Role of Surfactant and pH on Dissolution Properties of Fenofibrate and Glipizide—A Technical Note

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INTRODUCTION

Dissolution test for oral solid dosage forms was first introduced in *United States Pharmacopeia (USP)* 18 in 1969. The rational behind this test is that a drug should be appropriately dissolved within the gastrointestinal tract (GIT) in order to be absorbed. Dissolution hence has become the most important test to determine product quality and drug release behavior in addition to other applications outlined in Figure 1.[1-4]

In general, drug dissolution can be defined by the extent and the rate of dissolution and involves 2 steps, drug release from the dosage form (liberation process) and drug transport within the dissolution medium (convection process). Several factors influence drug dissolution including: (1) physicochemical properties of drug (eg, solubility, crystalline forms, particle size, molecular structure, diffusivity in the dissolution medium), (2) formulation characteristics (eg, additives, coatings, manufacturing parameters), (3) dissolution method (eg, apparatus type; volume, surface tension, ionic strength, viscosity, and pH of the medium; and hydrodynamic conditions).[5] Furthermore, the GI conditions must be maximally simulated in a well-designed dissolution testing. An appropriate dissolution method also should be discriminative (ie, sensitive to product quality in terms of release characteristics) and provide reproducible results.

Dissolution study is particularly important for insoluble or low solubility drugs, where absorption is dissolution-rate limited (class II drugs in respect to Biopharmaceutics Classification System, BCS). At the same time, development of a dissolution method for this group of drugs is very challenging. Dissolution medium must provide sink conditions (ie, saturation solubility is at least 3 times more than the drug concentration in the dissolution medium as outlined in *USP*).[6] According to some other references the drug concentration in the dissolution medium should not exceed 15% to 20% of saturation solubility of the drug in order to provide sink conditions.[1,7,8] Absence of sink conditions may result in unpredictable release kinetics and suppression of release profiles. Generation of dissolution data under non-sink condition can easily overweigh the role of formulation changes in the selection of candidate formulation (see Figure 1). Different techniques (eg, addition of organic solvents to aqueous medium or use of 2-phase solvent system),[2] use of large dissolution volume, removal of dissolved drug, pH changes, and addition of surfactants or their combinations have been employed by scientists to improve solubility and ensure sink conditions.[4,9] Of note, any modification applied should be relevant to real GI conditions. Among aforementioned approaches, pH modification and surfactant addition appear to be the simplest and can be tailored to resemble GI fluid environment. Finally, construction of in vitro-in vivo correlation provides the most valuable data for selection of the most appropriate dissolution method and testing conditions that can be prognostic of in-vivo dissolution.

This report describes dissolution quality assessments, in the evaluation of the rate of dissolution for 2 low solubility drugs, glipizide and fenofibrate. The influence of formulation, sink conditions, surfactant type, and medium pH on their dissolution behavior and discriminatory effect of dissolution testing is also presented. Glipizide is an oral antidiabetic agent and fenofibrate is a dyslipidaemic drug. Dissolution of immediate release commercial fenofibrate (Tricor 54-mg and 160-mg tablets) and controlled release 10-mg glipizide tablets developed by the authors[10] were studied.

MATERIALS AND METHODS

Materials

Fenofibrate and glipizide were obtained from the Sigma Chemical Co (St Louis, MO) and hydroxypropylmethyl cellulose (HPMC) K15M from the Dow Chemical Co (Midland, MI). Tween 80 (polyoxyethylene (80) sorbitan monolaurate), sodium lauryl sulfate (SLS), and buffer ingredients were purchased from Fisher Scientific (King of Prussia, PA). Deionized water was used in preparation of all test media.

Fenofibrate, 54-mg and 160-mg immediate release tablets, (Tricor) were obtained from Temple University Hospital and glipizide controlled-release matrix tablets were manufactured in our lab with full formulation described in Table 1.

