AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Mixed hydrotropic technique as a tool to Enhance the solubility of Poorly Water Soluble Drug: Olmesartan

Himani Tewari[1]*, Arun Kumar Singh[1], D. K. Sharma[1]
1. Devsthali Vidyapeeth, College of Pharmacy, Lalpur, Rudrapur- 263148, Uttarakhand, India

ABSTRACT

Current study was undertaken to improve solubility and bioavailability of poorly water soluble drug, Olmesartan. A mixed hydrotropic method was used to prepare the hydrotropes of Olmesartan. On the basis of screening Sodium Benzoate, Potassium Acetate and Tri Sodium Citrate hydrotropes were selected to prepare various hydrotropic solid dispersions of Olmesartan using selected hydrotropic agent in different ratio with the drug. The prepared solid dispersions were evaluated for solubility analysis, Drug Content Estimation, Fourier Transformed Infrared Spectroscopy, Differential Scanning Calorimetry, and *In-vitro* Dissolution Study of hydrotropes. From the study the results revealed that solubility was increased by using certain ratio (1:1:1:0.5) of drug with hydrotropic agents alone as well as in the combination. In the present study an attempt was made to prepare hydrotropes of a poorly water soluble drug Olmesartan to enhance the solubility and bioavailability of drug. The screening of different hydrotropic agents was performed to evaluate the best suited agent for drug hydrotrophs. On the basis of solubility analysis, the Sodium Benzoate, Potassium Acetate and Tri Sodium Citrate agents have the ability to enhance the solubility of the drug more than 3 times of its original solubility. The method is economical and simple, to enhance the solubility of Olmesartan.

Keywords: Hydrotropy Method, Co solvent, Olmesartan, Physicochemical property, Sodium Benzoate, Potassium Acetate, Tri Sodium Citrate.

*Corresponding Author Email: tewarihimanir@gmail.com
Received 21 August 2017, Accepted 01 September 2017

Please cite this article as: Tewari H *et al*., Mixed hydrotropic technique as a tool to Enhance the solubility of Poorly Water Soluble Drug: Olmesartan . American Journal of PharmTech Research 2017.

INTRODUCTION

The administration of only pure form of active pharmaceutical ingredient is not possible, but it can be made possible by development of suitable dosages form. Dosages form development is also dependent on the physicochemical property of drug, selection of excipients, route of administration and their stability for attaining their activity.

Many other examples of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used. Age is also an important aspect for designing the dosage forms. Liquid dosages form prepared for oral administration in case of infants and children below 5 years of age [1]

After the oral administration most of the drugs shows limited bioavailability because of their pH or enzymatic degradation, first pass metabolism or poor aqueous solubility. The major factor for poor bioavailability of drug is due to poor dissolution rate at the site of absorption.

So it is a difficult task for the formulation scientist to develop a dosages form with higher absorption rate or dissolution rate for BCS Class II drugs. Therefore it is important to increase the solubility of poorly soluble drugs with a novel technique to improve the dissolution rate at the site of absorption.

Solubility

It is often noted that the poor solubility and low dissolution rate of a poorly water soluble drugs in the aqueous gastrointestinal fluids often causes insufficient bioavailability. For class II (low solubility and high permeability) substances as per BCS classification, the bioavailability may be increased by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. This is because for BCS class II drugs absorption is not the rate limiting step, instead the drug release from the dosage form and the solubility in the gastric fluid are termed as the rate limiting step, therefore the solubility in turn increases the bioavailability for BCS class II drugs [2]

According to IUPAC, solubility may be defined as "The analysed composition of a solution which is saturated, it is determined in terms of the proportion of a particular solute in a particular solvent, is the solubility of that solute. The solubility may be expressed in terms of concentration, molality, mole fraction, mole ratio, etc.[3]

As per Indian Pharmacopoeia solubility is listed in terms of number of milliliters of solvent required to dissolve 1g of solute. In case of exact solubility is not known, the Pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in table:[4]

About 20 years ago it was reported that more than 41% of the failures in new drug development have contributed to poor biopharmaceutical properties, including water in solubility.[5]

