Improved Human Bioavailability of Vemurafenib, a Practically Insoluble Drug, Using an Amorphous Polymer-Stabilized Solid Dispersion Prepared by a Solvent-Controlled Coprecipitation Process

NAVNIT SHAH,[1] RAMAN M. IYER,[1] HANS-JUERGEN MAIR,[2] DUK SOON CHOI,[1] HUNG TIAN,[1] RALPH DIODONE,[2] KARSTEN FÄHNRICH,[2] ANNI PABST-RAVOT,[2] KIN TANG,[1] EMMANUEL SCHEUBEL,[2] JOSEPH F. GRIPPO,[3] SEBASTIAN A. MOREIRA,[3] ZENAIDA GO,[1] JAMES MOUSKOUNTAKIS,[1] THERESA LOUIE,[1] PRABHA N. IBRAHIM,[4] HARPREET SANDHU,[1] LINDA RUBIA,[2] HITESH CHOKSHI,[1] DHARMENDRA SINGHAL,[1] WASEEM MALICK[1]

[1]Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley, New Jersey, 07110

[2]Pharma Global Technical Development, F. Hoffmann-La Roche Ltd., Basel, Switzerland

[3]Clinical Pharmacology, Hoffmann-La Roche Inc., Nutley, New Jersey, 07110

[4]Non-clinical Development, Plexxikon Inc., Berkeley, California, 94710

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ABSTRACT: The present work deals with improving the solubility of vemurafenib, a practically insoluble drug, by converting it into an amorphous-solid dispersion using a solvent-controlled precipitation process. The dispersion containing vemurafenib and hypromellose acetate succinate (HPMCAS), an enteric polymer, is termed microprecipitated bulk powder (MBP), in which the drug is uniformly dispersed within the polymeric substrate. HPMCAS was found to be the most suitable polymer for vemurafenib MBP, among a series of enteric polymers based on superior physical stability and drug-release characteristics of the MBP. The MBP provided a greater rate and extent of dissolution than crystalline drug, reaching an apparent drug concentration of 28–35 μg/mL, almost 30-fold higher than solubility of crystalline drug at 1 μg/mL. The supersaturation was also maintained for more than 4 h. Upon exposure to high temperature and humidity, the MBP was destabilized, resulting in crystallization and lower dissolution rate. The control of moisture and temperature is essential to maintain the stability of the MBP. In a relative human bioavailability study, vemurafenib MBP provided a four- to fivefold increase in exposure compared with crystalline drug. Improving solubility with an amorphous-solid dispersion is a viable strategy for the development of practically insoluble compounds. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:967–981, 2013

Keywords: glass transition; amorphous; solid dispersion; precipitation; dissolution; solubility; X-ray diffractometry; thermal analysis; absorption; bioavailability

INTRODUCTION AND BACKGROUND

Because 85% of drugs sold around the world are orally administered, the properties of a drug molecule that govern oral absorption are critical to its development. The Biopharmaceutics Classification System (BCS) is a guide for predicting intestinal absorption based on the two parameters, aqueous solubility and intestinal permeability.[1,2] Although permeation enhancers could be used in a limited manner to improve permeability of poorly permeable drugs, from a formulation perspective, solubility enhancement using formulation intervention is the key driver for greater bioavailability. An increasing number of drug molecules being discovered belong to BCS class II or IV, with poor solubility being the primary concern. Based on the Noyes–Whitney theory of dissolution,[3] the dissolution rate is a function of the concentration gradient, which

Correspondence to: Raman M. Iyer (Telephone: +973-235-5862; Fax: +973-235-3769; E-mail: raman.iyer@roche.com)

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increases with the maximum solubility or saturated concentration achievable. Some of the more conventional approaches to enhance this solubility include the use of excipients such as solubilizers and lipid-based surfactants for micellar solubilization,[4–6] an increase in the surface area available for dissolution by micronization or nanoparticles using sizing-down (top down) or building-up (bottom up) technologies,[7,8] and complexation using cyclodextrins.[9]

