Title- Comparison of Solubility and dissolution behavior of Ibuprofen and Ketoconazole in FeSSIF (made from commercial powder and scratch) and corresponding USP buffer.

Purpose

Biorelevant media (BRM) simulate the gastrointestinal fluids by including the physiological surfactants, bile salt and lecithin. BRM are predominantly important for the development of poorly soluble drugs since these surfactants significantly increase drug solubility. FeSSIF enables formulation scientists to obtain solubility and dissolution profiles of drug and their formulations in vitro under fed state. The purpose of this study was to compare the equilibrium solubility and dissolution profiles of weakly acidic and weakly basic BCS class II drug substances (Ibuprofen and ketoconazole) in FeSSIF-V2 (made from commercial powder and scratch) and corresponding USP buffer. Comparing solubility values of drugs in FeSSIF with corresponding pH buffer will give an indication on how the drug solubility is affected by presence of bile salt and lecithin. Effects of sources of the BRM on the dissolution performance of drugs were evaluated by comparing the dissolution in FeSSIF prepared from scratch and biorelevant.com powder.

Methods

The BRM used in the studies is Fed State Simulated Intestinal Fluid (FeSSIF-V2 – pH 5.8) prepared from biorelevant.com powder and from scratch. USP buffer used in the studies is pH 5.8 phosphate buffer. The solubility studies were carried out at room temperature and 37 ºC for 24h. The stability chamber was used to maintain the temperature and the HPLC (Waters Inc.) was used for the quantitation. Appropriate amount of media and excess amount of drug were placed in vials and were agitated at same speed using magnetic stirrer bar, followed by filtration using syringe filters of 450-nm pore size. The dissolution tests for 200 mg Ibuprofen and Ketoconazole tablets were performed in 500ml of BRM as well as USP buffer using USP apparatus 2 for 75 minutes and samples were analyzed in HPLC.

Results

	T	Solubility (ug/ml)				
		FeSSIF	FeSSIF (Lit)	ScrFeSSIF	pH 5.8 Buffer	pH 5.8 Buffer (Lit)
Ibuprofen	RT	1904.89 ± 6.03	NA	1782.86 ± 34.33	448.68 ± 17.32	NA
	37 °C	2642.99 ± 47.17	1500	3171.56 ± 115.36	453.29 ± 8.92	~800
Ketoconazole	RT	222.84 ± 0.08	NA	270.93 ± 2.18	18.88 ± 0.37	NA
	37 °C	248.92 ± 2.26	~500	332.52 ± 9.18	23.5 ± 0.15	~11

Table 1. *The equilibrium solubility values of Ibuprofen and ketoconazole. (NA- Not available Lit- Literature value)*

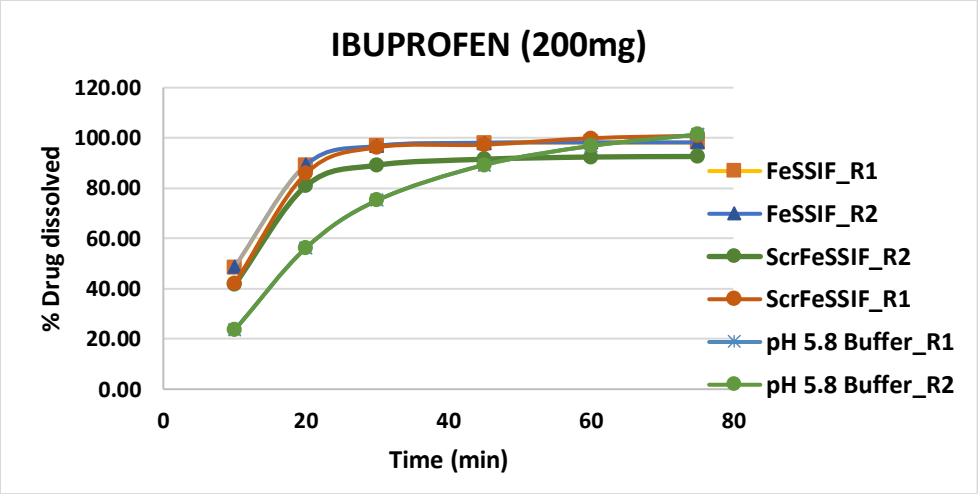

Figure 1. *Dissolution profiles of Ibuprofen in FeSSIF (commercial) and ScrFeSSIF (Scratch)*

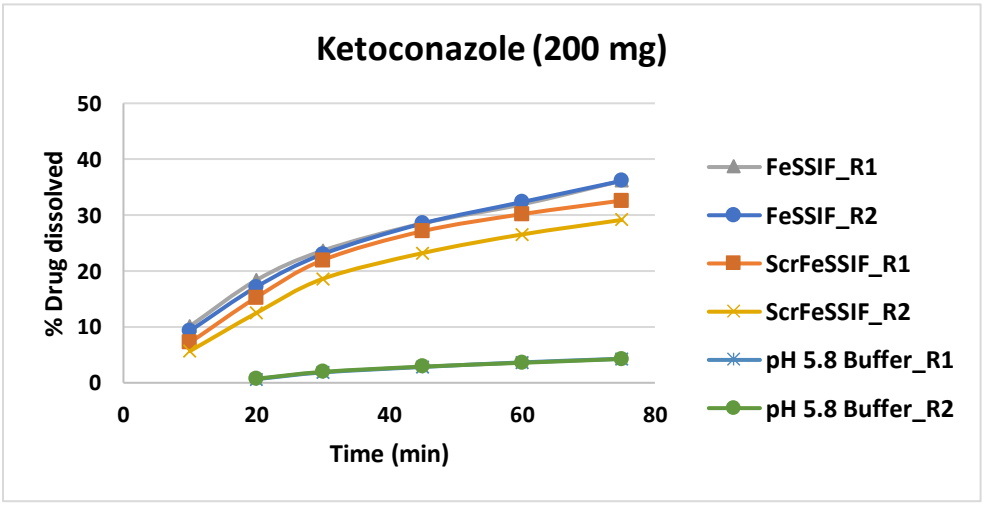

Figure 2. *Dissolution profiles of Ketoconazole in FeSSIF-V2 (commercial) and ScrFeSSIF (Scratch)*

As can be seen from Table 1, Ibuprofen and Ketoconazole both showed significantly higher equilibrium solubility in both FeSSIF compared to USP buffer. That is because of the presence of high amount of bile salts and lecithin in FeSSIF. Solubility of drugs in ScrFeSSIF (FeSSIF prepared from scratch) was overall slightly higher than the FeSSIF-V2 prepared from biorelevant.com powder due to difference in method of preparation. However, dissolution profiles of drugs in both types of FeSSIF were similar for both drugs (Figure 1 and Figure 2).

Conclusion

Evaluating solubility and dissolution profiles of poorly soluble drugs and drug products in BRM can help identify issues early on that may later occur in vivo. The solubility of Ibuprofen and

ketoconazole in both FeSSIF and pH 5.8 USP buffer were reported at room temperature as well as at 37 ºC. The dissolution profiles in each of the media made from scratch and the corresponding SIF Powder were similar. Thus, it is practical to switch from the more labor-intensive method to the use of standardized instant powders for preparing biorelevant media without affecting dissolution results.

Ibuprofen and Ketoconazole showed 7-fold and 15-fold higher solubility in both FeSSIF respectively compared to USP buffer. This indicates that in vitro results can be considerably affected in the presence of lecithin and bile salts. To conclude, the physiological solubility of these BCS class II drugs may be largely underestimated in in vitro solubility assays unless BRM is used.