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Research Article

ENHANCED SOLUBILITY STUDY OF SULPHASALAZINE USING DIFFERENT SOLUBILIZATION TECHNIQUES

Asija Rajesh*, Kalariya Nikunj, Asija Sangeeta

Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur, Rajasthan, India

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*Email: nikunjkalaria@gmail.com

ABSTRACT

The aim of present work was to perform a comparative study on effect of solubility of suphasalazine by using different solubilization techniques such as solid dispersion, hydrotropy and micellar solubilization. Hydrotropic studies were carried out using different hydrotropic agents (sodium acetate, sodium benzoate and lignocaine hydrocholride) and Micellar solubilization was carried out using different surfactant solutions (sodium lauryl sulphate, tween 80 and tween 20). Solid dispersion of suphasalazine was prepared by fusion method. PEG (Polyethylene glycol) 4000, mannitol and urea were used as carriers. The solubility enhancement of sulphasalazine by different solubilization technique was observed in decreasing order as hydrotropic solubilization > solid dispersion > micellar solubilization. It was observed that the solubility increased with the increase in the concentration of hydrotropic agents and amongst the various hydrotropic agents used, the solubility of sulphasalazine was enhanced greatest to 40 folds with sodium benzoate. This increase may be attributed due to aggregation of the hydrotropic molecules and inclusion of one of these aggregates at high concentration probably by reacting to form an associated product as a result of hydrogen bonding.

Key words: Solubility; sulphasalazine; Solid dispersion; Hydrotropy; Micellar solubilization.

INTRODUCTION

In fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It is commonly recognized in the pharmaceutical industry that on an average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor solubility of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics[1]. In the pharmaceutical analysis and formulation development fields it is most often required to increase the aqueous solubility of poorly water-soluble drugs. Most of the newly developed drug molecules are lipophillic in nature and poor solubility is one of the most difficult problems of these drugs. It is well known that drug efficacy can be severely limited by poor aqueous solubility. It is also known that the side effects of some drugs are the result of their poor solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects of drugs.

At the preformulation stage in the product development, it is important to realize the limit of absorbability of a drug i.e. the maximal or optimal rate and extent of absorption that can be achieved with the drug in its most readily available form. This is essential since a slow absorption results in an erratic and variable profile of drug level. Administration of a drug in any dosage form, except solution involves a dissolution step. Thus, it is required that the drug has to be present in the dissolved state at the site of absorption and then only it can be absorbed. In general, in order for a drug to exert its biologic effect, it must be soluble in and transported by the body fluids, transverse the required biological membrane barriers, escape widespread distribution to unwanted areas, endure metabolic attack, penetrate in adequate concentration to the sites of action and interact in a specific fashion, causing an alteration of cellular function[2].

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Currently, only 8% of new drug candidates have high solubility and permeability. The aqueous solubility of drugs is often a limiting factor in developing the most desirable dosage forms. Many drugs and drug candidates are poorly water-soluble which limit their clinical applications. Increasing number of newly developed drugs are poorly water-soluble and such poor water solubility causes significant problems in producing formulations of a sufficiently high bioavailability with reproducible effects[3].

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols[4].

In 1971, Chiou and Riegelman defined solid dispersion as “A dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent evaporation or melt-solvent method”. Solid dispersion when exposed to aqueous media, the carrier is dissolved; the drug is released as very fine colloidal particles[5] and widely used to increase intrinsic solubility or dissolution and further the bioavailability of drug[6,7] .Various carriers can be used for solid dispersion preparation which includes polyethylene glycol, poly vinyl pyrolidone, urea, mannitol, poloxamers etc. Solid dispersion can be prepared by conventional methods such as solvent evaporation method, fusion method and melt solvent method and novel methods used for preparation includes super critical fluid technology, electrospining, spray drying, lyophilization and melt extrusion method[8].

Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products. A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available. Despite the promising aspects of dissolution enhancement and simplicity of concept, the solid dispersion technique has

failed to gain popularity due to manufacturing, stability and scale-up issues[4].

Hydrotropic compounds are compounds that at high concentration solubilize poorly soluble molecule in water. The self- aggregation of hydrotropic agents is different from the surfactant self assemblies in that, hydrotropes form planar or open layer self assemblies instead of compact spheroid assemblies. Hydrotropic agents are characterized by a short, bulky compact moiety while surfactants have long hydrocarbon chain. In general, hydrotropic agents have a shorter hydrophobic segment, leading to high water solubility than surfactants. The hydrotropy is suggested to be superior to other solubilization methods such as micellar solubilization, cosolvency, miscibility and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification[5].

MATERIAL

Sulphasalazine was kindly received as a gift sample from Ronal Life Care Pvt Ltd, Patan, India. Poly ethylene glycol 4000 (PEG 4000), urea, mannitol, lignocaine hydrochloride , sodium acetate, sodium benzoate, sodium salicylate, sodium lauryl sulphate, tween 80 and tween 20 were purchased from CDH Laboratories, New Delhi. All other reagents used were of analytical grade.

