



HYDROTROPIC SOLID DISPERSIONS: A ROBUST APPLICATION TO UNDERTAKE SOLUBILITY CHALLENGES

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Abstract

The solubility is an inherent property of any solid, liquid or gas. The solubility of drug dictates the ease with which pharmaceutical formulations can be obtained. In pharmaceutical corporations, nearly 40 per cent of novel drugs showed poor water solubilization potential. Improving the solubility of complex poorly soluble compounds is a challenging task for scientists and pharmaceutical investigators. Hydrotropic solid dispersion (HSD) technique is commonly used to increase solvency to many folds using hydrotropes and has many advantages such as; it does not require chemical manipulation of hydrophobic products, the use of organic solvents or emulsification. Simple recovery of the dissolved solvent and feasible reuse of hydrotrope solutions render this technique a most productive especially at enormous scale. In addition, the benefit of many characteristics, such as the pH-independent solvent character, strong specificity, non-flammability, inexpensive and easy hydrotropic accessibility, renders this methodology preferable to other solubilization procedures. This review guides the followers *via* a comprehensive overview of the classification of the approaches of solubility improving techniques, advantages and characteristics of HSD, and application of HSD in different categories of drugs.

Key words: Solubility, Solubilization, Hydrotropic solid dispersion, Solubility enhancement techniques.

Introduction

The oral route is easiest and most appropriate mode of drug administration due to enhanced stability, simplicity of dosing, dosage precision, and consistent production (Argade *et al.*, 2013; Cid *et al.*, 2019; Sultana and Saifuddin, 2016; Yadav and Tanwar, 2015). Approximately 40 percent of the new chemical entities (NCEs) reported by monitoring programs in the drug industry have generally failed to implement due to poor water-solubility, that tends to make their formulation problematic or perhaps even difficult. The solvency problems which complicate the implementation of these new drugs also complicate the production of many medicines (Hite *et al.*, 2003; Lipinski, 2002; Hu *et al.*, 2004). The level of gastrointestinal absorption of class II drugs in the biopharmaceutical classification system (BCS) is specifically based on the solubility component. Solubility improvement of class II drugs would therefore be now the greatest challenge for the development of their oral dosage form. Fig. 1, illustrates different techniques for maximizing the solubility (Allawadi *et al.*, 2013; Sharma and Singh, 2019; Singh *et*

al., 2013; Singh *et al.*, 2015; Singh and Sarangi, 2017).

Solid dispersions are the dispersion of hydrophobic drugs as molecular / amorphous particles (clusters)/ crystalline particles in hydrophilic crystalline or amorphous matrix (Sharma and Jain, 2011; Saffoon *et al.*, 2011). Hydrotropic solid dispersion (HSD) is a solubilization concept under which the introduction of a huge quantity of a second solute outcomes in a rise in another solute's aqueous solubility (Fig. 2) (Reddy *et al.*, 2013; Kulkarni and Goswami, 2014; Jayakumar and Raja, 2014). Solute is composed of alkali metal salts of different organic acids. The ionic organic salts are hydrotropic agents. Additives or salts that boost or decrease the solubility of a specified solvent are also said to "salt in" or "salt out" the solute. Many salts with large anions or cations that are actually very water soluble contribute to the "salting in" of non-electrolytes termed "hydrotropic salts," a concept called as "hydrotropism." Because of high specificity, HSD is proposed to be preferable to other solubilization processes, and it does not involve emulsification, chemical alteration of hydrophobic products, and organic solvent usage. The

