Effect of Added Alkalizer and Surfactant on Dissolution and Absorption of the Potassium Salt of a Weakly Basic Poorly Water-Soluble Drug

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ABSTRACT: Telcagepant potassium salt (MK-0974) is an oral calcitonin gene-related peptide receptor inhibitor investigated for the treatment of acute migraine. Under gastric pH conditions, the salt rapidly gels, then converts to an insoluble neutral form that creates an impervious shell on the tablet surface, resulting in a slow and variable release dissolution rate and poor bioavailability. Early attempts to develop a solid dosage form, including solid dispersion and nanosuspension formulations, resulted in low exposures in preclinical studies. Thus, a liquid-filled soft gelatin capsule (SGC) formulation (oblong 20) was used for clinical studies. However, a solid dosage form was desirable for commercialization. The slow dissolution of the tablet formulations was overcome by using a basifying agent, arginine, and inclusion of a nonionic surfactant, poloxamer 407. The combination of arginine and poloxamer in the formulation created a local transient basic microenvironment that promoted the dissolution of the salt and prevented rapid precipitation of the neutral form on the tablet surface to form the gel layer. The tablet formulation achieved fast absorption and comparable exposure to the SGC formulation. The final optimized 280 mg tablet formulation was successfully demonstrated to be bioequivalent to the 300 mg SGC formulation. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: absorption; tablet; bioequivalence; dissolution; formulation; gels; oral absorption; solid dosage form; solubility; surfactants

INTRODUCTION

Telcagepant potassium salt (MK-0974) (Fig. 1) is an oral calcitonin gene-related peptide receptor inhibitor, which was developed and evaluated for the treatment of migraine headaches. It is a Biopharmaceutics Classification System (BCS) class II compound (low solubility, high permeability) with a projected efficacious dose ranging from 140 to 300 mg. Telcagepant has two pK_as: 2.2 (basic) and 9.6 (acidic). The crystalline neutral form has low aqueous solubility in the physiological pH range (0.08 mg/mL at pH 2 and 0.03 mg/mL at pH 6.0), but good solubility at pH 11 and above (>1 mg/mL). Crystalline neutral forms as well as amorphous and crystalline forms of the potassium salt were available for formulation development. In water, the solubility of the potassium salt is dependent of the total drug concentration because the compound can form micelles when it is in deprotonated under very basic pH. The critical micelle concentration (CMC) of telcagepant is estimated 10–15 mg/mL based on surface tension versus concentration measurements. Solubility of more than 300 mg/mL can be achieved with a final pH of 12.

A liquid-filled soft gelatin capsule (SGC) formulation was initially developed to support the clinical program. However, a solid dosage form was highly desirable for the market formulation to provide a smaller dosage form for patient compliance and to enable the development of fixed-dose-combination dosage forms with other therapeutic agents. Tablet formulations with the jet-milled neutral form, or nanocrystalline suspension or amorphous solid dispersion of the neutral form were explored without success.

Microenviromental pH control has been used to modify the dissolution of pharmaceutical formulations.[1–3] Salt forms have been widely used to improve the bioavailability of insoluble compounds. Although crystalline hydrate and ethanolate forms were identified for the potassium salt, the proof-of-concept study was initially conducted with the amorphous salt form. The hydrate and ethanolate forms were later evaluated to mitigate the possible physical stability risk associated with the amorphous salt form and the ethanolate. Because a robust process of making the hydrate form with controlled particle size was not developed, the ethanolate was selected for formulation development. The ethanolate converts to the hydrate above 10% relative humidity (RH) and the hydrate deliquesces above 75%RH. All three forms are chemically stable in the solid state. As demonstrated subsequently, these different forms of the potassium salt provided comparable oral bioavailability in the optimized solid dosage form.

A formulation containing conventional excipients may not always deliver the full benefit of salts. Initial solid formulation approaches using the potassium salt forms were not successful in providing a dosage form with high exposure, rapid onset and pharmacokinetic (PK) targets similar to the SGC formulation. For example, tablet and capsule formulations containing telcagepant potassium salt and different types of surfactants could not reach the same exposure as the SGC formulation in either preclinical studies or in the clinic. Salts of weak acids convert to the less-soluble neutral forms during dissolution in the stomach. This in some cases causes gelling of the drug in

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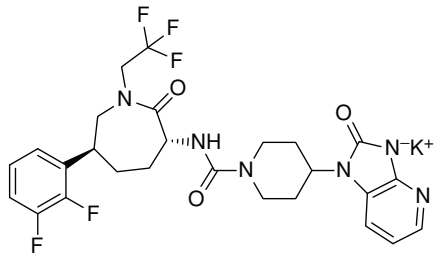

Figure 1. Chemical structure of MK-0974 N-[(3R, 6S)-6-(2,3-difluorophenyl) hexahydro-2-oxo-1-(2,2,2-trifluoroethyl)-1H-azepin-3-yl]-4-(2,3-dihydro-2-oxo-1H-imidazo [4,5-b] pyridin-1-yl)-1-piperidinecarboxamide potassium salt.

