

# Dissolution rate of BCS Class II drugs: Influence of pH, surfactants, and sink condition on discriminatory power of dissolution testing

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## Introduction

"Dissolution testing is required for all solid oral pharmaceutical dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect" [1]. Dissolution study is particularly important for insoluble or low soluble drugs where absorption is dissolution rate limited (BCS Class II drugs). It is required that dissolution medium provide sink condition, i.e. saturation solubility is at least three times more than the drug concentration in the dissolution medium as outlined in USP [1]. Different techniques have been employed to ensure sink condition, among them pH modification and surfactant addition appear to be the simplest and can be tailored to resemble GI fluid properties [2, 3].

## Objectives

To evaluate the influence of pH, surfactants, and sink condition on dissolution rate of three drugs, fenofibrate, glipizide, and levothyroxinesodium (Fig.1).

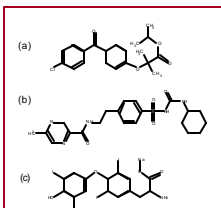


Fig. 1. Chemical structure of (a) Fenofibrate, (b) Glipizide, and (c) Levothyroxinesodium.

## Methods

Saturation solubility of fenofibrate and glipizide were determined at room T (25°C) after stirring excess amount of the drug in the respective medium (See Tables 1-3). The pH solubility data of levothyroxinesodium is listed in Table 4.

Dissolution tests were conducted at 37°C using USP apparatus II (paddle):

- CR 10mg glipizidetablet [4]: 900ml medium at 75rpm
- IR fenofibrate54mg and 160mg tablet: 1000ml medium at 75rpm
- IR levothyroxinesodium 300µg tablet: 500ml medium at 50rpm

Table 1. Saturation solubility and relative sink conditions of fenofibrate at different surfactant concentrations.

Medium	Saturation solubility (µg/ml)	C <sub>s</sub> /C <sub>0</sub> * (54 mg tablet)	C <sub>s</sub> /C <sub>0</sub> * (160 mg tablet)
DI Water	0.795	0.0147	0.00497
0.025M (+0.72%) SLS	195.274	3.616	1.22
0.05M (+1.44%) SLS	445.966	8.257	2.767
0.075M (+2.16%) SLS	728.145	13.84	4.551
0.1M (+2.88%) SLS	910.825	16.867	5.693
2% (+0.015M) Tween 80	133.493	2.472	0.834

\*C<sub>s</sub>: Saturation solubility of fenofibrate  
\*C<sub>0</sub>: Concentration of fenofibrate after complete tablet dissolution in 1000ml medium.

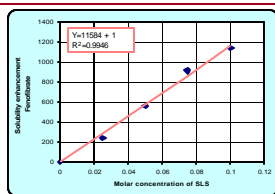


Fig. 2. Solubility enhancement of fenofibrate as a function of SLS concentration

## Results and Discussion

### a. Fenofibrate

Fenofibrate (Fig.1a) is a lipophilic compound and practically insoluble in water. In the presence of surfactants solubility increased significantly (Table 1). Fig. 2 shows that solubility enhancement by SLS is linearly correlated with increases in SLS concentration. This is attributed to the significant micellar solubilization of fenofibrate by SLS.

The equilibrium coefficient, k\* was determined to be 11584 L/mol by linear regression analysis of the data fitted to Eq. 1 [5].

$$\frac{S_{\text{total}}}{S_{\text{water}}} = 1 + k^* C_{\text{surfactant}} \quad (\text{Eq. 1})$$

S is solubility and C<sub>surfactant</sub> is molar concentration of SLS. k\* is the equilibrium coefficient (  $\frac{[C_s] - [C_0]}{[C_0] - [C_s]}$  ). The C<sub>s</sub>/C<sub>0</sub> ratio (Tables 1-4) having values of ≥3 represent existence of sink condition. Accordingly SLS at 0.025M level and above provides sink condition for 54mg fenofibrate tablet.

In Fig. 3, lower dissolution rate in 2% tween 80 compared with 0.025M SLS (f<sub>2</sub>=49.4) can be attributed to lower surfactant concentration and larger micellar structure with decreased diffusivity (concentration of 0.015M vs. 0.025M SLS, and micelles aggregation weight of 76,000 versus 15,900/mol) [6]. Dissolution profiles in 0.05M and 0.025 SLS are similar (f<sub>2</sub>=51.33), although C<sub>s</sub>/C<sub>0</sub> ratio is twice as high in the former. In practice, the net change in dissolution rate is the sum of solubility enhancement, and decline in effective diffusivity of dissolved species [6].

Dissolution profile of the 160mg fenofibrate tablet in 0.025M SLS is significantly different from that of 54mg tablet (f<sub>2</sub>=44.08) (Fig. 4). This can be explained by the low C<sub>s</sub>/C<sub>0</sub> ratio for higher dose (C<sub>s</sub>/C<sub>0</sub>=1.22) and absence of sink condition.