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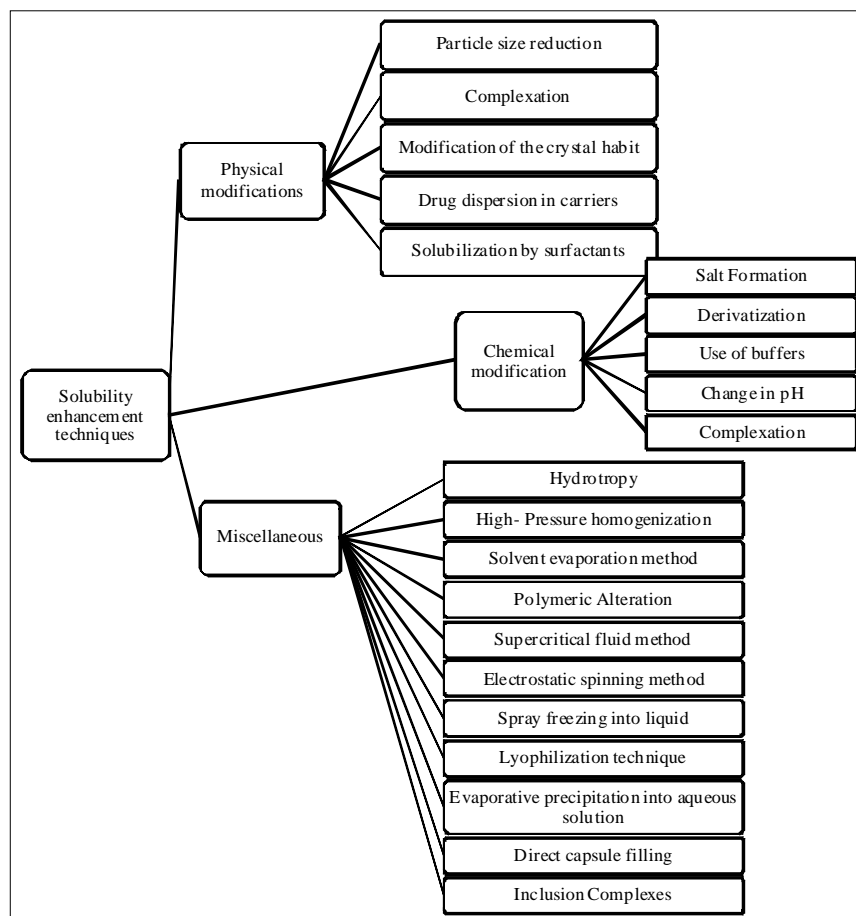


Fig. 1: Diverse methods for improving solubility.

HSDs are processed and transported in either aqueous solutions or granular solids, usually at an activity level of 30-60%, or 90-95%, respectively. Liquid product is developed in a closed system, whereas spray drying creates granular hydrotropes (Sajid and Choudhary, 2012; Kim *et al.*, 2010; Kapse *et al.*, 2016; Kapadiya *et al.*, 2011; Dhapte and Mehta, 2015). Characteristics of HSDs

are represented in fig. 3. mixture containing niacinamide and sodium benzoate (Yadav *et al.*, 2018). Amaravathi *et al.*, 2012 illustrated that dissolution profile of tablets of potato starch citrate-mefenamic acid HSD was found improved in comparison to tablets prepared using microcrystalline cellulose and lactose. Kadam *et al.*, 2016 synthesized stable and effective parenteral dosage form for acute pain

