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FORMULATION AND EVALUATION OF GLIMEPIRIDE TABLET BY IMPROVING AQUEOUS SOLUBILITY OF DRUG USING HYDROTROPY TECHNIQUE

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ABSTRACT

The purpose of this research study was to formulate and evaluate Glimepiride tablet by improving aqueous solubility of drug using hydrotropy technique. The pharmacological response of drug mainly depends on its absorption rate, which in turn depends on drug's solubility which is an important parameter. Glimepiride is an oral anti hyperglycaemic agent useful in lowering the blood glucose level in normal subjects with type 2 diabetics, has poor aqueous solubility. The poor aqueous solubility of medicament results in decreased bioavailability and insufficient therapeutic effect. In the present research, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug Glimepiride by mixed hydrotropy technique using hydrotropic solutes, such as sodium citrate, sodium salicylate and sodium benzoate. Different ratios of hydrotrops were prepared by solid dispersion technique and optimized was selected for final tablet formulation. To increase the disintegration of the tablet formulation some super disintegrants are used such as crosspovidone and sodium starch glycolate. Preparation of tablet by direct compression and evaluation were done. This study revealed the influence of hydrotropic agents in the improvement of solubility of Glimepiride. Compatibility between drug and excipient examined by FTIR and DSC study and on the basis of all the parameters the conclusion and results were drawn.

KEYWORDS: Pharmacological, Anti hyperglycaemic, Hydrotropy, Bioavailability, Disintegrants.

INTRODUCTION

The present major issue in the pharmaceutical manufacturing is tactics for increasing medication solubility. This is because water solubility is an issue for roughly 40% of newly identified medication users. One of the most important variables in getting the intended effect of medical research is melting. A drug's therapeutic impact is determined by its bioavailability and, eventually, its commercialization. To increase the melting and dispersion of oral bioavailability profiles, a variety of design approaches are available.

The technique of hydrotrope solubilization theoretically reduces the size of drugs to the colloidal and even molecular level, thus helping to facilitate the dissolution of poorly water-soluble drugs by overcoming crystal lattice energy. When the solid dispersion is exposed to gastrointestinal fluids, the carrier dissolves leaving the drug in a molecular state, improving drug dissolution. A "hydrotrope" is a compound that can increase water solubility. Many hydrotropes are available such as sodium citrate, sodium benzoate, sodium gluconate, urea, sodium ascorbate, sodium acetate used in hydrotrope technology. Capsules and tablets are manufactured for easy handling and self-administration for systemic use and oral administration. other therapeutic conditions such as motion sickness, nausea, and vomiting; and also influences dosage form design. Rapidly disintegrating tablets dissolve quickly in saliva without the need for water. It is mainly a fast-dissolving tablet, intended for bedridden patients, the elderly, and pediatrics.

MATERIALS AND METHODS

Glimepiride was obtained as a gift sample from FDC Labs, Goa, India. Microcrystalline cellulose and other ingredients were obtained from Fine Chem Industries, Mumbai. All the other raw materials were of pharmacopoeial grade.

Experimental studies

Pre-formulation study

Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer (UV-1800A, SHIMADZU). Solubility analysis of drug in various solvents including water, phosphate buffer pH 6.8 and organic solvents like methanol was carried out.(table 1.1)

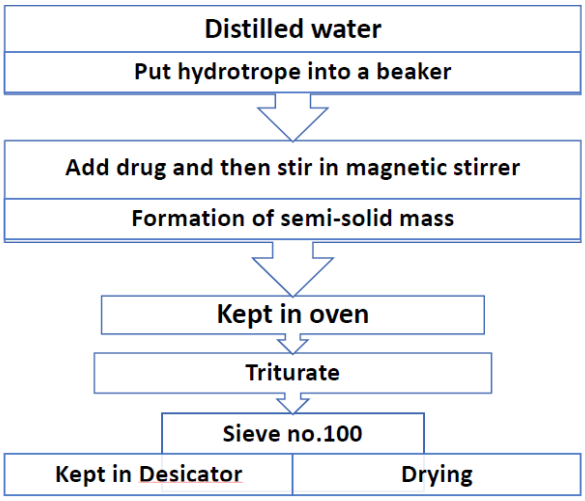
Formulation of hydrotropes

Screening of hydrotropes with glimepiride

The First step was the screening of various hydrotropes with Glimepiride. In this step, the drug glimepride was used to screen different hydrotropes for the final selection of hydrotropes for the development of different hydrotropes of drugs by the mixed hydrotrophic solid dispersion technique. A list of different hydrotropes used for drug screening is shown in the table1.2