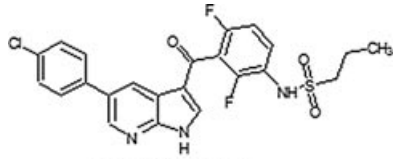
Over the past two decades, solid dispersions in polymeric carriers have been investigated as a means of improving the bioavailability of poorly soluble drugs.[10–16] The polymeric carriers reportedly increase the rate and extent of drug dissolution, in turn leading to greater bioavailability. The polymers seem to maintain the drug in a dissolved state at levels higher than their thermodynamic solubility limits for several hours, albeit as an unstable system. Because drug dissolution precedes absorption, the dissolved drug could be absorbed before the unstable system reaches its thermodynamic equilibrium state via precipitation of the drug and loss of bioavailability. Seen in this manner, the carrier excipient becomes a critical component that governs the drug's solubility and bioavailability. Several techniques are available to create a stabilized drug-carrier solid dispersion where the drug exists in varying states of crystallinity or in an amorphous state.[17] Non-polymer-based amorphous conversion such as comilling/cogrinding with inorganic silicates[18] has been used for select drugs. Polymer-based techniques of solid dispersion could be simple, moderately difficult, or complex. Comelting and melt quenching[19] are simple approaches, whereas examples of moderate ones are solvent evaporation under vacuum,[20] spray drying,[21] and lyophilization.[22] Solvent–antisolvent precipitation and hot–melt extrusion are examples of complex techniques where solubility differences, thermal stability, and so forth, play a major role in the type of solid dispersion obtained.[23,24] The most challenging of these are the ones where the drug is converted from a crystalline to an amorphous state and maintained with a stabilizing polymer. The present work deals with the conversion of crystalline vemurafenib into an amorphous-solid dispersion stabilized with an enteric polymer using a solvent-controlled precipitation process. The amorphous-solid dispersion is termed MBP and stands for "microprecipitated bulk powder."

MATERIALS AND METHODS

Vemurafenib is a practically water insoluble compound with a melting point around 272°C and the structure shown below. Its physicochemical properties and solubility are summarized in Table 1. The solubility of vemurafenib in various conventional organic solvents was ≤5 mg/mL at 25°C, with the exception of dimethylacetamide (DMA), in which the solubility was >500 mg/mL.

Table 1. Physicochemical Properties of Vemurafenib

Molecular formula	$C_{23}H_{18}ClF_2N_3O_3S$
Molecular weight	489.93 Da
Melting point (by DSC)	272.1°C
Glass transition (T_g)	105°C–107°C
Partition coefficient	3.0
Aqueous vehicles (μg/mL)	
Aqueous buffers (pH 3 and 7)	<0.1
Fasted simulated intestinal fluid	<2
Organic solvents (mg/mL)	
Dimethyl sulfoxide	>50
Methanol	4.57
Acetonitrile	1.40
Dichloromethane	1.95
Isopropanol	3.56
Acetone	<6



VEMURAFENIB

Preparation of MBP by Coprecipitation

Vemurafenib was prepared by Chemical Synthesis at Roche (Nutley, New Jersey) in a crystalline form and used for preparation of amorphous MBP. Hypromellose acetate succinate (HPMCAS) NF (Aqoat AS-LF) and hypromellose phthalate (HPMCP) NF (HP-55) were obtained from Shinetsu Corporation, Japan. Eudragit®L 100-55 was obtained from Evonik Corporation, New Jersey. All the excipients were used as received. The measured T_g value (rounded off to the nearest whole number) of HPMCAS was ~120°C, whereas that of Eudragit®L 100-55 and HPMCP are ~110°C and 133°C, respectively, from the literature.[24,25] All the polymers evaluated are enteric in nature and soluble at pH of 5.5 and above.

Amorphous-solid dispersions were prepared by a solvent-controlled coprecipitation process as shown in Figure 1. In this process, drug and polymer in a ratio of 40:60 (w/w) were dissolved in DMA to a solids content of 15% (w/w). The DMA solution was introduced at ambient temperature into 0.01 N HCl maintained at 2°C–5°C. The DMA–acid ratio was maintained at 1:10 (w/w). The resulting precipitate was washed with cold, dilute 0.01 N HCl followed by cold water to result in a DMA content of less than 0.2% (w/w). The wet precipitate was dried under vacuum at a temperature of 35°C to get a moisture content of 2% (w/w) or less. The resulting dry solid dispersion sample, designated as MBP, was analyzed as outlined below.

The amorphous MBP of vemurafenib prepared using HPMCP, HPMCAS, and Eudragit®L 100-55