Introduction

Nowadays, the Pharmaceutical Industry faces huge challenges in the development of new efficient drugs. Challenges include low bioavailability (solubility and permeability of the drug), poor drug delivery and the existence of polymorphism. Consequently, all the previous challenges end up affecting the drug absorption.

Methotrexate (MTX), see figure, is a synthetic organic compound, which belongs to the anti-folate therapeutic group and is class IV of the BCS. This drug is most used in chemotherapy to typically treat brain and lung tumours.

MTX acts as an antifolate antimetabolite. MTX is taken up into the cells and inhibits the conversion of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is the active form of folic acid which is necessary for the synthesis of nucleotides of both RNA and DNA.

Is it important to note that Methotrexate is an ionic compound under physiological pH (see figure on the left) which makes solubility a much more difficult challenge.

MTX is a toxic drug with a very low therapeutic index. MTX is also highly ionized and generally hydrophilic, and it crosses the biological barriers very poorly. Although MTX works as a potent chemotherapeutic agent, it is limited in clinical significance due to its poor aqueous solubility (0.05 g/L). For that reason, it is usually applied as sodium salt.

The goal of this research was to prepare and characterize non-toxic ionic liquids and deep eutectic solvents derived from natural compounds and to study them in solubilization of MTX as a novel form for drug solubilization in order to increase their solubility, stability, and anti-tumoural activity.

Objectives

Several types of studies were performed, such as solubility, permeability and thermal studies, to assess if there was any improvement in relation to the pharmaceutical problems associated with the active form of the drug used in this research project.

Methods

Methotrexate (MTX) was prepared by dissolving 5 mg of MTX in 300 mg of ILs/ESs. All tests were made in triplicate to make sure the results were consistent. All tested ILs formulations and one ES improved significantly MTX solubility (>100 times).

Results and Discussion

The solubility studies showed that the ILs formulations have, on average, 1100 times better solubility, when compared with MTX alone. However, most formulations containing Eutectic Systems (ES) did not show any improvement, and the only ES formulation that was able to match the results obtained by the ILs was the one with choline acid which registered a solubility value of 54.5 g/L, (since the one with lactic acid precipitated after a day).

The permeability study showed that the formulation containing citric acid proved to slightly improve the Kow (6 times higher than MTX alone).

Regarding the thermal study, the IL formulation containing choline gluconate proved to be the most promising since glass transitions were able to be observed meaning the compound is amorphous.

Conclusions and Outlook

The permeability study performed by spectrophotometric determination of octanol-water partition coefficients (Kp), MTX has a negative value which indicates that the drug prefers to remain in the aqueous layer than to carry over to the octanolic phase. The Kp value of IL formulation is still negative but 6 times higher than in case of MTX alone.

References


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