Preparation of hydrotropes

The hydrotropes of Glimepiride were prepared by mixed hydrotropy solid dispersion method after the selection of suitable hydrotropic agents, in different ratios. The hydrotropes of Glimepiride with different ratios of suitable hydrotropic agents were prepared.(Table 1.3)



Evaluation of the hydrotropes

Solubility analysis

In solubility analysis a weighed quantity of hydrotrope equivalent to 40 mg of Glimepiride of different drug: hydrotropic agent ratio was conveyed to a volumetric flask having 10 ml of distilled water. These hydrotropes containing flasks were kept for 24 h. Next morning all the samples were analyzed in UV spectrophotometer at λmax 228 nm. (Table 1.1)

Drug content estimation

In drug content estimation a measured quantity of hydrotrope equivalent to 40 mg of Glimepiride was dissolved with methanol in volumetric flask of 100 ml, the volume was marked up to 100 ml mark and assayed for drug content was analysed spectrophotometrically at 228 nm and similarly drug content of other hydrotropes was estimated.

Drug – Carrier interaction study

Fourier transformed infrared spectroscopy

Fourier Transformed Infrared Spectroscopy of samples, selected hydrotropes and Pure drug i.e. Glimepiride were attained using FTIR spectrophotometer (Table 1.6,1.7).

Differential scanning calorimetry

Differential Scanning Calorimetry of the selected formulation was obtained to the study of drug- excipient interaction. DSC profile of Glimepiride and selected hydrotropes are shown in Figure 1.2,1.3.

In vitro dissolution study of hydrotropes

Dissolution Study of hydrotropes was done by using USP basket type apparatus for 2 h. The basket rpm was set at 50 rpm, pH 7.8 phosphate buffer was used as a dissolution medium (900 ml), temperature was controlled at 37 ± 10 C, hydrotropes equivalent to 40 mg of Glimepiride was used for dissolution studies, at different time intervals sample are withdrawn and analyzed by UV spectrophotometer at 228 nm (Table 1.6).7

Formulation of tablet

Hydrotropic solid dispersions so prepared were then finally formulated into Tablet by using super disintegrants. Fast disintegrating tablet of so prepared hydrotrophic solid dispersion contain a quantity equivalent to 40 mg of drug (Glimepiride) additionally by incorporating super disintegrants such as crospovidone or sodium starch glycolate are added, and citric acid are supplemented, magnesium stearate and talc are used as a lubricant, to minimize the tablet defects like capping, etc.; and to mask the bitter taste of tablet mannitol is used as a sweetening agent.

Weight variation

From each formulation twenty tablets were randomly selected and determined their average weight. Then individual tablet was weighed and was compared with average weight.

Friability

Friability test apparatus was used to examine the friability of tablet. Initially weighed tablet (Winitial) were placed in friabilator. The percentage friability was determined by following formulae.(Table 1.9)

$$F = W_{(initial)} - W_{(final)} \times 100 / W_{(final)}$$

Hardness

Pfizer Hardness tester was used to examine the hardness of tablet. It is expressed in kg/cm2. (Table 1.9)

Disintegration test

Disintegration test apparatus was used to examine the disintegration time of fast dissolving tablet (Table1.9)

In-vitro dissolution study

In-vitro dissolution study was done using USP type II apparatus or paddle type apparatus which was rotated at 60 rpm.8,9

Methods to compare dissolution profiles

Model dependent methods

Glimepiride release kinetics was analysed by various mathematical models, which were applied considering amount of drug released in 0to 60 min. Based on these estimations; mathematical models were described for dissolution profiles. The model fitting was represented in the form of following plots: cumulative percent drug release versus time (zero order kinetic models); log cumulative percent drug remaining versus time (first order kinetic model); cumulative percent drug release versus square root of time (Higuchi model); cube root of percent drug remaining versus time (Hixson-Crowell cube root law).