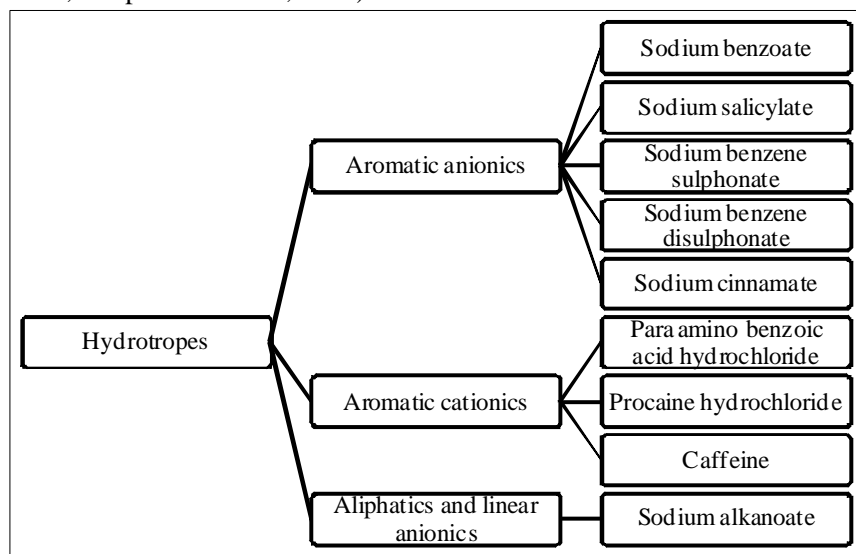


Fig. 2: Classification of hydrotropes.

are represented in fig. 3.

Method of preparation of HSD

Hydrotropes in different ratio are dissolved in distilled water followed by addition of drug and stirred at magnetic stirring until semisolid mass is obtained. The semisolid mass is triturated with mortar-pestle, spread on watch glasses and placed in oven maintaining at temperature of 60-65°C. After drying, it passes through sieve # 100 and kept in desiccators till complete drying (Fig. 4) (Kim *et al.*, 2010; Kapadiya *et al.*, 2011).

Application of HSD

Non-steroidal anti-inflammatory drugs (NSAIDs) Another researcher studied improved solubility of mefenamic acid by HSD production using 0.5 M sodium citrate. Dissolution studies had shown 62% increase in solubility of mefenamic acid in comparison to pure drug (Shelke, 2018). Other researchers found superior dissolution rate of flupirtine maleate through formation of HSD by solvent

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management using etodolac-HSD prepared using sodium acetate (10%), sodium citrate (5%) and sodium benzoate (25%). In another research HSD of aceclofenac were prepared using hydrotropic blend (20% urea and 10% sodium citrate) to enhance aqueous solubility and chemical stability of drug (Maheshwari and Indurkhya, 2010). In another research, HSD of flupirtine were synthesized using hydrotropic combination of sodium benzoate and a niacinamide to achieve superior dissolution rate and increased oral bioavailability (Yadav *et al.*, 2018). Sharma and his colleagues augmented the solubility of meloxicam through HSD technique using urea, nicotinamide

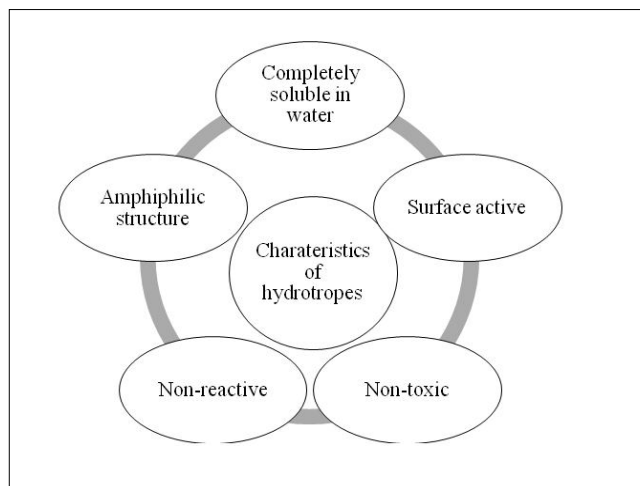


Fig. 3: Characteristics of hydrotropic solid dispersion.

and sodium citrate and further, manufactured mouth dissolving tablets of meloxicam HSD using super-disintegrating agents *i.e.* cross-carmellose sodium and cross-povidone and subliming agent *i.e.* camphor (Sharma *et al.*, 2015). Table 1, describes HSD of several drugs.