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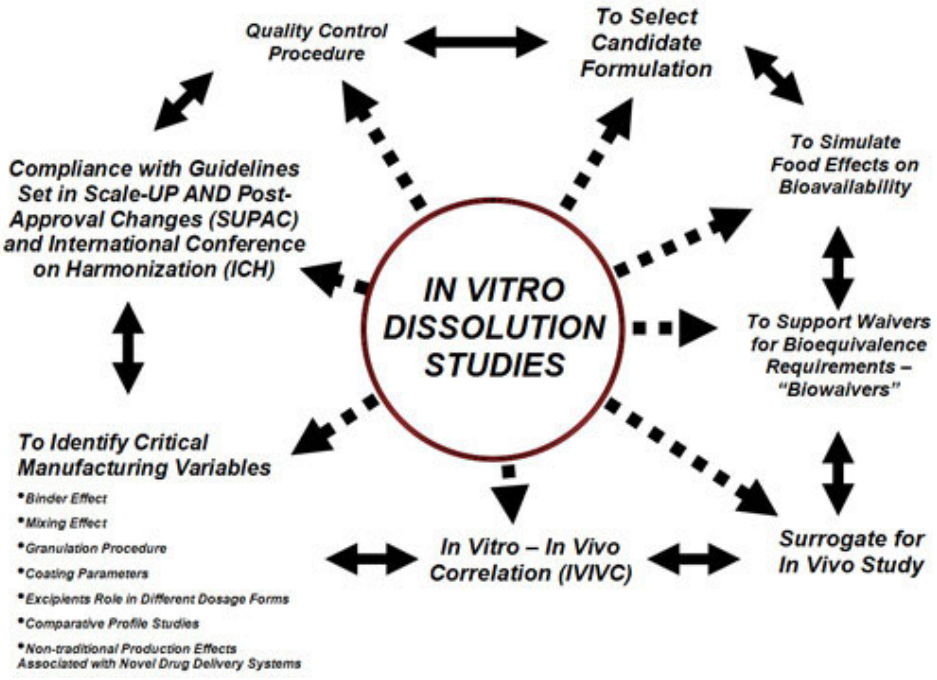

Figure 1. Applications of in vitro dissolution studies.

Methods

Saturation Solubility Studies

Saturation solubility of fenofibrate and glipizide were determined following standard approach by stirring excess amount of the active pharmaceutical ingredient (API) in the respective medium in 100-mL volumetric flasks at room temperature (25ºC) for 15 hours. The glipizide-containing flasks were covered by aluminum foil to protect against light exposure. Samples were taken manually and filtered through 0.45-µm filters. The UV absorbance of the solutions after appropriate dilution was determined at 290 nm and 276 nm for fenofibrate and glipizide, respectively (Cary-50 UV-visible [UV-vis] spectrophotometer), and the amount of drug dissolved was calculated using respective calibration curve. This procedure was repeated until the maximum concentration of the API was achieved (concentration remained constant).

Saturation solubility of fenofibrate was determined in 0.025, 0.05, 0.075, and 0.1 M SLS solution, in deionized water, and in 2% Tween 80 solution. Saturation solubility of glipizide was determined in pH 2 HCl/KCl buffer; pH 4.4 acetate buffer; deionized water (pH 5.2); and pH 5.8, 6.8, 8, and 10 phosphate buffer. In addition, the effect of HPMC K15M on saturation solubility of glipizide in pH 6.8 buffer was determined at 0.025, 0.05, 0.075, 0.1, 0.5, and 1 mg/mL polymer concentration.

Table 1. Composition of Modified Release Glipizide Formulation*

Ingredients	Amount (mg)	Amount (%)
Glipizide	10	6.6
HPMC K15M	35	23
HPMC K100LV	55	36
Spray-dried lactose monohydrate	50	32.8
Colloidal silicon dioxide	1.5	1
Magnesium stearate	0.75	0.5
Total	152.25	100

*HPMC indicates hydroxypropylmethyl cellulose.

Dissolution Studies

Dissolution tests were conducted in 900 mL (for glipizide) and 1000 mL (for fenofibrate) medium maintained at 37ºC using *USP* apparatus 2 (paddle) at 75 rpm (VK 7000, Vankel, Cary, NC). Dissolution method for glipizide controlled-release matrix tablets was modified by insertion of a mesh in each vessel to provide unconstrained and free 3-dimensional hydration and swelling.[11] Samples were taken automatically except for 160-mg fenofibrate tablets, where manual sampling and dilution were necessary. Samples were passed through 35-µm filters and UV absorbance was determined at 290 nm and 276 nm for fenofibrate and glipizide, respectively, using Cary-50 UV-vis spectrophotometer.