Hydrotropic Solubilization

The ability to increase the aqueous solubility of a drug (usually a sparingly soluble organic compound) by a concentrated solution of a chemical compound is termed as Hydrotropy. Thus 'hydrotropes' are the compounds that have ability to increase aqueous solubility. When it comes to characterized the hydrotropic agents structurally it is explained as bulky in nature, short and a compact moiety such as an aromatic ring.[6]

Talking about the chemical structure of hydrotropic salts as per Neuberg's concept, is the one which has two important parts:

- an anionic group
- a hydrophobic aromatic ring

The use of anionic group is in, to increase aqueous solubility, which is essential for a hydrotropic substance. A hydrophobic part is important for the proper mechanism of hydrotropic solubilization.[7]Additives acts as a key ingredient which is responsible for the increment or decrement o the solubility of a solute in a solvent.[8]

Urea, sodium gentisate, sodium salicylate, sodium benzoate, sodium gluconate, lysine, tryptophan, sodium acetate are some of the examples of hydrotropic agents. The main function of a hydrotropic agent is that it increases the solubility towards water of the selected drugs which are hydrophobic in nature , but it has been identified to have the capability solubilize all hydrophobic drugs. Therefore it is necessary to screen a number of hydrotropes for selecting the correct hydrotropic agents for a poorly soluble drug.

Mixed Hydrotropic Solubilization

Mixed hydrotropic solubilization technique is a method used to increase the solubility of poorly water soluble drugs by adding different types of hydrotropic agents in combination.

Solid Dispersions[9,10,11]

"Solid Dispersion" is the word which is used to describe a group of dosage forms in which the drug is dispersed in an inert matrix, which results in an increment of the oral bioavailability. As early as in 1961, Sekiguchi *et al*. developed the concept of solid dispersion to increase the absorption capacity of poorly water-soluble drugs. In this type drug forms eutectic mixtures with the carriers which are water-soluble, this happens by melting of their physical mixtures. Once the carrier dissolves completely, drug starts precipitating in water.[9]

Various methods have been applied for increasing the solubility, the methods are Fusion Method.[10] Solvent Evaporation Method, Lyophillization Technique[11], Melt Agglomeration Process, Extruding Method, Supercritical Fluid Technology.

MATERIALS AND METHOD

Olmesartan was obtained as a gift sample from Sun Pharma, Jammu. All other chemicals and reagents were of analytical grade

Determination Of λ_{max} in Methanol [12]

Olmesartan(10mg) was dissolved in 10ml of methanol, and the content was transferred into 100ml volumetric flask. The volume was made up to the mark with methanol to obtain a stock solution of 1000µg/ml final concentration.

From the stock solution the λ_{max} was determined by UV-Visible spectrophotometer 1800 at 200-400nm. Further the different concentration i.e. 5,10,15,20 and 30 (µg/ml) were prepared from the stock solution and absorption of each dilutions was determined at selected λ_{max} and standard graph was plotted between concentration and absorption.

Determination Of λ_{max} in Phosphate Buffer 6.8 pH [12]

Olmesartan(10mg) was dissolved in 1ml of methanol into 100ml volumetric flask. The volume was make up to the mark with phosphate buffer pH 6.8 to obtain a stock solution of 1000µg/ml final concentration. The solution was further sonicated for 10 minutes to obtain a clear solution.

From the stock solution and λ_{max} was determined by scanning at 200- 400nm. Further the absorption of different dilution i.e. 2,4,6,8,10,12,14,16,18 and 20 (µg/ml) were prepared and determined at selected λ_{max} and standard graph was plotted between concentration and absorption.

Determination of λ_{max} in Water[12]

For determination of λ_{max} of Olmesartan in water 10mg of Olmesartan was dissolved in 1ml methanol, and 2ml water the content was transferred into 100ml volumetric flask. The volume was marked upto mark with water to obtain a stock solution of Olmesartan with 1000µg/ml final concentration. The solution was further sonicated for 10 minutes to obtain a clear solution.

From the stock solution and λmax was determined by scanning at 200- 400nm. Further the absorption of different dilution i.e. 2, 4,6,8,10,12,14,16,18 and 20 (µg/ml) were prepared and determined at selected λ_{max} and standard graph was plotted between concentration and absorption.

