilization of hydrophobic drugs in aqueous environments. Solubilization can be defined as the spontaneous dissolving of a substance by reversible interaction with the micelles of a surfactant in water to form a thermodynamically stable isotropic solution with reduced thermodynamic activity of the solubilized material¹⁴. With the advent of non-ionic surfactant their utility as solubilizing system is increased. The surfactant molecules aggregate and form micelles at particular concentration called critical micelle concentration (cmc) with formation of hydrophobic interior core and hydrophilic external environment. Micelles have an anisotropic water distribution within their structure *i.e.* the concentration of water varies in whole of the micellar system. The concentration of water decreases from the surface towards the core of the micelle, with a completely hydrophobic core. Consequently, the solubilized drug distribute itself in a micelle on basis of its polarity which means that non-polar molecules will get solubilized in the micellar core, and substances with intermediate polarity will get distributed along the surfactant molecules in certain intermediate positions¹⁵. Some example of surfactant used for solubilization of hydrophobic drug include cremophor EL, tween 80, poloxamers, brij 54, sodium lauryl sulphate, cetrimide etc¹⁶.

MATERIALS

Rosuvastatin was kindly received as a gift sample from Windlaas Pharmaceuticals, Dehradun, Uttarakhand. Poly ethylene glycol 4000 (PEG 4000), urea, mannitol, cetrimide, sodium acetate, sodium benzoate, sodium salicylate, sodium lauryl sulphate were purchased from CDH Laboratories, New Delhi, Tween 80 was procured from Oxford Laboratories, Mumbai (M.S.). All other reagents used were of analytical grade.

METHODS

Preparation of Solid dispersion

Rosuvastatin and different carriers PEG 4000, urea and mannitol were weighed accurately in various ratios (1:2, 1:4, 1:6, and 1:8) and dissolved in sufficient quantity of ethanol which was evaporated on rotary vacuum evaporator to obtain solid dispersion. The resulted solid dispersion were kept in dessicator for drying and finally passed through sieve no.60 and stored in well closed container for further use¹⁷.

Solubility study of solid dispersion

Solubility studies were conducted by adding excess of solid dispersion to 25 mL of distilled water and mixture was shaken for 24 hrs in mechanical shaker. After achieving of equilibrium samples were withdrawn and filtered through Whatman filter paper no. 41 and finally diluted suitably and the concentration of Rosuvastatin was measured in UV spectrophotometer at 274 nm. The experiment was repeated in triplicate¹⁸.

Hydrotropic solubilization

The solubility study of Rosuvastatin with different hydrotropic agents (sodium acetate, sodium benzoate and sodium salicylate) was performed by adding excess of Rosuvastatin to a series of hydrotropic solution (0.4, 1.2 and 2.0 N) in 50 mL of screw capped glass vial. The vials were shaken for 12 hrs on mechanical shaker. After 24 hrs when equilibrium was reached, the solutions were centrifuged for 10 min and supernatant were filtered through Whatman filter paper no.1 and suitably diluted. The concentration of Rosuvastatin in supernatant was analyzed spectrophotometrically at 274 nm¹⁹.

Micellar solubilization

Different concentration (0.2, 0.4, 0.6, 0.8, 1.0 % w/v) of surfactants (Sodium lauryl sulphate, cetrimide and tween 80) were prepared. An excess of Rosuvastatin was added to 10 mL each of the surfactant solution taken in 25 mL of stoppered flasks. The flasks were shaken for 24 h. At equilibrium samples were withdrawn and properly diluted and filtered through filter of pore size of 0.22 mm and finally analyzed for concentration of Rosuvastatin spectrophotometrically at 274 nm¹⁶.

