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NMR study of haloperidol in weak acid solutions

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Acid-base supersolubilizaton (ABS) is recently developed method to prepare highly soluble amorphous despersions of drugs practically insoluble in water.[1] It was shown that haloperidol, weakly basic, antipsychotic, and very hardly solube drug, becomes supersoluble when mixed with weak acids. This is a good way to overcome the common ion effect known to lower the solubility in drug solutions when salts are formed.[2] Till today, it was shown that this principle is working for several well known hardly soluble drugs,[3,4] but it was not shown what are the main interactions causing the supersolubilization. This study is a part of our ongoing research on the main interactions causing ABS. We have used haloperidol as a model drug, deuteroacetic, malic and tartaric acids as model weak acids and trifluoroacetic and methanesulfonic acids as model strong acids. Solubility of haloperidol in solutions of different acid concentration was determined by shake-flask method followed by HPLC-DAD analysis. NMR spectroscopy (^{1}H and NOESY) was used to study interactions in solutions after the equilibrium was established and solid precipitate removed by centrifugation. Our results of solubility experiments in D_2O are in good accordance with previously reported results in aqueous solutions of weak acids: solubility of haloperidol in 3 M or higher concentrations of weak acids is approx. 25 to 35 times higher than solubility of haloperidol in hydrochloric acid.[1] Chemical shifts of all haloperidol protons in ^{1}H NMR spectra recorded in higher concentrations of all used acids have lower values. This trend in chemical shifts changes follows the trend of increasing haloperidol solubility in the presence of weak acids. ^{1}H NMR spectra have also shown that in lower concentrated (0.1 M) acid solutions chemical shifts of haloperidol protons remain almost the same, independent of solution pH value. In 1.0 M solutions of weak acids chemical shifts of all haloperidol protons are similar among used acids, but different compared to chemical shifts in strong acids solutions. NOESY 2D NMR spectra have shown that some NOE correlations are changed as acids' concentration is increased. We hope that in our future work a broad variety of available NMR techniques, accompanied with molecular modeling, will give us more pronounced insight in interactions between hardly soluble drugs and weak acids/bases that lead to supersolubilization.

References:

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