RESULTS AND DISCUSSION

Solubility analysis

Solubility analysis of drug in various solvents including water, Phosphate buffer pH 6.8,7.8 and organic solvents like methanol was carried out.

Table no. 1.1: Solubility analysis in different media.

Media	Solubility of drug (ug/ml)
0.1 N HCl	0.1
Phosphate buffer 4.5 acetate	1.128
Phosphate Buffer 6.8	3.70
Phosphate Buffer 7.8	8.56

Solubility analysis of screen hydrotropes

In solubility Analysis a weighed quantity of hydrotrope equivalent to 40mg of Glimepiride of different drug: Hydrotropic agent ratio was conveyed to a volumetric flask having 10ml of

distilled water. These hydrotropes containing flasks were analysed in uv spectrophotometer at ƛ max 228 nm. (Table-1.3)

Table no. 1.2: Solubility of glimepiride in various hydrotropic solvents.

Hydrotropes	Solubility enhancement ratio
Sodium benzoate	40
Sodium acetate	38.4
Sodium citrate	28.5
Sodium chloride	13.8
Urea	6.16
Sodium acetate +Sodium benzoate +Sodium citrate	135.6

Formulation of hydrotropes

The hydrotropes of Glimepiride were prepared by mixed hydrotropy solid dispersion method after the selection of suitable hydrotropic agents, in different ratios. The hydrotropes of Glimepiride with different ratios of suitable hydrotropic agents were prepared.

Table no. 1.3: Composition of various hydrotropes.

Batch no.	Drug (mg)	Sodium acetate (mg)	Sodium benzoate (mg)	Sodium citrate (mg)
1	200	100	100	100
2	200	200	100	100
3	200	100	200	100
4	200	100	100	200
5	200	200	200	100
6	200	200	100	200
7	200	100	200	200
8	200	200	200	200

Table no. 1.4: Solubility analysis of prepared batches.

Batch Number	Concentration (mg/ml)
1	83.5
2	82.5
3	91.4
4	69.5
5	98.9
6	82.7
7	88.5
8	84.5

Among the prepared hydrotropes formulations Maximum solubility of drug was found in the batch no. 3, 5, 7. This increase was directly related to increase in solubility of Glimepiride(Table 4).

***In vitro* dissolution studies of prepared hydrotropes**

On the basis of the solubility analysis the three batches (3, 5, 7) were optimized for further work. From the dissolution studies it was resulted that only 14 % of drug was released in 45 minutes.

Table no. 1.5: *In vitro* dissolution data for pure Drug and Different batches of hydrotropes.

Time (minutes)	%Drug release			
	Pure Drug	(Batch.no.3)	(Batch.no.5)	(Batch.no.7)
5	9.72	10.84	17.43	16.79
15	10.85	12.22	21.47	27.98
30	12.22	13.75	29.67	36.67
45	13.43	18.97	44.63	48.41
60	14.07	25.49	46.57	53.25
90	15.68	35.30	54.85	59.84
120	17.93	46.56	56.39	73.43