RESULTS AND DISCUSSIONS

Different methods viz solid dispersion, hydrotropy, micellar solubilization, applied for enhancement of solubility of Rosuvastatin showed an improvement in solubility behaviour of Rosuvastatin. The order of enhancement of solubility of Rosuvastatin with various approaches was found to decrease in order of hydrotropic solubilization > solid dispersion technique > micellar solubilization. From the solubility profile of Rosuvastatin with respect to the different techniques, it can be concluded that best solubility results were obtained from hydrotropic solubilization method. The effect of various hydrotropes such as sodium acetate, sodium benzoate and sodium salicylate on the solubility of Rosuvastatin was investigated. Figure 2 shows the solubility profile of Rosuvastatin with various hydrotropic agents in different concentration. Solubility of Rosuvastatin was increased with increase in concentration of hydrotropes. From the solubility profile it was observed that solubility of Rosuvastatin decreases in the following order as: sodium salicylate > sodium benzoate > sodium acetate. Sodium salicylate (2.0 M) increases the solubility of Rosuvastatin by 55 folds. The hydrotropic solubilization of Rosuvastatin at lower hydrotrope concentration may be attributed to weak ionic interactions involving a complexation while that at higher hydrotrope concentration may be due to molecular aggregation and inclusion of one in these aggregates at high concentration. Sodium salicylate has hydroxyl group which may lead to the hydrogen bonding and formation of aggregation product. In case of solid dispersion formulation solubility in descending order can be observed as Mannitol > Urea > PEG 4000. Increased solubility in case of solid dispersion formulation may be attributed to increased wettability, prevention of the aggregation of drug hydrophilic nature of carrier and reduction in drug crystallinity. The mechanism by which the solubility and the dissolution rate of the drug was increased includes firstly, the particle size of a drug is reduced to sub micron size or to molecular size in the case where solid solution is obtained. Secondly, the drug is changed to amorphous form, the high energetic state that is highly soluble and finally the dissolved carrier improves the wettability of drug particle²⁰. It was observed that there was increase in solubility of rosuvastatin with increased concentration of carrier, greater extend of solubility was observed with mannitol. The increase in solubility of rosuvastatin using solid dispersion technique mannitol, was found to 42 folds with mannitol. The study also evaluated and compared solubility enhancement of Rosuvastatin using three different surfactants i.e. sodium lauryl sulphate, tween 80 and cetrimide. Tween 80 was found to be the most efficient surface active agent, improving solubility by nearly to 36 folds. Thus from this comparative solubility analysis of rosuvastatin using different solubilization techniques can further be successfully applied for development and formulation of liquid or semisolid dosage forms of Rosuvastatin.

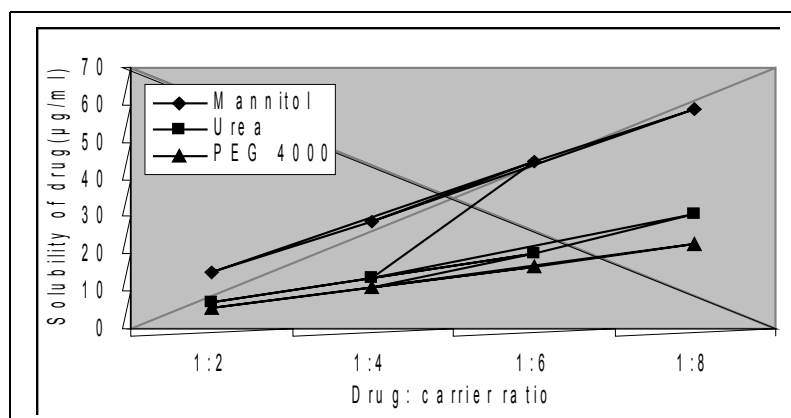


Fig. 1: Solubility profile of Rosuvastatin with solid dispersion formulations with PEG 4000, Urea and Mannitol.

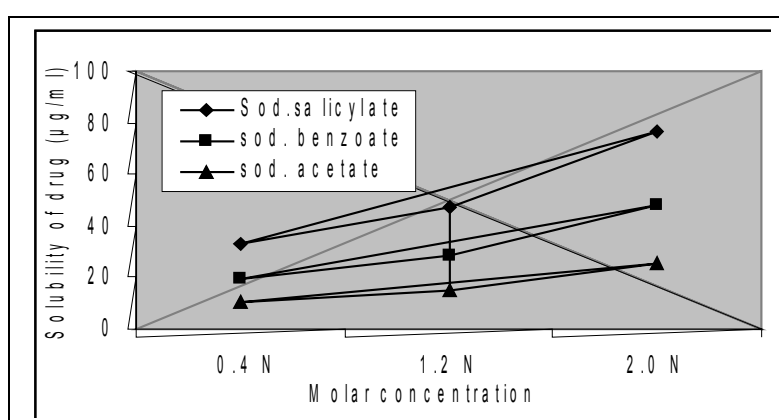


Fig. 2: Solubility profile of Rosuvastatin with hydrotropic solution of sodium salicylate, sodium benzoate and sodium acetate