Antibiotic

Another group of researcher investigated solubility enhancement of Miconazole and Fluconazole through mixed hydrotropic solubilization using sodium benzoate, urea and niacinamide as hydrotropes (Kaushik and Jat, 2017a; Kaushik and Jat, 2017b). Aqueous solubility as well as dissolution profile of Norfloxacin was improved by formulating HSD using sodium benzoate, urea and a niacinamide. Through *in-vivo* study, approximately 6.90-fold increase in AUC and five times amplification in C_{max} was observed for norfloxacin-HSD in comparison to pure drug (Kamble *et al.*, 2017). The solubility of nevirapine was determined in aqueous solution of urea (10 % w/v), lactose (20% w/v), citric acid 320% w/v), and mannitol (40% w/v), and maximum solubility was found in citric acid: lactose (25:15). Furthermore, fast dissolving nevirapine solid dispersion was manufactured (Madan *et al.*, 2017). Saibabu and his co-workers found solubility enhancement of Efavirenz through mixed hydrotropy using 10% w/v aqueous solutions of sodium acetate, urea,

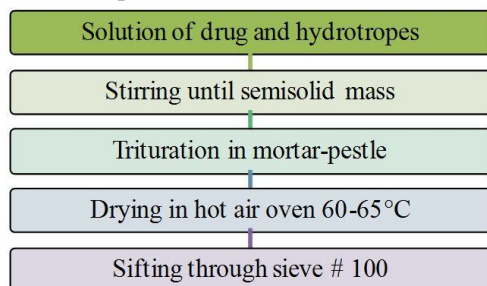


Fig. 4: Methodology for hydrotropic solid dispersion manufacturing.

sodium citrate, and sodium benzoate. Maximum solubility was achieved with 10% w/v aqueous solution of sodium benzoate (Saibabu *et al.*, 2015). Hydrotropic solubilization method was used for solubility enhancement of norfloxacin using one part of drug with 1-4 parts of sodium benzoate which increases 6.29, 7.09, 8.59 and 9.56-fold aqueous solubility of norfloxacin with 1:1, 1:2, 1:3 and 1:4 drug: polymer ratios, respectively (Pai *et al.*, 2014). Another research team manufactured HSD metronidazole using urea for enhancing the aqueous solubility of drug (Aseri *et al.*, 2013).

Antipsychotic/Anti-depressant/Antiepileptic

Novel fast dissolving oral dosage form of lurasidone hydrochloride using HSD technology were formulated and found highest solubility and bioavailability with 15:20:5 ratio of nicotinamide, sodium benzoate and sodium citrate (Madan *et al.*, 2015). In 2013, Shah *et al.*, enhanced the aqueous solubility of mixture of quetiapine fumarate, nortriptyline, propranolol and haloperidol using urea, niacin and niacinamide for improving their bioavailability (Shah *et al.*, 2013). Another research team formulated HSD of escitalopram oxalate using niacinamide and found 8-fold enhancement aqueous solubility with two-molar niacinamide (Choudhary *et al.*, 2012). Beig and his co-workers investigated solubility-permeability profile of carbamazepine using urea and nicotinamide. Both hydrotropes induces 30-fold increase in solubility while 17-and 9-fold decline in permeability with nicotinamide and urea, respectively (Beig *et al.*, 2016).

Rheumatoid arthritis

In 2012, Asija and his colleagues carried out comparative solubility enhancement study of suphasalazine using solid dispersion, hydrotropy and micellar solubilization techniques. They found superlative results with hydrotropic solubilization (40-folds increase with sodium benzoate) while least increase with micellar solubilization (Asija *et al.*, 2012). Aqueous solubility of diacerein was enhanced by synergistic combination of sodium citrate and sodium acetate as hydrotropic agents (Bhoir *et al.*, 2012).

Anti-diabetic

Madan and his research group increases the solubility of gliclazide using sodium salicylate, lactose, nicotinamide, urea, sodium acetate, sodium benzoate and trisodium citrate. They found maximum solubility with sodium salicylate and sodium benzoate in 25:15 ratios (Madan *et al.*, 2017). Through *in-vitro* as well as *in-vivo* studies, Li and his co-workers established increase in solubility and bioavailability of HSD of glimepiride fabricated using meglumine as hydrotrope (Li *et al.*, 2015).

