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A modified emulsion gelation technique to improve buoyancy of hydrogel tablets for floating drug delivery systems

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ABSTRACT

The use of buoyant or floating hydrogel tablets is of particular interest in the sustained release of drugs to the stomach. They have an ability to slow the release rates of drugs by prolonging their absorption window in the upper part of the gastrointestinal (GI) tract. In this study we synthesized bioactive hydrogels that have sustainable release rates for drugs in the stomach based on a hydrogel preparation technique that employs emulsifying surfactants. The emulsion gelation technique, which encapsulates oil droplets within the hydrogels during crosslinking, was used to decrease their specific gravity in aqueous environments, resulting in floating drug release depots. Properties such as swelling, buoyancy, density and drug release were manipulated by changing the polymer concentrations, surfactant percentages and the oil:polymer ratios. The relationship between these properties and the hydrogel's floating lag time was documented. The potential for this material to be used as a floating drug delivery system was demonstrated.

1. Introduction

Oral delivery is the most preferable route for the delivery of drugs that are not sensitive to the conditions in the gastrointestinal (GI) tract. Oral delivery has several clinical advantages such as ease of administration, patient compliance and flexibility in formulation [23,27]. However, not all drugs benefit from this type of delivery due to a narrow absorption window in the upper part of the GI tract (i.e., stomach and small intestine). This is a consequence of the relatively short transit time of the dosage forms in these anatomical segments. A controlled release substance typically leaves the upper GI tract after less than 2 h and is released in the non-absorbing distal segments. Drugs that are absorbed in the proximal part of the GI tract [28], and drugs that are less soluble in or are degraded in the lower parts of the GI tract may benefit from prolonged gastric retention [6,20]. Therefore, prolonging the gastric retention of a delivery system can be desirable for achieving greater therapeutic benefits including improved bioavailability, therapeutic efficacy and possible reduction of dose size [26].

As a case in point, verapamil HCl – a calcium channel blocker used in treatment of angina pectoris, hypertension, and supraventricular tachyarrhythmia [21] – can have vastly improved therapeutic benefits if presented with prolonged gastric retention. In atrial fibrillation, for example, verapamil HCl can be much more effective than digoxin for controlling ventricular rate [17] but, it is absorbed rapidly following its oral administration, and reaches a maximum plasma concentration within 1–2 h. Specifically due to first-pass effect, the oral form of verapamil HCl has remarkably low bioavailability (10–20%) and a short circulation half-life (4 h), thus requiring high oral dosing frequency [24]. Hence, the physicochemical properties of verapamil HCl make it a suitable candidate for sustained drug delivery in the stomach.

Several approaches have been developed for improving the gastric retention of solid dosage forms of drugs. These include mucoadhesion [25], sedimentation [5], expansion [37], modified shape systems [7] and the simultaneous administration of pharmacological agents [10] that delay gastric emptying. Another strategy to prolong gastric absorption is with the floating drug delivery system (FDDS), or dynamically controlled systems. This approach uses a low-density drug vehicle that has sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate [27]. In this context, the FDDS provides tremendous opportunities for designing new controlled and delayed release of existing oral drug formulations without the need for costly pharmaceutical development efforts.

FDDS systems can be divided into two main types [8]: the effervescent systems, where flotation is achieved by entrapping gas bubbles within a polymeric matrix, and the non-effervescent systems such as colloidal gel barrier systems [29], microporous compartment systems [11], and hollow microspheres [15]. Hydrogel beads, e.g. polysaccharide

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beads [2], are another version of non-effervescent system prepared from hydrophilic polymers. These have several advantages compared to other sustained release vehicles. Their structural characteristics, such as mesh size, may impact the penetration rate of liquid into the beads and thus influence the drug release profiles. Changes to the physical properties of the beads may also lead to different drug-release patterns in different parts of the GI tract, thus providing a number of control parameters to regulate the drug delivery.

The preparation procedures for the non-effervescent hydrogel beads are generally quite simple and low cost [8]. Several such methods exist, including polyelectrolyte complexation [1], incorporation of both oils and waxes [33], and emulsion gelation [13]. In the latter technique, a hydrophilic polymer such as a polysaccharide is dissolved in water, followed by the addition of oil to the polymer solution – under constant stirring – to form an oil-in-water emulsion to which the drug is added. In the next stage of the procedure, an ionotropic gelation method is used to prepare the hydrogel beads. The formed beads are filtered, washed and dried prior to oral administration. Factors like oil concentration, curing time, curing agent and drug-to-polymer ratio influence drug entrapment efficiency, floating lag time, bead morphology and drug release profiles [2,8,9,14,16,31,32,34–36].

There are few reports of the emulsion gelation technique using surfactant emulsifiers for the preparation of the hydrogel [22,30]. Nevertheless, even in these few studies that employ surfactants, the effects of surfactant concentration (e.g., span 80 or tween 20) on hydrogel characteristics were not comprehensively reported despite their well-known ability to stabilize emulsions and impact their final characteristics [38,41]. Singh et al. reported that the density of the formulated beads prepared with a span 80 formulation was in the range between 0.101 and 0.182 g/cm^3, and the beads formulated using 15% w/w linseed oil were more uniform in shape, exhibiting maximum buoyancy and minimal oil leakage [30]. The influence of mineral oil and castor oil over the morphology of hydrogel beads prepared with tween 20 was also reported [22]. These hydrogels were similar in dimensions, but differed in appearance, surface and structure.

