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Release of dextromethorphan hydrobromide from freeze-dried enzyme-degradable hydrogels

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Dextromethorphan hydrobromide was incorporated into albumin-crosslinked polyvinylpyrrolidone hydrogels by equilibrating the gels in a saturated drug solution followed by freeze drying to entrap the drug in the network. Through freeze drying, highly porous hydrogels containing uniformly dispersed drug were produced. Drug content in the gel increased as a function of the number of drug loading-freeze drying cycles. Solvent penetration into freeze-dried gels resulted in an initial isotropic collapse of the network followed by a gradual increase in gel size due to swelling. In the presence of pepsin, freeze-dried networks degraded at a much faster rate than non-freeze-dried control samples. Drug release from freeze-dried hydrogels was degradation-independent and inconsistent with conventional solute transport mechanisms through swellable low surface area devices. The rate of drug release was dependent on the amount of drug loaded into the freeze-dried matrix. The potential use of these devices for long-term oral drug delivery is discussed.

Keywords: Freeze drying; Hydrogel; Albumin; Pepsin; Enzymatic degradation; Solute transport; Drug delivery

Introduction

Polymeric devices have been used extensively in the area of controlled drug delivery [1–6]. A variety of drug-loaded devices have been fabricated using techniques involving solvent casting [7,8], injection molding [9], compression molding [10–12], and microencapsulation [13–18]. With respect to hydrogels, drug loading has primarily been limited to the equilibration of gels in a drug-containing solvent followed by drying [19–24] or by incorporating the drug during synthesis of hydrogels [25–28]. In the former case, upon removal of the solvent, undesirable drug migration to the surface of the gel can result depending on the properties of the solvent and drug [22]. When solute migration is apparent, both drug content and drug uniformity within the matrix become limited. In the latter case, when the drug is loaded during the formation of the network, events such as autoacceleration can lead to the degradation of thermally labile drugs. In addition, purification of the hydrogel network could result in unnecessary and even costly loss of drugs. Consequently, for the practical application of hydrogels as long-term drug delivery devices, drug content, drug uniformity and drug stability should be carefully considered to ensure therapeutic activity and to minimize undesirable release properties. Recently, albumin-crosslinked hydrogels have been developed as poten-

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tial platforms for oral drug delivery [29–31]. Since hydrogel retention was observed in the canine stomach for up to 60 h [32], the use of these systems for long-term oral drug delivery is promising. With this in mind, the development of an efficient means for drug loading into enzyme-digestible hydrogels using the process of freeze drying was initiated. As a first step towards this goal, the effects of freeze drying on hydrogel swelling, hydrogel degradation, multiple drug loading and drug release properties was studied.

Materials and Methods

Hydrogel preparation

Albumin-crosslinked polyvinylpyrrolidone (PVP) hydrogels were prepared in distilled deionized water using 1-vinyl-2-pyrrolidinone (Aldrich, Milwaukee, WI, U.S.A.) at 36% (w/v),2,2-azobis(2-methylpropionitrile) (Eastman Kodak, Rochester, NY, U.S.A.) as initiator at 0.5% (w/w) of the monomer, and 90% alkylated albumin as a crosslinking agent at 6.5% (w/w) of the monomer [29,30]. The monomer solution was degassed and purged with nitrogen three times followed by polymerization at 60°C for 18 h under nitrogen. Once polymerization was complete the gels were removed and cut into discs (12 mm diameter×5 mm thickness). The gels were then purified and dried as described previously [30]. The swelling and degradation of freeze-dried gels were compared with those of air-dried gels. The gels were frozen in the swollen state at −70°C and then freeze dried using a model USM-15 freeze dryer (Virtus Co., Gardiner, NY, U.S.A.).

Drug loading

Dextromethorphan hydrobromide (Hoffmann-LaRoche, Nutley, NJ, U.S.A.) was loaded into hydrogels by equilibrating the gels in a drug-saturated solution (37.6 mg/ml) at 37°C for 48 h. Following drug incorporation, some hydrogels were air dried for 4 days followed by oven drying at 60°C for 24 h while other hydrogels were freeze dried. A total of 4 drug loading cycles were carried out on both air-dried and freeze-dried gels by re-equilibrating drug-loaded gels in a drug saturated solution in the manner described above.