Table 1: Description about HSD of various drugs.

Drug	Hydrotropes	Drug Category	Dosage Form	References
Mefanamic Acid	0.5 M Sodium citrate	NSAID	HSD	Shelke <i>et al.</i> , 2018
Flupirtine maleate	Niacinamide and sodium benzoate	NSAID	HSD	Yadav <i>et al.</i> , 2018
Mefenamic acid	Potato starch citrate	NSAID	Solid dispersion tablet	Amaravathi <i>et al.</i> , 2012
Etodolac	Sodium citrate, Sodium acetate, Sodium benzoate	NSAID	Injections	Kadam <i>et al.</i> , 2016
Aceclofenac	Urea, Sodium citrate	NSAID	HSD	Maheshwari and Indurkhya, 2010
Flupirtine	Sodium benzoate, Niacinamide	NSAID	HSD	Yadav <i>et al.</i> , 2018
Meloxicam	Urea, Nicotinamide, Sodium citrate	NSAID	Mouth dissolving tablets	Sharma <i>et al.</i> , 2015
Miconazole	Sodium Benzoate, Niacinamide, Urea	Antibiotic	Solid dispersion tablets	Kaushik and Jat, 2017a
Fluconazole	Sodium Benzoate, Niacinamide, Urea	Antibiotic	HSD	Kaushik and Jat, 2017b
Norfloxacin	Sodium Benzoate, Niacinamide, Urea	Antibiotic	HSD	Kamble <i>et al.</i> , 2017
Nevirapine	Urea, Lactose, Mannitol, Citric Acid	Antibiotic	Fast dissolving tablets	Madan <i>et al.</i> , 2017
Efavirenz	Sodium Benzoate, Sodium Citrate, Sodium Acetate, Urea	Antibiotic	Immediate release tablets	Saibabu <i>et al.</i> , 2015
Norfloxacin	Sodium benzoate	Antibiotic	HSD	Pai <i>et al.</i> , 2014
Metronidazole	Urea	Antibiotic / Anti-protozoal	HSD	Aseri <i>et al.</i> , 2013
Lurasidone	Sodium Benzoate, Nicotinamide, Urea	Anti-psychotic	Fast dissolving tablets	Madan <i>et al.</i> , 2015
Quetiapine Fumarate, Nortriptyline, Propanolol	Urea, Niacin, Niacinamide	Anti-psychotic	HSD	Shah <i>et al.</i> , 2013
Escitalopram oxalate	Niacinamide	Anti-depressant	HSD tablets	Choudhary <i>et al.</i> , 2012
Carbamazepine	Urea, Nicotinamide	Anti-epileptic drug	HSD	Beig <i>et al.</i> , 2016
Sulphasalazine	Sodium benzoate, Sodium acetate, Lignocaine hydrochloride	Rheumatoid arthritis	Solid dispersion tablets	Asija <i>et al.</i> , 2012
Diacerein	Sodium citrate, Sodium acetate, urea, Sodium salicylate, Sodium benzoate	Rheumatoid arthritis	HSD Capsules	Bhoir <i>et al.</i> , 2012
Gliclazide	Sodium salicylate, Lactose, Urea, Nicotinamide, Sodium acetate Sodium benzoate, Tri-sodium citrate	Anti-hyperglycemic agent	Fast dissolving tablets	Madan <i>et al.</i> , 2017
Glimepiride	Meglumine	Anti-hyperglycemic agent	HSD	Li <i>et al.</i> , 2015
Furosemide	Urea, Sodium acetate, Sodium benzoate, Sodium citrate	Diuretics	Fast dissolving tablets	Maheshwari and Jagwani, 2011
Azilsartan medoxomil	Sodium acetate, Sodium citrate, Urea, Sodium benzoate	Anti-hypertensive agent	HSD Tablets	Surwade <i>et al.</i> , 2015

Diuretics

Another researchers formulated HSD of furosemide using urea (10% w/v), sodium acetate (20% w/v), sodium benzoate (30% w/v), and sodium citrate (40% w/v) (Maheshwari and Jagwani, 2011).