Partition Coefficient [13]

The Partition Coefficient of olmesartan was determined by Shake Flask Method**.** It was determined by using n-octanol (as oil phase) and water (as aqueous phase). 100 mg of Olmesartan was accurately weighed and taken in a separating funnel (250 ml) containing 50 ml each of n-octanol and water.

The separating funnel was shaken for a period of 1.5 hour, until equilibrium was reached and kept for 24 hours. Content in the oil phase and the aqueous phase was analyzed spectrophotometrically for the calculation of the amount of drug partitioned in aqueous phase and oil phase after the appropriate dilutions.

The log P value of Olmesartan was calculated. All data shown in table no 1

Aq= Aqueous; Abs.= Absorbance

Drug Excipient Compatibility

The different formulation components involved in the development of the hydrotropes of Olmesartan were physically mixed with Olmesartan in the ratio of 1:1 and filled in glass vials properly, capped and sealed. The vials of each sample were kept at room temperature for one month period. After every week the vials were withdrawn and the changes in physical appearance (if any) and color of the contents were observed.

Preparation of Hydrotropes

Screening method for selection of hydrotropic agents

Excess amount of Olmesartan was transferred to a volumetric flask containing water as a solvent , 5 mg of hydrotropic agent (Potassium Acetate) was accurately weighed and transferred to the volumetric flask and was allowed to stand for overnight. The next day 1ml of the solution was pipetted out and was diluted upto 10ml, the absorbance was recorded in a UV Spectrophotometrically. The same procedure was followed for screening of other hydrotropic agents. The list of hydrotropic agents used for screening is All data shown in table no 2

Preparation of Olmesartan Hydrotropes by Mixed Hydrotropic Technique[14]

After screening hydrotropic agents were selected for the preparation of the hydrotropes of Olmesartan by mixed hydrotropy solid dispersion method. The different ratios of the selected hydrotropic agents were used for the preparation of hydrotropes of Olmesartan.

Procedure:

10ml of distilled water was warmed in a beaker and the temperature was maintained to 80^{o}C. In another beaker the selected hydrotropes were placed and the warm water was added, the stirring was continued until a clear solution was obtained. Further it was cooled to 40^{0}C. Drug was incorporated in the beaker containing the solution of the hydrotropic agents. This as a whole was

allowed for stirring for at least 2 hours or until a semisolid mass was obtained, which was transferred to a petridish and was allowed to get dry in a hot air oven for 1 hour. Further after 1 hour the solid mass obtained was pasteurized and was triturated in a mortar & pestle, and passed through sieve no. 100, to obtain a fine uniform powder, which was further dried in oven. The final step used to obtained hydrotropes was to place the petridish containing fine powder of hydrotropes for 4 days (at least) in a desiccator containing silica pellets and all data mention in table no 3

Evaluation of the Hydrotropic Solid Dispersion

Solubility Analysis

The excess amount Olmesartan hydrotropes prepared from different drug carrier ratio was taken into a volumetric flask and 5ml of distilled water was added. These flasks were kept on shaker for 24 hrs to achieve equilibrium state. The aliquots of all the samples were withdrawn and after proper dilutions, the content was analyzed by UV spectrophotometer.

Drug Content Estimation

An accurately weighed quantity of the hydrotropes equivalent to 20mg of Olmesartan was weighed and placed in 100ml volumetric flask, and distilled water was added upto 100ml mark, and assayed for drug content using UV spectrophotometer and drug content was estimated in the prepared hydrotropes.

Fourier Transformed Infrared Spectroscopy-

The Fourier Transformed Infrared Spectroscopy of Hydrotropes and pure drug were obtained using FTIR spectrophotometer.

Differential Scanning Calorimetry

Selected formulations were subjected to DSC study for drug-excipient interaction and molecular assay.