Dynamic swelling studies

To assess the effects of freeze drying on the swelling behavior, freeze-dried and air-dried gels were allowed to swell from the dried state in pepsin-free simulated gastric fluid at 37°C [33]. Homogeneous gel swelling was achieved by placing a steel wire mesh in the swelling containers to prevent freeze-dried gels from floating on the surface of the medium. At timed intervals the weight, diameter, and thickness of the gels were recorded. The diameter and the thickness were measured using a ruler. The swelling ratio (Q) was then determined from the following relationship:

$$Q = W^*/W$$

where W^* and W are the weights of the swollen and dry gels, respectively.

To characterize the degradable properties of freeze-dried hydrogels, freeze-dried and air-dried gels were added to pepsin-containing simulated gastric fluid at 37°C. The concentration of pepsin (Sigma, 2500 units/mg) used for all degradation studies was 250 units/ml. This concentration was selected to avoid concentration-dependent changes in the degradation behavior [34]. It was found previously that at lower pepsin concentrations gel degradation was concentration-dependent. During the uptake of penetrants, the weight of the swollen gels was recorded until pepsin digestion rendered them unsuitable for continued measurements.

Studies on the PVP release from degrading gels

Freeze-dried and air-dried gels were added to pepsin-containing simulated gastric fluid in the USP II dissolution apparatus (VanKel Industries, Inc.) at 37°C. The paddle speed was maintained at 50 rpm. At timed intervals, 10-ml aliquots were removed from the 1 liter vessels and replaced with 10 ml of fresh-pepsin-containing

simulated gastric fluid. The samples were then analyzed spectrophotometrically against appropriate blanks at 211 nm for PVP using an absorptivity of 3.185×10^{-2} $cm^2 \mu g^{-1}$ that was determined in pepsin-free simulated gastric fluid. The pepsin concentration was maintained at 250 units/ml.

Drug release studies

The release of dextromethorphan hydrobromide from freeze-dried hydrogels and air-dried hydrogels was examined using a USP II dissolution apparatus. The paddle speed was maintained at 50 rpm. Release studies were performed at 37°C using both pepsin-free simulated gastric fluid and pepsin-containing simulated gastric fluid (250 units/ml). Over timed intervals, 10-ml aliquots were removed from the 1 liter vessels and replaced with 10 ml of fresh solvent. Drug release was determined spectrophotometrically against appropriate blanks at 278 nm using an absorptivity of 5.833 $cm^2 mg^{-1}$ that was determined in pepsin-free simulated gastric fluid. The release kinetics of dextromethorphan hydrobromide were analyzed using the following equation:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the total amount of drug released, k is a release constant, and n is the release exponent [23,35,36].

Results

Dynamic swelling

Through the use of freeze drying techniques, non-glassy, highly porous, polymer networks were formed. Hydrogels prepared by the air-drying method showed glassy network structures while freeze-dried gels were highly porous and comparable in size to the pre-freeze dried swollen state. Dynamic swelling studies showed that there was no apparent difference in the dynamic swelling behavior over time, although freeze-dried and non-freeze-dried gels were structurally distinct (Fig. 1). Solvent penetration into freeze-dried

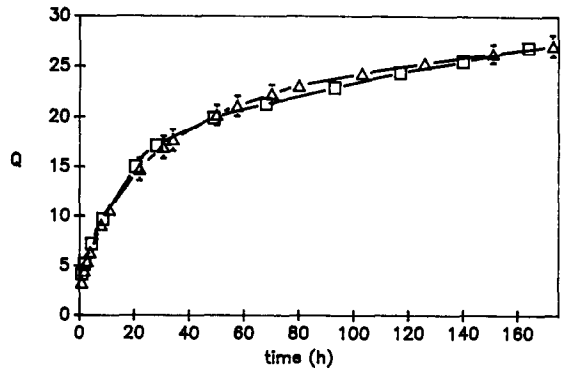

Fig. 1. Swelling kinetics of freeze-dried (□) and air-dried (△) hydrogels in simulated gastric fluid without pepsin at 37°C. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=4$).

