Effect of Soluplus® and its concentration on the precipitation of Albendazole and Felodipine: Screening the 'parachute' effect

Effect of Soluplus® and its concentration on the precipitation of Albendazole (Abz) and Felodipine (Fel): Screening the 'parachute' effect

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Introduction

- **Amorphous solid dispersions** (ASD) are widely used to increase the aqueous solubility and hence for increasing the bioavailability of poorly water-soluble drugs.
- **The dissolution profile of ASD** in the aqueous medium can be divided into the **'spring'** and **'parachute'** phases, and **proper concentration of polymer** to **inhibit precipitation** effect is of criticality for ASD formulation.
- **This study investigated the precipitation of Abz and Fel**, in the 0.1 N solution of HCl (pH 1.2) or phosphate buffer solution (PBS; pH 6.8) and **three level of Soluplus® concentration**.

Results

- The **equilibrium solubility of Abz** in **DI water** was determined at the level of 0.003±0.001 mg/ml (Av. ±S.D.), while in the **0.1 N solution of HCl** it was approx. 3 times higher (0.098±0.001 mg/ml) and increased 9, 12 and 13 times along with addition and increase of Sol concentration.
- At the same time, the **equilibrium solubility of Abz in PBS pH 6.8**, as well as **Fel in all medias**, was not UV-detected (**Table**), whereas, Fel solubility in water was reported as $3.83*10^{-4}$mg/ml [1].
- No **precipitation of Abz** in pH 1.2 solutions with 1, 0.5 and 0.05 mg/ml of Sol was observed during 6 h, thus the concentration of Abz remained at 0.22 mg/ml. At the same time, the precipitation of Abz in pH 6.8 solutions was Sol-concentration dependent. While the precipitation of Abz in pH 6.8 solutions was Sol-concentration dependent and increased along with the decrease of Sol concentration (Fig. 1). In pH 6.8 solutions with 1, 0.5 and 0.05 mg/ml of Sol after 6 h of test the dissolved amount of Abz corresponded to 82, 27 and 15 % of introduced Abz, respectively.
- **Fel precipitation** in pH 1.2 and pH 6.8 solutions with Sol has shown the same trend, at 1 and 0.5 mg/ml of Sol after 6 h the dissolved concentration Fel was equal to approx. 70 and 80% of introduced Fel (Fig. 2). While at the concentration of 0.05 mg/ml for the same time almost all dose was precipitated.

Discussion

- **Abz** has shown lower solubility and faster precipitation in pH 6.8 media. The lower precipitation of Abz in pH 1.2 media correlate with higher equilibrium solubility of Abz in pH 1.2 media and its increasing in presence of Sol. The concentration of Sol of 1.0 mg/ml demonstrated the best Abz precipitation inhibition (at pH 1.2 and 6.8) and corresponds to **Abz-Sol ratio of 18:82 (w/w)**.
- The equilibrium solubility of **Fel** was not UV-detected, allowing us to conclude the solubility of Fel is lower than the detectability limit and very close to zero. The difference between the anti-precipitation efficiency of Sol in concentrations of 1 and 0.5 mg/ml (at pH 1.2 and 6.8) was minimal and allowed to keep more than 70% of the introduced drug in the dissolved state for 6h. The Sol concentration of 1 and 0.5 mg/ml corresponds to **Fel-Sol ratio of 29:71 and 44:56 (w/w)**, respectively.

Conclusion

The described in this work **precipitation test** (as part of preformulation investigation) **can help to narrow down the drug-polymer ratio** for the preparation of ASD which will have the potential **to be successful in the dissolution test**.