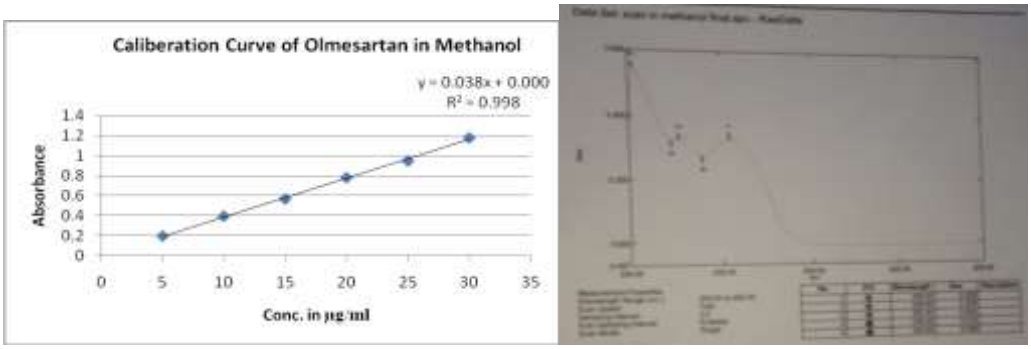
***In-vitro* Dissolution Study of hydrotropes**

Dissolution test was carried out by using USP paddle test apparatus for 2 hrs. The stirring rate was kept at 100rpm, and Phosphate buffer was used as a dissolution medium (900 ml), temperature was maintained at 37± 1^0C, the hydrotropes equivalent to 20mg of Olmesartan was used for dissolution studies, samples were withdrawn at different time intervals, and analyzed by UV spectrophotometry .

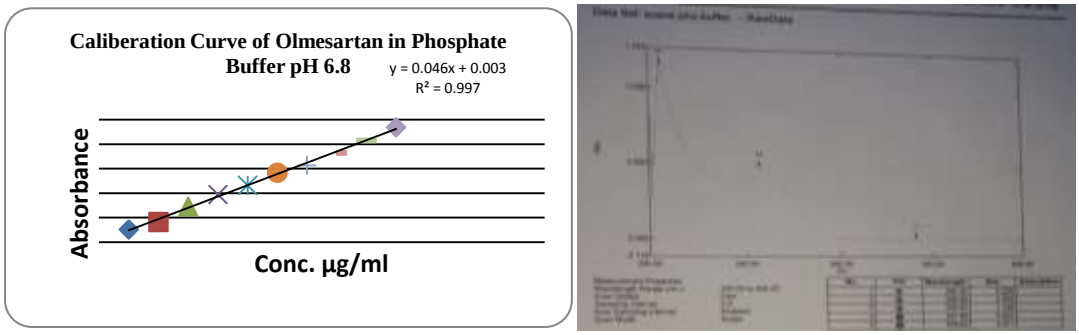
RESULTS AND DISCUSSION

Preformulation Studies of Olmesartan

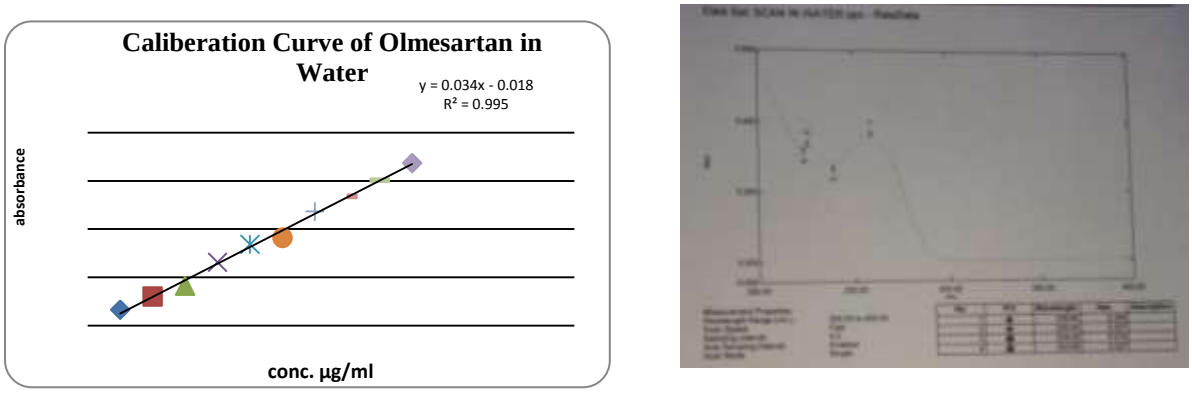
Standard Curve: The λ_{max} in methanol, distilled water and pH 6.8 was observed as 257nm, 252 nm, and 256nm respectively. The Standard curve for Olmesartan also showed linearity and it followed the Beers-Lamberts law in all the solvents used (methanol, distilled water and pH 6.8) all calibration shown in Figure 1.