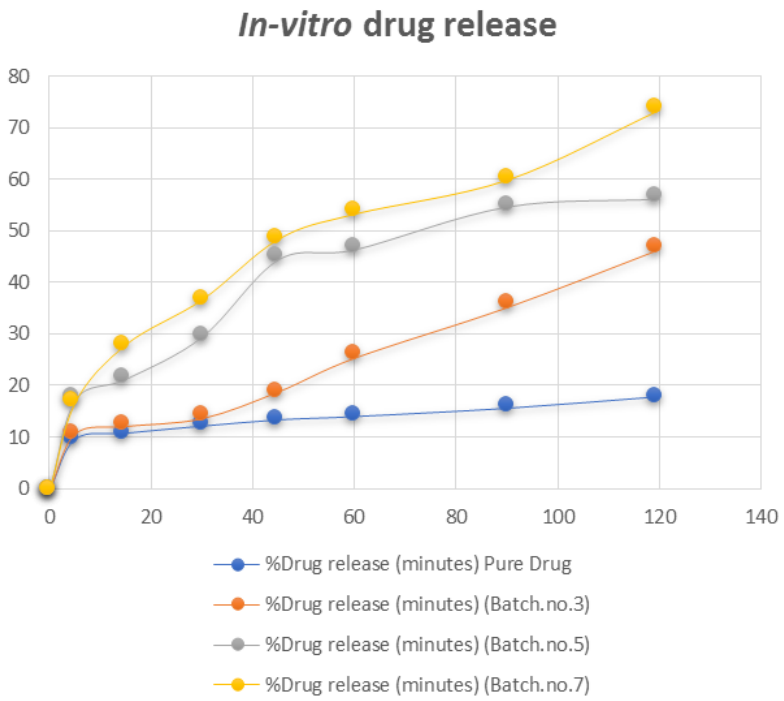


Figure no. 1.1*: In vitro* Dissolution Data for Pure Drug and Different batches of hydrotropes.

Differential Scanning calorimeter (DSC)

DSC curve of Glimepiride showed sharp endothermic peaks at 213.85º. While the DSC curve of physical mixture and solid dispersion both showed endothermic peak near 228.71º and 313.56º which indicates the absence of any complex formation in case of solid dispersion or physical mixture.

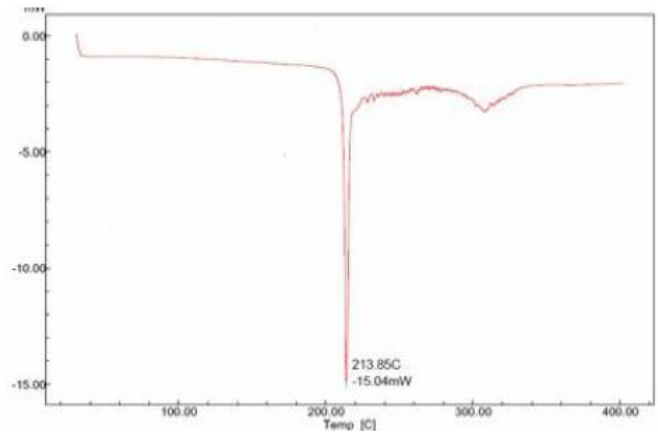


Figure no. 1.2: Dsc curve of Glimepiride.

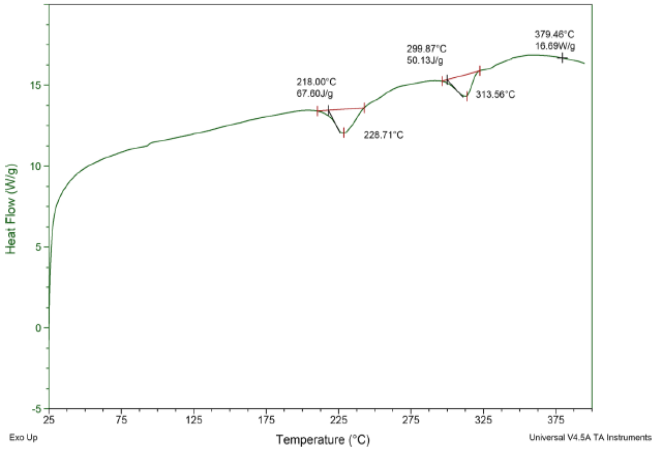


Figure no. 1.3: Dsc curve of mixed hydrotropes.

FTIR

Optimized formulation containing drug and hydrotrope were characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics from the result, It was concluded that there was no interference in the functional group as the principal peak of glimepiride were found to be unaltered in the spectra of the drug-hydrotrope mixture.

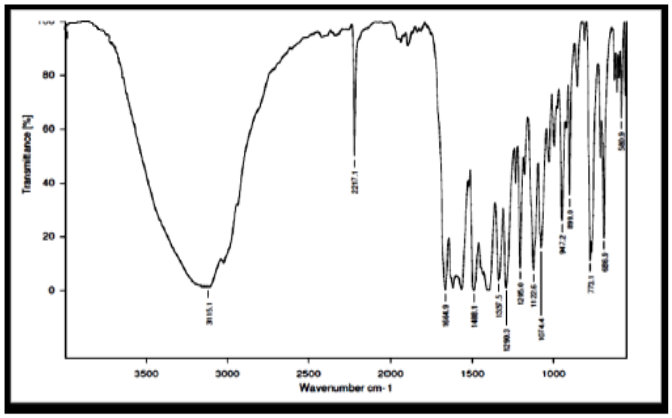


Figure no. 1.4: FTIR Spectra of glimepiride.