Results and Discussion

Fenofibrate

Fenofibrate (Figure 2) is a lipophilic compound and practically insoluble in water. Hence, dissolution study of fenofibrate dosage forms necessitates modifications in the dissolution medium to increase the solubility. Having no ionizable group, fenofibrate solubility was not influenced

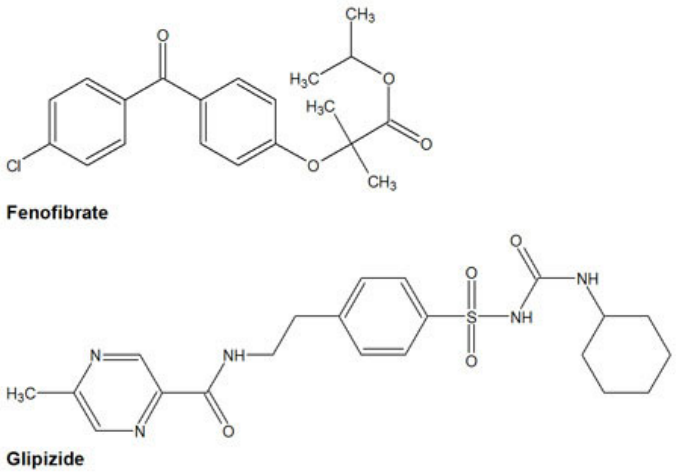

Figure 2. Chemical structure of fenofibrate and glipizide.

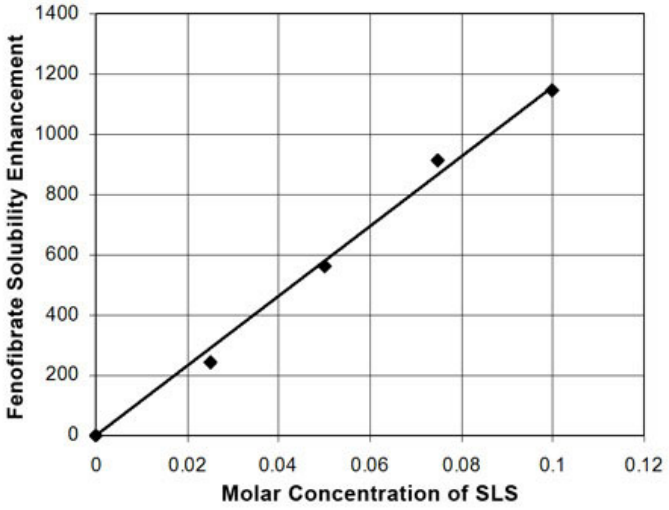

Figure 3. Solubility enhancement of fenofibrate as a function of SLS concentration.

by changes in medium pH. However, the addition of surfactants is a reasonable approach, which if implemented correctly can approximate the GI fluid condition.

Table 2 lists the saturation solubility values of fenofibrate in different media. Solubility was linearly increased from 244-fold (compared with water) at 0.025 M SLS to 1139 fold at 0.1 M SLS as shown in Figure 3. This significant increase is attributed to the micellar solubilization by SLS, considering that the concentrations of SLS examined in this study are well above its critical micelle concentration (CMC ~ 0.008 M).[12] Solubility enhancement data were fitted to Equation 1[13]:

$$\frac{S_{total}}{S_{water}} = 1 + k^* C_{m(b)}, \qquad (1)$$

where S is solubility, and $C_{m(b)}$ is molar concentration of SLS. The equilibrium coefficient, k*, is defined as follows[14]:

$$[C_s] + [C_m] \overset{k^*}{\leftrightarrow} [C_{sm}], \qquad (2)$$

where C_s is the drug concentration in water (solubility), C_m is the micelle concentration, and C_{sm} is the concentration of drug-loaded micelle. The equilibrium coefficient, k*, was determined to be 11584 L/mol by linear regression analysis. This high value indicates the very effective solubilization of fenofibrate by SLS.