(a) (b)



(c) **(d)**



(e) **(f)**

Figure 1 a) Calibration curve of Olmesartan in methanol; b) Scanning of Olmesartan in Methanol c) Calibration curve of Olmesartan in Phosphate Buffer pH 6.8; d)Scanning of Olmesartan in Phosphate Buffer pH 6.8 ; e) Calibration curve of Olmesartan in water ; f) Scanning of Olmesartan in Water.

Partition Coefficient:

Partition coefficient value was found to be 2.113 which shows that the drug is lipophilic in nature.

Table 1: Partition coefficient value of Olmesartan

Organic solvent/ Aq. Phase	Abs. in oil phase Df= 100	Abs. in aq. phase	P = C1/ C2	Log P
N-octanol/distilled water	0.148	0.143	129.8	2.113
	0.147	0.145		
	0.149	0.142		
Average value	0.148	0.1433		

Aq= Aqueous; Abs.= Absorbance

Table 2: List of Hydrotropic Agents Used.

S.No	Hydrotropic agent Used
1	potassium Acetate
2	Citric Acid Anhydrous
3	Sodium Benzoate
4	Urea
5	Sodium Tri Citrate
6	Gaiadu
7	Tapioca
8	Gahat

Drug Excipient Compatibility:

There was no physical incompatibility between drug and the hydrotropic agents in table no 4

Solubility Screening of Different Hydrotropic Agents

Solubility analysis of drug in different hydrotropic agents showed that sodium benzoate, tri sodium citrate and potassium acetate were reported to provide high solubility as compared to other hydrotropic agents. Therefore sodium benzoate, tri sodium citrate and potassium acetate were selected for preparation of hydrotropes of olmesartan by solid dispersion method Shown in Figure 2.

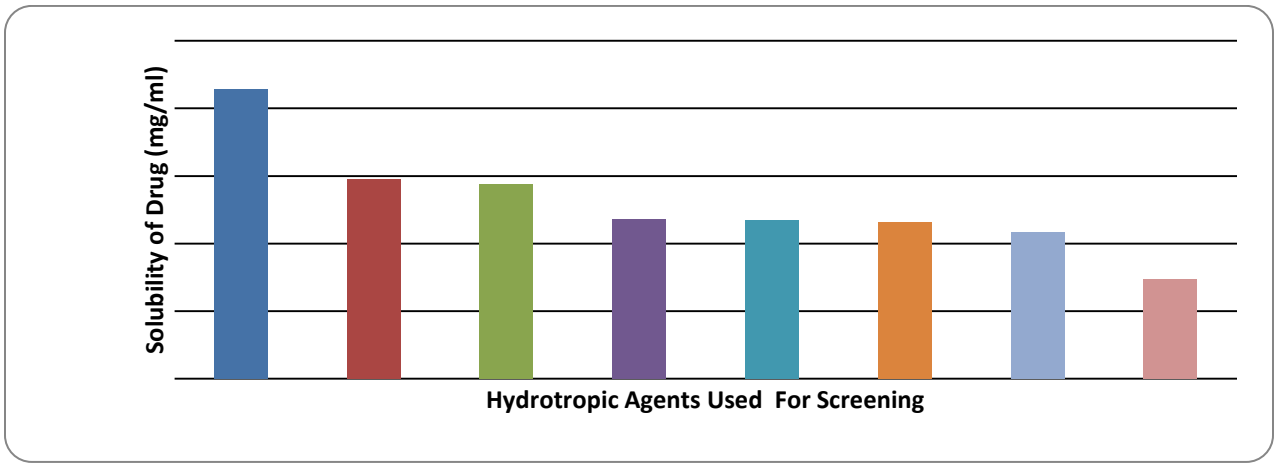


Figure 2: Graphical representation of solubility of Olmesartan in aqueous solutions of individual Hydrotropic Agents.

Screening of Different Hydrotropic Agents with Olmesartan

From the above graphical representation maximum increase in solubility was observed in Tri Sodium Citrate solution followed by sodium benzoate, urea, potassium acetate, gaiadu tapioca, gahat and anhydrous citric acid respectively. So, to minimize toxicity due to higher concentration of single solubilizer, mixed blend of solubilizers were used for the preparation of hydrotropes.