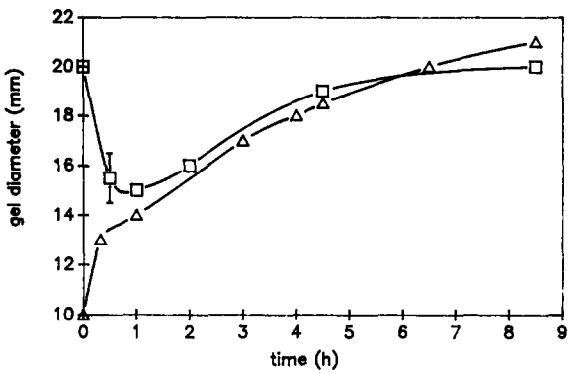

Fig. 2. Dynamic changes in gel diameter of freeze-dried (□) and air-dried (△) hydrogels resulting from solvent absorption. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=4$).

gels, however, was unique in that a substantial isotropic collapse of the network occurred initially (Fig. 2). Within the first 30 min of solvent penetration, the average diameter of the freeze-dried gels was reduced from 20 mm to 15 mm while the average thickness was reduced from 8.3 mm to 6.8 mm. Over the next 8 h, the gel diameter increased back to its original diameter. Solvent penetration was characterized by a rubbery gel front moving through an air-entrapped porous polymeric core. The rubbery outer core was found to resemble the pre-freeze-dried swollen state of the hydrogel. The air-entrapped inner core was

made up of a combination of dry porous polymer at the center and hydrated polymer near the rubbery front. After 72 h of swelling, the air bubbles could no longer be visualized inside the gel. Because of the slow release of air bubbles from the hydrogel, the rate of solvent penetration was believed to be reduced since the penetrant must first displace the air from inside the gel for further swelling to occur. Thus, the collapse of the gel network suggests that the characteristic relaxation time of the polymer in response to solvent absorption is much shorter than the characteristic diffusion time of the penetrant into the gel [37] while the rate of swelling appears to be dependent on the displacement of air from inside the gel.

Enzymatic degradation

The rate and extent of PVP release from freeze-dried hydrogels was found to be significantly higher than that of air-dried control samples (Fig. 3). Over a 7-day period, freeze-dried gels lost up to 40% (w/w) of the total PVP content while control samples lost only 18% (w/w) of the total PVP content. With respect to the air-dried samples, an initial 12 h lag period was observed prior to PVP release. The possible mechanism underlying these distinctly different degradation profiles is described below.

As seen in previous studies [30,31], swelling of both freeze-dried and air-dried hydrogels in the

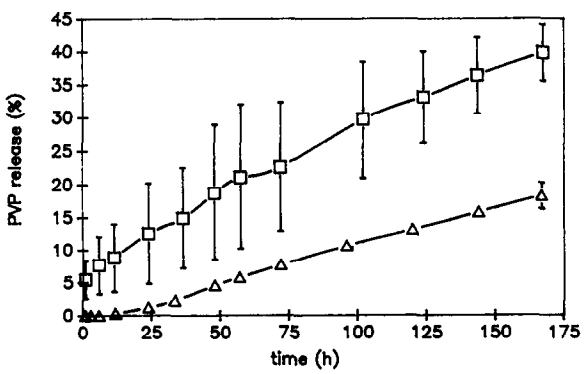

Fig. 3. Release of PVP as a function of time from freeze-dried (□) and air-dried (△) hydrogels in the presence of pepsin. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=4$).

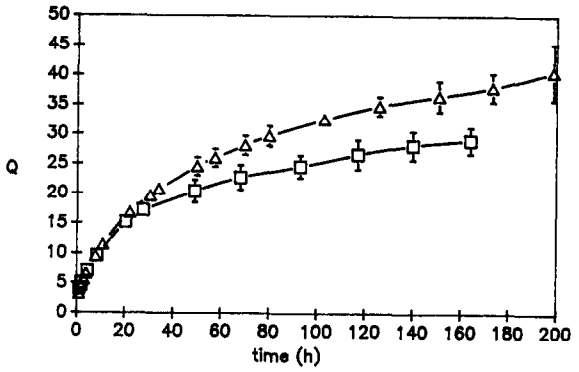

Fig. 4. Swelling kinetics of freeze-dried (□) and air-dried (△) hydrogels in the presence of pepsin. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=4$).

presence of the pepsin was attributed to bulk degradation. Bulk degradation was characterized by an increase in swelling ratios as compared to non-degrading control samples and a reduction in bulk integrity over time leading to complete gel disruption. Freeze-dried gels were found to swell to a lesser extent and degrade at a faster rate compared to air-dried gels (Fig. 4). The earlier onset of gel disruption and the reduction in Q was largely attributed to the more rapid loss of polymer chains from freeze-dried gels than from the air-dried samples.

