Journal of Pharmaceutical Sciences xxx (2017) 1-7

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Solubilization of a Poorly Soluble B-Raf (Rapidly Accelerated Fibrosarcoma) Inhibitor: From Theory to Application

Linda Bao, Le An, Yingqing Ran*

Department of Small Molecule Pharmaceutics, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080

ARTICLE INFO

Article history:
Received 4 August 2017
Revised 25 September 2017
Accepted 27 September 2017

Keywords:
solubility
solubilization power
cosolvents
surfactants
cyclodextrins

ABSTRACT

The oral bioavailability of a drug candidate is influenced by its permeability, metabolism, and physicochemical properties. Among the physicochemical properties, solubility and dissolution rate often are the most critical factors affecting the oral bioavailability of a compound. The increasing challenge for the pharmaceutical industry is to achieve reasonable oral bioavailability of poorly water-soluble drug candidates. G-F is a potent and selective B-Raf (rapidly accelerated fibrosarcoma) inhibitor with poor water solubility and moderate permeability, which resulted in an absorption-limited exposure in preclinical safety studies. The intrinsic solubility of G-F is 8 μg/mL (i.e., 0.0188 nM). In this study, pH adjustment combined with cosolvency, micellization, or complexation was applied as a technique to enhance the solubility of G-F. pH 9.5 and 4 buffers were selected to combine with the solubilization agents based on G-F's acidic p*K*a of 7.47. The solubilization power of each solubilization agent was determined based on the experimental data. The solubility G-F can be increased up to 4000-fold in a selected combination. The advantage of combination over individual solubilization agent was demonstrated. In this study, the understanding of the solubilization power of each solubilization agent played an important role in the formulation development of this development candidate.

Introduction

It has been a common challenge for the pharmaceutical industry to develop poorly soluble compounds, which would result in limited exposure. The use of computational methods and high throughput screening has been very supportive in designing and screening more new drug entities.[1] However, more than 40% of new drug entities developed in the pharmaceutical industry are practically insoluble in water.[2] Solubility becomes one of the major challenges for chemists to design compounds and for formulation scientists to develop formulations to support preclinical studies.

Formulation development of a poorly soluble compound can be highly challenging, especially in toxicology studies, which require the exposure of the compound to be multiple folds of the efficacious exposure.[3] Numerous approaches have been used to improve the solubility and dissolution rate including pH adjustment, salt formation (if the compound has a p*K*a within the physiological range), solubilization by adding cosolvents, surfactants, and complexation agents (such as cyclodextrins), as well as multiphasic systems such as nanosuspension by wet milling, lipid-based formulation, and amorphous solid dispersion.[3-19] The properties of the drug, especially crystallinity and polarity, are the key factors for the solubility. This article focuses on the modification of the solvent by adding solubilization agents combined with pH adjustment. Depending on the properties of the drug, the power of the solubilization agents could be very different.

Therefore, it is important to understand the physicochemical properties of a compound before testing any formulation. For example, melting point, polarity, and ionizable group at physiological pH range are the critical attributes, which can point to the direction of the solubility enhancement approach for a poorly soluble compound like G-F.

G-F (Fig. 1), a potent (B-Raf^{V600E} IC_{50}: 4.8 nM; phospho-ERK (Malme-3M) EC_{50}: 19 nM) and selective B-Raf (rapidly accelerated fibrosarcoma) kinase inhibitor, is a highly crystalline compound with a melting point ranging from 190°C to 228°C depending on the polymorphs.[20] It has a poor intrinsic aqueous solubility of 8 μg/ml and is nonhygroscopic (<0.2% water intake at 95% relative humidity) with no hydrate form observed upon high humidity. G-F has 2 acidic p*K*as of 7.47 and 11.4; it has one basic p*K*a of 0.68. When the pH is higher than 7.5, the solubility will increase exponentially; p*K*a of 11.4 and 0.68 have a negligible impact on solubility in physiological environment. This study aims to

* *Correspondence to:* Yingqing Ran (Telephone: 650-467-1423; Fax: +1 650-225-6238).
E-mail address: yran@gene.com (Y. Ran).

https://doi.org/10.1016/j.xphs.2017.09.023
0022-3549/

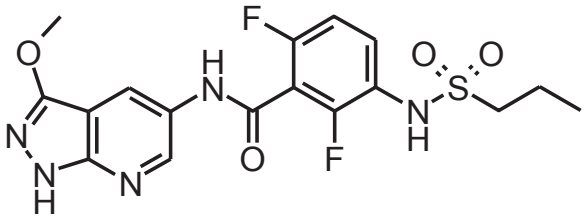

Figure 1. Chemical structure of G-F.

investigate the combination of pH control with cosolvents, surfactants, or complexation agents to solubilize this drug. The 3 approaches are described in detail in the following section.

pH Control

For a weak acid, the solubility could increase if the pH is greater than its acidic p*K*a. The solubility can be increased up to 100-fold when the pH is 2 or more units higher than its acidic p*K*a. A phosphate buffer at pH 9.5 is selected for this study based on a p*K*a value of ~7.5 and the feasibility of the formulations supporting preclinical studies. The total solubility of a solute (S_{tot}) is the sum of the solubility of unionized species (S_u) and the solubility of ionized species (S_i), as described by the Henderson-Hasselbalch equation:

$$S_{tot} = S_u\left(1 + 10^{(pH-pKa)}\right) \quad (1)$$

When the pH is higher than p*K*a, the solubility of the drug would increase exponentially with increased pH. When the pH of the drug is far (i.e., 2 units) lower than p*K*a, the solubility of ionized species is much less than the solubility of unionized species. If the compound has a workable p*K*a within physiological range, then pH adjustment is a powerful approach, which is often the first attempt for ionized compounds.