Solubility Analysis of the Prepared Hydrotrope

From the data analysis, it was observed that solubility of drug is more in Batch 1,2 and 6 all data show in table no 5

From the FTIR interpretation, It was found that there is no considerable change in the peak of the prepared hydrotropes, when compared with pure olmesartan drug. FTIR studies revealed that there is no physico-chemical interaction between Olmesartan and the prepared hydrotropes.

From the DSC of pure drug (Olmesartan) and the optimized hydrotropes, it was observed that the melting point of Olmesartan (pure drug) is 183.55 ºC, whereas the melting points of the three hydrotropic agents are 62.73, 122.43 and 155.76 ºC respectively. In the hydrotropic formulation prepared, the absence of the melting thermogram peak of the drug at 183.55 ºC indicated that the drug has been converted by the hydrotropic agents into a molecularly dispersed state and in such cases the solubility of the drug is markedly increases. This shows that the hydrotropic formulation was prepared.

In-Vitro Dissolution Study of the Prepared Hydrotropes

On the basis of the solubility analysis the three batches (1,2,6) were optimized. From the dissolution studies it was resulted that only 11.29% of drug was released in the first 15 minutes from the pure drug, whereas 26%, 46% and 57% of drug was released in the first 15 minutes from

the prepared hydrotropes respectively, which indicates that there is a rapid release of drug from the hydrotropes. Total release of drug from hydrotropes after 2 hours was found to be 43.75%, 55.34%, 74.56% respectively, whereas only 29.89% of drug was released from the pure drug. The dissolution study of the prepared hydrotropes revealed that, dissolution of drug was greatly increased approximately more than double of the pure drug, this may be attributed to higher surface area.

Table 3: Composition of Various hydrotropic solid dispersion (in ratio form).

Batch No.	Drug (mg)	Sodium Benzoate	Potassium Acetate	Sodium Tri Citrate
1	1	0.5	0.5	0.5
2	1	1	0.5	0.5
3	1	0.5	1	0.5
4	1	0.5	0.5	1
5	1	0.5	0.5	1
6	1	1	1	0.5
7	1	0.5	1	1
8	1	1	1	1

Table 4: Observations of Drug Excipient Compatibility Studies.

S. No.	Drug solubilizers (1:1 blend)	Initial Observation	Refrigerated condition (2-8 ° C)				Room temperature (25°)			
			1wk	2wk	3wk	4wk	1wk	2wk	3wk	4wk
1.	Olmesartan	White Powder	NC	NC	NC	NC	NC	NC	NC	NC
2.	Olmesartan + Sodium benzoate	White Powder	NC	NC	NC	NC	NC	NC	NC	NC
3.	Olmesartan +Tri Sodium citrate	White Powder	NC	NC	NC	NC	NC	NC	NC	NC
4.	Olmesartan + Potassium Acetate	White Powder	NC	NC	NC	NC	NC	NC	NC	NC

NC= No Change

Table 5: Solubility Analysis of the Prepared Hydrotropes.

Batch No.	Conc. (µg/ml)	Amount (mg/ml)	Solubility enhancement
1	2.94	29.4	4.1 times
2	2.88	28.8	4.102 times
3	2.79	27.9	3.97 times

4	1.82	18.2	2.5 times
5	1.97	19.7	2.80 times
6	3.02	30.2	4.30 times
7	2.67	26.7	3.80 times
8	2.82	28.2	4.01 times