Table no. 1.6: FT-IR study of drug glimepiride.

Functional group	Observed Frequency	Frequency
C-H	1488.1,1337.5	1500-1300
N-H	3115.1	3700-3000
S=O	1074.4	1140-1325
C=O	1664.9	1900-1590

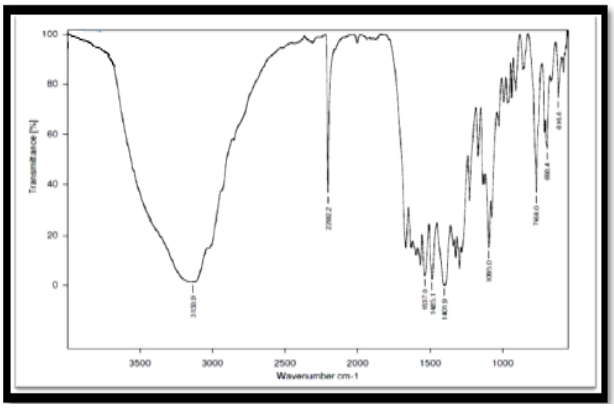


Figure no. 1.5: FTIR Spectra of hydrotrope formulation.

Table no. 1.7: FT-IR study of drug glimepiride.

Functional group	Observed Frequency	Frequency
C-H	1485.1	1500-1300
N-H	3133.9	3700-3000
S=O	1401.9	1140-1325
C=O	1537.0	1900-1590

Table no. 1.8: Preformulation studies.

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose (0)	C.I (%)	H.R
F1	0.725	0.785	27.75	7.64	1.08
F2	0.766	0.814	27.18	5.89	1.06
F3	0.758	0.810	24.56	6.41	1.06
F4	0.776	0.824	23.55	5.82	1.06
F5	0.735	0.794	25.27	7.43	1.08
F6	0.775	0.824	26.56	5.94	1.06
F7	0.772	0.832	24.58	6.48	1.04
F8	0.658	0.702	24.08	8.67	1.03
F9	0.723	0.895	28.70	6.72	1.06
F10	0.698	0.763	30.53	7.85	1.09
F11	0.704	0.847	32.00	5.28	1.05

Table no. 1.9: Post-formulation studies of prepared batches.

Evaluation parameter	Hardness(kg/cm^3)	Drug Content	Friability	Disintegration time(sec)	Wetting time(sec)
F1	3.1	99.1	1.07	4	12
F2	3.3	102.4	0.70	3	14
F3	3.2	93.35	0.78	4.4	10
F4	2.9	101.1	1.04	4.5	11
F5	3.1	99.7	0.77	5	13
F6	2.8	102.2	.069	4	15
F7	3.0	98.65	1.14	6	10
F8	3.1	94.85	1.06	8	12
F9	2.92	99.55	0.85	5	14
F10	3.01	100.4	1.01	6	15
F11	3.2	99.4	0.61	4	13

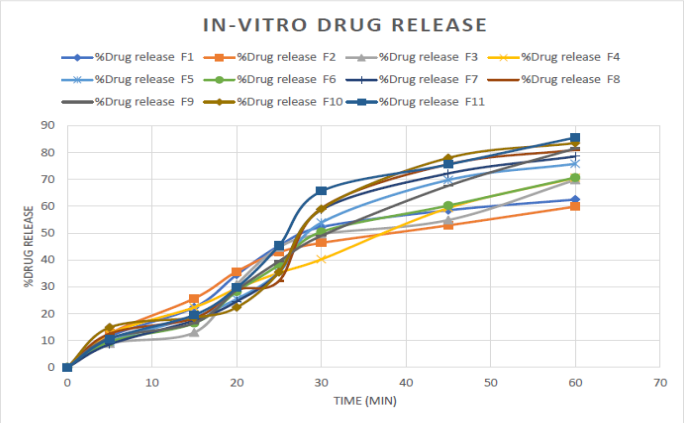


Figure no. 1.6: Comparison of % cumulative drug released from the formulation varying in the amount of F11 (use of crospovidone and sodium starchglycolate)

Table no. 1.10: Regression values of in vitro release kinetic study of optimized formulation (F11).

