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 the 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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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.

**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 evaporation technique using hydrotrropic 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 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 hydrotrropic blend (20% urea and 10% sodium citrate) to enhance aqueous solubility and chemical stability of drug (Maheshwari and Indurkhy, 2010). In another research, HSD of flupirtine were synthesized using hydrotrropic 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.

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**Fig. 1:** Diverse methods for improving solubility.

**Fig. 2:** Classification of hydrotropes.
and sodium citrate and further, manufactured mouth dissolving tablets of meloxicam HSD using superdisintegrating 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). Another research team manufactured HSD metronidazole using urea for enhancing the aqueous solubility of drug (Aseri et al., 2013). Saibabu and his co-workers found solubility enhancement of Efavirenz through mixed hydrotropy using 10% w/v aqueous solutions of sodium acetate, urea, 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 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).
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</table>
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