Table. *The* ***equilibrium solubility*** *(mg/ml) of* ***Abz*** *in DI water and 0.1 N solution of HCl without and with Sol.*

	DI water	0.1 N solution of HCl (pH 1.2)			
	no Sol	no Sol	0.05 Sol	0.5 Sol	1 Sol
Av.	0.003	0.098	0.091	0.120	0.128
S.D.	0.001	0.012	0.029	0.020	0.029

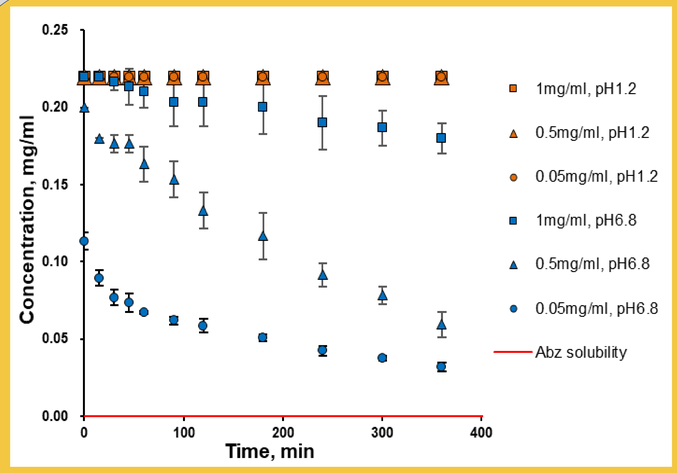

Fig. 1. *The precipitation of* ***Abz*** *in media at pH 1.2 and pH 6.8 and different Sol concentrations.*

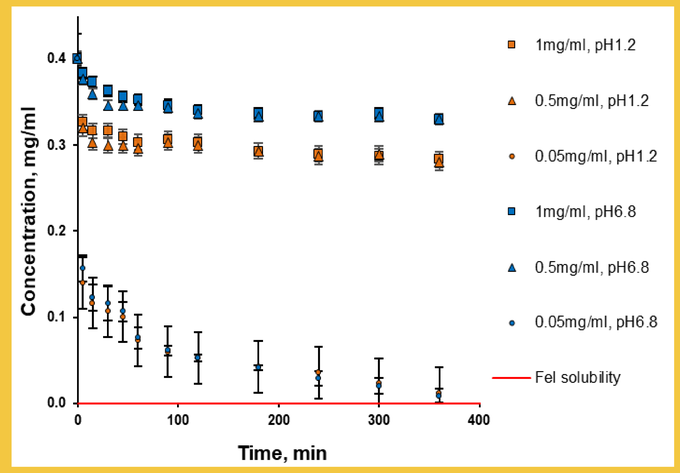

Fig. 2. *The precipitation of* ***Fel*** *in media at pH 1.2 and pH 6.8 and different Sol concentrations.*

Materials and Method

- **Abz** and **Fel** was bought (Kemprotec Ltd, UK) and **Soluplus®** (**Sol**) was kindly provided by BASF SE (Germany). NaH_2PO_4 and Na_2HPO_4, 37% w/w HCl, acetone and methanol were purchased from Sigma-Aldrich (UK).
- To determine the **solubility** of Abz and Fel, 4 mg of substance were accurately weighted and placed in glass sample vials with 10ml of DI water, pH 1.2, or pH6.8, optionaly with predissolved polymer. Those vials were store in shaker at 37℃ for four days.
- For the **precipitation test**, 0.11 ml of 20mg/ml Abz solution (equal to 2.2 mg of Abz) or 0.2ml of 20mg/ml Fel solution (equal to 4 mg of Fel) were introduced into the vials with 10 ml of media. Those solution were kept at 25ºC without mixing for 6 hours and drug concentration was periodically measured. The amount of drug and volume of media in this precipitation test is proportional to the dose of the drug per 900 ml of media in the dissolution test.
- The **UV-quantification of drug concentration** was done utilizing in-situ fibre-optic UV-probes, equipped with 2 mm path length tips and connected to the Rainbow® µDISS Profiler™ (Pion Inc., MA, USA) and calibration curves at a wavelength of 290nm ($C=0.2428*A-0.010$; $R^2=0.996$) for Abz and 330nm ($C=0.6956*A+0.001$; $R^2=0.999$) for Fel.

Reference: Perlovich, G.L., et al., Polymorphs and solvates of felodipine: analysis of crystal structures and thermodynamic aspects of sublimation and solubility processes. CrystEngComm, 2012. 14(24): p. 8577-8588.

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