Combination of pH Control and Cosolvency

The cosolvents form homogeneous mixture with water, when the polarity of a solvent is less than water, the polarity of the mixture will be less than water. The solubility of nonpolar solutes would increase because of the reduced polarity of aqueous solution. For a weak electrolyte, the combination of buffer and cosolvent will help to solubilize both ionized and unionized species. The total solubility of a solute (S_{tot}) can be expressed by Equation 2,[3,8-11]

$$S_{tot}^{cos} = S_u 10^{\sigma u f_c} + S_u 10^{(pH-pKa)} 10^{\sigma i f_c} \quad (2)$$

where S_{tot}^{cos} is the total solubility of solute in the mixture of cosolvent with buffer; S_u is the solubility of the unionized solute; f_c is the volume fraction of cosolvent; σ_u and σ_i are the solubilization power of cosolvent for unionized and ionized solutes, respectively; the subscript "u" and "i" represent the unionized and ionized solutes, respectively. In general, cosolvent has a greater effect on unionized solute. Thus, σ_u is larger than σ_i. However, when the pH is much higher than p*K*a of a weak acid, or when the pH is much lower than p*K*a of a weak base, the solubility of ionized solute could be dominant, which contributes to the majority of total solubility of the solute. The Equation 2 shows the log-linear model, which is based on the assumption that there is no change in crystal structure of the solute and the dissociation constant of a weak electrolyte stays the same, in another word, no change of p*K*a of weak acid or base. In reality, the crystal form and p*K*a may be changed, which may lead the experimental data deviated from the equation. Previous studies have shown p*K*a value of weak acids may increase up to 1 to 2 units depending upon the percentage of cosolvents in the aqueous media. The change of p*K*a is due to both electrostatic and nonelectrostatic contributions, and the p*K*a change can be calculated with the Born equation.[12]

Combination of pH Control and Micellization

Another method to increase the solubility of a poorly soluble solute is the addition of surfactants to the aqueous solution. The solubilization capacity of a surfactant depends on the structure of the surfactant and the solute. A surfactant in water forms micelle when the composition of surfactant in aqueous solution is higher than its critical micelle concentration (CMC). An organic solute would be partitioned into micelles, the more nonpolar the solute (i.e., the unionized G-F), the more likely it is to be incorporated near the core or center of the micelle. Likewise, the more polar the solute (i.e., the ionized G-F), the more likely it is to be located near the surface or in the bulk water.[3,8-11] When the pH control and micellization are combined, the total solubility of a weak acid can be described using Equation 3

$$S_{tot}^{surf} = S_u + S_u 10^{(pH-pKa)} + K_u S_u C_{mic} + K_i S_i C_{mic} \quad (3)$$

And then,

$$S_{tot}^{surf} = S_u + S_u 10^{(pH-pKa)} + K_u S_u C_{mic} + K_i S_u 10^{(pH-pKa)} C_{mic} \quad (4)$$

where S_{tot}^{surf} is the total solubility of a solute in surfactant solution; S_u is the solubility of unionized solute; K_u and K_i are the solubility capacities of unionized and ionized solutes by surfactant, respectively; C_{mic} is the concentration of the micellar surfactant in the solution and $C_{mic} = C_{surf} - CMC$, where C_{mic} is the concentration of micellar surfactant, C_{surf} is the total surfactant concentration, and CMC is the critical micelle concentration.

When the concentration of a surfactant is much higher than the CMC or when CMC is negligible, the micelle concentration is approximately equal to the surfactant concentration and Equation 4 can be rewritten as Equation 5.

$$S_{tot}^{surf} = S_u + S_u 10^{(pH-pKa)} + K_u S_u C_{surf} + K_i\ S_u 10^{(pH-pKa)} C_{surf} \quad (5)$$

$$S_{tot}^{surf} = S_u + S_u 10^{(pH-pKa)} + \kappa_u C_{surf} + \kappa_i C_{surf} \quad (6)$$

where $\kappa_u = K_u S_u$ and $\kappa_i = K_i S_u 10^{(pH-pKa)}$

κ_u and κ_i are the molar solubility capacities of unionized and ionized solute by surfactant, respectively; which can be described by the slopes of the solubility versus surfactant concentration. κ is the number of moles of the solute that can be solubilized by one mole of micellar surfactant. At a fixed pH, the total solubility of a solute should be at a linear relation against the concentration of surfactant in the solution. For a neutral solute, the molar solubilization capacity of surfactant is much larger for unionized species. But when the pH is larger than p*K*a, the solubilization capacity of surfactant for ionized species is significant.

Combination of pH Control and Complexation

Solubilization of a poorly soluble solute by using complexation agents is another typical strategy in pharmaceutical industry. Cyclodextrins have been used in this study to boost the solubility of G-F. This method has stricter geometric structural requirement on