METHODS

Calibration curve of sulphasalazine in 0.1N sodium hydroxide

10 mg of sulphasalazine was weighed accurately and transferred to 100 ml volumetric flask. The drug was dissolved with the help of 10 ml 0.1N sodium hydroxide solution the volume was made up to 100 ml with the distilled water so as to obtain stock solutions of 100 µg/ml. Appropriate dilutions from the stock solutions were made with the de-mineralized water to give solution containing 10, 20, 30, 40, 50, 60, and 70µg/ml. The absorbance of the resulting drug solutions were read on UV spectrophotometer (Shimadzu® 1700) at 359 nm against the respective blank.

Preparation of Solid dispersion

Sulphasalazine and different carriers PEG 4000, urea and mannitol were weighed accurately in various ratios (1:2, 1:4, 1:6, and 1:8) and dissolved at 40° C with the help of waterbath, add slowly drug slowly with stirring. The resulted solid dispersion were kept in desiccators for drying and finally passed through sieve no.60 and stored in well closed container for further use[9].

Solubility study of solid dispersion

Solubility studies were conducted by adding excess of solid dispersion to 25 ml of distilled water and mixture was shaken for 24 hrs in mechanical shaker. After achieving of equilibrium samples were withdrawn and filtered through Whatmann filter paper no. 41 and finally diluted suitably and the concentration of suphasalazine was measured in UV spectrophotometer at 359nm. The experiment was repeated in triplicate[10].

Hydrotropic solubilization

The solubility study of sulphasalazine with different hydrotropic agents (sodium acetate, sodium benzoate and lignocaine hydrochloride) was performed by adding excess of sulphasalazine to a series of hydrotropic solution (5%, 10%, and 20%) in 50 ml of screw capped glass vial .The vials were shaken for 12 hrs on mechanical shaker . After 24 hrs when equilibrium was reached, the solutions were centrifuged for 10 min and supernatant were filtered through Whatmann filter paper no.1 and suitably diluted. The concentration of sulphasalazine in supernatant was analyzed spectrophotometrically at 359 nm[11].

Micellar solubilization

Different concentration (0.2. 0.4, 0.6, 0.8, 1.0 % w/v) of surfactants (Sodium lauryl sulphate, tween 20 and tween 80) were prepared. An excess of suphasalazine was added to 10 ml each of the surfactant solution taken in 25 ml of stoppered flasks. The flasks were shaken for 24 h. At equilibrium samples were withdrawn and properly diluted and filtered through filter of pore size of 0.22 mm and finally analyzed for concentration of suphasalazine spectrophotometrically at 359 nm[12].

RESULTS AND DISCUSSIONS

Different methods like solid dispersion, hydrotropy, micellar solubilization, applied for enhancement of solubility of sulphasalazine showed an improvement in solubility behavior of sulphasalazine. The order of enhancement of solubility of sulphasalazine with various approaches was found to decrease in order of hydrotropic solubilization > micellar solubilization > solid dispersion technique. From the solubility profile of sulphasalazine with respect to the different techniques, it can be concluded that best solubility results were obtained from hydrotropic solubilization method. The effect of various hydrotropes such as sodium acetate, sodium benzoate and lignocaine hydrochloride on the solubility of sulphasalazine was investigated. Figure 2 shows the solubility profile of sulphasalazine with various hydrotropic agents in different concentration. Solubility of sulphasalazine was increased with increase in concentration of hydrotropes. From the solubility profile it was observed that solubility of sulphasalazine decreases in the following order as: sodium benzoate > lignocaine hydrochloride > sodium acetate. Sodium benoate (20 %) increases the solubility of sulphasalazine by many folds. The hydrotropic solubilization of sulphasalazine at lower hydrotrope concentration may be attributed to weak ionic interactions involving a complexation while that at higher hydrotrope concentration may be due to molecular aggregation and inclusion of one in these aggregates at high concentration.

In case of solid dispersion formulation solubility in descending order can be observed as Urea > Mannitol > PEG 4000. Increased solubility in case of solid dispersion formulation may be attributed to increased wettability, prevention of the aggregation of drug hydrophilic nature of carrier and reduction in drug crystallinity. The mechanism by which the solubility and the dissolution rate of the drug was increased includes firstly, the particle size of a drug is reduced to sub micron size or to molecular size in the case where solid solution is obtained. Secondly, the drug is changed to amorphous form, the high energetic state that is highly soluble and finally the dissolved carrier improves the wettability of drug particle[13]. It was observed that there was increase in solubility of sulphasalazine with increased concentration of carrier, greater extend of solubility was observed with urea. The increase in solubility of sulphasalazine using solid dispersion technique urea, was found with urea.