Drug loading

Drug loading by the freeze-drying method resulted in dosage forms with greater drug uniformity as compared to the air-drying method. Although the content of drug increased as the loading cycle increased (Fig. 5), drug uniformity was not maintained by air drying (Fig. 6). Drug loading by the air-drying method resulted in drug migration to the gel surface upon solvent removal. Over multiple loading cycles, the amount of drug contained on the surface of air dried samples increased significantly. As a result, the weight and diameter of air-dried gels were comparable to that by the freeze-drying method after multiple drug loading cycles (Figs. 5 and 6). Thus, multiple drug loading by the air-drying method could not uniformly disperse the drug within the glassy

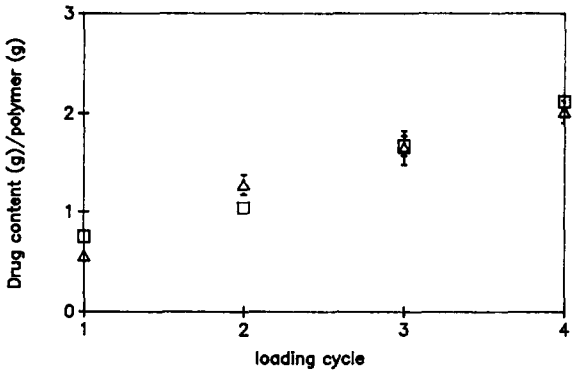

Fig. 5. The content of dextromethorphan hydrobromide in freeze-dried (□) and air-dried (△) hydrogels as a function of loading cycle. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=4$).

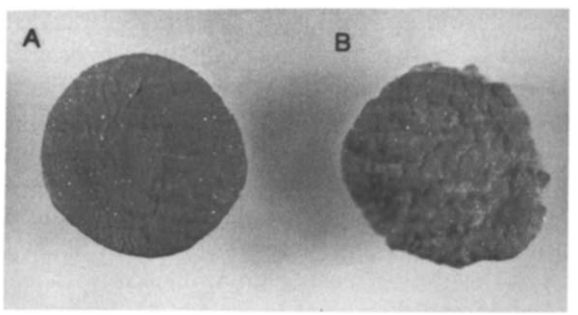

Fig. 6. Freeze-dried (A) and air-dried (B) hydrogels after 4 drug-loading cycles. Dextromethorphan hydrobromide was found to be more uniformly dispersed in the freeze-dried hydrogel compared to the air-dried gel where the drug resided mainly on the surface.

gel. In freeze-dried gels, however, a large fraction of the drug was localized within the network after single and multiple loading cycles. The surface of the freeze-dried gels was much more uniform after drug loading, and no visual evidence of drug migration to the surface was seen.

Drug release in the absence of pepsin

The process of freeze drying had a profound influence on the release of dextromethorphan hydrobromide from hydrogels (Fig. 7). After a swelling time of 90 min, an average of 63.7% (w/w) of the total loaded drug was released from air-dried gels while only an average of 38.6% (w/w)

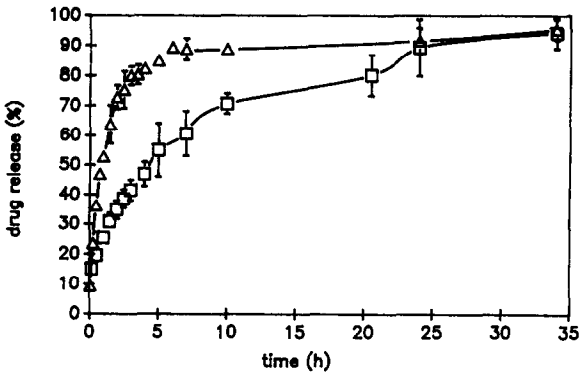

Fig. 7. Percent drug release as a function of time from freeze-dried (□) and air-dried (△) hydrogels in simulated gastric fluid without pepsin at 37°C. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=3$).