Anti-hypertensive

Azilsartan medoxomil solubility was enhanced using mixed hydrotropy using sodium acetate, sodium citrate, urea and sodium benzoate and highest solubility was achieved with 5:20:15 ratio of urea, sodium acetate and sodium benzoate (Surwade *et al.*, 2015).

Conclusion

Solubility is the drug's key important fundamental attribute for the production of different dosage forms along with oral bioavailability in its formulations. In the method of HSD solubilization, adding an additional quantity of second solvent leads in quite a great increase in the aqueous solubility of another solution. The HSD therefore evolves as a valuable method for improving the solubility and dissolution rate pattern of a certain chemical entity which belongs to the BCS class II.

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Conflict of interests

The authors report no conflicts of interest in this work.

References

- Allawadi, D., N. Singh, S. Singh and S. Arora (2013). Solid dispersions: a review on drug delivery system and solubility enhancement. *International Journal of Pharmaceutical Sciences and Research.*, **4(6)**: 2094-2105.
- Amaravathi, V., S. Firoz, D. Kishore, Y.C. Mouli and M. Venkataramudu (2012). Formulation and evaluation of mefenamic acid tablets by using modified starch. *Asian J. of Pharmaceutical Science & Technology.*, **2(2)**: 46-53.
- Argade, P.S., D.D. Magar and R.B. Saudagar (2013). Solid Dispersion: Solubility Enhancement Technique for poorly water soluble Drugs. *Journal of Advanced Pharmacy Education & Research.*, **3(4)**: 427-439.
- Aseri, A., D. Duggal, J. Katewa and A. Nayak (2013). Enhancement of solubility of poorly water soluble drug-metronidazole by hydrotropy. *Asian J. of Pharmaceutical Research and Development.*, **1(2)**: 98-102.
- Asija, R., N. Kalariya, S. Asija and M.T. Arvind (2012). Enhanced solubility study of sulphasalazine using different solubilization techniques. *International Research Journal of Pharmacy.*, **3(8)**: 187-190.
- Beig, A., D. Lindley, J.M. Miller, R. Agbaria and A. Dahan (2016). Hydrotropic solubilization of lipophilic drugs for oral delivery: The effects of urea and nicotinamide on carbamazepine solubility-permeability interplay. *Frontiers in Pharmacology.*, **7**: 379.
- Bhoir, S., S. Dhole, N. Kulkarni, P. Sangole, S. Thorat and D. Bhoite (2012). Novel and validated spectrophotometric estimation of diacerein in bulk and capsule formulation using mixed hydrotropic solubilisation approach. *International Journal of Pharmacy and Pharmaceutical Sciences.*, **4(4)**: 501-504.
- Choudhary, N.H., M.S. Kumbhar, D.A. Dighe, P.S. Mujgond and M.C. Singh (2012). Solubility enhancement of escitalopram oxalate using hydrotrope. *International J. of Pharmacy and Pharmaceutical Sciences.*, **5(1)**: 121-125.
- Cid, A.G., A. Simonazzi, S.D. Palma and J.M. Bermúdez (2019). Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. *Therapeutic Delivery.*, **10(6)**.
- Dhapte, V. and P. Mehta (2015). Advances in hydrotropic solutions: An updated review. *St. Petersburg Polytechnical University Journal: Physics and Mathematics.*, **1(4)**: 424-435.
- Hu, J., K.P. Johnston and R.O. Williams III (2004). Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. *International Journal of Pharmaceutics.*, **271**: 145-154.
- Jayakumar, C. and C. Raja (2014). A review on solubility enhancement using hydrotropic phenomena. *International J. of Pharmacy and Pharmaceutical Sciences.*, **6(6)**: 1-7.
- Kadam, P.S., V.V. Pande, S.K. Vibhute and M.A. Giri (2016). Exploration of mixed hydrotropy strategy in formulation and development of etodolac injection. *Journal of Nanomedicine Research.*, **3(4)**: 1-7.
- Kamble, R., S. Sharma and P. Mehta (2017). Norfloxacin mixed solvency based solid dispersions: An *in-vitro* and *in-vivo* investigation. *Journal of Taibah University for Science.*, **11**: 512-522.
- Kapadiya, N., I. Singh, K. Mehta, G. Karwani and J. Sen (2011). Hydrotropy: A promising tool for solubility enhancement: A Review. *International Journal of Drug Development & Research.*, **3(2)**: 26-33.
- Kapse, V.N., V.M. Dharashive, S.R. Devne and G. Ajit (2016). Effect of hydrotropes on solubility of drugs. *International Journal of Pharmaceutical and Chemical Sciences.*, **5(1)**: 48-52.
- Kaushik, A. and R.K. Jat (2017a). Solubility enhancement of miconazole by formulation of hydrotropic solid dispersions, *Journal of Drug Delivery and Therapeutics.*, **7(3)**: 117-126.
- Kaushik, A. and R.K. Jat (2017b). Solubility enhancement of fluconazole by formulation of hydrotropic solid dispersions. *Journal of Biomedical and Pharmaceutical Research.*, **6(3)**: 129-140.