## Results and Discussion

### b. Glipizide

Glipizide (Fig.1.b) is a weak acid with pKa of 5.9 and pH dependent solubility (Fig. 5). Based on the C<sub>s</sub>/C<sub>0</sub> value at pH 6.8 (2.392), the sink condition for pure drug compound is not fully met (Table 2). Since in the CR dosage forms the polymer, HPMC, is used and it is known to have limited surface activity, its influence on glipizide solubility was investigated (Table 3). The increase in solubility up to a certain level is attributed to reduction in surface tension of the dissolution medium with subsequent enhancement in drug particles wettability. The critical HPMC concentration appears to be around 0.025mg/ml dissolution medium, which tends to complement the pH effect and provides the necessary sink condition. The low rate of dissolution in acidic pHs (Fig. 6) is due to the low solubility of the drug in acidic media and the obvious lack of sink condition (Table 2).

Table 2. Saturation solubility of glipizide at different pHs and relative sink.

Medium pH	Saturation solubility (µg/ml)	C <sub>s</sub> /C <sub>0</sub> * (10 mg tablet)
2	1.095	0.099
4.4	1.318	0.119
5.22 (DI Water)	3.924	0.393
5.8	4.927	0.443
6.8	26.573	2.392
8	280.730	25.266
10	888.906	80.902

Table 3. Saturation solubility and relative sink conditions of glipizide at different concentrations of HPMC in pH 6.8 phosphate buffer.

Medium	DI Water	pH 6.8	0.025	0.05	0.075	0.1	0.5	1
Saturation Solubility (µg/ml)	3.924	26.573	37.288	42.019	37.777	32.902	40.502	35.402
C <sub>s</sub> /C <sub>0</sub> **	0.393	2.392	3.596	3.782	3.4	2.961	3.645	3.186

\*C<sub>s</sub>: Saturation solubility  
\*\*C<sub>0</sub>: Concentration of drug after complete tablet dissolution in the dissolution medium.

Table 4. Saturation solubility of levothyroxinesodium at different pHs and relative sink.

pH	Saturation solubility (µg/ml)	C <sub>s</sub> /C <sub>0</sub> * (300 µg tablet)
1	6.53	10.88
2	0.878	1.46
3	0.313	0.52
4	0.257	0.43
5	0.254	0.42
6	0.284	0.47
7	0.585	0.98
8	3.6	6
9	33.75	56.25
10	251.77	419.62
11	1495.45	2392.42
12	13272.25	22120.42

\*C<sub>s</sub>: Saturation solubility  
\*\*C<sub>0</sub>: Concentration of drug after complete tablet dissolution in the dissolution medium.

### c. Levothyroxine sodium

The pH solubility profile of levothyroxine sodium is shown in Fig. 7 [7]. The preliminary study of SLS effect on dissolution profile of levothyroxinesodium 300µg tablet is shown in Fig. 8, which clearly demonstrates the significance of surfactant effect. The amphoteric nature of levothyroxinesodium is evident in Fig. 1c and Fig. 7

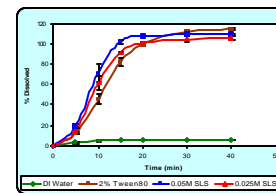


Fig. 3. Dissolution profiles of fenofibrate 54mg tablets in water and different surfactant media at 75rpm.

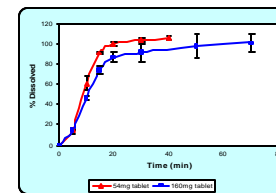


Fig. 4. Dissolution profiles of fenofibrate 54mg and 160mg tablets in 0.025M SLS medium at 75rpm.

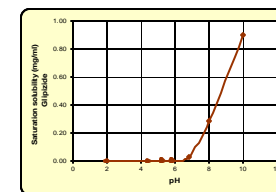


Fig. 5. pH-Solubility profile of glipizide.

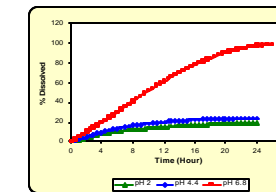


Fig. 6. Dissolution profiles of 10mg glipizide tablets in different pHs, at 75rpm.

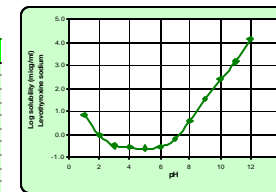


Fig. 7. pH-Solubility profile of levothyroxine sodium [7].

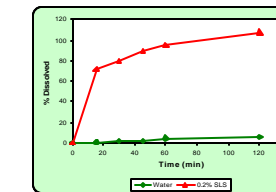


Fig. 8. Dissolution profiles of 300µg levothyroxinesodium tablets at 50rpm.

## Conclusions

Depending on the dose size and solubility characteristics of low solubility drugs, a meaningful and discriminatory power of dissolution rate testing can be demonstrated. Saturation solubility of fenofibrate and glipizide in different media were determined. Solubility of fenofibrate increased directly with SLS concentration. For a 54mg fenofibrate tablet, SLS at 0.025M level is required for a discriminatory dissolution test, while for 160mg tablet, dissolution condition and levels of SLS should be optimized; higher concentrations may be effective (i.e., 0.052M, ~1.5%). A pH 6.8 phosphate buffer medium is appropriate for glipizide 10mg tablet dissolution study, when formulation ingredients include excipients with surface activity (e.g. HPMC). As far as levothyroxinesodium is concerned, 0.2% SLS in an appropriate pH medium may provide for reproducible dissolution profiles.

## References

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