Review Article

Utilization of Mixed-Solvency Approaches for Formulations and Analysis

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Abstract

Solubility of drug is considered to be one of the crucial parameter to achieve its desired concentration in systemic circulation and better pharmacological response. As most of the drugs available are poorly aqueous soluble, solubility enhancement has become major challenge to the formulators in the product development of many orally administered drugs. Therapeutic response of drug as well bioavailability can be limited by poor aqueous solubility of drugs.

Keywords: Mixed-Solvency, Formulations, solubility Enhancement

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INTRODUCTION

Solubility is the major concern related to the drug's efficacy in the pharmaceutical industry. Most of the drugs have poor aqueous solubility resulting into very low bioavailability of the drug in respective dosage form, more particularly in the oral and parenteral forms. Almost 90% of the drug products are orally administered and it is estimated that more than 40% of the Active Pharmaceutical Ingredients (API 's) & New Chemical Entities (NCEs) are poorly aqueous soluble compounds. Improvement in the solubility in the aqueous medium does provides better drug absorption, sufficient and reproducible bioavailability, and enhanced pharmacokinetic profile of orally administered drug substance[1-3].

Solubility is an important attribute to achieve optimum drug concentration in systemic circulation and have desired pharmacological responses. There are almost more than 40% new molecules drugs which are lipophillic candidates and these fails to reach the market due to poor availability although these may exhibit better pharmacodynamic activities [4-5].

What is 'Solubility?'

Solubility is defined as, 'the concentration of the solute in a saturated solution at a certain temperature'. This is a quantitative definition [2-3].

'Solubility may be defined as the spontaneous interaction of two more substances to form a homogeneous molecular dispersion.'

The pharmacopeia description of the solubility is in terms of number of milliliter of solvent required to dissolve 1 gm of solute. The solubility of a substance is described in term of –

- Very soluble - 1 part of solute in less than 1 part of solvent
- Freely soluble - 1 part of solute in 1- 10 part of solvent
- Soluble - 1 part of solute in 10- 30 part of solvent
- Sparingly soluble - 1 part of solute in 30- 100 part of solvent
- Slightly soluble - 1 part of solute in 100- 1000 part of solvent
- Very Slightly soluble - 1 part of solute in 1000- 10000 part of solvent
- Insoluble &Practically insoluble - 1 part of solute in > 10000 part of solvent

Solubility – Requirement & Its Mechanism

In case of orally administered drug products the therapeutic efficacy is directly related to the drug substance solubility and thereby better and improved bioavailability. Therefore, it makes solubility a most critical attribute to achieve the desired concentration of the drug in systemic circulation which ultimately determines the pharmacological response. An aqueous soluble drug does show better absorption and improved bioavailability in comparison to the lipophillic drug molecule. The lipophillic drug will require higher dose to attain requisite optimum pharmacological actions.

About 40% of new chemical entities coming from discovery are all insoluble in aqueous medium and poor bioavailability. Poor bioavailability limits to the performance of a drug, requiring administration a much higher dose than strictly required from a pharmacologic point of view. This can induce critical side effects or lead to problems related to the economics of overall treatment. Poor bioavailability may also allow considering the formulator to select injection route instead of more acceptable oral route. For good oral bioavailability drug must be soluble in gastro-intestinal fluids i.e. aqueous soluble and also possess permeability properties for good membrane diffusion in order to reach the bloodstream[6].

Improvement in Solubility

There are various techniques to improve the solubility of the poorly water soluble drugs. However, first of all it requires understanding the process of solubilization. The process of solubilization predominantly involves

the breaking of inter- ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion Hydrotropy is an emerging powerful drug solubilization strategy, which has been shown to significantly improve the solubility of many drugs (Booth et al., 2012). Hydrotropy refers to the process by which a large amount of solute (the hydrotrope) enhances the solubility of another compound (the drug), by a mechanism that is not yet fully understood (Shimizu et al., 2013). Hydrotropy is a unique solubilization techniques in which certain chemical compounds termed as ' Hydrotropes' can be used to affect the several fold increase in the aqueous solubility of the sparingly soluble solute under normal conditions. This is achieved mainly due to the formation of organized assemblies in hydrotrope molecules at critical concentrations.

Hydrotropes generally are water soluble and surface active compounds which can significantly enhance the solubility of organic solutes such as esters, acids, alcohols, aldehydes, ketones, hydrocarbons and the fats.

Hydrotropic agents are typically characterized by an amphiphilic molecular structure yet distinguished from surfactants because their hydrophobicity is not sufficient to produce well organized self-associated aggregates such as micelles. Hydrotropic drug solubilization is also mechanistically different from cosolvency. For instance, while cosolvents enhance drug solubility by minimizing the polarity gap between the solvent and the drug, it was reported that hydrotropes preferentially concentrate nearby the drug molecules. A number of mechanisms or their combinations are responsible for hydrotropic drug solubilization, including the depression of water activity and drug-hydrotrope interactions. It can be said that hydrotropy is a distinctive standalone drug solubilization technique, which may dramatically increase the apparent solubility of drugs.