- Kim, Y., S.W. Kim, M. Papp, K. Park and K. Pinal (2010). Hydrotropic solubilization of poorly water-soluble drugs. *Journal of Pharmaceutical Sciences.*, **99**: 3953-3965.
- Kulkarni, S. and A. Goswami (2014). Research on application of hydrotrophy: a review. *International Journal of Science, Engineering and Technology Research.*, **3(10)**: 2617-2619.
- Li, H., L. Ma, X. Li, X. Cui, W. Yang, S. Shen and M. Chen (2015). A simple and effective method to improve bioavailability of glimepiride by utilizing hydrotrophy technique. *European Journal of Pharmaceutical Sciences*, **77**: 154-160.
- Lipinski, C. (2002). Poor aqueous solubility-an industry wide problem in drug delivery. *American Pharmaceutical Review.*, **5**: 82-85.
- Madan, J.R., V.J. Kamate, R. Awasthi and K. Dua (2017). Formulation, characterization and *in-vitro* evaluation of fast dissolving tablets containing gliclazide hydrotropic solid dispersions. *Recent Patents on Drug Delivery & Formulation.*, **11(2)**: 147-154.
- Madan, J.R., V.J. Kamate, K. Dua and R. Awasthi (2017). Improving the solubility of nevirapine using a hydrotrophy and mixed hydrotrophy based solid dispersion approach. *Polymers in Medicine.*, **47(2)**: 83-90.
- Madan, J.R., K.T. Pawar and K. Dua (2015). Solubility enhancement studies of lurasidone hydrochloride. *International Journal of Pharmaceutical Investigation.*, **5(2)**: 114-120.
- Maheshwari, R.K. and A. Indurkha (2010). Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of hydrotropic solid dispersion of aceclofenac. *Asian Journal of Pharmaceutics.*, **4(3)**: 235-238.
- Maheshwari, R.K. and Y. Jagwani (2011). Mixed hydrotrophy: novel science of solubility enhancement. *Indian journal of pharmaceutical sciences.*, **73(2)**: 179-183.
- Pai, G.K., S. Divya, S.M. Reddy, L. Kumar and V.T. Krishna (2014). Solubility enhancement of norfloxacin by hydrotrophy technique. *International Journal of Pharmacy and Pharmaceutical Sciences.*, **6(8)**: 395-397.
- Reddy, R.M., P.V.S. Srikanth, B. Bonthagarala and P.K. Desu (2013). A review on hydrotrophy. *Journal of Pharma Research.*, **2(4)**: 5-6.
- Saffoon, N., R. Uddin, N.H. Huda and B.S. Sutradhar (2011). Enhancement of Oral Bioavailability and Solid Dispersion: A Review. *Journal of Applied Pharmaceutical Science.*, **01 (07)**: 13-20.
- Saibabu, S., J. Pasam, K. Ratnaraju, M. Prathap and A. Kumar (2016). Formulation and evaluation of efavirenz immediate release tablets by using mixed hydrotropic solubilization technique. *World Journal of Pharmacy and Pharmaceutical Sciences.*, **5(2)**: 1533-1556.
- Sajid, A. and V. Choudhary (2012). Solubility enhancement methods with importance of hydrotrophy. *Journal of Drug Delivery & Therapeutics.*, **2(6)**: 96-101.