The ratio of solubility over drug concentration (after complete dissolution of the drug in 1000 mL medium), expressed as C_S/C_D, represents the closeness to the sink conditions; values greater than 3 being considered sink according to *USP*.[6] For a 54-mg tablet, SLS at concentration level of 0.025 M and above provides sink conditions. In deionized water, only 6% of the drug was dissolved in 1 hour (Figure 4). This is related to the very low C_S/C_D ratio. In 2% Tween 80, the dissolution profile is different from 0.025 M SLS based on the calculated f_2 value (f_2 = 49.4), using dissolution of 54-mg tablet in 0.025 M SLS as reference (Figure 4). In this case, surfactant concentration is lower (0.015 M Tween 80 versus 0.025 M SLS), and sink conditions cannot be met. Moreover, as was mentioned before, drug dissolution is the result of drug liberation and drug diffusion into the dissolution medium. In this respect, the diffusivity of dissolved specimens (drug molecule and drug-micelle complex) plays an important role. The diffusivity of drug-micelle complex is several-fold less than the drug alone, and the net change in the dissolution rate is the sum of solubility enhancement

Table 2. Saturation Solubility and Relative Sink Conditions of Fenofibrate at Different Surfactant Concentrations*

Medium	Saturation solubility (μg/mL)	C_S/C_D (54 mg tablet)	C_S/C_D (160 mg tablet)
DI water	0.8	0.015	0.005
0.025 M (~0.72%) SLS	195.3	3.6	1.22
0.05 M (~1.44%) SLS	445.9	8.26	2.79
0.075 M (~2.16%) SLS	728.1	13.48	4.55
0.1 M (~2.88%) SLS	910.8	16.87	5.69
2% (~0.015 M) Tween 80	133.5	2.47	0.83

*C_S indicates saturation solubility of fenofibrate; C_D, concentration of fenofibrate after complete dissolution of tablet in 1000 mL dissolution medium; DI indicates deionized; and SLS, sodium lauryl sulfate.

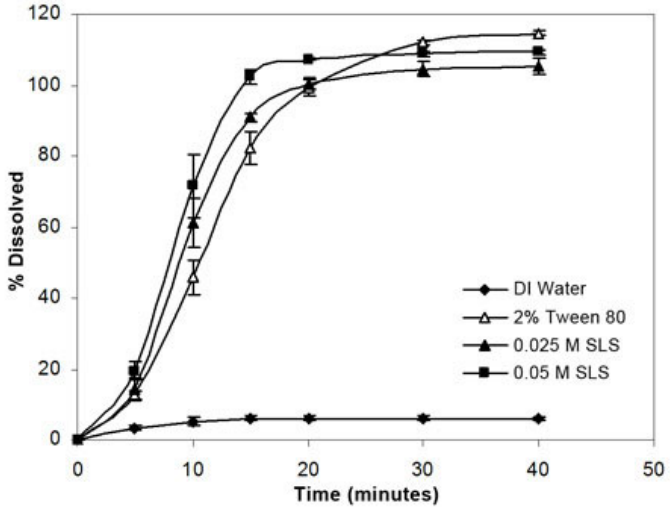

Figure 4. Dissolution profiles of fenofibrate 54-mg tablets in water and different surfactant media at 75 rpm.

and decline in effective diffusivity.[15,16] The higher molecular weight of Tween 80 (1310 versus 288.4 g/mol) and the greater aggregation weight of its micelles (76 000 versus 15 900 g/mol)[17,18] compared with SLS result in lower diffusivity of drug-micelle complex and hence reduce the dissolution rate.[16]

Dissolution profile in 0.05 M SLS (Figure 4) is relatively similar to that of 0.025 M SLS (f_2 = 51.33). Although saturation solubility in 0.05 M SLS is approximately twice as high as in the 0.025 M SLS (Table 2), the dissolution rate is not significantly different. This can be attributed to the effect of decreased drug-micelle diffusivity, since at higher concentrations of SLS more drug molecules will be loaded in micelle structure.

However, for 160-mg tablet, much higher concentration of SLS was required to achieve the necessary sink conditions.