Hydrotropes are frequently anionic aromatic (e.g., salicylate, benzoate) or non-aromatic compounds (e.g., citrate), but can also be neutral (e.g., urea). Urea is widely used as a hydrotropic agent, as it was shown to enhance the aqueous solubility of many lipophilic drugs including diclofenac (250-fold), hydrochlorothiazide (74-fold), and many others. Urea constitutes a near-ideal mixture with water; in contrast to several other hydrotropes, urea exhibits weak self-association in water, and since hydrotrope self-association reduces the solubilization capacity, urea exhibits very minor loss of solubilization efficiency. Nicotinamide, the product of nicotinic acid (niacin) *in vivo* conversion, is another effective and commonly used hydrotrope, which has been demonstrated to solubilize a wide variety of lipophilic drugs[7-8].

Selection of Hydrotropes for Drugs having poor solubility

A suitable hydrotropes can be selected by determining the approximate solubility determination method. The method involves –

Take 25 ml of distilled water / hydrotropic solution in 50 ml glass bottle and note the gross weight (including the cap weight).Transfer few mg of the drug to the bottle and shake vigorously manually. Once the drug is dissolved, transfer more drug qty. to the bottle and shake vigorously again. Same operation is repeated until some excess drug remains un-dissolved after vigorous shaking for 10 minutes. Note the gross weight again. Calculate the difference in the weight and determine the approximate solubility. A ratio, solubility enhancement ratio, is calculated by observing the same as solubility in hydrotropic solution / solubility in distilled water.

What are the Advantages of Solubility enhancement by using hydrotropic solubilization method?

Following are the major advantages -

1. Hydrotropy is preferred method (superior) than the other techniques e.g. Miscibility , micellar solubilization, co solvency and sating in , as the solvent character is independent of p H , highly selectivity and does not require emulsification.
2. It is simple and requires only mixing of the drug with hydrotrope in water
3. No need of Chemical modification of hydrophobic drugs, use of organic solvents or preparation of emulsion system.

Mixed Hydrotropy

It is a solubilization technique, which involves the phenomenon of increasing the solubility of drug substance exhibiting poor aqueous solubility by means of using blends of hydrotropic agents. These blends of hydrotropic agents are selected in such a way that these give improved or enhanced solubility by virtue of synergistic effect on solubility of the poorly soluble drug. It is also termed as mixed solvency.

For instance, if it requires 3 different hydrotropic agents to solubilize a particular drug, the concentration of each of the hydrotropic agent will reduce to 1/3rd level of qty. of agent if only a single hydrotrope is used. This will allow reducing the toxic effects of the hydrotrope used[7-8].

Advantages of Mixed Solvency approach

1. It reduces the total concentration of single hydrotrope.
2. Synergistic enhancement of solubilization leads to further decrease in the qty. of the overall hydrotropes used.
3. This is new, simple, efficient, cost effective & safe approach.
4. Its environment friendly as well as good for method of analysis used.
5. It eliminates the use of organic solvents, thus avoid the problems of organic residuals impurities / toxicities.
6. Pharmaceutical Application of Mixed Solvent in Formulation and Their analysis

Quantitative Estimation of Poorly water soluble Drugs

As it eliminates the use of Organic solvents (costly, toxic & polluting), Titrimetric & Spectrophotometric

method can be used effectively.

Hydrotropic Solid Dispersion for improving the dissolution rate

Similar to solid dispersion techniques, a hydrotropes based solid dispersion can be prepared which does not has toxic, impurity inheriting and polluting organic solvents. Since, mixed hydrotopes approach shall use water as the solvent, it produces a solid mass after water evaporation, which is a novel technique to produce drug solid dispersion know as 'Hydrotropic Solid Dispersion'

Liquid Oral Formulations – Specialized techniques are required to dissolve the ingredients is a liquid oral formulation. Hydrotropic solubilization has been explored to develop liquid oral solutions of the poorly water soluble drugs, to give better bioavailability (in comparison to suspensions)

Dry Syrup Formulations – The API's having insufficient stability in aqueous solution / suspensions, dry powder form is obvious option. In these formulations hydrotropic agents are used to produce solution is water after reconstitution of poorly water soluble drugs.

Injection Formulation (Injectables) – The solubility of the API is enhanced by using mixed hydrotropy. This mixed hydrotropy approach allows reduced toxicity in the final preparation e.g. use of 20% urea and 10% sodium citrate solution enhanced the aqueous solubility of aceclofenac by 250 fold as compared to solubility in distilled water. When these hydrotropes are used as alone in 30% urea and 30% sodium citrate solution the solubility is 25 folds and 5 folds respectively. Thus, mixed hydrotropy allowed using lesser conc. of Hydrotrope and much enhanced water solubility of the API.[8]

Similarly use of Hydrotropic Polymer micelle system for drug loading and suitable mixed hydrotropic approach also utilized for aqueous suspension preparations.

CONCLUSION

Overall, as a conclusion of the article it is well understood that Solubility of the API is most important attribute which actually control the performance of the drug product. Therefore, it is considered to be one of the critical aspects for various formulation approaches.Dissolution is the rate determining step for oral absorption of the poorly water soluble drugs. The hydrotropic solubilization techniques described herein can be used for enhancement of aqueous solubility of the drug substance.

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