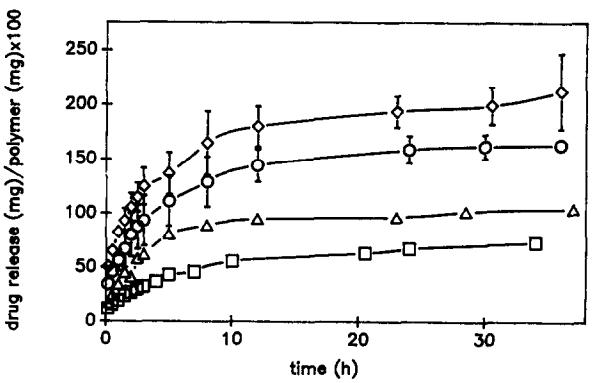

Fig. 8. Drug release from freeze-dried hydrogels as a function of time in simulated gastric fluid without pepsin at 37°C. □, one loading cycle; △, two loading cycles; ○, three loading cycles; ◇, four loading cycles. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=3$).

of the total loaded drug was released from freeze-dried gels. The more prolonged release of drug from the freeze-dried gel is not surprising since the drug was more uniformly dispersed in the freeze-dried gels compared to the air-dried gels where the localization of large amounts of drug at the surface was prominent. One may argue that differences in diffusional path lengths arising from the initial size of freeze-dried gels versus air-dried gels could account for the more sustained release of drug from freeze-dried gels. However, Fig. 2 shows that the freeze-dried and air-dried gels are

comparable in size after the first hour of swelling. Thus, differences in diffusional path lengths may have a minimal contribution to the drug release profiles observed in this study. Furthermore, if the drug was uniformly dispersed within the air-dried glassy gel, a more sustained release of drug would result due to the presence of a glassy/rubbery transition front which would restrict the release of drug to the rubbery phase of the gel. In contrast, freeze-dried gels would be expected to release the drug more readily since the highly porous network can facilitate drug release instead of restricting it. Fig. 7 indicated that the rate of drug release from air-dried gels was more rapid than from freeze-dried gels. Thus, the lack of drug uniformity within the air-dried network is further supported.

The exponential term (n) in eqn. 1 was used to determine the mechanism of drug release for the first 60% of the total drug released. Air-dried hydrogels were found to release drug by an anomalous transport mechanism ($n=0.67$). Drug release from the freeze-dried gel was not consistent with either Fickian ($n=0.5$), anomalous ($0.5<n<1.0$), or case II ($n=1.0$) transport mechanisms, since $n=0.44$. Although this phenomenon requires further investigation, it is conceivable that the collapse of the freeze-dried network upon solvent penetration may have influenced the kinetics of drug release significantly.

The release profiles of dextromethorphan hydrobromide from multiple loaded freeze-dried hydrogels were found to be consistent with drug release from related freeze-dried systems [16,17]. As the content of drug increased inside the hydrogel, an increase in the rate of drug release was observed (Fig. 8). The exponential term (n) for drug release was found to range from $n=0.44$ for gels loaded once to $n=0.32$ for gels loaded four times.

Drug release in the presence of pepsin

The release of dextromethorphan hydrobromide from both air-dried and freeze-dried hydrogels in the presence of pepsin was determined to be degradation-independent. The release of drug from degrading hydrogels was not significantly different from that of non-degrading hydrogels (Fig. 9). Degradation-independent drug release may have arisen due to two factors. First, the high solubility of dextromethorphan hydrobromide led to a rapid rate of drug dissolution and release upon solvent penetration. Second, the slower relative rate of hydrogel degradation did not significantly alter the drug-releasing environment with respect to non-degrading hydrogels. Degradation-dependent drug release would be expected if gel degradation was more prevalent. Further studies are needed to support this concept.

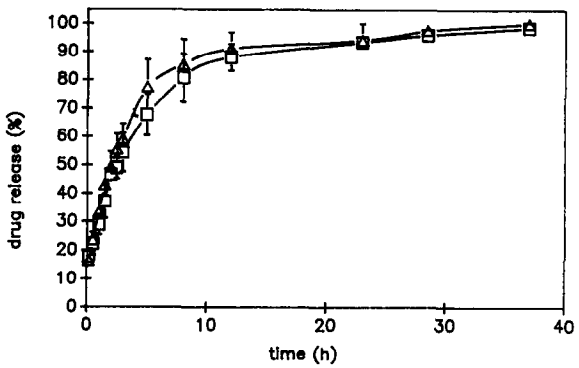

Fig. 9. Percent drug release as a function of time from freeze-dried hydrogels in the absence of pepsin (△) and in the presence of pepsin (□). The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n=3$).

