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Modulation of microenvironmental pH and crystallinity of ionizable telmisartan using alkalizers in solid dispersions for controlled release

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ABSTRACT

The present work is an original evaluation of the microenvironmental pH (pH_M) and crystallinity of an ionizable drug in order to enhance its dissolution using alkalizers in polyethylene glycol 6000 (PEG 6000) based solid dispersions (SDs). Telmisartan (TEL) was chosen as a model drug due to its poor and pH-dependent water solubility. The nine alkalizers used to modify the pH of TEL were MgO, NaOH, KOH, Na_2CO_3, $NaHCO_3$, bentonite, Na_2HPO_4, K_2HPO_4 and arginine. MgO, NaOH, KOH and Na_2CO_3 in the SD system significantly increased the drug dissolution rate in intestinal fluid (pH 6.8) and water. Modulation of pH_M was clearly observed as a function of time at different fractional dimensions of tablet. Structural change in drug crystallinity to an amorphous form was also a contributing factor based on differential scanning calorimetry (DSC) thermograms and powder X-ray diffraction (PXRD) patterns. The drug frequency of the C=O band decreased and the O–H broad band in the Fourier transform infrared (FTIR) spectra disappeared when these alkalizers were added. It was evident that the alkalizers in PEG 6000 based SDs synergistically enhanced dissolution of TEL not only by modulating pH_M but also by changing drug crystallinity to an amorphous form via molecular interactions.

1. Introduction

Numerous studies have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. A common method used to improve the dissolution rate of a poorly water-soluble drug is by formation of a solid dispersion (SD) with hydrophilic polymers such as polyethylene glycol, hydroxypropylcellulose, polyvinylpyrrolidone, and other diverse carriers [1–3]. Briefly, an SD is defined as a molecular mixture of drug in carriers. The changes of drug crystallinity to an amorphous form and the reduced particle size for better wettability are the main mechanisms whereby SD enhances drug dissolution.

Alternatively, it has also been reported that the modulation of pH in dosage forms is a promising way to modify the release rate of several pH-dependent and ionizable drugs [4–6]. For example, the addition of water soluble or insoluble pH modifying agents to mini tablets was found to maintain high pH values within the tablets, thus resulting in improved release of 8-prenylnaringenin, a weakly acidic drug with an extremely poor solubility [6]. Incorporation of weak acids as pH modifiers in hydrophilic matrix tablet also enhances release rate of weakly basic drugs by reducing the microenvironmental pH (pH_M) [5]. The pH_M can be defined as the pH of the saturated solution in the immediate vicinity of the drug particles and has been used to modify the dissolution of ionizable drugs from pharmaceutical formulations in a predictable manner.

The importance of pH_M control on the dissolution behaviors of water-insoluble drugs in SD systems became apparent a decade ago [7,8]. For example, an internal buffer system comprised of disodium hydrogen orthophosphate and citric acid incorporated into frusemide-polyvinylpyrrolidone SD was used to control the pH_M and consequently increased the dissolution rate of weakly acidic frusemide in acidic media and retarded the rate in alkaline media [7]. Still, it is not clear how the inclusion of the buffered system into the SD is related with drug crystallinity. Dissolution enhancement of a basic drug with hydrophilic polymers by using a mixed solvent of 1 N hydrochloric acid and methanol in a SD of the salt form was studied. However, no information of pH modifiers was described [8].

One disadvantage of the SD method and modulation of pH_M is the limited solubilization capacity, especially with a high drug-loaded system. Furthermore, no detailed attempt has been made to understand the modulating mechanism of pH modifiers in SD systems or how these potential changes of drug crystallinity and pH_M control are correlated with enhanced dissolution of poorly water-soluble drugs.

Telmisartan (TEL) was selected as a model drug. Therapy with this drug offers a good quality of life for hypertensive patients due to the minimal side effects [9]. TEL is manufactured and supplied in the free acid form and is characterized by a very poor solubility, resulting in low bioavailability [10]. According to the chemical structure of TEL, the TEL is readily ionizable and subsequently the solubility is also pH-dependent.

The aim of this study was to investigate the effect of incorporating alkalizers into PEG 6000 based SDs on the dissolution rate of TEL. The alkalizers MgO, NaOH, KOH, Na_2CO_3, $NaHCO_3$, bentonite, Na_2HPO_4,

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K_2HPO_4 and arginine were selected on the basis of their strong alkalinity. PEG 6000 was selected as the carrier in the manufacture of SD using the solvent method. The modulation of pH_M and drug crystallinity were extensively characterized. The structural behavior and molecular interaction of the SD containing alkalizers were also examined by instrumental characterization using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FTIR). The gradient changes of pH_M when TEL was in tablet form were also investigated as a function of time at different fractional distances of tablet length to elucidate the pH modifying mechanism.

2. Materials and methods

2.1. Materials

TEL was purchased from NJMMM Co. (Nanjing, China). PEG 6000 was purchased from Yakuri Pure Chemicals Co., Ltd., (Osaka, Japan). Magnesium oxide (MgO) from Junsei Chemical Co., Ltd., (Japan), sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), arginine, acid citric, acid malic, acid ascorbic and acid alginic from Sigma-Aldrich (USA), bentonite from Mineral and Pigment Solutions, Inc., (USA), disodium hydrogen phosphate (Na_2HPO_4) and dipotassium hydrogen phosphate (K_2HPO_4) from Showa Chemical Co., Ltd., (Japan), and sodium hydroxide (NaOH) and potassium hydroxide (KOH) from Duksan Chemical Co., Ltd., (Korea). The solvents used were high performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Solubility study