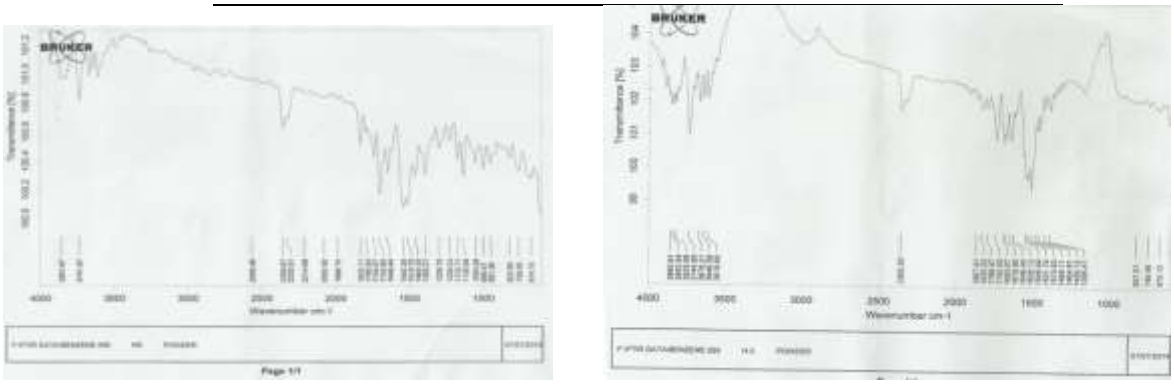
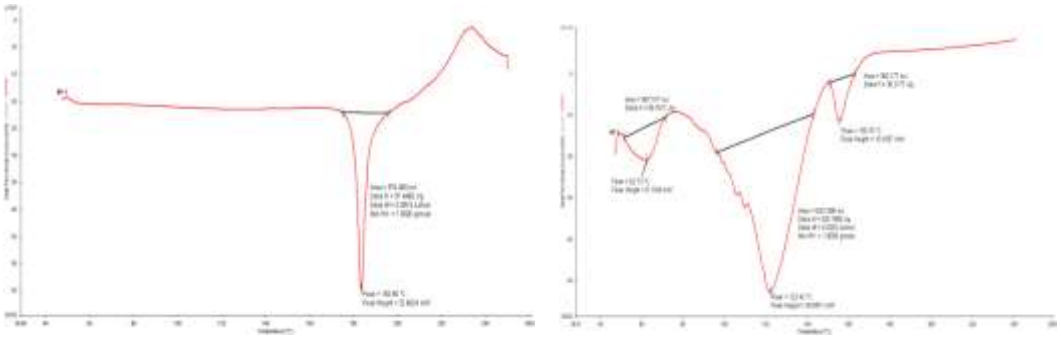
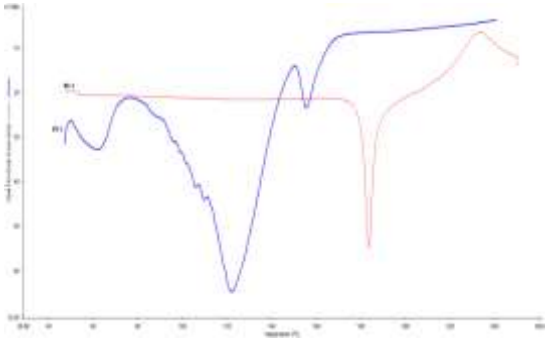


Figure 3: a) FTIR of Pure Olmesartan b) FTIR of optimized Hydrotropes of Olmesartan Fourier Transformed Infrared Spectroscopy



(a) **(b)**



(c)

Figure 4: a) Graphical Representation of DSC of Olmesartan. b)Graphical Representation of DSC of optimized Hydrotropes. c) Graphical Representation of Both the Pure Drug and the optimized Hydrotropes. Differential Scanning Calorimetry

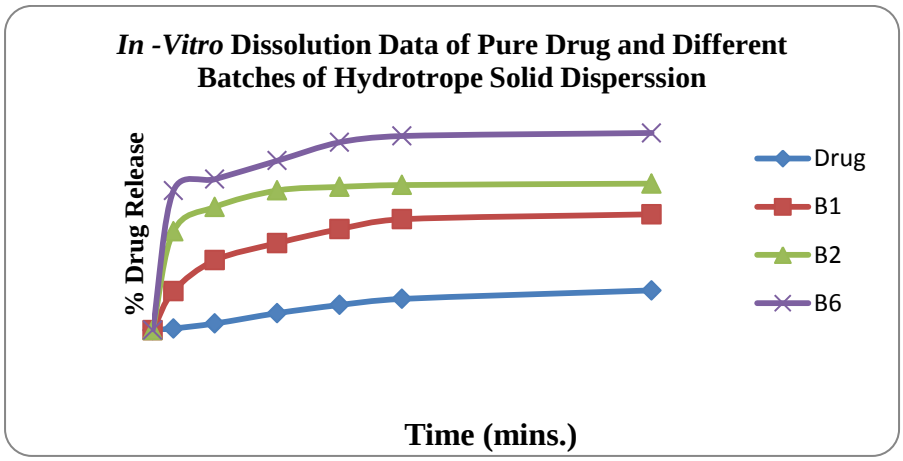


Figure 5: *In-Vitro* Dissolution Data of Pure Drug and different Batches of Hydrotropic Solid Dispersions.