The study also evaluated and compared solubility enhancement of sulphasalazine using three different surfactants i.e. sodium lauryl sulphate, tween 80 and tween 20. Tween 80 was found to be the most efficient surface active agent, improving solubility. Thus from this comparative solubility analysis of sulphasalazine using different solubilization techniques can further be successfully

applied for development and formulation of liquid or semisolid dosage forms of sulphasalazine.

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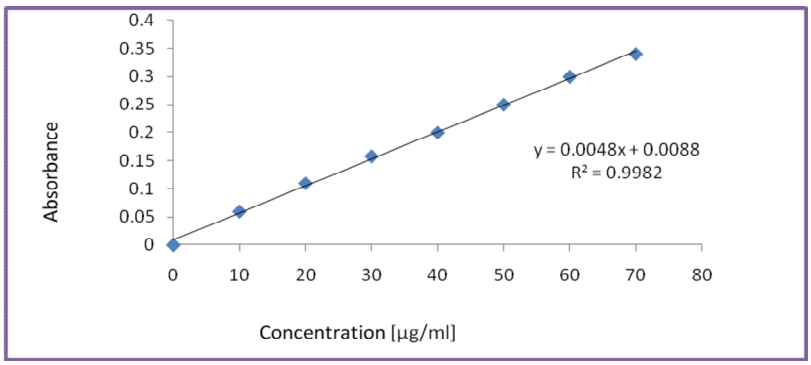

Figure 1: Calibration curve of sulphasalazine in 0.1N sodium hydroxide

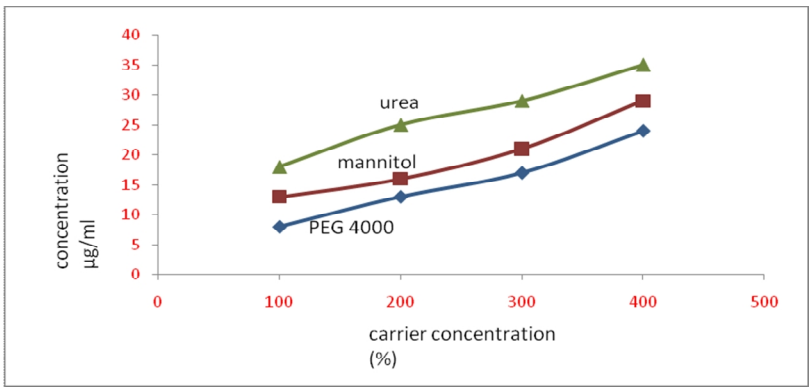

Figure 2: solubility profile of sulphasalazine solid dispersion

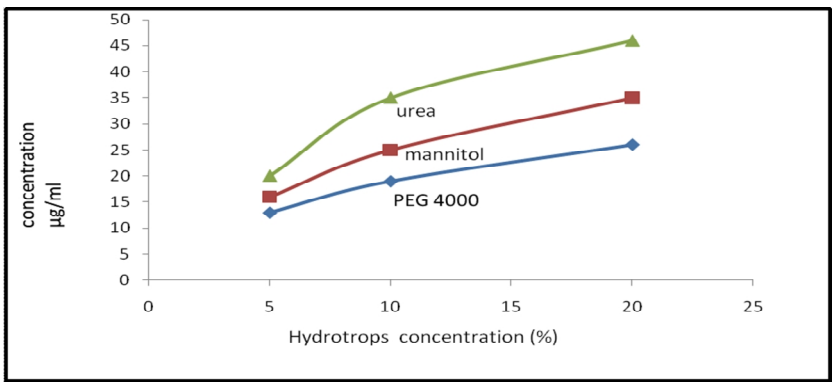

Figure 3: solubility profile of sulphasalazine with hydrotropic agents

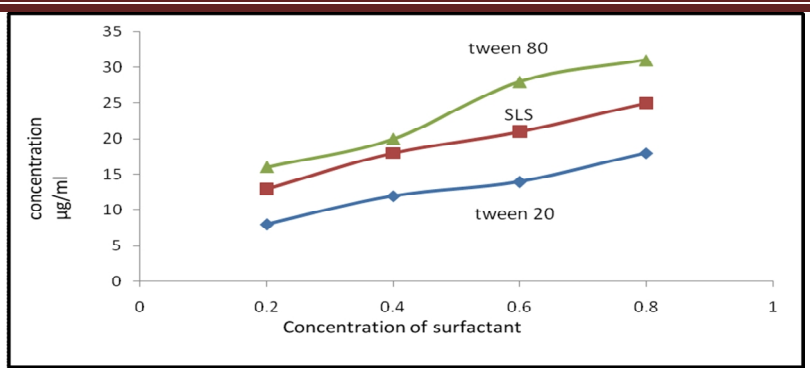

Figure 4: solubility profile of sulphasalazine with surfactants

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