The solubility of TEL was determined in triplicate in enzyme-free simulated gastric fluid (pH 1.2) prepared by dissolving NaCl in deionized water and adjusted by 7.4% HCl solution, enzyme-free simulated intestinal fluid (pH 6.8) prepared by dissolving KH_2PO_4 in deionized water and adjusted by NaOH 1 N solution, phosphate buffer (pH 10) adjusted by 1 N NaOH solution, distilled water and in a 1% w/v solution of the pH modifiers (NaOH, KOH, MgO, acid citric, acid malic, acid ascorbic and acid alginic) by adding an excess amount of TEL to snap-cap Eppendorf tube (Hamburg, F.R.G) containing 1 mL of media. 10 mg of TEL was added except for cases of three alkalizers—NaOH, KOH and MgO about 130 mg of TEL was added gradually due to significantly high solubility in alkalizers' solution. The phosphate buffer (pH 10) was used instead of some other buffer material, like Na_2CO_3 to investigate the pH effect on TEL solubility without any interfering property of other agents.

The resulting mixture was thoroughly vortexed and then placed in a 37 °C incubator for two days. Aliquots were centrifuged at 1000 g for 10 min. The supernatant layer was carefully removed and then diluted with a solution whose components provided the mobile phase for HPLC analysis based on the preliminary solubility test. The concentration of TEL was then measured using HPLC by comparison with a standard calibration curve. All of the solutions prepared in the whole study were surely degassed prior to use.

2.2.2. Preparation of SD formulations

PEG 6000 was placed in a beaker with a magnetic stirrer and melted to a liquid using a hot plate (60 °C). Ethanol (100 mL/1 g TEL to be added) was then added to the beaker containing the melted PEG 6000 and mixed at room temperature. When a clear solution was obtained, alkalizer was added. Finally, TEL was added and stirred until a uniform mixture was obtained. The system was evaporated and then dried in a vacuum dryer. The weight ratio of alkalizers, drug and PEG 6000 used to prepare ternary SDs was kept at 1:8:24. A binary SD consisting of PEG 6000 and drug was also prepared as a reference for comparison. Formulations in this paper are named according to the alkalizer in the formulation.

2.2.3. In vitro dissolution

Dissolution studies were conducted using a USP II paddle method (50 rpm, 37 °C, and 900 mL dissolution medium) with a DST-810 dissolution tester (Labfine, Seoul, Korea). The SD powder or its tablet equivalent to 80 mg TEL was exposed for 1 h to three different media: gastric fluid (pH 1.2), intestinal fluid (pH 6.8), and water. Samples were withdrawn from the dissolution medium at predetermined intervals (10, 20, 30, 40, 50 and 60 min) and then drug concentration was determined by HPLC. An equivalent amount of fresh medium was added to maintain a constant dissolution volume.

2.2.4. Determination of pH in dissolution media

The pH of the dissolution medium after the dissolution test was measured using a pH meter (InoLab pH level 2, WTW, Germany) with the pH electrode SenTix 81.

2.2.5. Determination of microenvironmental pH (pH_M)

To further understand the effect of alkalizers on the pH_M, SD-based tablets were prepared with all of the alkalizers apart from NaOH and KOH, which were unsuitable due to their high hygroscopicity. The round shape tablets (400 mg) with diameter of 12 mm were prepared by the direct compressing method.

Tablets were removed from the dissolution medium after specific time intervals and let them strain off water adequately for 5 min in an ambient temperature. Immediately after that, the pH_M was determined potentiometrically using a surface pH electrode (Metoxy pH Meter HM-17MX, DKK-TOA Corp., Japan). The gradient pH_M from the surface to the inner tablet center was determined as a function of time. Tablets were cut into three slices. Depending on the fractional dimension of tablet length, the tablet surface and inner regions were determined and designated as $d/d_0 = 0$, 1/3, 2/3 or 1, respectively. The d_0 was the distance from the edge to the center. We assumed that the pH gradients from the center of the tablet to both margins are similar. $d/d_0 = 1$ represents the center, whereas $d/d_0 = 0$ indicates the edge (surface) of the tablet. The pH_M was plotted as a function of time at different fractional distances (d/d_0).

2.2.6. HPLC analysis

TEL was analyzed by the Waters™ HPLC system consisting of a pump (600 Controller), a UV–VIS tunable absorbance detector, a 717 autosampler, and an in-line degasser with a reverse phase column (150×4.6 mm, Luna 5u C18). The mobile phase consisted of a 75:25 (%v/v) mixture of methanol and 51.8 mM ammonium acetate; the flow rate was 1.0 mL/min; the detection wavelength was 296 nm; the injection volume was 20 μL; and the running time was 6 min. The entire solution was filtered using a 0.45 μM membrane filter (Millipore Corp., Bedford) before running the HPLC analysis.

2.2.7. Thermal analysis (DSC)

A TA Instruments differential scanning calorimeter (Model 2910, USA) was used to investigate the thermal behaviors of the raw material of TEL, PEG 6000 and the different SD powders. The amount of sample used ranged from 1 to 2 mg for the SD powder and PEG 6000, and was 0.4 mg for pure TEL. The samples were weighed in a standard open aluminum pan, while an empty pan of the same type was used as a reference. The heat running for each sample was set from 19 to 300 °C at 10 °C/min, using nitrogen as a purge gas. Calibration of temperature and heat flow was performed with indium.

2.2.8. Powder X-ray diffraction (PXRD)

PXRD patterns were obtained with a D5005 diffractometer (Bruker, Germany) using Cu-K radiation at a voltage of 40 kV and a current of 50 mA. The samples, which included the raw material of TEL, PEG