Here we report on a modified emulsion gelation technique which incorporates a biocompatible surfactant to create a stable emulsion just prior to hydrogel gelation. For the first time we report how this technique is used to fine-tune the hydrogel structure and physical characteristics. Moreover, we provided a comprehensive characterization of the physical properties of the hydrogel tablets in response to changing polymer content and oil percentage. The release profiles of the hydrophilic drug verapamil HCl were investigated in correlation to hydrogel buoyancy and floating lag times. Finally, a relationship between the hydrogel structure and its physical characteristics was proposed. This use of emulsifiers to control hydrogel structure and drug release characteristics could open the door to a new generation of improved vehicles for FDDS.

2. Materials and methods

2.1. Preparation of PEG hydrogel tablets

Poly(ethylene glycol) (PEG) (molecular weight 10 kDa) hydrogel tablets were prepared using the emulsion gelation method at different oil:polymer ratios. Briefly, 10 or 15% (w/v) kolliphor® p188 (BASF™) was added to 80 or 85% (v/v) polymer precursor solution of PEGDA with 5, 10 or 15% (w/v) polymer at 4 °C in 20 ml glass vial until complete dissolution of the surfactant was achieved. The solution was mixed with 1% (v/v) photoinitiator stock solution [10% (w/v) Irgacure®2959 in 70% ethanol and 30% deionized water]. Paraffin oil (Bio-Lab Ltd.) was added dropwise to the solution under constant stirring to a final emulsion volume of 2.5 ml. The oil percentage was 15 or 20% v/v, unless otherwise stated. An overhead mechanical stirrer with a 1.5 cm diameter propeller was used, rotating at an angular velocity of 1950 rpm. Stirring was continued for 15 min after the oil was added. The emulsion (0.5 ml) was transferred into a round Teflon mold with a 14 mm diameter. The emulsion was then irradiated with UV light (365 nm, 4–5 mW/m^2) for 5 min in order to achieve chemical crosslinking resulting in hydrogel tablets in the gel state.

2.2. In vitro buoyancy experiments

The ability of the PEG hydrogel tablets to float in aqueous media was determined by buoyancy studies. Eight samples of hydrogel tablets were prepared as described in Section 2.1. The tablets were submerged in a 50 ml plastic vial containing 30 ml of 0.1 M HCl pH 1.2 and agitated at 100 rpm in a water bath at 37 °C. The floating lag time was defined as the time passing between transferring the tablet to the vial until the tablet floated in the solution. The buoyancy time was defined as the time passing between initial floating of the tablet until it sank again to the bottom of the vial. Both floating lag time and buoyancy time were determined by visual inspection to the tablets in solution.

2.3. Swelling experiments

The swelling of the PEG hydrogel tablets was measured based on a modified protocol described previously [39]. Briefly, hydrogels were submerged in 50 ml of 0.1 M HCl pH 1.2 while the swelling ratio was determined gravimetrically as follows:

$$Q = \frac{(m_W - m_D)}{m_W} \times 100 \quad (1)$$

where m_W is the weight of the swollen hydrogel, and m_D is the weight of the polymer and water in the hydrogel immediately after casting. Several hydrogel groups were characterized, including those made with several oil:polymer ratios, polymer concentrations and surfactant percentages. Swelling measurements were performed in quadruplicate.

2.4. Density measurements

The mean weight of a 0.5 ml PEG hydrogel tablet was measured and used to calculate the hydrogel density using the following relation:

$$\rho = \frac{M}{V} \quad (2)$$

where ρ is the density of the tablets; M is the weight of the tablets; and V is the volume of the tablets. Density measurements were performed in quadruplicate.

2.5. In vitro drug release studies

Verapamil HCl (Sigma-Aldrich) was used as a class I hydrophilic drug (according to the BCS classification) with a log p of 3.8 [40], for release experiments. The drug (10 mg/ml) was dissolved in aqueous phosphate buffer saline (PBS) solution containing different PEG concentrations. This solution was used to create hydrogels containing emulsions with different oil:polymer ratios and surfactant concentrations, as described in Section 2.1. Hydrogel tablets were submerged in a 50 ml plastic vial containing 30 ml of 0.1 M HCl pH 1.2 and agitated at 100 rpm in a water bath at 37 °C. During the course of the 24 hour release experiments, samples of 0.2 ml were withdrawn from the supernatant at several time intervals and replenished with fresh 0.1 M HCl pH 1.2. Spectroscopic analysis of the sample was performed at 228 nm using a synergy HT™ multi-mode microplate reader (Biotek). The concentration of the drug was determined from a calibration curve.

2.6. Statistical analysis

Statistical analysis was performed using Microsoft© Excel software. Data from independent experiments were quantified and analyzed for