CONCLUSION

The mixed hydrotropic method as used for the preparation of olmesartan hydrotrophs. Further screening of different hydrotropic agents was performed to evaluate the best suited agent for drug hydrotrophs. on the basis solubility analysis, the Sodium Benzoate, Potassium Acetate and Tri Sodium Citrate agents have the ability to enhance the solubility of the drug more than 3 times of its original solubility. Although Urea has a potential to enhance the solubility of olmesartan as similar to the hydrotropes mentioned in above line but being toxic and showing more adverse effect in human body the use of urea was avoided for the preparation of the hydrotropes. From the FTIR study it was concluded that there is no interaction between drug and agents and DSC analysis clearly showed the absence of the melting thermo gram peak of the drug. It indicates that the drug has been converted by the hydrotropic agents into a molecularly dispersed state so that the solubility of the drug is markedly increases.

REFRENCES:

1. Allen.L.V., Popovich .N.G , and Ansel. H.C., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams & Wilkins, 2011, 9, 90.
2. Chaudhary, A.; Nagaich, U.; Gulatti, N.; Sharma, V. R.; Khose, L., Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications:A recent review Journal of advanced pharmacy,education and research **2012,** 2 (1), 32-67.
3. Varshney S, Tiwari A, Negi D, Khulbe P, and Singhal P, Solubility enhancement of norfloxacin: a review, J. Sci.,2012,2(1), 30-32.

4. Indian Pharmacopoeia, Government of India. The Controller of Publications: Delhi, 1996; Vol. II, p 684.
5. Liu. R., Water Insoluble Drug Formulation. 2nd ed.; CRC Press Taylor and Francis Group London New York, 2008.
6. Jayronia S, Y. K., Sharma B, Jain S, Maheshwari R. K., Hydrotropy: A Novel approach in estimation of poorly aqueous soluble drugs by TLC. International journal of pharmacy and pharmaceutical sceiences **2013,** 5 (2), 175-178.
7. Kapadiya N., Singhvi I. , Mehta K. , Karwani G. and Sen D.J. , Hydrotropy: a promising tool for solubility enhancement: a review ; IJDDR , 2010 , 3(1), 26-33.
8. Da Silva R. C.; Spitzer, M.; Da Silva, L. H. M.; Loh, W., Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes. Thermochimica Acta **1999, ,** 328 (1/2), , 161-168.
9. Vasanthavada M, T. W., Serajuddin ATM, Development of Solid Dispersion for Poorly Water-Soluble Drugs. In, Rong liu. Water-insoluble drug formulation. 2nd edition ed.; CRC press: London,, 2008; p 499-523.
10. Sharma. D. K. and Joshi. S. B. , Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: a review, Asian J Pharm Sci, 2007, 1(1), 9-19.
11. Das. S.K, Roy.S, Kalimuthu.Y, Khanam.J, and Nanda.A. Solid dispersions an approach to enhance the bioavailability of poorly water-soluble drugs, IJPPT, 1(1) , 37-46.
12. Patel S.K, Kumar D.,Waghmode A.P.,and Dhabale A.S., Solubility enhancement of ibuprofen using hydrotropic agents, IJPLS. 2011; 2: 542-545.
13. Lachman L, Lieberman HA, Kanig JL., The Theory And Practice Of Industrial Pharmacy. 3rd ed; pg no. 188-189,Varghese publishing house: Bombay.1990.
14. Maheshwari, R. K.; Indurkhya, A., Formulation and Evaluation of acceclofenac injection made by the use of mixed hydrotropic solubilization technique. Iranian Journal of Pharmaceutical Research .2010; 9 (3): 123-132.