Development of Ionic Liquids and Eutectic Systems for Drug-Formulations

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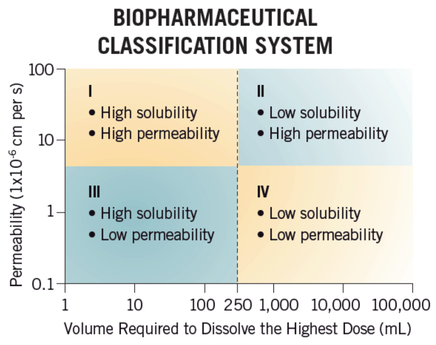
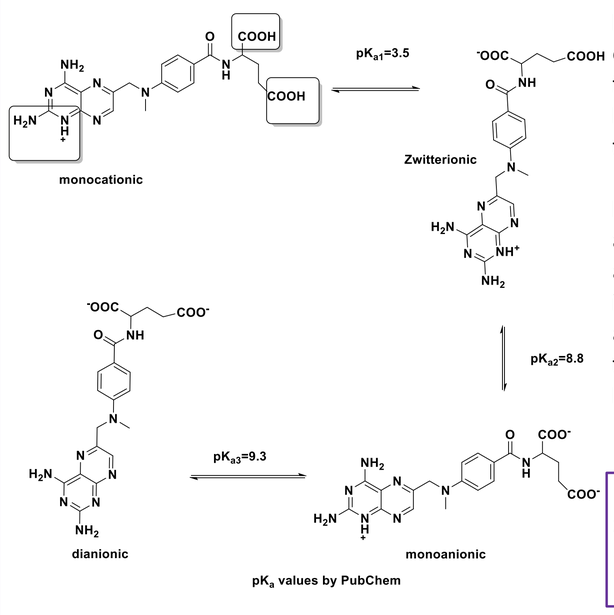
Introduction

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[1].



Methotrexate (MTX)



Methotrexate (MTX, see figure), is a synthetic organic compound, which belongs to anti-folate therapeutic group and to Class IV of the BCS[2,3]. This drug is most used in chemotherapy to typically treat brain and lung tumours.

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

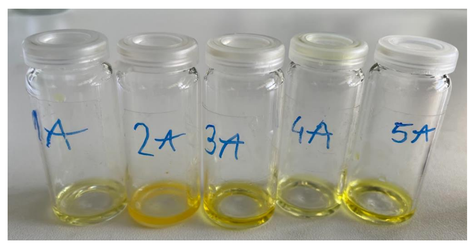
Is it important to note that Methotrexate is zwitterionic compound under physiological pH (see figure on the left) which makes solubility a much more difficult challenge.

Objectives

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[2]. 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 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-tumoral activity.

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.



Prepared Compounds

Ionic Liquids (ILs)

[Ch][Hexanoate]

[Ch][Glycolate]

[Ch][Gluconate]

Eutectic Systems (ES)

ChCl:Urea (1:2)

ChCl:Glycerol (1:2)

ChCl:Lactic Acid (1:2)

ChCl:PEG200 (1:5)

ChCl:Citric Acid (1:1)

Results and Discussion

Solubility Studies

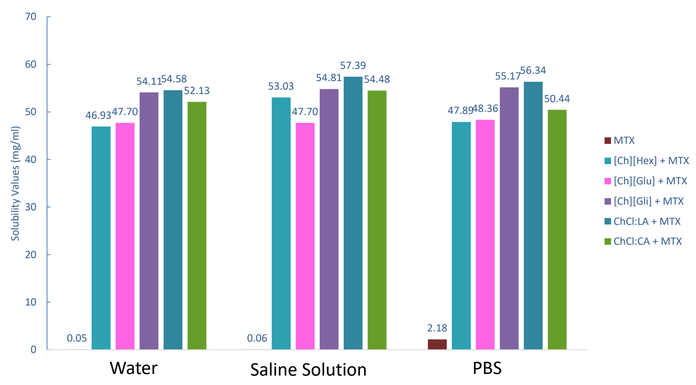
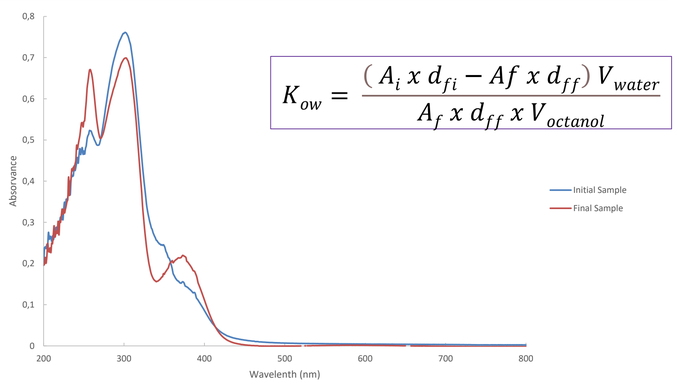


Figure 1: Results of Formulations from solubility studies

MTX has a poor water solubility, being experimentally determined a value of 0.05 g/L. Slightly better solubility was determined in saline and PBS solutions (0.06 and 2.18 mg/ml respectively).

MTX formulations were prepared by dissolving 5 mg of MTX in 300 mg of ILs/ESs. All test were made in triplicate to make sure the results were consistent. All tested ILs formulations and one ES improved significantly MTX solubility (>1100 times).

Permeability Studies



$$K_{ow} = \frac{(A_i \, x \, d_{fi} - Af \, x \, d_{ff}) \, V_{water}}{A_f \, x \, d_{ff} \, x \, V_{octanol}}$$

Figure 2: UV/Vis Absorvance of Choline Hexanoate + MTX

Compound and Formulation	Calculated log Kow
Methotrexate (MTX)	-1.85
Choline Hexanoate + MTX	-1.05
Choline Chloride:Citric Acid (1:1)	-1.99

The permeability study was performed by spectrophotometric determination of octanol-water partition coefficients (K_{ow}).
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 K_{ow} value of IL formulation is still negative but 6 times higher than in case of MTX alone.

Thermal Studies

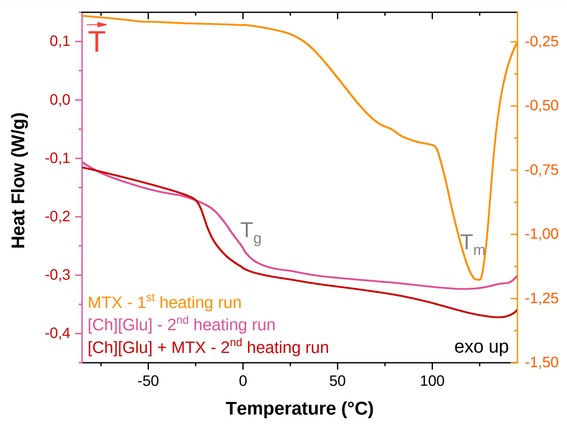


Figure 3: Thermograms of MTX, Choline Gluconate, and Choline Gluconate+MTX

The calorimetry analysis showed that all samples exhibited traces of adsorbed water, as in the first heating was observed a broad endotherm due to water evaporation.
Neat MTX is crystalline. The glass transition observed in all runs indicates that Choline Gluconate is a glass former and an amorphous material.
For the formulation (Choline Gluconate + MTX), a single glass transition was detected with no need of thermal treatment, confirming the drug amorphization.

Conclusions and Outlook

The solubility results 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 **citric 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.
To conclude with certainty if the addition of choline based ILs are able to solve some pharmaceutical problems associated with MTX, we would need to perform more studies such as anti-tumoral activity and cytotoxicity tests.

References

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Acknowledgements

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