Kinetic study model	R2
Zero order	0.8793
First order	0.9585
Higuchi	0.9467
Kross-peppas	0.9696
Hixson-Crowell	0.9382

The in vitro dissolution data of Glimepiride immediate release tablets (F11) were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixson-Crowell and Korse Meyer- Peppas equation; and the graphs were plotted figure. The KorseMayer Peppa's kinetic plots were found to be fairly linear As indicated by their highest regression values (0.9696) for F11 formulation. The release exponent 'n' for optimised formulation F11 was

found to be 0.932 (0.5 < n < 1), that appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study in vitro drug release kinetic of Glimepiride immediate release tablet followed Peppas release kinetic model and the drug release mechanism was said to be anomalous diffusion coupled with erosion. The regression values of all the release kinetics were presented in the table 6.15.

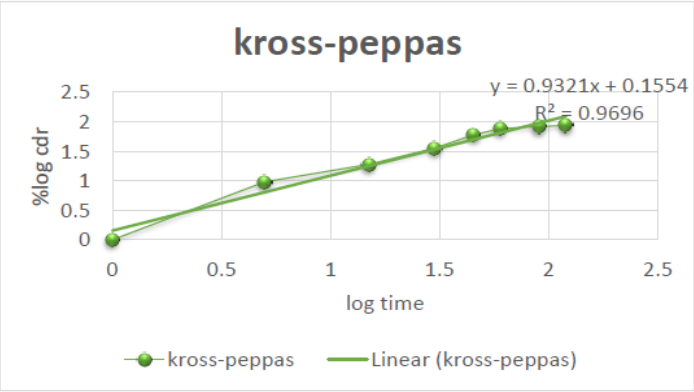


Figure 1.7: Kross mayers peppas release.

Chemical Stability Testing of Hydrotropic Solid Dispersions and Physical Mixtures of Drugs Different hydrotropic solid dispersions and physical mixtures of drugs were subjected to chemical stability testing. Powders of various formulations were kept in 10ml colourless glass vials and vials were plugged and sealed. Vials were kept at room temperature, at 55°C in oven (Khera Instruments Pvt.Ltd., Delhi). The samples were withdrawn at different time intervals and drug contents were determined spectrophotometrically. To calculate the drug content, the formulations were analysed by the same procedures which were applied to determine their drug contents after their formulations. The initial drug content for each formulation was considered as 100.00%. The percent residual drug for each formulation at different time intervals are recorded in Table.

Table no. 1.11: Chemical Stability data of Glimepiride hydrotropic solid Dispersion and Physical mixtures.

Condition	Time(months)	%residual drug in formulation (mean±sd)
Room temperature	1	98.76±2.30
Room temperature	3	98.52±0.931
Room temperature	6	98.31±0.59

CONCLUSION

In conclusion, currently pharmaceutical industry has reached the factor in which the invention of recent drugs has grow to be very tough and high-priced. Exploiting the maximal price that can be generated of current compounds now constitutes an critical motive force of sales and hydrotropy is an answer for pharmaceutical organizations to enhance the existence cycle of the prevailing merchandise wherein poor solubility is a prime challenge. Many useful tablets can be abandoned due to negative pharmacokinetic homes along with negative water solubility. through hydrotropy, water solubility of a drug can be improved for that reason enabling protection of drugs inside the existing products pipeline.it may be concluded that the idea of combined hydrotropic solid dispersion is novel, safe and fee powerful technique for boosting bioavailability of poorly water-soluble capsules by using dissolving drug in nonionized shape. the magical enhancement in solubility of Glimepiride is apparent indication of its potential to be used in destiny for different poorly water soluble pills wherein low bioavailability is most important situation.