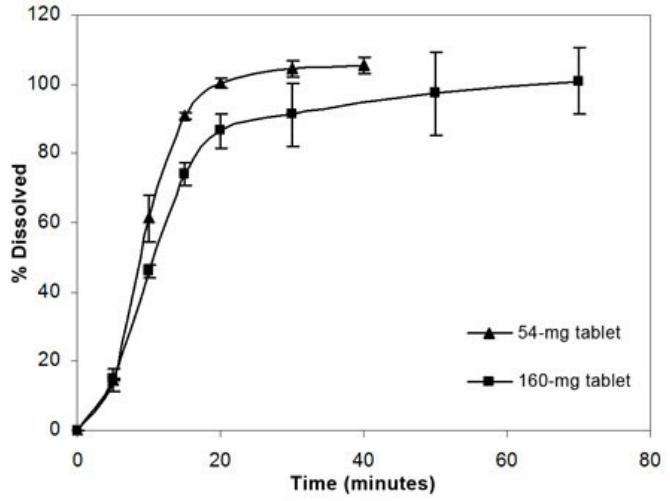

Figure 5. Dissolution profiles of fenofibrate 54-mg and 160-mg tablets in 0.025 M SLS medium at 75 rpm.

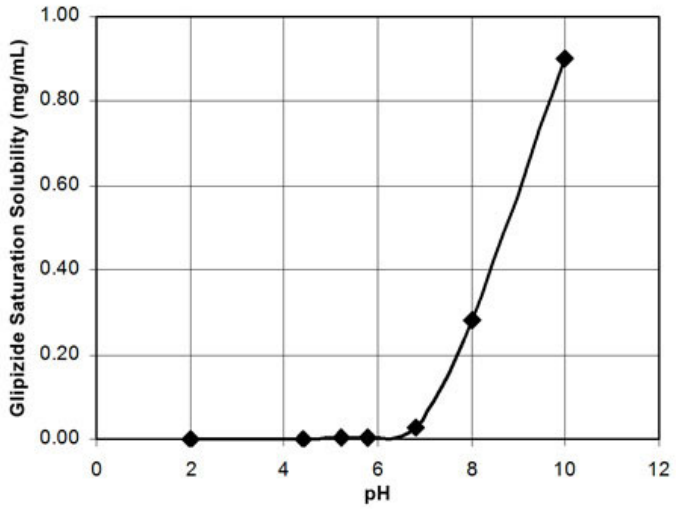

Figure 6. pH-Solubility profile of glipizide.

In Figure 5, the dissolution profiles of the 54- and 160-mg fenofibrate tablets in medium containing 0.025M SLS are shown. The dissolution profile of the 160mg fenofibrate tablet in 0.025 M SLS is significantly different from that of 54-mg tablet (f_2 = 44.08). The slower dissolution rate can be explained by the low C_S/C_D ratio for higher dose in this particular medium (1.22 versus 3.6). Based on the results of the study and the above discussion, 1000 mL 0.025 M SLS dissolution medium for a 54-mg fenofibrate tablet is suitable. For a 160-mg tablet, the SLS concentration should be much higher, around 0.052 M (~1.5%) to provide sink conditions, and this requires further investigation.

Glipizide

Glipizide (Figure 2) is a weak acid with pK_a of 5.9. The solubility is expected to increase by rise in pH. Figure 6 depicts pH solubility profile for glipizide. As expected, immediately above the pK_a, the solubility increased significantly. In Table 3, the solubility values along with corresponding C_S/C_D values are listed. It is recommended to study the dissolution of glipizide at pH 6.8 buffer.[19] Based

Table 3. Saturation Solubility and Relative Sink Conditions of Glipizide at Different pH*

Medium pH	Saturation Solubility (μg/mL)	C_S/C_D (10 mg tablet)
2	1.1	0.1
4.4	1.3	0.12
5.22 (DI water)	3.9	0.35
5.8	4.9	0.44
6.8	26.6	2.39
8	280.7	25.27
10	898.9	80.9

*C_S indicates saturation solubility of glipizide; C_D, concentration of glipizide after complete dissolution of tablet in 900 mL dissolution medium; and DI, deionized.

