Application of Acid-Base Supersolubilization Principle to Increase Aqueous Solubility of Indomethacin and its Dissolution from ASD Prepared by Hot-Melt Extrusion

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Purpose
This work demonstrates the potential of the acid-base supersolubilization (ABS) principle to overcome extremely low solubility challenges. ABS between a weak acidic drug, indomethacin (IND), and a weak base, tromethamine (Trom), improved the solubility of the drug in water from <1 mg/mL to an outstanding >240 mg/mL. Furthermore, the research shows the application of ABS to lower the processing temperature of hot melt extrusion (HME) and form amorphous solid dispersion of IND.

Methods
The aqueous solubility of IND, with various weak bases, was determined using the shake-flask method at 25oC, and samples were analyzed using HPLC. Amorphous solid dispersions (ASD) were prepared using HME (Thermo Scientific Process11mm extruder). Rheology as a function of temperature, hot-stage microscopy, DSC, and PXRD were performed to determine HME experimental conditions and characterize ASDs. In vitro dissolution testing of 25-mg IND equivalent was performed in 250mL 0.1M HCl (pH 1.2) using USP II apparatus at 50 RPM and 37oC.

Results
While literature showed ≤15% indomethacin drug release at pH 1.2 due to its poor solubility (<0.001 mg/mL at pH 1.2), formulations formed using ABS showed remarkably high drug release of >80%. The solubility of IND (mg/mL) in 0.1M solutions of the weak bases histamine, lysine, arginine, and tromethamine was 1.77, 1.05, 48.31, and 137.98, respectively; increasing concentration displayed acid-base supersolubilization around pH 7.5-8. In contrast, strong bases like sodium hydroxide and bicarbonate caused salt formation above pH 7.2, limiting solubility enhancement versus non-salt forming weak bases. Tromethamine showed the highest ABS, with IND solubility reaching >240 mg/mL around pH 8. Using the ABS principle, a solid ASD was formed by the solvent-free HME process at a very low temperature of 80 oC. IND-Trom mixture at a 1:2 molar ratio and the polymer-KollidonVA64 (KVA64), along with or without added surfactant, Poloxamer-407(P407) at 10 and 20% levels, was used for ASDs. Physically and chemically stable ASDs were formed in all cases.

Conclusion
The application of the acid-base supersolubilization (ABS) principle allowed the formation of ASD of IND at a low temperature of 80oC, and it greatly enhanced indomethacin's (IND) solubility in water and the dissolution rate from ASD.

Keywords: acid-base supersolubilization (ABS), Hot-melt extrusion (HME), Amorphous solid dispersion (ASD)