REFERENCES

1. Biopharmaceutics and Pharmacokinetics-by sunil b jaiswal TuitouE, Godin B, Weiss C. Enhanced delivery into and across the skin by ethosomal carriers. Drug Dev Res, 2000; 50: 406-45.
2. Banker GS, Rhodes CT. Modern Pharmaceutics: Basic Principles and Systems. New York: Marcel Dekker Inc, 2002; 4: 200.
3. Jain S, Umamaheshwari RB, Bhadra D, Jain NK. Ethosomes: A novel vesicular carrier for enhances transdermal delivery of an Anti-HIV agent. Indian J Pharm Sci, 2004; 66: 72-81.
4. Jain S, Umamaheshwari RB, Bhadra D, Jain NK. Ethosomes: A novel vesicular carrier for enhances transdermal delivery of an Anti-HIV agent. Indian J Pharm Sci, 2004; 66: 72-81. delivery. Pharm Rev, 2004; 1: 41-60.
5. Jun ginger HE, Hofland HE, Bouwrtra JA. Development of a topical anti-inflammatory gel from vitexnegundo extract and evaluating it. Pharm Ztg, 1991; 136: 9-24.
6. Divya L, Keerthana LP. Enhancement of solubility of raloxifeneHCl by formulating immediate and controlled release solid dispersion. Asian J Pharm Technol, 2015; 5: 238-48.

7. Kaplun-Frischoff Y, Touitou E. Testosterone skin permeation enhancement by menthol through formation of eutectic with drug and interaction with skin lipids. J Pharm Sci, 1997; 86: 1394-9.
8. Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E, et al. Cannabidioltransdermal delivery and anti-inflammatory effect in a murine model. J Control Release, 2003; 93: 377-87.
9. Ranade VV. Drug Delivery Systems. Boca Raton, Florida: LLC Publishing Group, Taylor and Francis, 2002; 199-205.
10. Jain NK. Advances in Controlled and Novel Drug Delivery. New Delhi: CBS Publication, 2001; 428-51.
11. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 2000; 50: 47-60.
12. Sonawale P, Patil A, Kamble A, Bhutkar M. Solubility enhancement of lipophilic drugs-solid self-micro emulsifying drug delivery system. Asian J Pharm Techno, 2016; 6: 155-8.
13. Neuberg C. Hydrotropy. Biochemistry, 1916; 76: 107-109.
14. Rajawardhan Reddy M, Prasanna Kumar D. A Review on Hydrotropy. Journal of Pharmaceutical Research, 2013; 2(4): 5-6.
15. Friberg E, Brancewicz C. O/W Microemulsions and Hydrotropes: The Coupling Action of a Hydrotrope, Langmuir, 1994; 10: 2945-2949.
16. Hatzopoulos M, Eastoe J, Peter J, Rogers S, Heenan R, Dyer are Hydrotropes Distinct from Surfactants, Langmuir, 2011; 27: 12346-12353.
17. Vemula V.R, Lagishetty V, Lingala S. Solubility Enhancement Techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41-51.
18. Asmat Majeed, Syed Naiem Raza, Nisar Ahmad Khan. Hydrotropy: Novel Solubility Enhancement Technique: A Review. International Journal of Scientific progress and research, 2019; 10(3): 10251036.
19. Vividha Dhapte, Piyush Mehta. Advances in Hydrotropic Solutions: an Updated Review. St.Petersburg Polytechnical University. Journal Physics and Mathematics, 2015; 1: 424-435.
20. Dhapte V and Mehta P: Advances in hydrotropic solutions:An updated review. St. Petersburg Polytechnical University Journal: Physics & Mathematics, 2015; 1: 424-435.

21. Verma G, Aswal VK, Fritz-Popovski G, Shah CP, Kumar M and Hassan PA: Dilution induced thickening in hydrotrope-rich rod-like micelles. Journal of Colloid and Interface Science, 2011; 359: 163-170.
22. Neumann MG, Schmitt CC, Prieto KR and Goi BE: The photophysical determination of the minimum hydrotrope concentration of aromatic hydrotropes. Journal of Colloid and Interface Science, 2007; 315: 810-813.
23. De Paula WX, Denadai AML, Santoro MM, Braga ANG, Santos RAS and Sinisterra RD: Supramolecular interactions between losartan and hydroxyl propyl-β-CD: ESI mass spectrometry, NMR techniques, Phase solubility, Isothermal titration calorimetry and antihypertensive studies. Inter Jour of Pharmaceutics, 2011; 404: 116-123.
24. Szabo K, Wang P, Peles-Lemli B, Fang Y, Kollar L and Kunsagi-Mate S: Structure of aggregate of hydrotropic p toluene sulfonate and hydroxyaceto phenome isomers. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2013; 422: 143-147.