- Shah, M., Z. Farooqui, J. Shah, N. Shah and S. Sheorey (2013). Solid dispersion- a way to enhance solubility of quetiapine fumarate. *American Journal of PharmTech Research.*, **6**: 732-748.
- Sharma, A. and C.P. Jain (2011). Solid dispersion: A promising technique to enhance solubility of poorly water. *International Journal of Drug Delivery.*, **3(2)**: 149-170.
- Sharma, N. and S. Singh (2019). Central composite designed ezetimibe solid dispersion for dissolution enhancement: synthesis and *in vitro* evaluation. *Therapeutic Delivery.*, **10(10)**: 643-658.
- Sharma, S., V. Chauhan, Neha and M.K. Khan (2015). Formulation optimization of mouth dissolving tablets of Meloxicam using mixed hydrotropic solubilization technique. *Journal of Scientific and Innovative Research.*, **4(2)**: 76-82.
- Shelke, S.P. (2018). Enhancement of solubility of mefenamic acid by hydrotrophy based solid dispersion. *International Journal of Scientific Research in Science and Technology.*, **4(8)**: 147-149.
- Singh, N., D. Allawadi, S. Singh and S. Arora (2013). Techniques for Bioavailability Enhancement of BCS Class II Drugs: A Review. *International Journal of Pharmaceutical and Chemical Sciences.*, **2(2)**: 1092-1101.
- Singh, N. and M. Sarangi (2017). Solid Dispersion-a novel approach for enhancement of bioavailability of poorly soluble drugs in oral drug delivery system. *Global Journal of Pharmaceutical Sciences.*, **3(2)**: 1-8.
- Singh, S., Y.P. Singla and S. Arora (2015). Box-Behnken Design, Statistical, diagnostic and response surface analysis of nefopam hydrochloride nanospheres using 3⁵ box-behnken design. *International Journal of Pharmacy and Pharmaceutical Sciences.*, **7(10)**: 89-101.
- Sultana, S. and A.H.M. Saifuddin (2016). Review article: Solid dispersion currently practiced in pharmaceutical field. *International Journal of Advancements in Research & Technology.*, **5(3)**: 170-175.
- Surwade, K.S. and R.B. Saudagar (2015). Solubility enhancement of azilsartan medoxomil using mixed hydrotrophy. *World Journal of Pharmacy and Pharmaceutical Sciences.*, **4(7)**: 1167-1179.
- Yadav, B. and Y.S. Tanwar (2015). Applications of solid dispersions. *Journal of Chemical and Pharmaceutical Research*, **7(2)**: 965-997
- Yadav, N.K., T. Shukla, N. Upmanyu, S.P. Pandey and M.A. Khan (2018). Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate. *Journal of Drug Delivery and Therapeutics.*, **8(5)**: 481-488.
- Yadav, N.K., T. Shukla, N. Upmanyu, S.P. Pandey and M.A. Khan (2018). Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate. *Journal of Drug Delivery and Therapeutics.*, **8(5)**: 481-488.