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Research paper

Solid molecular dispersions of poorly water-soluble drugs in poly(2-hydroxyethyl methacrylate) hydrogels

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Abstract

The applicability of cross-linked hydrogels in forming solid molecular dispersions to enhance the delivery of poorly soluble drugs has not been fully explored. The purpose of this study is to characterize physicochemical parameters affecting the formation of solid molecular dispersions of poorly water-soluble drugs in poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels and to investigate the effect of storage humidity levels on their physical stability. Samples were prepared by an equilibrium solvent loading process, using diclofenac sodium, piroxicam and naproxen as model drugs. These were characterized by X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), as well as changes in the physical state during storage under different humidity conditions. The results show that a threshold drug loading level of about 30% exists in these solid molecular dispersions, above which amorphous to crystalline transition may occur. At any given drug loading, the onset of such change in physical state is accelerated at higher relative humidity levels during storage. The presence of hydrogen bonding between the polymer and the drug, as reflected in the observed FTIR band shifts, improves the compatibility between the drug and the polymer. This, together with a decreased mobility in the glassy polymer, helps to retard the crystallization event below the loading threshold. An increase in dissolution rate is also observed from the polymeric solid molecular dispersion as compared with that of the crystalline pure drug. These physicochemical results indicate that solid molecular dispersions based on PHEMA hydrogels can effectively enhance the dissolution and therefore should be potentially useful in improving the oral bioavailability of poorly water-soluble drugs.

Keywords: Solid dispersion; Poly(2-hydroxyethyl methacrylate); Hydrogel; Poorly water-soluble drug; Solubility enhancements; Physicochemical characterization; Storage stability; Effect of relative humidity; Dissolution

1. Introduction

One major challenge in the oral drug delivery area has been the low bioavailability of many compounds exhibiting poor solubility characteristics. With the advent of high throughput screening in drug discovery, the number of poorly water-soluble drug candidates has increased significantly [1]. As a result, the enhancement of bioavailability of these compounds has become one of the major challenges in drug development. Among various methods employed to improve the rate of dissolution for poorly water-soluble drugs, the preparation of solid molecular dispersions (or solid solutions) in pharmaceutically acceptable water-soluble polymers such as polyvinylpyrrolidone (PVP) has been shown to be particularly effective in enhancing the rate of dissolution and the oral bioavailability. This is a result of the higher aqueous solubility of the amorphous drug in the solid molecular dispersion which generates a transiently supersaturated solution, thereby, enhancing the driving force for absorption [2–5].

Despite the fact that the utility of solid molecular dispersion has been known for many years, it has only been employed in a handful of commercial products [6]. Other than being limited by the complexity in the method of

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preparation and manufacturing scale up (e.g., spray drying from organic solvents, hot melt extrusion, etc.) as well as the reproducibility of its physicochemical properties, the lack of a wider commercial application is mainly a result of long-term stability issues such as the appearance of crystalline drug and the resulting decrease in dissolution rate on aging of the amorphous solid molecular dispersion. To be able to take full advantage of this promising approach to improve bioavailability for poorly water-soluble drugs, it is necessary to establish a more in-depth understanding of physicochemical factors affecting, and criteria determining, the physical state and stability of such amorphous systems.

The mechanism of crystallization inhibition in solid molecular dispersions is not completely understood. Factors such as reduced molecular mobility in polymers with high glass transition temperatures (T_g), change in the interfacial energy and specific hydrogen-bonding interaction between the drug and polymer have been identified in the pharmaceutical literature as responsible for the inhibition of drug crystallization in amorphous drug-PVP solid solutions/dispersions [7–11]. However, the effect of humidity level on the stability of such systems has not been investigated to any great extent in terms of time-dependent changes in the state of the entrapped drug. Another inadequately understood aspect involves factors determining the maximum level of amorphous drug that can be safely incorporated into the polymer without risking crystallization during storage. A better understanding of such governing physicochemical factors therefore becomes essential in devising new strategies to enhance the long-term stability of such amorphous solid dispersion systems.

Despite the interest in using water-soluble polymers in forming solid molecular dispersions, the application of cross-linked glassy hydrogels to stabilize entrapped drug in an amorphous state for the purpose of enhancing the dissolution and bioavailability of poorly soluble drugs has not been fully explored. Such hydrogel systems will be the focus of the present study. Cross-linked glassy hydrogels, especially those based on polymers or copolymers of 2-hydroxyethyl methacrylate (HEMA), are generally inert and biocompatible with a history of clinical use in drug delivery systems and contact lenses [12–14]. The major advantage of using cross-linked hydrogels rather than water-soluble polymers to form solid molecular dispersions of poorly soluble drugs lies in its ease of manufacture and the substantial reduction of organic solvent emission associated with conventional spray drying of solid dispersions based on soluble polymers such as PVP. In addition, these cross-linked hydrogels are inert and insoluble, and therefore will not be absorbed in oral delivery applications. Previous studies on hydrogel controlled release systems by Lee [12,15] suggest that amorphous dissolved or dispersed drug can be readily formed in cross-linked hydrogels as a result of the unique equilibrium drug loading process, and a threshold loading concentration exists above which drug crystallization may occur in the polymer. Throughout this manuscript, the term ''amorphous dissolved'' is intended to indicate amorphous drug that is dissolved in the polymer as opposed to being dispersed. In this study, we focus on the aspect of solubility and dissolution rate enhancement and examine in detail physicochemical parameters affecting the state of poorly water-soluble model drugs molecularly dispersed in PHEMA hydrogels. In particular, the effect of storage humidity condition on the stability of such solid molecular dispersions is also assessed.

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate 98% (HEMA) and ethylene glycol dimethacrylate 98% (EGDMA), both obtained from Sigma–Aldrich Canada, were distilled under vacuum prior to use to remove the hydroquinone inhibitor. Methyl methacrylate 99% (MMA), from Fluka Germany, was purified to remove hydroquinone stabilizer by adsorption with aluminum oxide powder. Benzoyl peroxide, diclofenac sodium salt, naproxen, and piroxicam were purchased from Sigma–Aldrich Canada and used without further purification. All other chemicals were reagent grade obtained commercially and used as received.

2.2. Polymer synthesis

PHEMA sheets of various cross-linking agent concentrations (0.5, 0.66, 1, 3, 5, 10 mol%) and copolymers of HEMA with different MMA content (10, 20, 40, 50% v/v) at a fixed cross-linking agent concentration of 0.66 mol% were synthesized by free radical bulk polymerization using 0.1 mol% of benzoyl peroxide as the initiator and EGDMA as the cross-linking agent. Monomer mixtures were injected into a custom mold consisting of two glass plates lined with Mylar sheets (0.003 in.), separated by a silicon rubber spacer (0.06 in.) and held together with multiple binder clips. The polymerization was carried out at 80 °C for 3 h followed by 1 h at 100 °C to decompose any remaining initiator. After the completion of polymerization, the hydrogel sheets were extracted in a 50:50 water:methanol (v/v%) bath for 2 days to remove any unreacted extractables. After further equilibration in distilled water, circular disc samples were cut from the swollen hydrogel sheets followed by drying at 50 °C under vacuum over a 24 h period. The dried discs (average diameter of 0.31 in.) were stored in desiccators before use.

For the dissolution comparison study, PHEMA beads of 180–230 μm size range were synthesized by suspension polymerization of HEMA monomer with 0.66 mol% of EGDMA as the cross-linking agent and 0.1% mol/mol of benzoyl peroxide as the initiator according to previously reported procedures [12]. Afterwards, the PHEMA beads were extracted in a Soxhlet with methanol for 2 days, dried