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A comparative study of solubility enhancement of enalapril using formulation of solid dispersion and using hydrotropic solubilization technique

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ABSTRACT

In this work, an attempt has been made to enhance dissolution and solubility of poorly water soluble drug Enalapril by formulation of solid dispersion using solvent evaporation method and by hydrotropic solubilization method for attainment of effective absorption and improved bioavailability. Excipients used for solvent evaporation method, are mannitol, methanol and dichloromethane while for hydrotropic solubilization method, are urea and tripotassium citrate monohydrate. Solubility of pure drug was found to be 129 µg/ml. This experiment concluded that solubility enhancement through formulation of solid dispersion is better than hydrotropic solubilization method.

Keywords: Solid dispersion, hydrotropic solubilization technique, Enalapril, solubility enhancement.

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INTRODUCTION

The solubility is defined as a maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature [1]. In the other words, the solubility can also define as the ability of one substance to form a solution with another substance. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water [2]. Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on Solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble [3]. Enalapril belongs to class ACE inhibitor and it competitively inhibits angiotensin I–converting enzyme, preventing conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that also stimulates release of aldosterone. Enalapril blocks the conversion of angiotensin I to angiotensin II, decreasing blood pressure, decreasing aldosterone secretion, slightly increasing serum potassium levels, and causing sodium and fluid loss; increased prostaglandin synthesis may also be involved in the antihypertensive action [4]. Results in decreased blood pressure, reduced sodium absorption and potassium retention but having low soluble property. More than 70 companies have developed advanced drug delivery technologies for poorly water-soluble drugs. These approaches include solid dispersions [5-7], microemulsions [8], self- emulsifying systems, inclusion complexation with ß-cyclodextrin [9], use of lipid carriers [10] & creation of nanocrystals [11]**.** Chiou and Riegelman defined the term solid dispersion as “A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”. Sekiguchi and Obi suggested that the drug in solid dispersion is present in a eutectic mixture in a microcrystalline state [12].

There are several other techniques which enhance the solubility mainly include physical modifications such as Particle Size Reduction, Modification of crystal habit, Drug dispersion in carriers, Complexation and Chemical Modifications. In solvent evaporation method, the inner phase is constituted by a polymer solution in organic solvent. The removal of organic solvent by heat or vacuum results in the formation of fine aqueous dispersions which are collected and then purified. Polysters and polymers like PEG copolymers, PLA, PLGA are used in this method [13]. In hydrotropic solubilization method, an increase in solubility is caused by presence of large amount of additives. The Phenomenon is closer to complexation but change in solvent characteristics play a significant role as well [14].

MATERIALS

Enalapril, Methanol, Mannitol, Dichloromethane, Urea and Tripotassium Citrate Monohydrate.

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EXPERIMENTAL

Solubility determination

To obtain solubility of the drug, it was added in excess amount in a beaker containing 10 ml of distilled water. Drug was added intermittently until saturation point reaches and precipitation occurs. It was kept for 24 hrs and sonicated. The resultant solution was filtered through 0.45 µm membrane filter. This filtrate was analysed by ultraviolet spectrophotometer.

Formulation of solid dispersion using solvent evaporation method

Drug was dissolved in solvent blend of methanol and dichloromethane (1:1) to get a clear solution in a 100ml Round bottom Flask. Excipient used was mannitol (1:1, 1:2 and 1:3) which was then added and dispersed. The solvent mixture was removed by evaporation at 50^0C while mixing content. The mass obtained was pulverized, mixed and then passed through sieve number 60.

Hydrotropic Solubilization Method

In 250 ml beaker, drug was mixed with hydrotropic blends of Urea (20%) and Tripotassium Citrate Monohydrate (10%) in the ratio (1:1, 1:2, 1:3). Powder was finally passed with sieve number 60 and stored in air tight glass bottle.

RESULTS AND DISCUSSION

Drug was evaluated for its identification. The melting point of drug was found to be 142-143^{o}C. Concentration of active pharmaceutical ingredient was found to be 129 µg/ml at 207.5 nm. Dry mixing brings the drug in close contact with the mannitol. The increased dissolution rate can thus be explained as being due to increased wettability and dispersibility of Enalapril. During the experiment it was noticed that the mixture immediately sinks to bottom of the dissolution vessel whereas the pure Enalapril floats for a longer period. All the mixtures and samples showed improved dissolution of Enalapril.

In solvent evaporation method, there was an increase in the concentration as concentration of mannitol increases. Table 1.1 shows concentration at different level of excipients at 207.5 nm.

Table 1.1: Varying concentration in solvent evaporation method.

S. No.	Drug : Mannitol	Concentration in µg/ml
01.	1:1	136
02.	1:2	145
03.	1:3	157

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In hydrotropic solubilization method, there was an increase in the concentration as concentration of hydrotropic blend increases. Table 1.2 shows concentration at different level of hydrotropic blends at 207.5 nm.

Table 1.2: Varying concentration of blend in hydrotropic solubilization method.

S. No.	Drug : hydrotropic blend	Concentration in µg/ml
01.	1:1	134
02.	1:2	140
03.	1:3	150

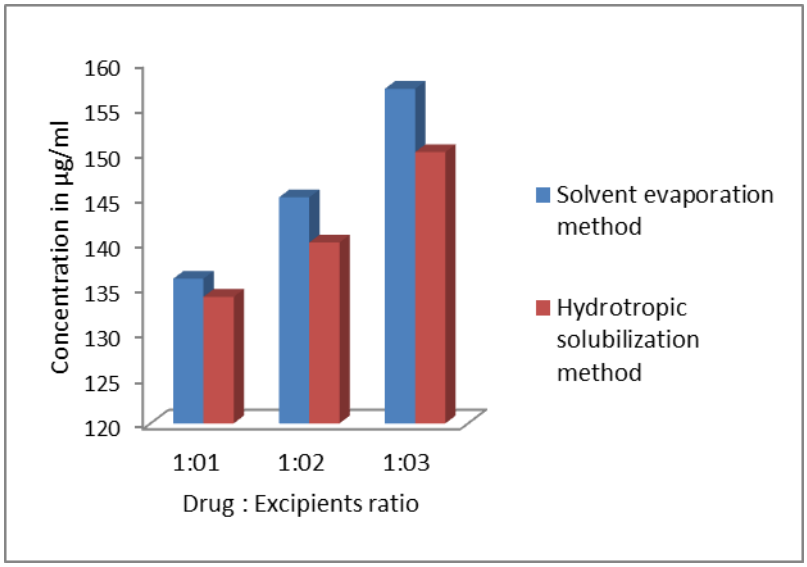

Figure 1: Comparative study of solubility enhancement of drug.

Different ratios of drug and excipients were taken in solvent evaporation as well as hydrotropic solubilization method. In solvent evaporation method, as excipient concentration is increased as compare to drug in different ratio, solubility of drug increased. The concentration was found to be 157 µg/ml in ratio 1:3. While in hydrotropic solubilization method, as excipient concentration is increased as compare to drug, solubility of drug increased. Concentration was found to be 150 µg/ml in ratio 1:3.

CONCLUSION

From above experiment, it was concluded that formulating solid dispersion is better than hydrotropic solubilization method for solubility enhancement of drugs. Therefore to improve absorption, oral bioavailiability and to enhance pharmacokinetic profile, the solid dispersion can be a suitable alternative to other available dosage form.

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