Discussion

A large amount of a hydrophilic drug was uniformly incorporated into enzyme-degradable hydrogels by freeze drying. The content of the loaded drug increased linearly as a function of the number of loading cycles. In the swollen state, since 95% of the hydrogel is water, a large portion of the solvent-occupied volume could be utilized for further incorporation of drugs. Consequently, the use of freeze drying enables one to minimize the amount of polymeric materials required for dosage form preparation while maximizing the total drug content in the delivery system. In short, the three step process consisting of gel preparation, drug loading, and freeze drying may be a useful

technique for uniformly loading hydrophilic drugs into hydrogels.

The swelling kinetics of both freeze-dried and air-dried hydrogels were comparable even though structural changes arising from solvent penetration were distinctly different. Solvent penetration into freeze-dried hydrogels resulted in a 25% reduction in gel size over the first 30 min. The time required for the freeze-dried network to regain its original dry state dimensions was approximately 8 h. It should be noted, however, that this 8-h time constraint is likely to vary depending on the initial size and porosity of the network.

The release of PVP from freeze-dried hydrogels in the presence of pepsin was found to be more prominent than that from air-dried gels. A 12-h lag phase in PVP release was observed for air-dried gels while PVP release from freeze-dried gels was less than 1 h. Network digestibility may be explained by considering the extent of conformational constraints on oligopeptide segments that exist between polymer chains before and during solvent uptake. When the extent or degree of conformational constraints is high, the rate of enzymatic degradation is expected to be low due to the limited access to cleavable sites on the protein segments. When the degree of constraints become low as a result of swelling, enzymatic degradation is expected to be enhanced since the protein segments are more accessible to cleavage.

In the case of air-dried gels, the presence of a "glassy" polymer significantly reduces the probability of enzymatic degradation by limiting the conformational freedom of the oligopeptide segments. During solvent uptake, the degree of constraint is reduced due to swelling. Consequently, segment constraint is highest in the "glassy" phase and lowest in the rubbery phase. Since the degree of conformational constraint is largely influenced by the presence of a glassy core, gel degradation is expected to be enhanced once the glassy core has disappeared due to swelling. At that point, large constraints on oligopeptide segments are liberated and the hydrogel becomes more susceptible to enzymatic degradation. Gel degradation by the above mechanism is consistent with the 12-h lag period observed in this study for PVP release from air-dried gels. In the case of the freeze-dried network, the absence of a glassy/rubbery transition front combined with the porous structure of the freeze-dried network served to enhance the release of PVP. During solvent uptake, gel swelling was characterized by a rubbery gel front moving through an air entrapped porous polymeric core. Because a glassy/rubbery transition front does not exist, no significant barrier is present to constrain the oligopeptide segments during swelling. As a result, the average degree of conformational constraint is largely reduced at an earlier stage in swelling and thus the rate of gel degradation is enhanced. Compared to air-dried glassy polymers, the release of PVP from freeze-dried networks was more rapid as seen in Fig. 3.

Drug release from both air-dried and freeze-dried hydrogels was found to be degradation-independent. Drug release from freeze-dried gels was determined by a transport mechanism that may be controlled by the collapse of the network and the presence of a porous/rubbery swelling front during solvent absorption. As the drug load increased, however, only the rate of drug release was found to increase. The use of a hydrophilic drug in our study largely contributed to the limited sustained release properties from the device. With respect to long-term oral drug delivery, however, diffusion-controlled release may have a minimal effect on drug release from the stomach due to the presence of gel surface erosion under fasted and fed conditions [32]. Thus, it may be possible to utilize both erosion-controlled and diffusion-controlled mechanisms to provide sustained drug release even when the drug is hydrophilic.

In summary, the use of freeze drying represents a new means of homogeneously incorporating and dispersing hydrophilic drugs in enzyme-degradable hydrogels. The application of this process in the development of long-term oral drug delivery systems is promising.

Acknowledgements

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