151a Molecularly Designed Mucoadhesive pH Responsive Tethered Biomaterials

Joshua B. Thomas, James W. McGinity, and Nicholas A. Peppas

Introduction

The oral route remains the most favored method of therapeutic administration. The ease of administration associated with this delivery route leads to a higher patient compliance which aids in increasing the overall effectiveness of the drug. For drugs that possess high solubility and high permeability (Biopharmaceutics Classification System (BCS) Class I) along the gastrointestinal tract, the oral delivery method poses very few challenges. However, for drugs with either low solubility (II), low permeability (III) or both (IV), challenges exist in the successful development of these compounds into oral dosage forms.

Polar compounds, including peptides and proteins, and those transported through facilitated mechanisms absorb in the upper gastrointestinal (GI) tract with little to no absorption in the large intestine. These compounds have a relatively narrow absorption window as compared to those that have the ability to be absorbed along the entire GI tract. For therapeutics possessing a narrow absorption window, a need exists to alter the GI transit so that the drug remains at its ideal site of absorption for an extended period of time. Bioadhesion affords the ability to slow upper GI transit by maintaining the dosage form at the site of absorption through interactions with the intestinal mucosa.

Drug delivery systems capable of following normal GI transit but possessing the capability to increase residence time in the small intestine have been molecularly designed. Through a synergistic combinatorial approach, particles capable of hydrating to control release, creating a highly viscous suspension, and interpenetrating into the mucus to develop enhanced physical bridging have been developed to create a delivery system capable of increasing the residence time of a therapeutic.

Materials and Methods

Microparticles composed of poly((meth)acrylic acid) were synthesized using a precipitation polymerization. The linear polymer poly(ethylene glycol) (PEG) was grafted on the poly((meth)acrylic acid) (P(M)AA) backbone of the microparticles through a thermally initiated free-radical precipitation polymerization. In a typical synthesis, glacial AA and/or MAA, PEGMMA, deionized distilled water (ddH2O), and potassium carbonate were combined and sonicated to ensure a homogeneous mixture. Ethyl acetate was added to a round bottom reaction flask. To the solvent mixture, the monomer solution and crosslinker dissolved in ethyl acetate were added and purged for 20 minutes with nitrogen. At the completion of the purge, BCHPC was dissolved using the solvent and combined into the reaction flask. The flask and contents were further purged for an additional 10 minutes and placed in a thermostatic water bath at 50°C. The resultant slurry was transferred to a single-neck round-bottom-flask, and the solvent was removed at reduced pressure and elevated temperature (29.5 in Hg, 50°C). The polymer powder was then allowed to further dry in a vacuum oven at 40°C and 28.5 in Hg until further use.

Infrared spectra of the microparticles prepared were obtained in the wavenumber range of 400-4000 cm^{-1} on a Thermo Mattson Infinity Gold FTIR spectrophotometer in transmission mode equipped with a KBr beamsplitter and DTGS detector. Each spectrum is an average of 64 scans at a resolution of 1 cm^{-1}. The thermal properties of the microparticles were characterized using a differential scanning calorimeter (DSC, TA Instruments MDSC 2920). Approximately 10 mg samples were analyzed at a sample rate of 10°C/min from -40°C to 160°C. Particle suspensions of the microparticles were prepared using ethyl acetate, and the particle size distribution was determined with a Malvern Mastersizer-S (Malvern Instrument Co., UK). The measurement was repeated three times. A Hitachi Model S-4500 scanning

electron microscope (SEM, Hitachi Ltd., Tokyo, Japan) was used to obtain SEM photographs. The vacuum-dried polymer microparticles were mounted on an aluminum stage using double-sided carbon conductive tape and coated with gold for 45 seconds using a Pelco Model 3 sputter-coater in an argon atmosphere.

Approximately 4.0 g of the prepared polymer microparticles previously dried at 30°C and 28 inHg were added to 350 mL of an agitated aqueous solution containing the appropriate amount of NaCl to achieve the specified ionic strength. After a 15 minute hydration period, the pH of the microparticle slurry was adjusted accordingly using 1 N NaOH, and a sufficient volume of ddH2O was added to make the final volume of liquid 400 mL. One mL of the polymer gel was placed on the lower of the two cylindrical (D = 19 mm) agarose sample mounts (0.5 g Agarose in 50 mL of ddH2O) in a tensile tester (Instron 4301, 10 N load cell, Canton, MA) at 22°C. The upper sample mount was brought into contact with a 42 mN impingement force, and the gel was allowed to relax for five minutes. The upper sample mount was raised at 6 mm/min until failure of the gel bond occurred, and the detachment force was measured as a function of displacement.

Results and Discussion

The structure of the microparticles was characterized using FT-IR, and the presence and influence of the PEG chains was noted in the spectra. Inter- and intramolecular hydrogen bonding occurs within PAA particles and is observed by the presence of the carbonyl peak at ~1710 cm^{-1} and bonded and free hydroxyls at 3150 and 3500 cm^{-1}, respectively. The presence of the ether oxygens of the PEG units provides an additional complexation event between the hydroxyl groups of the polyacid. This interactions causes a shift in the carbonyl peak to ~1725 cm^{-1} and perturbation in the ether oxygen at ~1100 cm^{-1}.

The thermal properties of the microparticles were analyzed using a heat/cool/heat method of DSC. The microparticles were heated to 160 °C and cooled to -20 °C to erase the thermal history of the various compositions, and the Tg was determined using the inflection of the thermogram. Crosslinked PAA exhibited a Tg of approximately 131 °C which reflects the lowered mobility of the chains due to the crosslinks and the presence of potassium acrylate (Tg ~ 194 °C) units in the polymer. Upon incorporation of PEG, phase separation within the particles occur as evidenced by the decreasing ΔCp and the two Tg's for the $\sigma = 9$ composition. Upon incorporation of larger amounts of PEG, a continuous phase is once again developed and exhibits a significantly lowered Tg.

The gel adhesion of hydrated gels composed of the microparticles was performed using tensiometry. This type of technique attempts to elucidate the capacity of the highly hydrated and neutralized gel that occurs at the periphery of the dosage form as it swells in the small intestine. A force versus elongation curve is obtained and split into two regions. The area under the curve up to the peak is defined as adhesion, and the area after the peak is defined as cohesion. These two areas combined are referred to as the total work of adhesion. The concentration of the carboxyl groups in the microparticles is the dominant factor in determining the adhesive capacity of the gels created. No detrimental effects are observed until the $\sigma = 30$ composition where all the parameters are significantly lowered.

Conclusions

The incorporation of the PEG imparts interesting thermal properties on the microparticles by inducing phase separation at lower concentrations. FT-IR analysis indicates the presence of complexation between the ether oxygen of the PEG and the hydroxyl groups of the PAA. This is valuable for these

particles as drug delivery vehicles due to their ability to limit diffusion at lowered pH. Gel adhesion results indicate the carboxyl groups are the dominant factor in creating gel adhesion, and the addition of large amounts of PEG has detrimental effects on the gel's behavior. However, with the addition of small amounts of PEG, there are no significant differences observed indicating that the surface energy of the particles are able to be modified with little effect on the adhesive capacity of the gel.

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