Table 4. Saturation Solubility and Relative Sink Condition of Glipizide at Different Concentrations of HPMC in pH 6.8 Phosphate Buffer*

			HPMC Concentration (mg/mL) in pH 6.8 Buffer					
Medium	DI Water	pH 6.8	0.025	0.05	0.075	0.1	0.5	1.0
Saturation solubility (μg/mL)	3.9	26.6	37.3	42.02	37.8	32.9	40.5	35.4
C_S/C_D	0.35	2.39	3.36	3.78	3.40	2.96	3.65	3.19

*C_S indicates saturation solubility of glipizide; and C_D, concentration of glipizide after complete dissolution of tablet in 900 mL dissolution medium.

on the C_S/C_D value (2.39), at this pH, sink conditions are not fully met. On the other hand, dissolution study at higher pH may not be biorelevant.

It is well known that the nature of the drug formulation can also influence the dissolution process. To investigate this effect, solubility of glipizide at different concentrations of HPMC (the release modifying ingredient of the developed formulation) was studied. This was based on the assumption that polymer dissolution during the time course of study changes the surface tension of the medium and increases drug solubility. A significant increase in solubility was observed in the concentration range studied (Table 4). This can be attributed to the surface activity of the polymer. The surface tension of water (at 20ºC) is ~72 mN/m and that of HPMC polymer class at the same temperature ranges from 42 to 64 mN/m.[20] This reduction in surface tension can increase the wetting of the drug particles and as a result, increase the solubility. The change in the solubility at levels above 0.05 mg/mL HPMC may be attributed to the change in the viscosity of the medium.

Figure 7 depicts the dissolution profile in 900 mL pH 6.8 phosphate buffer of a controlled-release 10-mg glipizide formulation containing 35 mg HPMC K15M and 55 mg HPMC K100LV (Table 1).[10] In pH 2 and 4.4, although the tablet completely disintegrated and disappeared by the end of the experiment, the amount of the drug detected was very low (<25%). This is the result of very low solubility of drug particles in acidic media (Table 3). At pH 6.8, however, dissolution was complete. Based on the results achieved, the use of pH 6.8 buffer medium is justified only if the formulation itself can provide some additional degree of solubility enhancement. In the absence of such contribution by formulation components, the nature of release profile may not represent the exact release behavior under sink conditions.

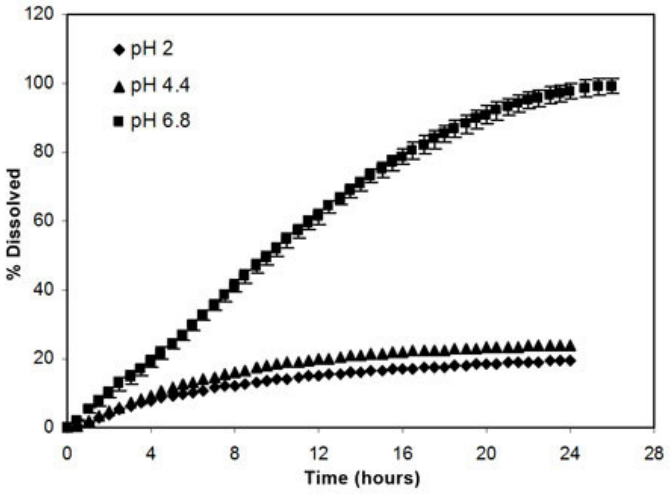

Figure 7. Dissolution profiles of 10-mg glipizide tablets in different pH at 75 rpm.

It is generally recognized that in vitro dissolution tests should be able to predict in vivo drug release. Tang and coworkers showed that for a low solubility drug, increase in solubility by addition of surfactants to meet sink conditions (based on bulk drug solubility data) may not always produce biorelevant results.[21] Similar conclusion was made by Gu et al regarding the selection of biorelevant dissolution volume.[22] In most cases, however, better correlation between dissolution and bioavailability have been achieved when sink conditions have prevailed.[8]

Summary and 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 54-mg fenofibrate tablet, SLS at 0.025 M level is required for a discriminative dissolution test, while for 160-mg tablet, dissolution condition and levels of SLS should be optimized; higher concentrations may be effective (ie, 0.052 M, ~1.5%). A pH 6.8 phosphate buffer medium is appropriate for glipizide 10-mg tablet dissolution study, when formulation ingredients include excipients with surface activity (eg, HPMC).

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