the tablet formulation and in other cases formation of a layer of free acid or neutral form on the surface of the dosage form.[4] As a result, the drug release from the tablet formulation is either retarded or in some cases completely hindered. Some of the most common approaches employed to overcome this issue are addition of surfactants, inorganic salts, disintegrants, polymers, or pH modifiers to provide a more favorable local environment for drug release, control active pharmaceutical ingredient (API) particle size, and dilution of the tablet with more excipients.[2,5–8] In the present study, the combined effect of a basifying agent (arginine) and a nonionic surfactant (poloxamer 407) was explored to overcome tablet gelling encountered during formulation development. The authors hope to demonstrate the power of "enabling" excipients to enhance the bioperformance of salts through this case study.

MATERIALS AND METHODS

Materials

Telcagepant (N-[(3R,6S)-6-(2,3-difluorophenyl)hexahydro-2-oxo-1-(2,2,2-trifluoroethyl)-1H-azepin-3-yl]-4-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxamide potassium salt) three potassium forms (amorphous, hydrate, and ethanolate), were provided by Merck Sharp & Dohme Corporation (West Point, Pennsylvania, USA). The excipients poloxamer 407 (Lutrol® Micro 127; from BASF Corporation, Washington, New Jersey, USA), L-arginine (from Kyowa Hakko Kogyo- HOFU, Yamaguchi, Japan), mannitol (SD 200; JP-D-mannitol, from Roquette France, Inc., Lestren, France), crospovidone (Polyplasdone XL; from ISP Technologies, Inc., Calvert City, Kentucky, USA), starch 1500® (from Colorcon, West Point, Pennsylvania, USA), sodium lauryl sulfate (from Mutchler, Inc., Harrington Park, New Jersey, USA), and Mg stearate (nonbovine, from Mallinckrodt Chemical, Inc., St. Louis, Missouri, USA), all were compendial. The coating material, Opadry® white 20A18334 (HPC, HPMC and TiO_2) was obtained from Colorcon.

General Formulation Selection Strategy

After evaluation of the impact of various excipients including surfactants and polymers on the drug release, tablets containing poloxamer and arginine were selected as the lead formulation option. The formulation composition was optimized for arginine, poloxamer and magnesium stearate levels and particle size of the arginine and the API. Major compositional changes were evaluated *in vitro* and formulations with good dissolution profile were chosen for *in vivo* PK studies in dogs to assess their potential to match the PK parameters (including C_{max}/T_{max}) of the SGC. The formulations with acceptable performance in dogs were selected for further evaluation in human relative bioavailability studies.

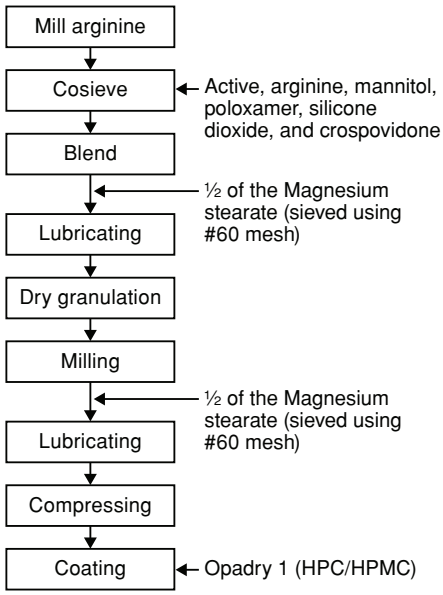

Figure 2. Manufacturing process flow diagram.

Manufacturing Process

A roller compaction (RC) dry granulation process was selected for manufacturing of the prototype telcagepant tablets containing arginine. The arginine containing formulations were produced by blending drug and excipients (excluding magnesium stearate) in a diffusion blender. The blend was roller compacted and the resulting ribbons were milled. The milled granulation was mixed with the remaining magnesium stearate and compacted to tablets using oval-shaped tooling. The tablets selected for the clinical studies were coated to about 3% weight gain with Opadry® I coating formulation. Figure 2 shows the manufacturing process flow diagram.

In Vitro Studies: Dissolution Studies

Early screening of formulation compositions was conducted via dissolution of 300 mg-dose strength tablets in simulated gastric media at pHs of 1 and 2 with and without surfactant. The surfactant, Tween 80, was added to enable complete solubilization of the drug. The dissolution data were obtained using simulated gastric fluid (SGF) prepared with 0.08 N HCl (pH ~1) or 0.008 N HCl (pH~2) plus 0.2% (w/w) NaCl and 0.5% Tween 80 in a USP II apparatus with paddle speed of 100 rpm. The pH 1 medium provided the most discriminating power with respect to tablet composition and thus was used as a worst case scenario for screening purposes. The pH 2 medium was also used for screening as well as for studies of materials attributes and process parameters on the formulation. It was also subsequently used for testing of clinical batches.

Dog PK Studies

Formulations were screened preclinically in male beagle dogs (Marshall Farms, North Rose, New York). The animals were

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