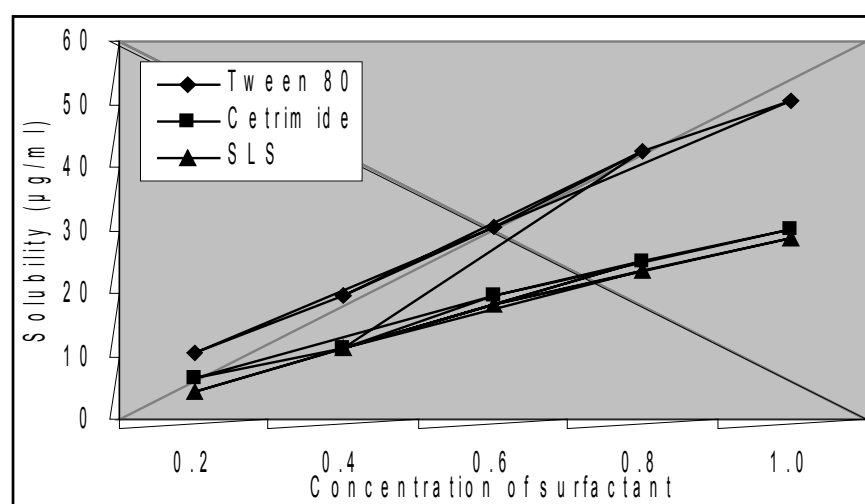


Fig. 3: Solubility profile of Rosuvastatin with surfactant solution of Sodium lauryl sulphate (SLS), cetrimide, Tween 80.

ACKNOWLEDGEMENTS

Authors are thankful to Mr. Rajesh Ramola (Production Head, Windlaas Pharmaceuticals, Dehradun, Uttarakhand) for providing gift sample of Rosuvastatin.

REFERENCES

1. Adel Aly M Muzen Qato K Mahrous Ahmad O Enhancement of dissolution rate and bioavailability of Rosuvastatin through cyclodextrin inclusion complex. *Drug Del Ind Pharm* 2002; 32: 578-584.
2. Chiou WL Reigelman S. Pharmaceutical applications of solid dispersions. *J Pharm Sci* 1971; 60:1281-302.
3. Serajuddin TM Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthrough. *J Pharm Sci* 1999; 88 (10): 1058-1066.
4. Chiou WL Riegelmann S Preparation and dissolution characteristics of several fast release solid dispersion of griseofluvin. *J Pharm Sci* 1969; 58:1505-1059.
5. Sharma D K Joshi SB. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A Review. *Asian J Pharmaceutics* 2007; 1 (1):9-19.
6. Neuberg C Hydrotropy. *Biochemische Zeitschrift*. 1916; 76: 107-176.
7. Swarbrick J Encyclopedia of pharmaceutical Technology, 3rd ed., Marcel Dekker, (NY), 2007 p. 2919.
8. Coffman RE Kildsig D Hydrotropic solubilization- mechanistic studies. *Pharm Res* 1996; 13(10): 1460-1463.
9. Lee J Lee SC Acharya G Chang C Parke R Hydrotropic solubilization of Paclitaxel. *Pharm. Res* 2005; 20(7), 1022- 1030.
10. Truelove J Bawarshi-Massac R Chen NR Hussain A Solubility enhancement of some developmental anti-cancer analog by complexation ith nicotamide. *Int J Pharm* 1987; 19, 17-25.
11. Agrawal S Pancholi SS Jain NK Agrawal GP Hydrotropic solubilization of nimesulide for parenteral administration *Int J Pharm* 2004; 274: 149-155.
12. Jain NK Patel VV Taneja LN Hydrotropic solubilization of nifedipine. *Pharmazie* 1998; 43(3):194
13. Blake Martin Loyd E Harris The action of solubility agents on the solubility of xanthine derivatives in water: The application of partition studies to theophylline and caffeine combinations. *J Amer Pharm Ass* 2006; 41, (10), 521-523,
14. Rosen M J Surfactants and interfacial phenomena, 1989, second edition, John Wiley & Sons, New York,
15. Yagui R Oliveira C Pessoa A Jr. Tavares LC. Micellar solubilization of crystals. *J Pharm. Sci* 2005; 8(2), 147-163.
16. Modi A Tayade P A comparative solubility enhancement profile of valdecoxib with different solubilization approaches. *Indian J. Pharm Sci* 2007; 69 (2) 274-278.
17. Vadnere MK Coprecipitates and Melts. In: Swarbrick J Boylan J Eds Encyclopedia of Pharmaceutical Technology. 2nd ed. NY, Marcel Dekker Inc. 2002; 641-643.
18. Higuchi T Connors KA. Phase solubility techniques. *Adv Anal Chem Instr.* 1965; 4:117-212.
19. Kulkarni PK Balaji NJ Prabhuling VR Hydrotropic solubilisation of albendazole. *Indian J.Pharm.Educ.Res.* 2007; 412: 150-154.
20. Sammour OA Hammad MA Megrab NA Zidan AS Formulation and optimization of mouth dissolve tablets containing Rofecoxib solid dispersion. *AAPS Pharm Sci Tech*; 2006; 7 (2): 55.